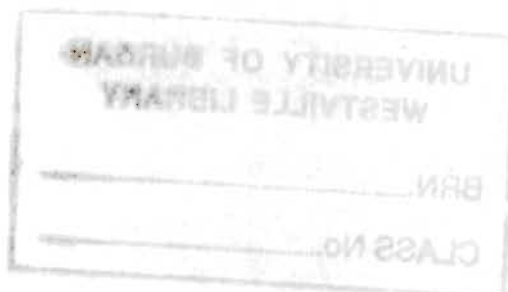# A STUDY OF THE RELATIONSHIP BETWEEN THE PHARMACOKINETICS AND THE PHARMACODYNAMICS OF ATENOLOL IN BLACK AND WHITE SUBJECTS USING AN EFFECT MODELLING TECHNIQUE

Margaret Lynn McFadyen

A Thesis Submitted to the Faculty of Health Science, University of Durban-Westville, Durban, in fulfillment of the requirements for the degree of Doctor of Philosophy.

Durban 1991

To Jean and Don

DECLARATION

I declare that this thesis is my own, unaided work with the exception of the areas indicated in the acknowledgements. It is being submitted to the University of Durban-Westville for the degree of Doctor of Philosophy. It has not been submitted to any other university.

....
M L McFadyen

..23rd. day of ...December........, 1991

ii

ACKNOWLEDGEMENTS

ABSTRACT

Although beta-blockers are considered among first line antihypertensive agents, it is well recognized that not all patients respond to usual doses with an adequate drop in blood pressure. Beta-blockers have been reported to be less effective in blacks and the elderly although the reasons for the inadequate blood pressure response have not been determined with any certainty.

Accordingly, the objectives of the study were to administer 50 mg of IV atenolol to normotensive healthy black and white volunteers and to:

i)   document any ethnic differences in blood pressure heart rate and plasma renin activity responses;

ii) assess the pharmacokinetics of atenolol in blacks and whites;

ii) define the atenolol concentration effect relationship with respect to reduction in exercise HR in individuals. in order to ascertain if any ethnic differences exist with respect to maximal effect or sensitivity to beta$_1$-blockade.

Sixteen normotensive subjects (8 black and 8 white) between the ages of 20 and 30 years participated in the study, which was placebo controlled, single blind and crossover in design. Blood was sampled at intervals for 36 hours after placebo or atenolol administration in order to measure atenolol concentrations (14 subjects) and plasma renin activity (5 black and 5 white subjects). Supine and erect systolic and diastolic BP were measured at intervals after drug and placebo administration as was resting and exercise HR. The periodic sub-maximal exercise entailed bicycle ergometry for 3 minutes, at a constant load predetermined to raise HR to at least 140 beats per minute in that individual.

Initially, the pharmacodynamic data (BP, HR and PRA) was

analyzed in isolation from concentration. Analysis of variance (ANOVA) was used to discern if the drug caused any effect relative to placebo at each time point of measurement, and if so whether the effect might differ between the races. The difference in area under the curve (AUC) from 0 to 12 hours after placebo and atenolol was employed as an alternative approach in assessing an individual or group's overall response to atenolol. Responses to atenolol were similar to those reported by other investigators. As expected atenolol had the greatest and most consistent effect on exercise tachycardia. The effects of atenolol on resting HR, systolic and diastolic BP were slower in onset and were influenced to a far greater extent by factors other than treatment, leading to baseline noise in the measurements. The PRA showed great intra- and inter-individual variation. There were no marked racial differences in treatment response in the ANOVA time point analysis for any of the effects measured. However, using AUC differences, supine systolic BP was found to be lowered significantly less in black individuals compared to whites. Moreover, this supine systolic BP response in individuals showed a significant correlation with baseline PRA (r^2=0.5782, p<0.0107). Unfortunately, there were insufficient measurements to detect possible differences in the regression line between blacks and whites.

The atenolol plasma-concentration time data was analyzed in 14 volunteers, by model independent methods as well as by compartmental modelling using two and three compartment open pharmacokinetic models. The compartmental modelling involved the use of two alternative approaches:

i)   the standard two stage (STS) method where data from an individual was used to generate pharmacokinetic parameters for that individual by extended least squares (ELS) regression. The individual data was then grouped and the black and white groups compared.

ii)   NONMEM analysis of data from all volunteers was used

to give group parameter estimates with quantitation of inter- and intra-individual variation in parameters. Race as a possible factor affecting inter-individual parameter variation was evaluated.

Model independent mean estimations of CL (17.4 L/hr) and V_{ss} (126 L) were consistent with STS two compartment modelling (CL of 17.2 L/hr and V_{ss} of 126 L). However, NONMEM analysis indicated that a three compartment model described the data better than a two compartment model. The three compartment NONMEM parameter estimations of CL and V_{ss} were 13.6 L/hr and 151.6 L respectively. Although terminal elimination half-life was consistent with literature values, the model independent and two compartment CL and V_{ss} values were larger than published values. The 3 compartment NONMEM CL value was much closer to reported values of 11-12 L/hr for healthy young volunteers. None of the methods showed any ethnic differences in the disposition of atenolol.

The last stage of the study involved the fitting of pharmacodynamic models to the effect data (in individuals by ELS regression and in the group by NONMEM) with the pharmacokinetic parameters constrained to those from the best fit pharmacokinetic analysis. The linear, log-linear E_{max} and sigmoid E_{max} models were evaluated. Because of the inadequate design of the study in that too few measurements were carried out when effect was undergoing maximal change, the fitting of individual effect data was problematic. In 11 of the 14 subjects the E_{max} or sigmoid E_{max} model gave a reasonable fit with no significant differences noted between blacks and whites in either E_{max} or IC_{50} values. Using NONMEM, the sigmoid E_{max} model appeared the most appropriate with estimated parameter values for E_{max}, IC_{50} and slope (n) of 42.7 bpm, 32.4 ng/ml and 0.783 respectively. Race did not influence the inter-individual variation in either E_{max} or IC_{50} to any significant degree.

In conclusion, there was no significant ethnic difference

in the pharmacokinetics of the drug nor was there any difference in the sensitivity of the $beta_1$-receptors responsible for exercise tachycardia. In the light of the above, the finding of a significantly lower overall systolic BP response as measured by difference in AUC between placebo and atenolol in normotensive blacks when compared to whites was surprising. The difference needs to be confirmed by further studies in hypertensive patients. The utilization of NONMEM for pharmacokinetic-dynamic modelling and dose ranging studies with beta-blockers where effect variability is related across a continuum to factors such as PRA, is a potentially powerful tool in elucidating the mechanism of action of these agents as well as the factors predicting response variability across populations.

CONTENTS

CHAPTER 1
AN OVERVIEW OF THE PHARMACODYNAMICS AND
PHARMACOKINETICS OF BETA-BLOCKERS

CHAPTER 2
AN OVERVIEW OF THE DOSE-CONCENTRATION-EFFECT RELATIONSHIP

CHAPTER 3
METHODS

CHAPTER 4
PHARMACODYNAMICS IN BLACK AND WHITE VOLUNTEERS
EXPERIMENTAL RESULTS AND DISCUSSION

CHAPTER 5
PHARMACOKINETICS IN BLACK AND WHITE VOLUNTEERS
EXPERIMENTAL RESULTS AND DISCUSSION

CHAPTER 6
PHARMACOKINETIC-DYNAMIC MODELLING
EXPERIMENTAL RESULTS AND DISCUSSION

APPENDIX 1
APPENDIX TO CHAPTER 3

APPENDIX 2
APPENDIX TO CHAPTER 4

APPENDIX 3
APPENDIX TO CHAPTER 5

APPENDIX 4
APPENDIX TO CHAPTER 6

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Since their introduction into clinical medicine in the mid-1960s the beta-adrenoceptor blocking drugs have become the most commonly prescribed drugs for cardiovascular diseases including hypertension, angina pectoris and cardiac arrhythmias (Weiner 1985). Their efficacy as antihypertensive agents is evidenced by their having been considered first line drugs in mild to moderate hypertension in many countries, especially in Europe. In the USA they were slower to gain acceptance and were generally considered the second line of treatment following thiazide diuretics (Kaplan 1983, Thadani 1983).

It is recognized that there are some patients who do not respond with an adequate fall in blood pressure when given usual antihypertensive doses of beta-blockers. Blacks and the elderly are amongst those reported to be less likely to respond to beta-blockade (Opie 1983, Thadani 1983).

Since the first report of limited efficacy of propranolol in hypertensive Jamaicans (Humphreys & Delvin 1968) many other studies have pointed to a relatively poor anti-hypertensive response to beta-blockers in blacks (Abson et al 1981, Richardson et al 1968, Seedat & Reddy 1971, Seedat 1980, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1982a, 1982b, 1983).

The South African black urban population appears to have a particularly high incidence of hypertension and this is associated with high morbidity and mortality (Seedat 1983). With increasing urbanization the problem is likely to become ever greater. It is therefore necessary to have safe and relatively cheap agents which can effectively lower blood pressure. The apparent lack of efficacy seen with beta-blockers is thus an important issue.

Although beta-blockers have been in use for over 25 years their mode of antihypertensive action remains unclear. Since all beta-blockers, regardless of ancillary properties, lower blood pressure to the same extent, it is certain that the antihypertensive effect is some function of $beta_1$-receptor blockade, albeit indirect and apparently delayed relative to chronotropic effects. On the other hand it has been claimed that there is no relationship between antihypertensive effect and either plasma concentration or $beta_1$-receptor blockade as measured by reduction in exercise tachycardia (McDevitt 1979). There are thus a number of questions to be answered:

i)   How do beta-blockers lower blood pressure?

ii)   What is the relationship between concentration and antihypertensive effect? (There must be some relationship even if it is not direct).

iii) Why is it that people do not all respond with an adequate fall in blood pressure?

iv)   Is the apparent poor response in the elderly and in blacks related to alterations in beta-receptor sensitivity or the intrinsic activity of the beta-receptor system or is it due to pathophysiology at another level of blood pressure regulation?

Accordingly, the objectives of the study were:

1.   To document any differences between black and white normotensive volunteers in blood pressure and heart rate responses to the administration of intravenous atenolol.

2.   To define the atenolol concentration-effect relationship with respect to inhibition of exercise tachycardia in individual volunteers.

3.   To ascertain whether racial differences exist in the above relationship with regard to maximal response and sensitivity to beta-blockers.

CHAPTER 1

AN OVERVIEW OF THE PHARMACODYNAMICS AND PHARMACOKINETICS OF BETA-BLOCKERS

1.1. PHARMACODYNAMICS OF BETA-BLOCKERS

Sir Henry Dale, among the first to study adrenergic blockade, recognized that adrenaline had two distinct sets of actions, only one of which could be blocked with ergot (Dale 1906). However, it took more than 40 years before Ahlquist (1948) introduced the concept of alpha- and beta-adrenergic receptors.

It took a further 10 years before the first beta-adrenergic blocking agent, dichloro-isoproterenol was described, although its clinical usefulness was limited by a high degree of intrinsic sympathomimetic activity (Powell & Slater 1958, Moran & Perkins 1958). Sir Jim Black's group conceived the idea of using beta-blockers to treat angina and introduced the first clinically relevant agent, pronethalol, which had to be withdrawn because of tumour production in mice (Black & Stephenson 1962, Dornhorst & Robinson 1962). Subsequently Black et al (1964) introduced propranolol which, to date, remains one of the most widely used beta-blockers.

On the basis of differential responses to beta-agonists, Lands et al (1967) suggested subdividing beta-receptors into $beta_1$- and $beta_2$-receptors. This led to a search for and the introduction of a relatively cardioselective $beta_1$-blocker, practolol (Sandler & Clayton 1970). Since then, many beta-blocking agents have been developed and marketed. In the 1970s and 1980s they were amongst the most widely used drugs in cardiovascular medicine.

1.1.1. Properties of Beta-blocking Drugs

Although all beta-blockers are competitive inhibitors of the effects of catecholamines at beta-receptors they differ

with respect to ancillary properties such as selectivity for beta-receptor subtypes, intrinsic sympathomimetic activity and membrane stabilizing activity.

They all have at least one asymmetric carbon atom and thus exist as pairs of optical isomers. Beta-blockade is a stereospecific effect and the laevorotatory (l) or (-) isomer is much more potent in this respect than the dextro-rotatary (d) or (+) isomer. The (-) isomer of propranolol has 50 to 100 times the beta blocking capacity of the (+) isomer (Gibson 1974). Most beta-blockers are, however, marketed as racemates with the exception of (-) timolol (Drayer 1986).

Beta-blockers with relative selectivity (Table 1.1.) for blocking the cardiovascular effects of catecholamines were developed in an effort to minimise the risk of side effects on the bronchi, blood vessels and metabolism, associated with blockade of beta$_2$-receptors (Cruikshank 1980, Shand 1983). Clinically, the selective agents may be preferable in smokers and in diabetics where a diastolic pressor response could occur under non-selective blockade (Cruikshank 1980).

A number of the beta-blockers show a measurable response in the absence of an agonist, indicating that they are partial agonists (Table 1.1.). This property is termed intrinsic sympathomimetic activity (ISA) or partial agonist activity (PAA). The clinical relevance of ISA has been much debated (Opie 1983, Thadani 1983, Shand 1983) but the suggestion that ISA conveys protection in heart failure and asthma has not been conclusively proved (Shand 1983). Agents with ISA cause less resting bradycardia, less reduction in cardiac output and have a flatter dose response curve (Harry et al 1979, Shand 1983). This is true in both normotensive and hypertensive patients and applies irrespective of the cardioselectivity of the blockers (Svendsen et al 1979,

Svendsen et al 1981, Svendsen et al 1985). Assessment of concentration response relationships of beta-blockers with ISA <u>in vivo</u> is complicated. The concentration of endogenous agonist present is variable and generally unknown and, particularly at low concentrations, will have a marked influence on the degree of beta blockade.

Many of the beta blockers possess membrane stabilizing (MSA) or 'quinidine-like' actions (Table 1.1.), with isomers being equipotent in this respect (Breckenridge 1983, Shand 1983, Wood 1984). This effect of slowing the rate of rise of the intracardiac action potential requires propranolol concentrations well above those associated with substantial beta-blockade (Wood 1984). At therapeutic doses used in angina and hypertension this effect is thought to be clinically unimportant.

Table 1.1. Pharmacodynamic properties of beta blockers. (Adapted from Shand 1983, Wood 1984).

	BETA$_1$- SELECTIVITY	ISA	MSA
Acebutolol	+	+	+
Alprenolol	0	+	+
Atenolol	+	0	0
Carteolol	0	+	0
Metoprolol	+	0	0
Nadolol	0	0	0
Oxprenolol	0	+	+
Penbutolol	0	0	+
Pindolol	0	+	±
Practolol	+	+	0
Propranolol	0	0	+
Sotalol	0	0	0
Timolol	0	0	0

It is generally believed that in the treatment of hypertension and angina all beta-blockers are equally

effective regardless of which of these ancillary characteristics they possess (Breckenridge 1983, Opie 1983, Prichard 1974, Shand 1983, Wood 1984). However, Cruikshank (1980) reported that cardio-selective beta-blockers may have a slightly greater effect in lowering diastolic blood pressure than non-selective agents.

Atenolol is a relatively cardioselective beta-blocker with no ISA or MSA (Harry 1977) (Table 1.1.). It is marketed as the racemate.

1.1.2. Cardiovascular and Haemodynamic Effects of Beta-blockers

The most important pharmacodynamic effects of beta-adrenergic blocking drugs involve the cardiovascular system. They have negative inotropic, as well as negative chronotropic effects (Weiner 1985), affect cardiac conduction and are antiarrhythmic (Pimenta & Pereira 1986). Rather surprisingly, they also lower blood pressure.

The negative inotropic action together with the reduction in heart rate leads to a reduction in cardiac output (Ulrych et al 1968). This results in a beneficial influence on angina (Gibson 1974, Opie 1983, Prichard 1974) and may be implicated in the antihypertensive action (1.1.2.2.3).

1.1.2.1. Effect on Heart Rate

In normal subjects heart rate is determined by the balance between sympathetic stimulation and para-sympathetic inhibition (Guyton 1986) superimposed on intrinsic heart rate. Intrinsic heart rate is the rate devoid of any autonomic influences. This can be assessed after the autonomic influences have been removed with atropine and propranolol (Jose 1966). It is altered by disease states such as cardiac disease, thyrotoxicosis and pyrexia (Jose 1966).

The effect of a beta-blocker on heart rate is therefore not simply related to the concentration of the drug at the chronotropic beta receptors. Assessment must take into account the background influences including the autonomic tone (both sympathetic and parasympathetic) (Joubert et al 1988), other reflex mechanisms (Shand 1983), cardioselectivity (Brown et al 1983) or ISA of the beta-blocker (Svendsen et al 1979), underlying disease states and even the age of the subject (Jose 1966).

1.1.2.1.1. Resting Heart Rate

In the supine position at rest, the parasympathetic system is dominant (McDevitt 1977, Robinson et al 1966). Under these circumstances beta-blockers have less effect than during sympathetic stimulation.

Beta-blockers lower resting supine heart rate in both volunteers (Fuller & Vallance 1982, Maling et al 1979) and patients (McDevitt 1977) to a variable degree depending on the dose, the initial heart rate (Gibson 1974) and the degree of ISA of the particular agent used (Carruthers & Twum-Barima 1981). The greater the degree of ISA the smaller the reduction in resting heart rate (Svendsen et al 1985). Resting heart rate is therefore not a suitable parameter for estimation of beta-blockade (McDevitt 1979).

Untreated hypertensive patients and volunteers show intra-subject variability in heart rate when measured over 24 hours, with the lowest levels during sleep (Mancia et al 1984). Beta-blockers, whilst reducing heart rate, do not alter the relative 24-hour variability (Mancia et al 1984).

1.1.2.1.2. Stimulated Heart Rate

Tachycardia evoked by various stimuli including exercise is mediated by increased sympathetic activity as well as parasympathetic withdrawal (Gibson 1974, Guyton 1986). The contribution of beta-blockers to reduction in tachycardia

would therefore be expected to be greater than that seen in the resting situation.

In both patients and volunteers, beta-blockers reduce the magnitude of the increases in heart rate induced by isoprenaline administration (infusions and bolus doses), exercise, orthostasis, tilt, Valsalva's manoeuvre and anxiety (Gibson 1974, McDevitt 1977, Shand 1983, Svendsen et al 1981).

The cardioselective beta-blockers inhibit isoprenaline induced tachycardia less than the nonselective agents, possibly because isoprenaline may have a direct cardiac $beta_2$-mediated effect or because it causes an indirect reflex response due to vasodilatation (Brown et al 1983, McDevitt 1977, Perucca et al 1981, Shand 1983). The mode of isoprenaline administration (bolus injection versus continuous infusion) has been found to elicit contrasting effects on vagal reflexes (Arnold & McDevitt 1986). This may affect isoprenaline dose ratio displacement curves in the presence of beta-blockers.

Agents with ISA eg. pindolol show little influence under moderate sympathetic stimulation such as that induced by orthostasis (Carruthers & Twum-Barima 1981).

The most consistent effect of beta-blockers on HR is on exercise tachycardia since this results largely from $beta_1$-receptor stimulation (Brown et al 1983, Hager et al 1981, Robinson et al 1966). Under these circumstances of high adrenergic stimulation the differences seen at lower levels of sympathetic stimulation between agents with and without ISA, largely disappear (Svendsen et al 1981, Svendsen et al 1985).

1.1.2.2. Effect on Blood Pressure

The ability of beta-blockers to reduce blood pressure (BP), although not anticipated, was discovered early in the development of these agents (Prichard 1964a, Prichard & Gillam 1964b, Prichard 1966). During long term therapy, all beta-blockers, irrespective of cardio-selectivity, ISA or MSA, have been found to lower blood pressure without causing postural hypotension (Harry et al 1979, Opie 1983, Prichard 1966, Prichard & Gillam 1969, Thadani 1983, Simpson 1974).

1.1.2.2.1. Acute Effect on Blood Pressure
1.1.2.2.1.1. Intravenous Administration

It was initially believed that intravenous (IV) administration of beta-blockers had no effect on blood pressure in either normotensive or hypertensive individuals (Mason & Winer 1976, Prichard 1964a, Prichard 1966, Ulrych et al 1968, Bühler et al 1975a).

Even in a more recent series of studies using seven beta-blockers with different ancillary properties in healthy volunteers and patients with ischaemic heart disease, only exercise systolic BP was significantly reduced, with no effects on resting blood pressure observed (Svendsen et al 1979, Svendsen et al 1981, Svendsen et al 1985). Effects were, however, only followed for at most an hour after the last dose.

It has now been clearly shown that IV administration does affect BP in volunteers (Fagan et al 1982a, Fitzgerald et al 1978, Wilson et al 1982) and hypertensive patients (Okubo et al 1981, Shinebourne et al 1967). The effects on systolic post-exercise BP are most marked but resting systolic and, to a lesser extent, resting diastolic BP are also decreased. The effects depend on dose and are time-lagged relative to the effects on HR (See 1.3.2.2.).

The magnitude of change appears to be somewhat greater in hypertensive patients than in normotensive subjects. Shinebourne et al (1967), recording intra-arterial pressure, found that systolic BP fell more than diastolic BP after propranolol (0.1 mg/kg) in hypertensive patients at rest, on standing and on exercise. The magnitude of these changes was greater in these hypertensive patients than in normotensive angina patients subjected to the same procedures. Okubo et al (1981) also found differential effects after pindolol (0.002 mg/kg) with no change in BP in normotensive subjects but a significant fall in hypertensive subjects.

The reasons for the initial reports of lack of effect in both volunteers and patients may have been:
i)   the relatively small doses administered;
ii) the short period of observation (under one hour after dose) thus possibly missing the time-lagged hypotensive effect (see 1.3.2.2. below);
iii) many studies only report differences that reach statistical significance.

1.1.2.2.1.2. Acute Oral Administration
Post-exercise blood pressure
A significant reduction in post-exercise systolic blood pressure has been shown with single oral doses of bisoprolol (Leopold et al 1986), carteolol (Stoll et al 1981), metoprolol (Leopold et al 1986), penbutolol (Giudicelli et al 1977) and propranolol (Leopold et al 1986). Much smaller effects were seen on diastolic BP. Similar results on exercise systolic pressure were seen with pindolol (7.5 mg), metoprolol (80.5 mg) and propranolol (78 mg) after 6 doses (2 days treatment) (Gugler et al 1980).

Resting BP

Single dose or short term oral beta-blocker administration has inconsistent effects on resting blood pressure.

O'Conner et al (1985) reported no consistent effects on resting or standing systolic and diastolic pressure in volunteers given oral atenolol in doses up to 100 mg.

However, a few single dose studies in volunteers have shown significant changes in resting systolic pressure but smaller changes in diastolic pressure using pindolol (5, 10 and 20 mg) (Jennings et al 1979) and propranolol (80 mg) (Giudicelli et al 1977). Although a dose of 20 mg penbutolol caused no significant reduction in systolic BP (Giudicelli et al 1977) higher doses (25, 50, 100 mg) significantly reduced systolic BP with lesser effects on diastolic BP (Jun et al 1979).

In a double blind placebo controlled study of 3 days of atenolol treatment (100 mg per day), resting mean arterial pressure and systolic pressure were significantly lower 5 hours after the dose (Fuller & Vallance 1982). Three days treatment with oral atenolol (50 mg per day) lowered resting and exercise systolic blood pressure (Hespel et al 1986). Thus with slightly more prolonged treatment a similar pattern of greater influence on systolic pressure compared with diastolic pressure was seen.

In contrast to the above reports, two studies in healthy volunteers demonstrated clear cut changes in both systolic and diastolic BP at rest (Fagan et al 1982a, Maling et al 1979). Single oral doses of atenolol (100 mg) and propranolol (200 mg) caused significant reductions in resting supine systolic and diastolic blood pressures (Maling et al 1979). Fagan et al (1982a) showed that a single 80 mg oral dose of propranolol reduced systolic,

diastolic and mean arterial pressure by 10% three hours after the dose.

In mild to moderately hypertensive patients, single oral doses of propranolol (40-320 mg) decreased standing and supine systolic and diastolic BP by 6-13% (Fagan et al 1982b). In another study using single 80 mg doses of propranolol a significant reduction in systolic but not diastolic BP was produced (Leenen et al 1982).

Similarly, metoprolol (single 100 mg doses) administered to hypertensive subjects caused significant reductions in both systolic and diastolic BP (Myers & Thiessen 1980). However, with smaller doses (50 and 80 mg) only systolic BP was significantly reduced (Bengtsson et al 1975, Collste et al 1980).

In only one study in hypertensives who received 100 mg atenolol, was a significant reduction of diastolic BP found without a corresponding significant effect on systolic BP (Holtzman et al 1986).

In summary then, as with IV administration, single oral doses of beta-blockers in patients and volunteers have produced relatively inconsistent effects on resting blood pressure. Effects on resting systolic pressure are more prominent than effects on diastolic BP but both are more pronounced with higher doses. Exercise systolic BP is generally reduced to a significant extent.

1.1.2.2.2. Chronic Treatment Effect on Blood Pressure
Numerous studies including open label, single blind and double blind placebo controlled designs, attest to the clinical efficacy of long term administration of beta-blockers in lowering systolic and diastolic BP. The use of these drugs in hypertension has been reviewed by various authors including McDevitt (1979), Prichard (1966),

Prichard (1979), Robertson (1983), Seedat (1975), Simpson (1974), Thadani (1983).

In the so-called stepped-care approach to hypertension (Hypertension Detection and Follow up Program Cooperative Group 1979a, 1979b) which became very popular in the 1980s, either beta-blockers or thiazide diuretics were recommended as the first step, the beta-blockers being more popular in Europe than in America (Moser et al 1977, Moser 1983).

A review of the literature regarding the hypotensive efficacy of beta-blockade reveals that the criteria by which efficacy is assessed differ among studies, making fair comparisons difficult. Most studies use one or more of the following assessment methods:

i)   the fall in BP expressed as a percentage of the baseline value;

ii) a significant fall in systolic and diastolic BP compared to pretreatment or placebo values;

iii) achievement of goal blood pressures eg. diastolic BP of 90 or 95 mm Hg; and at least a 5 mm Hg fall.

Depending on which method is used different conclusions could be drawn. Method i) is the least stringent and any percentage fall could be construed as a positive result. With method ii) if numbers in the study are small the chances of finding positive results will be reduced due to inter-patient variability. The use of method iii) would give better results in patients who start off at relatively lower blood pressures. To illustrate this, in a study of 15 patients on long term metoprolol (Rasmussen & Rasmussen 1979) falls of 11 and 8 % in systolic and diastolic BP respectively were found, constituting a statistically significant result. However 8 (53%) of the patients were actually considered to be non-responders because their diastolic BP did not drop below 95 mm Hg.

In many of the original trials frequently quoted as demonstrating the potent antihypertensive effects of beta-blockers, efficacy criteria and trial design were inadequate. In the often cited, first relatively large series of patients reported by Prichard & Gillam (1969) a claim of 84% response was made. However, only 14% of patients were on monotherapy and goal diastolic BP appears to have been 100 mm Hg. In another study, while propranolol reduced BP in 16 patients (84%,) 7 of these did not achieve diastolic pressures below 95 mm Hg (Frohlich et al 1968). Similarly, Paterson & Dollery (1966) in a crossover study reported that 240 mg propranolol lowered BP on average although it was slightly less effective than 50 mg hydrochlorothiazide. However, average diastolic BP did not fall below 100 mm Hg with either treatment.

A review of relatively large, well designed studies reveals that monotherapy with beta-blockers appears to reduce blood pressure in 50-60% of patients with mild-to-moderate hypertension with the magnitude of the reduction being in the range of 10-24 and 8-14 mm Hg for systolic and diastolic pressures respectively (Tarazi & Dustan 1972, Thadani 1983, Veterans Administration Cooperative Study Group on Antihypertensive Agents (VACSG) 1977, 1982a, 1982b, 1983).

The dose response curve for blood pressure reduction is relatively flat with little to be gained from resorting to very large doses (See 1.3.1.2.) although some investigators claim a biphasic response (Esler et al 1977, Hollifield et al 1976).

Notwithstanding their widespread use, the extensive research conducted and literature available on these agents, a number of inter-related questions have been extensively debated and remain essentially unanswered.

These include:

i)   What is the mode of the antihypertensive action of beta-blockers?

ii)   Why do some people not respond to beta-blockers?

iii) What is the time course of hypotensive actions?

iv)   Why is there apparently no relationship between concentration and the antihypertensive action?

These issues will be discussed in the following sections.

1.1.2.2.3. Mode of Hypotensive Action

Since all beta-blockers, regardless of ancillary properties, appear to lower blood pressure to about the same extent when used long term (Harry et al 1979, Vaughan Williams et al 1980) the hypotensive effect must be the consequence of blockade of $beta_1$-receptors albeit indirect and delayed relative to effects on heart rate (Connell 1986, Tarazi & Dustan 1972).

The hypotensive mechanism has been much debated (Connell 1986, Lowenthal et al 1984, Man in't Veld & Schalekamp 1983, Opie 1983, Prichard 1979, Robertson 1983, Seedat 1975, Simpson 1974, Thadani 1983). The following possibilities have been proposed but none are entirely satisfactory:

i)   resetting of baroreceptors (Prichard & Gillam 1964b);

ii)   fall in cardiac output (Frohlich et al 1968, Tarazi & Dustan 1972);

iii) suppression of renin release, activity and/or concentration (Bühler et al 1972);

iv)   interference with central sympathetic outflow in the vasomotor centre (Birkenhäger et al 1977);

v)   blockade of presynaptic beta-receptors thereby preventing neurotransmitter release (Langer 1977).

The first proposal is difficult to prove or refute. It suggests a long term adaptive regulatory response. Acute administration of oral propranolol and atenolol to normal

volunteers can cause 'resetting' of the baroreceptors (Deering et al 1988). Exactly how this relates to long term blood pressure reduction has not been elucidated.

Considering the second hypothesis, it has been shown that the inverse correlation between changes in cardiac output and vascular resistance, on long term beta-blocker therapy is shifted to a lower level of vascular resistance for a given cardiac output (Man in't Veld & Schalekamp 1983). Yet the beta blockers with ISA when given acutely, cause a much smaller reduction in cardiac output than those without ISA (Svendsen et al 1979, Svendsen et al 1981, Svendsen et al 1985) despite causing similar reductions in BP. Also the reduction in cardiac output by selective beta-blockers is not temporally related to the fall in BP (Tarazi & Dustan 1972). It is therefore difficult to envisage exactly how the reduction in cardiac output could be at the core of the hypotensive action.

Plasma renin activity is at least partially controlled by $beta_1$-receptors with $beta_2$-receptors playing a negligible role (Hespel et al 1986). A cardinal role for renin suppression in beta-blocker hypotension has many protagonists. The original theory by Laragh et al (1972, 1973) that essential hypertension can be divided into subtypes according to renin and other hormone profiling is supported by, amongst others, the large study of Bühler et al (1975a). This study showed a clearly different pattern of response to antihypertensive treatment (beta-blockers and diuretics) dependent on the renin-sodium index; those with a high index showed an excellent response (85%) to beta-blockade, those with normal renin levels a good but less consistent response whilst those with low renin-sodium index little or no response. The opposite pattern was evident with diuretics. The patients with a poor response and low renin-sodium index were generally older and had

higher diastolic pressures than those who showed a good response (See 1.1.2.2.4.2.).

There are a number of other studies which support a relationship between blood pressure reduction by beta-blockers and basal plasma renin activity (PRA) (Volpe et al 1983, Von Bahr et al 1976, Weber et al 1980) and plasma renin concentration (Amery et al 1977a). However, the extent of reduction of diastolic pressure by beta-blockade could not be related to the degree of PRA suppression (Holland & Fairchild 1982, Lehtonen et al 1977, Pedersen et al 1981, Salvetti et al 1977).

All beta$_1$-receptor blockers decrease plasma renin activity on exercise (Bühler et al 1975a) whereas only those without ISA have a significant effect on basal plasma renin activity (Bühler et al 1975b, Lijnen et al 1979, Stokes et al 1974, Traub et al 1980). This is used as an argument against the renin suppression theory (Stokes et al 1974) as all beta-blockers lower blood pressure to a similar extent.

Hollifield et al (1976) proposed a dual mechanism of action: a renin associated, low to moderate dose antihypertensive action and a high-dose, renin-independent action which might involve central effects. They showed that in both high and low renin hypertensive patients significant falls in BP unassociated with any changes in PRA occurred at doses above 160 mg of propranolol.

The argument against the beta-blockers having a central effect to limit sympathetic outflow from the vasomotor centre is that the accessibility of the various beta-blockers to the CNS bears no relationship to either the onset or magnitude of the hypotensive response (Man in't Veld & Schalekamp 1983). The acute haemodynamic effects of IV atenolol (limited CNS access) and metoprolol in

anaesthetized cats were found to be identical although metoprolol concentrations in CSF were 6-9 fold those of atenolol (Van Zwieten & Timmermans 1979).

The existence of presynaptic beta-receptors, which when stimulated lead to noradrenaline release, has been demonstrated (Langer 1977). It is postulated that raised plasma adrenaline in hypertension may facilitate noradrenaline release in this way. Blockade of these presynaptic receptors could conceivably reduce noradrenaline release on sympathetic stimulation, reduce vascular resistance and thus lower blood pressure (Man in't Veld & Schalekamp 1983).

The answer, to what the hypotensive mode of action of beta-blockers really is, probably lies in some complex combination of some or all of the above effects, particularly the sympathetic cardiovascular actions and renin-angiotensin fluid balance mechanisms interacting with the complex pathophysiology maintaining raised BP in hypertensive individuals.

1.1.2.2.4. Poor Response to the Hypotensive Effects of Beta-blockade

It was recognized quite early in the development of the beta-blockers that there are hypertensive patients who clearly do not respond with any fall in BP upon administration of beta-blockers alone, even in large doses. Patient groups who are reportedly less likely to respond to beta-blockers are blacks (Humphreys & Delvin 1968, Seedat & Reddy 1971, VACSG 1983) the elderly (Bühler et al 1975a) and patients with low basal PRA (Bühler et al 1972, Bühler et al 1975a, Distler et al 1978, Weber et al 1980).

Much debate on the reasons for a poor response to beta-blockers has centred on the renin status of patients. There is a reasonable amount of evidence that patients with low

renin levels will respond better to diuretic therapy and calcium channel blockers than to beta-blockers and angiotensin converting enzyme inhibitors while the opposite pattern of efficacy is found in high renin patients (Bühler et al 1975a, M'Buyamba-Kabanga et al 1986, Serlin et al 1980, Weber et al 1980). The higher incidence of so-called 'low renin hypertension' in blacks (Cruikshank & Beevers 1982) and the elderly (Bühler et al 1975a) seems to bear out the predictive role of renin status (see 1.1.2.2.3. above). The situation is less clear, however, in patients with intermediate renin activity and this may account for some of the conflicting results reported.

1.1.2.2.4.1. Poor Response in Blacks

Since the initial report by Humphreys and Delvin (1968) that propranolol was ineffective in hypertensive Jamaicans a number of other reports have suggested that beta-blockers are relatively ineffective in lowering blood pressure in blacks (Abson et al 1981, Hollifield et al 1978, Seedat & Reddy 1971, Seedat 1980, Richardson et al 1968).

These studies can be criticised on a number of grounds, including small numbers of patients and a relatively high pre-treatment diastolic BP. In the study of 25 patients where Seedat and Reddy (1971) showed a better response to propranolol in Indians than Blacks, pre-treatment diastolic BP was high, on average 136 mm Hg. This was also the case in the trials of Humphreys & Delvin (1968) and Abson et al (1981). Similar poor response rates (20-30%) have been found in other studies where patients who were presumably white had pre-treatment diastolic blood pressures above 110 mm Hg (Frohlich et al 1968, Paterson & Dollery 1966).

Studies in mild hypertension in black patients, comparing the efficacy of beta-blockers with diuretics, clearly show that diuretics are more effective than beta-blockers in lowering BP (Grell et al 1984, Moser & Lunn 1981,

Richardson et al 1968, Seedat 1980). This could be due to better efficacy of the diuretic and not necessarily poorer response to the beta-blocker. In one of the above comparative studies (Grell et al 1984) as well as other studies using only beta-blockers, a significant drop in BP in blacks was found (Oli 1982, Seedat & Stewart-Wynne 1972).

Beta-blockers could be termed mild hypotensive agents while diuretics are relatively potent blood pressure lowering agents in all patients.

The best evidence for a racial difference in response comes from studies involving both whites and blacks. The Veterans Administration cooperative study Group on Hypertensive Agents (1982a, 1982b) showed that overall (blacks + whites) hydrochlorothiazide (HCTZ) was more effective than propranolol in controlling BP (65.5% vs 52.8%) with HCTZ having a greater effect on systolic BP. This pattern was also seen when blacks and whites were considered separately. However, although the difference was not statistically significant, blacks showed a greater response than whites to HCTZ whilst whites showed a better response to propranolol than blacks. In another study nadolol was marginally more effective overall than bendroflumethiazide (49% vs 46%) (VACSG 1983). When whites and blacks were considered separately an equivalent response rate to diuretic was seen (46% in each) but more whites than blacks responded to nadolol (77% vs 31%). In a much smaller trial by Weber et al (1980) a greater response to diuretics was found in black than in white patients.

There is therefore some evidence that black patients with mild to moderate hypertension respond better than whites to diuretics with whites responding better to beta-blockers than blacks. The differences are, however, not dramatic.

A few attempts have been made to find the cause of the apparent racial difference in response to beta-blockers by looking more closely at cardiac beta-receptor sensitivity.

In healthy males, a significantly lower Emax/ED50 was found in whites compared with blacks when the effect of the beta-agonist, isoprenaline, on heart rate was assessed (Rutledge et al 1989). The authors caution however, that the mode of isoprenaline administration (bolus injection) leads to vagal withdrawal which may be subject to racial differences.

Although Venter & Joubert (1982, 1984a) initially claimed that black volunteers were less responsive than whites to the effects of beta blockade on exercise tachycardia they have subsequently demonstrated this to be a methodological artefact (Joubert et al 1988) due to ethnic differences in intrinsic heart rate and vagal withdrawal (Venter et al 1984b, Venter et al 1986).

Assessment of the beta-adrenergic pathway using isoprenaline stimulated cAMP production by lymphocytes has yielded conflicting results. Two reports indicated significantly higher cAMP production in blacks than in whites (Venter et al 1985, Rutledge et al 1990) although a third study reported lower cAMP levels in blacks than in whites (Stein et al 1987). Beta-receptor isotherm binding studies found no differences in B_{max}, sites per cell or k_d suggesting that if there was a racial difference it was probably distal to the receptor (Rutledge et al 1990). These studies were conducted in normotensive volunteers and involved the $beta_2$-receptor. It is therefore difficult to extrapolate these findings to hypertensive patients where the antihypertensive effect is assumed to be a $beta_1$-receptor mediated effect.

A much better case can be made for differences in the pathophysiology of hypertension in blacks and whites. In untreated hypertensives the percentage of black patients with volume expansion and low renin activity was double that in whites, whilst a higher percentage of whites were volume contracted with high plasma renin activity (Chrysant et al 1979). Racial differences in the pathophysiology and epidemiology of hypertension have been extensively reviewed by Aderounmu (1981) and M'Buyamba-Kabanga (1986). Evidence for differences include:

i)   differences in response to antihypertensive drugs including diuretics, beta-blockers and angiotensin converting enzyme inhibitors;

ii)   differences in complications with stroke and renal failure being much more common in blacks as opposed to ischaemic heart disease in whites;

iii) physiological differences in plasma and intra-cellular electrolytes and transmembrane fluxes, plasma renin activity, urinary kallikrein activity and plasma volume.

The above differences may be due to different environmental (socio-economic) factors overlaying the pathophysiology of hypertension, influencing the expression of the disease.

It has been suggested that the primary pathophysiological abnormality in essential hypertension is an increase in peripheral resistance (Rosendorff 1988) with two different mechanisms responsible for long term vasoconstriction identified (Laragh 1987). One mechanism is renin independent, requiring sodium retention and seems to be related to abnormal membrane transport of calcium and is clinically identified by low plasma renin and ionised calcium. The second is renin dependent and may involve an increase in cytosolic calcium (Laragh 1987).

In most black hypertensive patients the first mechanism appears to be operative and can be corrected by sodium depletion, calcium channel blockade or blockade of heightened sympathetic activity at the blood vessels by central adrenolytics or alpha-blockers (Rosendorff 1988). The second situation (more common in whites) would be expected to respond well to drugs which act on the renin-angiotensin system eg. beta-blockers and angiotensin-converting enzyme inhibitors.

There are suggestions that the racial difference in blood pressure response to beta-blockers may be less with beta-blockers with high ISA such as pindolol (Hall & Kong 1991) as well as the combined alpha and beta-blocker labetalol (Cubberley 1985, Flamenbaum et al 1985).

The efficacy in blacks, of drugs such as labetalol which also have alpha-blocking properties fit in with the above theories of renin independent mechanisms maintaining raised BP in blacks while renin sensitive mechanisms are operative in most whites.

The question of where those beta-blockers with strong ISA such as pindolol, fit into the picture, remains unanswered. These agents although reducing BP, do not reduce plasma renin activity. In a review of the effects of 10 different beta-blockers on basal haemodynamics in hypertensive patients it was concluded that all beta-blockers cause a shift in vascular resistance to a lower level which is always accompanied by a reduction in blood pressure during chronic therapy (Man in 't Veld & Schalekamp 1983). However, the acute response is based on a reflex response to cardiodepression which appears to differ depending on the level of ISA. Beta-blockers with strong ISA reduce BP in the face of a reduction of total peripheral resistance below pre-treatment levels without a net change in cardiac output, those with moderate ISA reduce BP without a net

change in total peripheral resistance but cause moderate cardiodepression while those without ISA cause gross cardiac depression with an elevated peripheral resistance above pre-treatment levels (Man in 't Veld & Schalekamp 1983). If the possession of ISA improves the hypotensive efficacy of beta-blockers in otherwise poor responders it may be the cardiodepressive effects possessed by those without ISA eg. propranolol and atenolol amongst others, which somehow negate the hypotensive effects common to all beta-blockers.

Beta-blockers without ISA (atenolol, propranolol, nadolol) were used in most of the studies suggesting a reduced hypotensive efficacy in blacks. Only one study comparing the acute haemodynamic effects in hypertensive Africans, of a beta blocker without ISA (propranolol 100 mg) and one with ISA (pindolol 20 mg) appears to have been done (Salako et al 1979). As expected the two beta-blockers differed in their effect on resting heart rate. Pindolol however, had a greater effect in reducing resting systolic BP than propranolol despite an almost identical reduction in exercise heart rate (Salako et al 1979). The relevance of this acute dose difference to long term BP reduction is uncertain. At this stage there appears to be very little evidence to support or refute the claim of better efficacy of beta-blockers with ISA in blacks. More studies need to be done to examine the effect of ISA on BP response in black hypertensives.

1.1.2.2.4.2. Poor Response in the Elderly.
A number of studies claim a reduced blood pressure response in elderly patients compared with younger patients (Bühler et al 1975a, Rasmussen & Rasmussen 1979). This poor response may be related to:
i)   reduced adrenoceptor sensitivity with age (Dillon
      et al 1980, Klein et al 1986, Vestal et al 1979);

ii) alterations in sodium excretion resulting in increased total body sodium and extracellular fluid volume. These changes are particularly prominent in patients with moderate myocardial insufficiency (Weiner 1985) which is more likely to occur in the elderly;

iii) age related reductions in renin status (Bühler et al 1975);

iv) higher pressures in the elderly (Bühler et al 1975a).

The evidence for reduced beta-receptor sensitivity is based on studies using the agonist, isoprenaline. Dillon et al (1980) showed a decreased maximal response and a displacement to the right of the dose response curve of isoprenaline stimulated cAMP production from the lymphocytes of the elderly. In two studies, the doses of isoprenaline required to raise heart rate by a given amount were significantly greater in elderly people compared with young volunteers (Klein et al 1986, Vestal et al 1979). In the one study the sensitivity to propranolol also appeared to be reduced, with an age related increase in the apparent dissociation constant (Vestal et al 1979). This contrasts with a study where timolol binding to cardiac beta-receptors has been shown to be unaltered by age (Klein et al 1986). These studies suggest a reduction in post-synaptic receptor sensitivity to agonists and antagonists.

In the elderly, BP is generally higher than in younger people and there is a higher incidence of low PRA possibly due to volume expansion. Points ii) to iv) are thus inter-related. Volume expansion could result in higher pressures and both higher pressures and volume expansion suppress renin.

There is evidence that failure to respond to beta-blockers with a drop in BP may be due to fluid retention. This possibility is strengthened by the appreciable fall in BP seen in non-responders to beta-blockers when a diuretic is added (Baber & Dawes 1979). This may be related to the opposite effects of the two classes of drugs on extracellular fluid volume (ECV). Rasmussen & Rasmussen (1979) showed that non-responders to metoprolol showed a significant 5% increase in ECV on metoprolol treatment whilst responders showed a non-significant 1% increase with no change in plasma volume in either group. The addition of a diuretic to metoprolol in the non-responders reduced the BP as well as the ECV. The non-responders were on average 20 years older than the responders.

1.2. PHARMACOKINETICS OF BETA BLOCKERS

The pharmacokinetics of a drug are determined to a large extent by its lipid solubility or polarity which is a consequence of its chemical structure. The lipid solubility determines its route(s) of clearance from the body as well as its penetration into tissue. While tissue penetration influences the intensity of effects, clearance will affect the duration of action.

The beta-blockers vary widely in their lipid solubility (Hinderling et al 1984) and thus in volumes of distribution, routes of clearance and elimination. The more lipid soluble, less polar agents are generally extensively metabolised by the liver, are more highly bound to serum protein, have larger volumes of distribution, more rapid clearance and thus shorter half-lives (Ochs et al 1985, Regardh 1982) (See Table 1.2). The pharmacokinetics of beta-blockers have been reviewed by Regardh (1982), Riddell et al (1987) and Ritschel (1980).

The pharmacokinetics of atenolol (one of the least lipid soluble beta-blockers) as well as those of the lipid soluble agent, propranolol, will be discussed in more detail. Propranolol is of interest because it has been used in many of the studies relating concentration to effect (see 1.3. below) and its kinetics contrast in many respects with those of atenolol.

1.2.1. The Pharmacokinetics of Propranolol
1.2.1.1. Absorption and Bioavailability
Propranolol, although well absorbed after oral administration, undergoes extensive pre-systemic (first pass) metabolism resulting in a variable and relatively low bioavailability ($\approx$30%). At low single doses (< 30 mg) bioavailability is very low but when the removal process

Table 1.2. Pharmacokinetic characteristics of some beta-blockers. The drugs are listed in increasing order of polarity. (After Regardh 1982, Riddell et al 1987).

DRUGS	F	$t\frac{1}{2}_\alpha$ (minutes)	V (L/kg)	Serum Protein Binding (%)	CL (L/kg/hr)	$t\frac{1}{2}_\beta$ (hours)	Organ of elimination
Propranolol	.3	5-10	3.6	93	1.0	3-4	liver
Alprenolol	.1	5-10	3.3	85	1.2	2-3	liver
Oxprenolol	.3	20	1.2	80	0.4	2-3	liver
Metoprolol	.5	5-10	5.0	10	1.0	3-5	liver
Timolol	.5	5-10	2.0	10	0.4	3-4	liver & kidney
Pindolol	.5-1	5-10	1.2	50	0.4	3-4	liver & kidney
Sotalol	.9	-	1.4	0	0.16	10-15	kidney
Nadolol	.3-.5	-	1.9	30	0.10	19	kidney
Atenolol	.5	20-30	0.7	5	0.10	5-7	kidney

F = bioavailability
$t\frac{1}{2}_\alpha$ = half-life of distribution
V = volume of distribution

CL = total clearance
$t\frac{1}{2}_\beta$ = half-life of elimination

becomes saturated at higher doses a larger fraction of the oral dose reaches the systemic circulation (Nies & Shand 1975). At steady state during 6 hourly dosing drug concentrations are essentially proportional to dose although hepatic extraction is still relatively high with only 20 to 50% of the dose reaching the systemic circulation (Nies & Shand 1975).

The extent of first pass metabolism is dependent on many factors (Riddell et al 1987, Routledge & Shand 1979) including dose, route and frequency of administration (Coelho et al 1983, Woods et al 1979). Since propranolol is a high extraction ratio drug, the bioavailability can be altered by changes in blood flow, concurrent food intake (Olanoff et al 1986, Routledge & Shand 1979) and other drugs which inhibit or induce enzymes. Propranolol itself reduces liver blood flow by reducing cardiac output and consequently can reduce its own elimination (Nies & Shand 1975). A 10-20 fold inter-individual variation in plasma concentration has been found in patients on the same dose (Esler et al 1977, Lehtonen et al 1977, Nies & Shand 1975, Serlin et al 1980).

1.2.1.2. Distribution

Propranolol has a relatively large volume of distribution and is rapidly distributed from the blood into various tissues including the brain (Riddell et al 1987).

As a basic drug, propranolol binds extensively (90-94%) to α_1-acid glycoprotein and to albumin (Riddell et al 1987). The extent of binding is highly variable (Steinberg & Bilezikian 1983) and can be altered by many conditions. This can influence the pharmacokinetics by changing distribution volume and altering half-life. The pharmacodynamics can also alter because it is essentially the free fraction which is active.

In inflammatory conditions where α_1-acid glycoprotein is raised increased binding of propranolol can occur (Regardh 1982). In one study a significantly higher degree of protein binding was demonstrated in hypertensive subjects compared with normotensive volunteers (McDevitt et al 1976).

1.2.1.3. Metabolism and Elimination

Propranolol is extensively metabolised by the liver to both inactive and active metabolites which include 4-hydroxypropranolol. In single dose studies where effects are measured shortly after oral dosing this metabolite may contribute to effect but because it has a shorter half-life than propranolol, effects seen at 6 hours are due mainly to propranolol (Nies & Shand 1975). In hypertensive patients on chronic therapy relatively low levels of 4-hydroxypropranolol have been found and it is unlikely that this metabolite contributes greatly to effect at steady state (Chidsey et al 1976, Wong et al 1979).

The oxidation of some beta blockers eg. metoprolol and timolol appear to be related to debrisoquine phenotype (Dayer et al 1985, Lennard et al 1986) which could account for some racial differences (Iyun et al 1986). Although propranolol also undergoes oxidation, its metabolism has been found to be unaffected by debrisoquine phenotype (Lennard et al 1986).

Bioavailability, protein binding and clearance are altered by liver disease, necessitating dose reduction (Regardh 1982).

There is a very wide inter- and intra-individual spread of propranolol concentration to dose ratios (Esler et al 1977, Hitzenberger 1979, Lehtonen et al 1977). This is the result of variation in bioavailability, serum protein binding and extent of metabolism including production of active

metabolites. Defining concentration effect relationships for propranolol is complicated by this pharmacokinetic variability.

1.2.2. Pharmacokinetics of Atenolol
1.2.2.1. Absorption and Bioavailability

The oral bioavailability of atenolol is approximately 50% (Brown et al 1976, Conway et al 1976, Kirch et al 1981, Mason et al 1979, Wan et al 1979). Bioavailability is unaffected by dose up to at least 600 mg (Kirch & Görg 1982). Unlike propranolol, atenolol dose and concentration are linearly related (Amery et al 1977b, Ishizaki et al 1983, Mason & Winer 1976, Shanks et al 1977). In contrast to dogs where absorption is complete, man, rats, mice, rabbits and rhesus monkeys absorb atenolol incompletely after oral administration (Reeves et al 1978a, Reeves et al 1978b). Using radiolabelled atenolol, Reeves at al (1978b) showed that after oral dosing 47% of the dose was recovered from urine and 53% from faeces in contrast to 88% urinary and 10% faecal recovery after IV dosing. This study confirmed that the incomplete urinary recovery after oral dosing seen in earlier studies (Brown et al 1976, Conway et al 1976, McAinsh 1977) was due to incomplete absorption and not to extensive first pass metabolism as with propranolol.

Peak levels occur 2-4 hours after oral administration with an approximately 4-10 fold inter-individual variation (Amery et al 1977a, Ishizaki et al 1983, McAinsh et al 1980). Administration of atenolol with food reduces the AUC by about 20% (Melander et al 1979). Hypothyroid patients have a lower maximum atenolol concentration and AUC after oral administration than after correction of the hypothyroidism (Levesque et al 1990) implying reduced bioavailability in this condition.

1.2.2.2. Distribution

Any variation in serum protein binding of atenolol is not likely to alter effect dramatically since serum protein binding is less than 5%.

The plasma concentration-time decay can be described by a two or three exponential expression reflecting a two or three compartment open model.

Studies in which the distribution characteristics of atenolol have been investigated are summarised in Table 1.3. When doses were small (5-10 mg) the two compartment model appeared to be most appropriate probably because serum/plasma levels declined to below the assay detection limits of 10-20 ng/ml before the slow terminal elimination phase became evident (Buck et al 1989, Kirch et al 1981, Rubin et al 1982). In studies where larger IV doses (50 mg or greater) were used a 3 compartment model appeared to fit best for most individuals (Mason et al 1979) since levels of atenolol were detectable at 24 hours or longer after administration. This would account for the shorter half-lives reported with lower IV doses as compared with 50 mg IV doses (Rubin et al 1982) and oral doses of 100 mg or more. This methodological explanation is more likely than the suggestion that a saturable non-glomerular elimination pathway is operative and becomes saturated at doses above 10 mg (Rubin et al 1982).

Atenolol is rapidly distributed to extra-vascular tissue (half-life of about 20 minutes) (Buck et al 1989). The volume of the central compartment has been calculated as between 12 and 20 litres with that of the peripheral compartment being between 50 and 100 litres (Kirch and Görg 1982).

1.2.2.3. Elimination

Atenolol is mainly eliminated unchanged by the kidneys with less than 10% being metabolised (Reeves et al 1978b). The influence of metabolites (active or inactive) is therefore negligible in terms of the dose-concentration-effect relationship.

Although one study showed that age did not appear to alter atenolol disposition dramatically (Rubin et al 1982) another study showed a significantly increased AUC associated with decreased clearance in elderly hypertensive subjects compared with healthy young volunteers (Rigby et al 1985). A number of studies show atenolol plasma levels and clearance correlate closely with creatinine clearance (Amery et al 1977a, Ishizaki et al 1983). Impaired renal function can substantially reduce the clearance of atenolol and the elimination half life is prolonged from 6 to more than 100 hours in anephric patients (McAinsh et al 1980). Dose or dose interval adjustment is necessary in severe renal failure (McAinsh et al 1980a, Regardh 1982).

Not surprisingly, neither clearance nor pharmacodynamics of atenolol are related to debrisoquine oxidation phenotype (Dayer et al 1985, Lennard et al 1986, Lewis et al 1985).

Atenolol's clearance is dependent only on renal function and therefore plasma levels show little intra-individual variation and relatively small inter-individual variations (Ishizaki et al 1983).

Table 1.3. Pharmacokinetic parameters of atenolol after IV dosing.

References	No of Patients	Dose (mg)	V (L/kg)	CL (L/hr)	$t_{\frac{1}{2}}$ (hr)	No of Compartments
Reeves et al 1978b	2	5	76.00 (L)	5.85	11.7	–
Kirch et al 1981	7	5	1.20	9.00	5.9	2
Buck et al 1989	7 (young)	0.1 (mg/kg)	0.83	0.15 (L/hr/kg)	4.6	2
Wan et al 1979	6 (young)	50	–	9–14	5.33	3
Rubin et al 1982	7 (young) 7 (elderly)	10 10	0.55 0.75	12.18 9.78	3.33 3.52	2 2
Brown et al 1976	4	10,20, 50 & 80	51.2 (L)	5.8	6.06	3
Kirch et al 1981	7-normal GFR 8-moderate ↓ 4-pre-uraemic	5 5 5	1.2 – 0.9	9.0 4.2 1.5	5.9 14.0 42.1	2
Mason et al 1979	12 (young)	50	1.26	0.144 (L/hr/kg)	6.06	3

1.3. DOSE-CONCENTRATION-EFFECT RELATIONSHIPS OF BETA-BLOCKERS

1.3.1. Dose-effect Relationship

The steepness of the dose-effect relationship depends on which effects of beta-blockers are under consideration.

1.3.1.1. Negative Chronotropic Effects

Resting bradycardia is dose dependent for all those beta-blockers without ISA. However, with pindolol, reduction in resting heart rate has been shown to be inversely related to dose when assessed 1 to 3 hours after dose but is reversed at 24 hours post dose (Jennings et al 1979).

In volunteers, a linear relationship between dose and inhibition of exercise tachycardia has been demonstrated for atenolol (up to 200 mg), metoprolol (up to 400 mg), sotalol (up to 400 mg) (Harron et al 1981, Shanks et al 1977) and timolol (up to 25 mg) (Singh et al 1980). Exercise tachycardia was increasingly reduced with increasing doses of metoprolol from 25 to 100 mg and propranolol 20 to 120 mg but pindolol increased effects only from 2.5 to 5 mg with minimal further increases at higher doses (Gugler et al 1980). The magnitude of maximal inhibition of exercise tachycardia was also less with pindolol (25%) than with the other two drugs (30%).

In a large volunteer study of the influence of varying dosage regimens of propranolol on exercise tachycardia, the degree of beta-blockade at the daily minimum propranolol level (trough) was related to total daily dose and not to dose frequency (Mullane et al 1982). Regardless of how the daily dose was divided (twice or four times daily) an equivalent degree of inhibition of exercise tachycardia was observed before the morning dose with equivalent daily doses.

1.3.1.2. Hypotensive Effects

The dose response curve for BP reduction appears to be less steep than that for heart rate. In responders little further reduction in BP was seen over 200 mg metoprolol (Collste et al 1980), 75-100 mg atenolol (Douglas-Jones & Cruikshank 1976, Ishizaki et al 1983, Myers et al 1976, Amery et al 1977a) and 80 mg propranolol (Leenen et al 1982, Serlin et al 1980) although resting bradycardia increased with higher doses.

In one study, although BP reduction was more pronounced with increasing doses of propranolol neither mean dose (160 to 480 mg/day) nor concentration (98 to 215 ng/ml) could be correlated with mean decrease in BP (Lehtonen et al 1977). The reason could be that dose and concentration were near maximal.

It has been suggested that there may be a difference in the dose response curves of systolic and diastolic BP. Amery et al (1977b) showed a maximal effect on systolic BP at doses of 150 mg atenolol with no further significant decrease with doses of 300 mg and even 600 mg in some patients. Diastolic, BP however, decreased successively with increments up to a total of 300 mg per day. This suggests different mechanisms may be involved.

There is some controversy as to whether there might be a biphasic BP response (Esler et al 1977, Hollifield et al 1976) and whether BP can be effectively lowered in patients who do not respond to low doses of propranolol by using large doses (M'Buyamba-Kabanga 1986, Seedat & Reddy 1971). This is of academic interest only because side effects including bradycardia limit the use of very large doses.

1.3.1.3. Plasma Renin Activity

Renin suppression appears to occur at lower doses than are usually needed for BP reduction (Prichard 1979). Ishizaki

et al (1983) showed that renin suppression was maximal at doses of 25 mg of atenolol daily, which in most patients had little effect on BP. Similarly 40 mg propranolol induced maximal suppression of supine and furosemide stimulated renin levels and 60% suppression of standing renin levels whilst BP decreases were seen at doses from 40-160 mg daily (Leonetti et al 1975).

1.3.2. Time Course of Action
1.3.2.1. Negative Chronotropic Effects

In most studies, the time course of inhibition of exercise tachycardia by beta-blockers is the same as that of plasma concentrations. After IV administration maximal reduction of exercise tachycardia is seen at the first point of assessment, 5-15 minutes after doses of timolol and propranolol (Achong et al 1976). When beta-blockers are administered orally, the peak effects on inhibition of exercise tachycardia usually occur at approximately the same time as the peak concentrations. This has been found with propranolol (Giudicelli et al 1977) metoprolol (Wieselgren et al 1989), and pindolol (Jennings et al 1979).

Penbutolol appears to be an exception, with a delay of about 1 hour to peak chronotropic effects (Brockmeier et al 1988, Giudicelli et al 1977). This may be the result of the production of unknown active metabolites (Brockmeier et al 1988).

Achong et al (1976) have shown that the time course of the negative inotropic and chronotropic responses to timolol and propranolol are identical.

1.3.2.2. Hypotensive Effects

The time of onset and the time to development of maximal antihypertensive effects have been the subject of much controversy. Many publications, especially the earlier

ones, claimed that the hypotensive action was slow in onset requiring dose titration and weeks to months for maximal effects to develop (M'Buyamba-Kabanga et al 1986, Prichard 1964a, Prichard & Gillam 1964b, Prichard & Gillam 1966, Prichard & Gillam 1969, Tarazi & Dustan 1972). Since most of these studies increased doses at intervals (usually two weeks) and the patients were only monitored at these intervals it is not clear whether it was dose or time which was responsible for the observed increase in effects. Very few single dose studies in the 1960s and early 1970s assessed blood pressure responses.

The development of the hypotensive effect of beta-blockers is time-lagged by hours when compared with negative inotropic and chronotropic effects and with blood levels. In the early studies the hypotensive effects of single doses were probably missed since attention was focused on the time course of heart rate effects.

1.3.2.2.1. Intravenous Administration

In volunteers, bolus IV doses of propranolol (0.2 mg/kg) modestly decreased resting systolic, diastolic and mean arterial pressure at 3 to 6 hours after the dose (Fagan et al 1982a). A study with atenolol (10 mg) showed different time courses for systolic and diastolic BP (Fitzgerald et al 1978). Systolic BP was reduced from 15 minutes to 8 hours post dosing whilst diastolic BP was significantly decreased only from 4 up to 24 hours after the IV dose.

1.3.2.2.2. Oral Administration

There is now much evidence that effects on BP are seen after the first oral dose or at least within a few days, with the effect on systolic BP preceding that on diastolic pressure. It has been suggested that the extent of the initial effect is dose dependent; the bigger the starting dose the quicker the onset of effect (Pedersen et al 1981).

Normotensive Volunteers

In volunteers, single oral doses of both atenolol (100 mg) and propranolol (200 mg) caused significant reductions in resting supine systolic and diastolic blood pressures with the fall beginning 1 hour after administration and remaining below control values for 24 hours (Maling et al 1979). Peak effects were seen between 2-4 hours and 6-8 hours with propranolol and atenolol respectively. Fagan et al (1982a) showed that a single 80 mg oral dose of propranolol reduced systolic, diastolic and mean arterial pressure by 10%, three hours after the dose.

Oral pindolol (5, 10, and 20 mg) given to normotensive volunteers reduced resting systolic blood pressure with peak effects occurring between 1 and 3 hours post-dose (Jennings et al 1979). The effects of the two lower doses had worn off by 7 hours.

Hypertensive Patients

In hypertensive patients given single doses of propranolol (Fagan et al 1982b, Leenen et al 1982), effects on BP were seen within 6 hours. In the first study these effects increased with further dosing and appeared to parallel propranolol cumulation; at 3 days 89-92% of the total effects seen at 6 days were observed (Fagan et al 1982a).

Collste et al (1980) found that single doses of metoprolol produced falls in systolic and diastolic pressures of 57% and 23% of those seen with long term therapy with relatively greater effect seen on systolic BP. In another study single oral doses of metoprolol (50 and 80 mg) given to hypertensive patients decreased systolic BP within half an hour of administration with no effect observed on diastolic BP up to 6 hours post dose (Bengtsson et al 1975).

A single 100 mg dose of atenolol decreased supine BP in hypertensives producing a maximum decrease of 17 mm Hg at 6 hours and of 11 mm Hg at 10 hours for systolic and diastolic BP respectively (Leonetti et al 1980). In another study, oral atenolol (200 mg) caused a significant reduction in systolic pressure from 45 minutes onwards with a return to normal by 24 hours (Fitzgerald et al 1978). In contrast, reduction of diastolic pressure was only evident from 3-4 hours after oral dosing but persisted up to 24 hours after dosing. Curiously, in the same study, the time courses of effects of intravenously administered atenolol (10 mg) on both systolic and diastolic BP, closely paralleled those of oral dosing.

In a long term study in 15 patients who carried out home BP measurements, the major fall in BP occurred 24-48 hours after initiation of treatment with 200 mg atenolol three times daily (Amery et al 1977b). In another study of atenolol the first 100 mg dose caused a prompt (3 hours) and prolonged (up to 24 hours) reduction of supine and standing systolic and diastolic BP (Leonetti et al 1980). The extent and time course of the effects were not altered by repeated daily (100 mg) dosing for two weeks.

Many studies have shown that, in responders to beta-blockers, effects that were seen at the first assessment viz. one week (Harry et al 1979) two weeks (Marshall et al 1977, Myers et al 1976, Serlin et al 1980) or 3 weeks (Paterson & Dollery 1966) were not significantly different from those seen at later times.

1.3.2.3. Tremorolytic Actions

The tremorolytic actions of beta-blockers although mediated mostly by beta$_2$-blockade are interesting in that the time course of onset of effect is delayed with respect to that of heart rate although off set rates are similar. Abila et al (1985) conducted a very interesting experiment using three beta-blockers with different kinetic and dynamic

characteristics. They showed significantly greater rate constants for onset of cardiac effects than for tremorolytic effects, irrespective of the magnitude of the effects seen. Differences in the rate constants for the three drugs within the heart rate and tremor responses were not however, significant. The authors concluded that the delay in tremorolytic actions was possibly due to the beta-receptors being located in a relatively inaccessible compartment rather than to rate-limiting post receptor events.

1.3.3. Concentration-Effect Relationships of Beta-blockers
1.3.3.1. Negative Chronotropic Effects
1.3.3.1.1. Resting Bradycardia

A linear relationship between reduction in resting heart rate and the log of metoprolol plasma concentration within the range of 20-100 ng/ml has been demonstrated (Bengtsson et al 1975).

Maximal resting heart rate responses to propranolol occur at concentrations of 100 ng/ml (Lehtonen et al 1977). Significantly greater effects on inhibition of resting heart rate occurred at pindolol concentrations above 20 ng/ml compared with below 20 ng/ml but little further inhibition was seen in the range 21-160 ng/ml (Jennings et al 1979).

Other studies showed a poor relationship between propranolol (Hager et al 1981, Hitzenberger 1979) penbutolol (Jun et al 1979) and oxprenolol (Hitzenberger 1979) concentrations and changes in resting heart rate.

1.3.3.1.2. Inhibition of Exercise Tachycardia

Many studies, both acute and chronic have found a linear relationship between inhibition of exercise tachycardia and the log of plasma concentration of various beta blockers, including atenolol (Amery et al 1977b, McAinsh 1977, Shanks

et al 1977), acebutolol (Quarterman et al 1979, Woods et al 1979), alprenolol (Åblad et al 1974), bisoprolol (Leopold et al 1986), metoprolol (Woods et al 1979), oxprenolol (Mason & Winer 1976) penbutolol (Müller et al 1979), propranolol (Coelho et al 1983, Coltart & Shand 1970, Hager et al 1981, McAinsh et al 1978, McDevitt & Shand 1975, Mullane et al 1982, Van den Brink et al 1980, Woods et al 1979), nadolol and pindolol (Kostis et al 1984).

Fujimura et al (1990) demonstrated a greater reduction of exercise tachycardia with morning oral dosing of propranolol than with evening dosing. They ascribed this to diurnal variation in plasma concentrations of propanolol resulting from an increased absorption rate in the morning. They found no difference between the morning and evening regression lines relating percentage reduction in tachycardia to the log of plasma propranolol concentrations.

A linear relationship between propranolol plasma concentration (up to 300 ng/ml) and reduction in exercise tachycardia has also been demonstrated (Serlin et al 1980). A similar linear relationship has been found for timolol plasma levels and percentage reduction in exercise tachycardia (Singh et al 1980).

The concentrations at which effects reach a plateau show inter-individual and inter-study variation, probably because of differences in the extent of sympathetic stimulation elicited by differing exercise protocols. Hager et al (1981) found inhibition of exercise tachycardia to plateau at propranolol concentrations of 200 ng/ml in 4 of 7 subjects whilst in the other 3 no plateau was demonstrated up to 450 ng/ml. Serlin et al (1980) also found plateau effects above 300 ng/ml of propranolol. On the other hand, inhibition of exercise tachycardia has been reported to be maximal at propranolol concentrations of 80

to 100 ng/ml (Chidsey et al 1976, Mullane et al 1982, Nies & Shand 1975).

Chidsey et al (1976) found an IC_{50} of 8 ng/ml for propranolol inhibition of exercise tachycardia at maximal exercise indicating a relatively flat dose response curve. The IC_{50} was 5 ng/ml and 3 ng/ml for moderate and mild exercise respectively (Chidsey et al 1976). (See 2.2.2.)

Coltart and Shand (1970) reported that for a given maximal effect on exercise tachycardia, higher concentrations (> 100 ng/ml) of propranolol are required after single dose IV administration than after oral administration (40 ng/ml). They ascribe the difference in response to a contribution by active metabolites formed after oral but not after IV administration. Since measurements were made 1.5 hours after dosing, active metabolites may well have contributed to the effect. (See 1.2.1.3.)

1.3.3.1.3. Inhibition of Isoprenaline Induced Tachycardia
A straight line relationship between log of mean plasma concentration of propranolol and the dose ratio of isoprenaline in the presence and absence of propranolol has been found (Coltart & Shand 1970, Zacest & Koch Weser 1972).

Hager et al (1981) have also reported a good relationship between isoprenaline dose ratio minus 1 (DR-1) and serum propranolol concentrations after chronic oral treatment with doses from 10 to 160 mg four times daily. This was also found after intravenous administration of propranolol with concentrations between 5 and 200 ng/ml (McDevitt & Shand 1975). A higher dose ratio was found by Shepherd et al (1991) than by McDevitt and Shand (1975) (22 versus 13).

In a study where subjects were given much smaller doses by intravenous infusion, McDevitt et al (1976) found a

relatively poor relationship between total propranolol plasma concentrations (range of 22 to 50 ng/ml) and isoprenaline DR-1. However, an excellent correlation between efficacy and free drug concentration was found. They concluded that the effects of propranolol are a function of free drug concentration according to the classical receptor theory of drug antagonism (See 2.2.2.).

When beta-blockade due to a small IV dose of timolol (0.25 mg) was assessed by determining the dose ratios of isoprenaline required to raise heart rate by 25 beats/minute a linear relationship between log of timolol concentration and log (DR-1) was found (Kaila et al 1991). The isoprenaline DRs and the pA2 (below 1 ng/ml) values for timolol are consistent in various studies (Achong et al 1976, Kaila et al 1991, Klein et al 1986) and indicate that the isoprenaline increased heart rate is extremely sensitive to timolol blockade.

1.3.3.2. Hypotensive Effects

Poor relationships between plasma concentration and fall in BP have been demonstrated for atenolol (Amery et al 1977b, Ishizaki et al 1983), carteolol (Giles et al 1984), propranolol (Hitzenberger 1979, Krediet et al 1980, Lehtonen et al 1977, Serlin et al 1980), metoprolol (Bengtsson et al 1975) and oxprenolol (Hitzenberger 1979, Myers & Thiessen 1980, Marshall et al 1977).

When Amery et al (1977b) divided their patients into 3 equal groups according to the hypotensive response to daily doses of 300 mg of atenolol, they found no differences between the groups with respect to beta-blockade (exercise tachycardia) or morning blood levels of atenolol which could account for the variability in response.

Most of the above authors concluded that the wide inter-patient variability in hypotensive response is unrelated to

plasma concentrations or degree of beta-blockade as assessed by reductions in exercise tachycardia.

Because there is a lag in the time course of the anti-hypertensive effects relative to chronotropic effects it is not surprising that the log-linear relationship found for concentration and negative chronotropic effects (See 1.3.3.1.2. above) should be inappropriate for BP.

Two other factors which may complicate the relationship between concentration and blood pressure response are the inclusion of non-responders and the disregard of maximal effects by many investigators.

A few studies have demonstrated some correlation between concentration of beta blocker and blood pressure response. Although there was great inter-individual variability an average level of 120 ng/ml of propranolol was associated with a good response (Chidsey et al 1976, Hansson et al 1974). Chidsey et al (1976) found significant effects on blood pressure at propranolol concentrations above 30 ng/ml which became progressively greater as the propranolol levels rose. They found a linear relationship between the log of propranolol concentration and percentage change in diastolic BP with no evidence of a plateau at the levels achieved in their patients. They concluded that much higher concentrations were necessary for BP reduction than for inhibition of exercise tachycardia and PRA. This conflicts with the idea that the dose response curve for BP is less steep than that for inhibition of exercise tachycardia (See 1.3.1.2. above). A modest but statistically significant linear relationship between minimum nadolol plasma concentration (25 to 275 ng/ml) and fall in diastolic BP in responders (>5% from pre-treatment) has been reported (Duchin et al 1980).

A biphasic plasma propranolol concentration-hypotensive effect relationship has been demonstrated by another group of investigators (Esler et al 1977). They suggested an early antihypertensive effect at propranolol concentrations of 10 ng/ml (related to basal plasma renin activity) with the later effect above 30 ng/ml (unrelated to renin status) and a plateau above 100 ng/ml. Concentrations were however, unrelated to falls in PRA but appeared to be related to higher plasma noradrenaline levels, a higher cardiac output and heart rate.

In a study investigating the effects of 14 days of metoprolol treatment on blood pressure, critical flash fusion and tremor, an E_{max} pharmacodynamic model was used to estimate values for the concentration giving 50% of maximal effect (IC_{50}) and the ratio of E_{max} to drug free baseline (Gengo et al 1985). Significantly different values for the different effects were found indicating distinct sites or mechanisms of action. The IC_{50} for BP reduction was 49.2 ng/ml and was between that found for the other two effects.

1.3.3.3. Plasma Renin Activity

One study with propranolol has shown a maximal effect on PRA at concentrations of 10 ng/ml to 30 ng/ml (Esler et al 1977). In another study, maximal effects on both supine and standing PRA were seen at 100 ng/ml of propranolol with an IC_{50} of 11 ng/ml, which closely resembled effects on heart rate (Chidsey et al 1976).

1.3.3.4. Anti-anginal Efficacy

As with hypertensive patients, patients with angina can also be categorised into responders and non-responders to beta-blockers (Johnsson & Regardh 1976). A significant reduction in anginal episodes in responders was consistently obtained with propranolol serum levels above 30 ng/ml (Alderman et al 1975, Johnsson & Regårdh 1976,

Pine et al 1975) whilst in non-responders much higher levels were without effect.

1.3.3.5. Myocardial Contractility

Corbo et al (1989) found that the pharmacokinetic-dynamic relationship for propranolol on myocardial contractility differed between normotensive and spontaneously hypertensive rabbits. There were no differences in pharmacokinetic parameters of propranolol between the two groups of rabbits including the elimination rate constant from the effect compartment (k_{e0} of 2.78 hr^{-1}) (See 2.3.2.4.). However, using the sigmoid E_{max} model, IC_{50} values of 12.7 and 6.9 ng/ml and slopes of 7 and 3 were obtained for the normotensive and hypertensive groups respectively suggesting altered sensitivity to propranolol in hypertension.

1.3.3.6. Antiarrhythmic Actions

Antiarrhythmic effects in patients who respond to propranolol have been demonstrated at concentrations of 40-85 ng/ml whilst concentrations of 20-700 ng/ml were ineffective in non-responders (Coltart et al 1971).

1.3.3.7. Central Nervous System Actions

Changes in psychomotor function as measured by flash fusion frequency were found to be related to metoprolol serum levels, although these changes lagged behind the time course of metoprolol concentrations (Gengo et al 1985a). This time lag with a half-time of 29 minutes was thought to be the result of accumulation of an active metabolite, hydroxymetoprolol rather than a delay in CNS penetration.

CHAPTER 2

AN OVERVIEW OF THE DOSE-CONCENTRATION-EFFECT RELATIONSHIP

CHAPTER 2

AN OVERVIEW OF THE DOSE-CONCENTRATION-EFFECT RELATIONSHIP

In order for any drug to bring about a desired therapeutic effect in a patient the drug must have the appropriate pharmacodynamic capability and it must reach its site of action in sufficient concentrations to elicit that effect. To achieve this the correct dosage regimen needs to be implemented. A thorough knowledge of the drug's pharmacodynamics as well as its kinetics and the sensitivity and variation of the target population will allow more rational drug choice, dose design and thus therapeutic application of medicines.

In the case of the beta-blockers although much is known about their pharmacodynamic effects their mode of anti-hypertensive action still eludes us. It is also far from clear why beta-blockers are ineffective in lowering BP in some patients. New, more sophisticated, computer based data analysis techniques are assisting in the elucidation of more subtle interindividual differences in kinetics and dynamics. This chapter gives a background to the development and application of the pharmacokinetic and pharmacodynamic techniques which have been utilised in the present study in an attempt to assess whether black and white normotensive volunteers differ in their sensitivity to atenolol.

2.1. DOSE-CONCENTRATION-TIME RELATIONSHIPS
PHARMACOKINETICS

A brief review of some aspects of pharmacokinetic data analysis which are pertinent to this thesis will be given below. It should in no way be considered a comprehensive review.

2.1.1. Methods of Pharmacokinetic Assessment

Certain pharmacokinetic parameters can be calculated without making as many assumptions as are made when compartmental models are used. It may therefore be useful to calculate these parameters using model dependent and model independent methods in order to confirm the applicability of the particular model(s) chosen.

2.1.1.1. Model Independent Assessment Methods

Noncompartmental methods for the assessment of certain pharmacokinetic parameters based on statistical moment theory are enjoying increasing utilization particularly in bioavailability studies.

The time course of drug concentration in plasma can usually be regarded as a statistical distribution curve. The first three moments are:

i)   Area under the curve (AUC);

ii) Mean residence time (MRT);

iii) Variance of the mean residence time (VRT).

These moments can be calculated by numerical integration using the trapezoidal rule (Gibaldi & Perrier 1982) although only the zero moment (AUC) and first moment (MRT) are used due to unacceptable error in the computation of the second moment (VRT) (Gibaldi & Perrier 1982).

In the usual single-dose pharmacokinetic study, estimation of AUC and Area-under-the-(first)-moment versus time curve (AUMC) is carried out in two stages. First the AUC or AUMC from the time of administration to the last blood sampling time is calculated. This is then added to the AUC or AUMC from this last sample time extrapolated to infinity (Gibaldi & Perrier 1982, Rowland & Tozer 1989).

The following parameters relevant to intravenous administration can be calculated using model independent methods:

i)   Clearance

ii)   Half-life

iii) Volume of distribution

(See Methods 3.5.2.1. for equations).

2.1.1.2. Model Dependent Compartmental Pharmacokinetic Assessment Methods.

Models are heavily relied upon in much of the work carried out in pharmacokinetic and pharmacodynamic analyses. 'Models' are simplified, mathematical forms, the constants (parameters) of which represent factors believed to be important in determining observations of either concentrations or effects of drugs (Holford & Sheiner 1982).

Rescigno & Beck (1987) have explicitly reviewed the limitations of modelling. Their definition of a model is a secondary system made with the purpose of verifying the validity of a hypothesis made on a primary system. In judging a simulator (a secondary system merely describing a primary system) only the closeness with which the simulator mimics the primary system need be assessed. However, in contrast to a simulator, when choosing a model three different points need to be judged: retrodiction, prediction and understanding (Rescigno & Beck 1987).

The description of concentration time data by means of compartmental models is a commonly used approach. It represents the body as a system of compartments, with the assumption that the rate of transfer (intercompartmental clearance) between compartments and the rate of elimination from compartments is linear (Gibaldi & Perrier 1982). These compartments may have no physiologic or anatomic reality (see 2.3.2.3. below). However, this approach is useful in relation to pharmacodynamics in the context of obtaining good predictions of concentrations at times when effects and not concentrations are measured. Thus, whether atenolol

concentration time data fits a two or three compartment model better in a particular individual has no clinical relevance. Nevertheless, the better the description of the pharmacokinetic data the less the uncertainty in the pharmacokinetic-pharmacodynamic modelling.

2.1.1.2.1. Nonlinear Least Squares Regression Analysis for Individual Patient Parameter Estimation

In model dependent analysis of pharmacokinetic data (and pharmacodynamic data) the mathematical form of a model is fitted to the observed data by using nonlinear regression procedures. The most commonly used method is ordinary nonlinear least squares analysis (OLS) which assumes a constant variance model (Sheiner & Beal 1985). Many pharmacokineticists make use of weighted least squares (WLS) where either some form of weighting (variance model) is assumed appropriate or different weightings require testing.

The method of extended least squares (ELS) regression (Beal & Sheiner 1979) overcomes the problem in that the variance model is specified explicitly rather than implicitly as in choosing weights for ordinary least squares regression (Peck et al 1984). Simulations have established that ELS regression behaves better when there is heteroscedasticity in the data (Sheiner & Beal 1985) as is usually the case with pharmacokinetic data.

2.1.1.2.2. The Use of NONMEM for Population Pharmacokinetic Parameter Estimation

Nonlinear Mixed Effect Modelling (NONMEM) is a technique developed to directly assess mean population pharmaco-kinetic parameters, their quantitative relationship (fixed effects) to individual physiology (eg. body size, age, renal function etc.) and their variability across populations (random effects and errors). It is ideally suited for the analysis of data collected from a large

number of patients (few data points per individual), in a relatively unstructured fashion in routine patient care (Sheiner et al 1977).

This method is also applicable to data arising from traditional experimental designs. When compared to a standard two stage (STS) method where each individual's data is fitted separately and the individual parameters are then combined, NONMEM's estimates are as good for mean parameters and residual variability (Grasela et al 1986, Sheiner & Beal 1981) but are better for interindividual variability. In a simulation study Sheiner & Beal (1981) demonstrated that the STS method consistently over-estimates interindividual variability due to the added error from each individual estimation.

In pharmacokinetic studies the estimate of interindividual variability by NONMEM although not biased is unacceptable in an absolute sense since it is highly imprecise (Grasela et al 1986). This is a consequence of the small number of subjects used in experimental studies. Additionally, they may not be representative of the population.

However, in the context of the present study it was thought appropriate to test NONMEM against the STS method in an attempt to highlight any possible racial differences in kinetic handling and pharmacodynamic response. At the same time it is recognised that a small number of individuals would make it difficult to identify statistically significant differences with either method.

2.2. IN VITRO CONCENTRATION-EFFECT RELATIONSHIP AND RECEPTOR THEORY

Most drug molecules exert their effects by interacting with functional macromolecular components of the organism, namely the receptors. The development of receptor theory began with the observations of Langley and Ehrlich in 1905 and 1906. Langley suggested that drug cell combinations and hence drug actions were probably governed by the law of mass action. Clark developed this view in the 1920s and 1930s and introduced many of the concepts still in use today. However, it was Ariëns, Simonis and Van Rossum (1964) who refined the theory, made it mathematically rigorous and examined the applicability of theory to experimental findings (Tallarida 1984).

2.2.1. Receptor Binding of Agonists

The original work involved indirect characterization of receptors by examining agonist and antagonist structure activity relationships, usually in carefully controlled in vitro isolated organ systems. In these isolated systems the concentration in the organ bath is assumed to be proportional to that in the biophase with transport and distribution processes having minimal influence. Under these circumstances relatively simple dose-response relationships can be studied (Ariëns et al 1964). The simple relationships described below underlie the more complex situation encountered when drugs are administered to patients.

Recent progress in receptor identification and characterization has involved the extensive use of radiolabelled ligand binding techniques whereby drug binding properties of receptors are studied directly. The earlier assumptions have been confirmed for a number of drug-receptor systems (Bourne & Roberts 1987). The quantitative assessment of drug action can be considered analogous to enzyme substrate interactions and ligand

binding reactions. If an agonist is assumed to interact
with a receptor in a reversible fashion and the resultant
effect is proportional to the number of receptors occupied
the following equation can be written:

$$\text{Drug (D) + Receptor (R)} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{DR} \rightarrow \text{Effect}$$
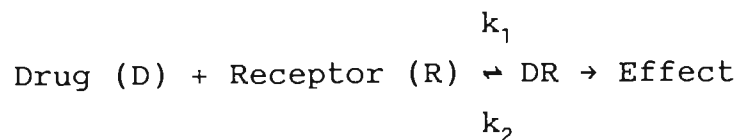
The magnitude of the effect (E) can be expressed in the
form of the Michaelis Menten equation:

$$E = \frac{E_{max}[D]}{K_D + [D]}$$

which can be rearranged to:

$$\frac{E}{E_{max}} = \frac{1}{1 + \frac{K_D}{[D]}}$$

where [D] is the concentration of free drug and K_D (equal to
k_1/k_2) is the dissociation constant for the drug receptor
complex. There is thus no effect when [D] = 0 and the
effect is half-maximal when [D] = K_D.

In the case of an agonist the term intrinsic activity (α)
refers to the relative ability of a compound to give rise
to a particular effect in relation to the maximal effect
(E_{max}) of the system (Ariëns et al 1964). Thus:

$$\frac{E_D}{E_{max}} = \frac{\alpha}{1 + \frac{K_D}{[D]}}$$

In the situation where two drugs (A and B) are competing
for occupation of the same receptor and both drugs are
agonists the combined effect (E_{AB}) can be described as
follows:

$$\frac{E_{AB}}{E_{max}} = \frac{\alpha}{1+(1+\frac{[B]}{K_B})\,(\frac{K_A}{[A]})} + \frac{\beta}{1+(1+\frac{[A]}{K_A})\,(\frac{K_B}{[B]})}$$

The combined effect is determined by the concentrations of the individual drugs ([A] and [B]), by their affinity for the receptor ($1/K_A$ and $1/K_B$) and by their intrinsic activities (α and β) (Arïens et al 1964).

2.2.2. Receptor Binding of Antagonists

If one of the drugs, B for example, is a competitive antagonist with no intrinsic activity ($\beta = 0$), only affinity, then the right hand term above becomes zero and the equation for effect would be:

$$\frac{E_{AB}}{E_{max}} = \frac{\alpha}{1+(1+\frac{[B]}{K_B})\,(\frac{K_A}{[A]})}$$

The concentration of a competitive antagonist which diminishes by 50% the observed response to a fixed agonist concentration is termed the IC_{50}. This IC_{50} differs for each concentration of agonist used because of the competitive nature of the interaction (Bourne & Roberts 1987).

The ratio of the concentration of an agonist necessary for a given degree of effect in the presence of a fixed concentration of antagonist (C') relative to the concentration required to give that same degree of effect in the absence of the antagonist (C) is called the dose ratio (DR) (Bourne & Roberts 1987). It is related to the dissociation constant of the antagonist (K_B) by the Schild equation:

$$\frac{C'}{C} = 1 + \frac{[B]}{K_B}$$

The experimentally derived K_B shows reasonable agreement with ligand binding studies of radiolabelled competitive antagonists to receptors (Bourne & Roberts 1987). Thus the degree of inhibition observed depends on both the concentration of antagonist as well as agonist present.

2.3. IN VIVO DOSE-CONCENTRATION-EFFECT RELATIONSHIPS

In the past, the assessment of the kinetics of drug effects (pharmacodynamics) in the whole animal has enjoyed less attention than has the delineation of the plasma concentration-time relationships (pharmacokinetics). Recently much more attention has been focused on the concurrent measurement of the pharmacodynamics and pharmacokinetics of drugs and interpretation of their inter-relationships (Holford & Sheiner 1981,1982, Paalzow 1984, Van Rossum & Burgers 1984). The assumption that there is a relationship between the desired or unwanted effect of a drug and its concentration in plasma is the basis of therapeutic drug monitoring. Thus better characterization of these relationships should improve therapeutics.

2.3.1. Pharmacodynamic Models

As already mentioned (2.1.1.2), much of the work carried out in the areas of both pharmacokinetics and pharmacodynamics relies heavily upon the use of models. Clearly the preferred pharmacodynamic models would be those which also offer some insight into the underlying physiological processes (Holford & Sheiner 1982).

A brief description of some simple pharmacodynamic models follows. It should be noted that these models all refer to the situation in which drug concentration at the effect site is either known or is in equilibrium with the sampled biological fluid. In a tissue bath it is assumed that the concentration in the tissue bath is in equilibrium with the effect site. In vivo, at steady state the tissue site of action may be in equilibrium with the blood or sampling site although this is not necessarily so. For some drugs the equilibration between tissue site and plasma is so rapid that concentration and effect can be directly related even in the non-steady state situation.

2.3.1.1. Fixed Effect Model

This is the simplest pharmacodynamic model. It relates drug concentration to an effect which may be either present or absent eg. seizures or to some degree of effect eg. 50% reduction of anginal episodes. It has only one constant, the concentration at which the effect appears. This constant, however, varies among individuals. The probability of a particular effect occurring at a given concentration can be modelled but the parameters of this probability distribution would need to be defined. Although a sigmoid curve is obtained when probability is plotted against concentration the theoretical basis is in the statistical theory of cumulative distribution function and not in receptor theory (Holford & Sheiner 1982).

This model has been successfully applied in determining plasma concentrations of alfentanil required to suppress various noxious stimuli (Ausems et al 1986). These concentrations were then used to programme a computer controlled infusion pump to provide more appropriate delivery of anaesthetic and hence better anaesthesia (Ausems et al 1988).

Although there do not appear to be any published applications of this model to beta-blocker effects it could be readily applied to relate average steady state concentrations to anti-anginal effects, antiarrhythmic effects and migraine prophylaxis.

2.3.1.2. Linear Model

This is the simplest relationship between concentration and effect, where the intensity of effect (E) is proportional to concentration (C) and the slope (S) is the only parameter:

E-S.C

This model predicts no effect when drug is absent but lacks the ability to estimate maximum effects. The parameters can be easily estimated by linear regression.

If effect has some value when drug is absent such as BP then the equation becomes:

$$E\text{-}S.C + E_0$$

where E_0 is the effect without drug. Whether E_0 is estimated as a parameter or not depends on the reliability of measurements of E_0 relative to E (Holford & Sheiner 1982).

This model is applicable as an empirical description of drug effects over the observed concentration range when it is not practicable to achieve maximum effects (Holford & Sheiner 1981) and the particular effect is studied in the range below 50% of E_{max} (Oosterhuis & Van Boxtel 1988).

It has been successfully applied to the effects of cardiac glycosides (Kelman & Whiting 1980) and total and unbound disopyramide (Thibonnier et al 1984, Whiting et al 1980) on the QT interval of the cardiac cycle.

Correlations between the effects of beta-blockers on heart rate and their mean steady state plasma concentrations are relatively weak (Duchin et al 1980, Von Bahr et al 1976). A linear relationship between propranolol concentration and the isoprenaline DR-1 was reasonably strong (Coltart & Shand 1970, Zacest & Koch-Weser 1972) (See 1.3.3.1.3).

2.3.1.3. Log-linear Model

The relationship between concentration and effect has traditionally been represented by a log transformation of concentration on the abscissa. The equation is:

$$E = S.logC + I$$

where E, S and C are the same as before and I is a constant with no physiological meaning.

There are two reasons why this transformation has enjoyed popularity. The first is ease of graphical representation by compression of a wide concentration range. The second is the convenience that the relationship between log concentration and effect is a linear approximation of the E_{max} model in the range of 20 to 80% of maximum effect. Prior to the availability of non-linear regression techniques, this enabled the use of linear regression to determine the slope of the line and tests of parallelism to compare effects after addition of antagonists (Holford & Sheiner 1981).

There are theoretical and practical disadvantages to using this model (Holford & Sheiner 1981, Oosterhuis & Van Boxtel 1988). The two major drawbacks are its inability to predict E when concentration is zero (Kelman & Whiting 1980) and its inability to predict a maximum effect (Holford & Sheiner 1981, 1982). Whilst this model holds within the range of 20 to 80% of maximal effect the practical difficulty remains how to ascertain that one is working within this range if E_{max} is not known. Additionally, the model is unable to accommodate a baseline effect and may lead to the abuse of a baseline effect as if it were known without error (Holford & Sheiner 1981). Graphical representation using a log transform of concentration may obscure the existence of a maximum effect and make recognition of the need for the sigmoid E_{max} model difficult (Holford & Sheiner 1981).

Much of the work quoted in Chapter 1 (1.3.3.) relating concentration of beta-blockers to effect makes use of the log-linear model. Although many authors claimed a significant correlation between log concentration and reduction in heart rate the correlation was relatively weak (Bengtsson et al 1975, Müller et al 1979, Quarterman et al 1979, Van den Brink et al 1980, Wilson et al 1982). Only a few researchers recognized a maximum effect (Esler et al 1977, Fitzgerald et al 1978, Hager et al 1981, Mason & Winer et al 1976, Nies & Shand 1975) and excluded concentrations above certain values (Serlin et al 1980) or below certain values (Leopold et al 1986). Lalonde et al (1987) clearly showed that the use of this model for predicting inhibition of exercise tachycardia by propranolol, underestimated the observed effects at lower concentrations and overestimated observed effects at higher concentrations.

2.3.1.4. E_{max} Model

The existence of a maximum drug effect when drug concentrations are allowed to increase indefinitely is an important biological attribute and this model can therefore be justified on theoretical grounds (See 2.2 above). It is described mathematically by the so-called E_{max} model:

$$E = \frac{E_{max} \cdot C}{EC_{50} + C}$$

where E_{max} is the maximum effect ascribed to the drug and EC_{50} is the concentration producing 50% of the maximum effect.

In common with the linear model, this model predicts no effect when concentration is zero. It can also accommodate a baseline effect in the absence of drug when the equation becomes:

$$E = E_0 + \frac{E_{max} \cdot C}{EC_{50} + C}$$

If the effect is inhibition of a physiological phenomenon such as lowering of exercise heart rate by a beta-blocker the equation can be modified to:

$$E = E_0 - \frac{E_{max} \cdot C}{IC_{50} + C}$$

where IC_{50} is the concentration of the antagonist producing 50% inhibition of E_{max}.

Holford & Sheiner (1982) maintain that the E_{max} model should be considered the basic pharmacodynamic model with the linear model being used as an approximation only when no maximum effect can be predicted or observed effects are always less than 50% of maximum.

They illustrate their point by showing how Singh et al (1980) erroneously concluded that there was only a weak correlation between timolol concentration and effect on exercise and resting heart rate after applying the log-linear model. Using the same data and the E_{max} model, Holford & Sheiner (1982) found a stronger relationship which predicted the lowest heart rates (E_{max}) achievable at rest and after exercise to be 56 and 68 beats per minute with concentrations of 10 and 12 ng/ml of timolol giving half-maximal effects (IC_{50}) respectively.

In Chapter 1 (1.3.3), much of the data quoted relating to beta-blocker concentration and effect might be more appropriately described by this model rather than the log-linear model (see 2.3.1.2. above). Some of the early studies on beta-blockade clearly demonstrated that the E_{max} model was applicable to the heart rate effects of these drugs when pooled patient data was used and that plateau effects were obtained with therapeutic doses (Chidsey et al

1976, McDevitt & Shand 1975). A few more recent studies have demonstrated the suitability of this model for predicting the effects of propranolol (Lalonde et al 1987) and metoprolol (Gengo et al 1985, Kendall et al 1991) on exercise tachycardia in individual subjects.

The receptor binding studies of Wellstein et al (1985a, 1985b) have also confirmed that this model is appropriate for atenolol and propranolol. These authors suggest that any deviations from the model may be indicative of additional compartments, active metabolites, partial agonist activity, counter-regulatory processes and adaptive mechanisms and should be verified.

2.3.1.5. Sigmoid E_{max} Model

This model has an additional parameter, n, which allows for differences in the shape of the relationship which now becomes the so-called Hill equation:

$$E = \frac{E_{max} \cdot C^n}{EC_{50}^n + C^n}$$

Holford & Sheiner (1981) warn that it is probably unwise to use the sigmoid E_{max} model if the effect is not clearly defined by the observations or by a known physiological limit such as total muscle paralysis. Noise in the effect measurement is the most likely explanation for small deviations from unity in which case the simpler E_{max} model may be preferable (Holford & Sheiner 1982).

Where there is a rapid equilibration of drug between plasma and tissue this model can be directly applied. In patients with varying degrees of renal dysfunction, Kleinbloesem et al (1985) related haemodynamic effects of nifedipine to plasma concentrations using the sigmoid E_{max} model. They found that although slopes did not differ, E_{max} was larger and EC_{50} smaller in patients with more severe renal failure.

This indicated increased sensitivity to the drug in severe renal failure patients, over and above the differences in nifedipine kinetics. The sigmoidal concentration effect relationship of nifedipine concentration to haemodynamic effects was unaltered by hypertension and liver cirrhosis (when corrected for altered protein binding) (Kleinbloesem et al 1987).

In healthy volunteers it was found that the sigmoid E_{max} model was the most appropriate one in most of the subjects in describing the direct relationships between left ventricular systolic function and heart rate and serum l-propranolol concentration (Clifton et al 1990). This study demonstrated that propranolol was significantly more potent in reducing heart rate (IC_{50} of 10 ng/ml) than left ventricular systolic function (IC_{50} of 19 ng/ml) but the E_{max} for the latter was significantly greater than for the former (47% versus 30%).

2.3.2. Methods of Assessing Pharmacokinetic-pharmacodynamic (PK-PD) Relationships in vivo

In the intact animal the situation is often more complicated as the concentration at the effect site is usually unknown and cannot always be assumed to be in equilibrium with the sampled site.

The overall relationship between dose and effect can be represented diagrammatically (Fig 2.1.). The common link between the pharmacokinetic model (PK) (relating dose to concentration) and the pharmacodynamic model (PD) (relating concentration to effect) is the concentration (C) in the biophase.

DOSE-----PK-----C-----PD-----EFFECT

Fig.2.1. The role of pharmacokinetics (PK) and pharmaco-dynamics (PD) in the dose-effect relationship

Pharmacokinetic-dynamic analysis becomes difficult when pharmacological effects are delayed in relation to levels of drug in the central (or sampled) compartment. Such equilibration delays become obvious when effect is plotted against concentration in the central compartment; when the points are joined in chronological sequence, a counter-clockwise hysteresis loop is generated. This counter-clockwise hysteresis may be the result of:

i)   an equilibration delay between the sampled compartment and the effect compartment;

ii)   an active metabolite being formed;

iii) the effect not being rapidly reversible;

iv)   acute development of sensitization.

(Oosterhuis & van Boxtel 1988).

2.3.2.1. Model Independent Methods

The most direct means of defining the PK-PD relationship would be to measure the effect and simultaneously the concentration at the effect site. There is then no need to define either the pharmacokinetic or pharmacodynamic model. In most instances it is obviously impractical to sample at the effect site and even if it were possible, any error in concentration measurement is ignored by this method.

Hull (1979) pointed out that meaningful correlations between plasma concentration and effect can also be made if effects are measured at several different steady state con-centrations when free drug in plasma and biophase should be in equilibrium. Prior to the advent of computer controlled infusion pumps this method was also impractical. It would have entailed very long periods of infusion of the drug at different rates of input.

A general approach for linking concentration and effect which is model independent has been proposed by Smolen (1976). Some aspects of a systems dynamics approach to the quantitative relationships between dynamics and kinetics of

drugs have been discussed by Van Rossum & Burgers (1984). The techniques of numerical deconvolution are potentially powerful tools for describing complex dose-concentration-effect relationships (Holford & Sheiner 1982) but are not easily understood or applied.

A method known as distributed lags analysis which is independent of compartmental modelling has been applied to the "high" caused by cocaine (Zahler et al 1982). This method can accommodate different effects when concentrations are rising and falling but may not be universally applicable. This approach does not appear to have been utilised by any other investigators.

2.3.2.2. Pharmacokinetic Compartment Modelling

Compartmental analysis is the usual method for modelling the time course of drug concentration in sampled biological fluids. It allows prediction of concentration in compartments not directly sampled and it enables prediction of concentration at any time. Thus effect and concentration need not be simultaneously measured.

A number of attempts have been made to relate the time course of effect to predicted concentration in a pharmacokinetic peripheral compartment. This has been fortuitously successful in a few cases such as the effect of clonidine on the cat nictitating membrane (Paalzow 1984). Galeazzi et al (1976) demonstrated that the effects of procainamide on prolongation of the QT interval appeared to be intermediate in time course between concentrations in the central and peripheral compartments but happened to coincide with procainamide saliva concentrations. In the main, however, this approach has been unsuccessful (Dahlström et al 1978, Paalzow 1984).

Kelman & Whiting (1980) have proposed a multicompartment method with partitioning of fractions of the effect among

the different pharmacokinetic compartments. This 'mixed compartment' approach whilst adequately describing the time course of the effects of disopyramide and two cardiac glycosides, is purely empirical. It is highly unlikely that a single effect is mediated by drug concentrations at sites with different pharmacokinetic properties ie. at different effect sites (Holford & Sheiner 1982, Oosterhuis & Van Boxtel 1988).

The requirement for modelling of effects on the basis of pharmacokinetic compartments to be successful is that the time course of effect-site concentration must parallel the distribution to tissue sites determining the multi-exponential concentration-time course (Holford & Sheiner 1982). The tissue sites must therefore have a relatively large drug capacity. Many sites of action may have slow drug penetration but a small capacity and therefore have no discernible influence on central compartment concentrations. Additionally, this cannot be applied to drugs where equilibration delays are observed but which show one compartment kinetics (Oosterhuis & van Boxtel 1988).

2.3.2.3. Effect Compartment Modelling

The concept that the time course of the effect itself could be used to define the rate of drug movement into the effect site was first mooted by Segre (1968). It was first applied by Forrester et al (1974) to calculate the equilibration half-times of effect of various cardiac glycosides after IV bolus administration. However, they ignored the fact that concentrations were decreasing in the plasma.

Hull et al (1978) in a study on pancuronium, proposed an additional effect site compartment with a negligibly small volume (1 ml), linked to the plasma compartment by a first order process represented by a single rate constant. They estimated this rate constant by iterative methods, solving for time points when both rising and falling concentrations

in the central compartment gave the identical intensity of effect. A conceptually similar method but involving complex mathematics and multiple effect compartments was applied to eliminate the lag between concentration and analgesic effect of morphine (Dahlström et al 1978).

Using these ideas as a basis, Sheiner et al (1979) proposed a simpler method to estimate the rate constant of the effect site equilibration. This method used an effect compartment as an extension of the pharmacokinetic compart- mental model (Schematically shown in Fig 2.2). The effect compartment was linked to the plasma compartment by a first order process but received a negligible amount of drug, therefore the input rate constant K_{1e} was negligible. The rate constant K_{e0} was not directed back to the plasma compartment and thus characterised the time dependent equilibration between plasma concentration and effect.
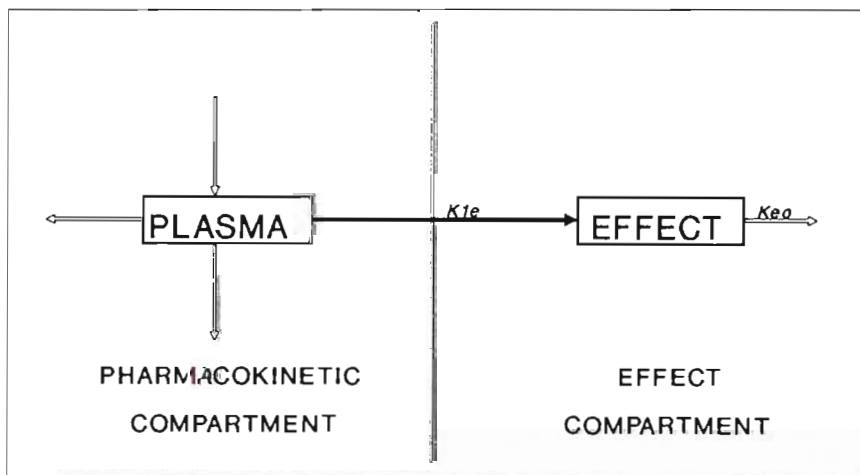
Fig 2.2. A pharmacokinetic-pharmacodynamic model showing the connection between the central compartment and the effect compartment.

The plasma concentration time course was used to estimate pharmacokinetic parameters. These parameters were then used to calculate concentrations in the hypothetical effect compartment which when combined with an effect model yielded the equilibration constant together with the effect model parameters. Sheiner's model allows the determination of the rate constant of dissociation of the drug from the effect compartment (K_{e0}). Time independent sensitivity to the drug can be expressed as the steady state plasma concentration that results in 50% of maximal effect (EC_{50}) if a plateau effect is obtained (Tfelt-Hansen & Paalzow 1985).

This approach has been criticized as inadequate on the grounds that it is purely descriptive; is based on compartmental modelling which relegates the different components contributing to the delay in effect to a "black box"; and predictions from different routes of administration as well as from single dose to multiple dosing do not always hold (Colburn 1981, Colburn 1987). Sheiner's reply (Sheiner 1987) to this criticism is that effect compartment modelling:"is simply a means to "correct" non-steady state data to the equivalent of steady state data so that a dose-(concentration)-response curve can be discerned, unobscured by hysteresis".

Whilst retaining a parametric pharmacokinetic model, Fuseau & Sheiner (1984) proposed a nonparametric form of the pharmacodynamic model which estimated K_{e0} as the value that caused the hysteresis curve to collapse to a single curve. Unadkat et al (1986) have extended the nonparametric approach to include both the pharmacokinetic and pharmacodynamic models but retained a parametric link model. This method is appropriate when the pharmacokinetic model is uncertain.

Many and varied studies have successfully used effect compartment modelling to describe temporal discrepancies between concentration and effect and to make clinically useful predictions. Some equilibration half-times for various drugs and effect measurements are given in Table 2.1. overleaf.

Knowledge of equilibration rate constants is of great assistance in ensuring the safe application of drugs. In anaesthetic practice for example, overdosage with drugs which are slow to equilibrate is far more likely to occur since dosing is influenced by clinical signs which are time lagged.

The effect of beta-blockers on heart rate has been considered to follow the same time course as the plasma concentration and therefore effect compartment modelling has, for the most, not been attempted. Most studies have measured effects at the earliest 5-15 minutes after administration and may have missed a disequilibration phase.

Corbo et al (1989) assessing the effects of propranolol on cardiac contractility in rabbits, have demonstrated a half-time of equilibration of 15 minutes. In a study measuring the changes caused by metoprolol on flash fusion frequency it was found that these CNS effects were delayed relative to metoprolol concentrations, with a disequilibration rate constant of 1.43 h^{-1} (Gengo et al 1985a).

Although the effects of beta-blockers on blood pressure are delayed relative to plasma concentration no one appears to have investigated this. Meaningful delineation of this relationship is probably hampered by variation in homeostatic feedback mechanisms but certainly needs some effort at investigation.

Table 2.1. Equilibration half-times for various drugs estimated using effect compartment modelling.

DRUG	EQUILIBRATION HALF-TIME (minutes)	EFFECT	REFERENCES
Diazepam	1.6	EEG changes	Bührer et al 1990b
Thiopentone	1.5	EEG changes	Stanski et al 1984
Disopyramide	2.0	QT prolongation	Whiting et al 1980
Methadone (IV)	3.6	Pain relief	Inturrisi et al 1987
Midazolam	4.8	EEG changes	Bührer et al 1990b
D-tubocurarine	4-5	Muscle paralysis	Sheiner et al 1979
Terbutaline	5-8	FEV_1, airway resistance & conductance	Oosterhuis et al 1986
Trimazosin Alkyl-OH-metabolite	6 36	Fall in systolic BP Fall in systolic BP	Meredith et al 1983
Vecuronium	7	Neuromuscular blockade	Shanks et al 1987
Quinidine	8	QT prolongation	Holford et al 1981
Propranolol	15	Cardiac contractility*	Corbo et al 1989
Metoprolol	29	Flash fusion frequency	Gengo et al 1985a
Cimetidine	116	Basal acid output	Ezra et al 1985
Digoxin	170-280	LVET shortening	Kelman & Whiting 1980b
Ergotamine	10-12 hrs	Peripheral systolic BP	Tfelt-Hansen & Paalzow 1985

* Rabbits

2.3.3. Therapeutic Application of the Pharmacokinetic-pharmacodynamic Relationship

2.3.3.1. Duration of Effect

The duration of a drug-induced effect cannot be directly equated to the drug's elimination half-life across the whole concentration range. The decay of an effect is also influenced by dose since this determines in which portion of the concentration effect curve one is operating.

The time course of drug effect can be divided into 3 phases (Holford & Sheiner 1981):

i)   When plasma concentration is above the concentration causing 80% of maximal effect the relationship between effect and concentration is shallow. Large changes in drug concentration cause small changes in effect (E_{max} model).

ii) When plasma concentration is in the range of concentration giving 20 to 80% of maximal effect the effect will decline linearly with time whilst concentrations decline exponentially. During this phase effect and log concentration are linearly related (Log-linear model).

iii) When effect is less than 20% of maximum then both concentration and effect decline exponentially and are directly proportional (Linear pharmacodynamic model).

The nonlinear relationship between concentration and effect in i) is the reason for the duration of beta-blocker effect being much longer than the elimination half-life would lead one to expect. Propranolol has a half-life of 2 to 3 hours but an IC_{50} of only 5-20 ng/ml for inhibition of exercise tachycardia (Lalonde et al 1987, Wellstein et al 1985b) and possibly also BP reduction (Esler et al 1977). Thus doses of 80 mg should maintain levels well above the IC_{50} for a good part of the day. This was discussed by McDevitt & Shand in 1975. It is therefore surprising that until recently it was seldom recognised by clinical investigators that the dose of the beta-blocker determines the time that

concentrations remain above E_{max} and therefore also influences the duration of action.

2.3.3.2. Dose Regimen Design

In terms of the E_{max} model if concentrations are greater than EC_{80} for most of the day there will be little difference between an infusion and intermittent dosing. However, the influence of dosing regimen is greatest when the average concentration is in the region of the EC_{50} and the dosing interval is much longer than the elimination half-life (Holford & Sheiner 1981). Knowledge of the pharmacokinetics as well as the E_{max} and EC_{50} of a drug can then be used to implement a rational dosing strategy.

The relatively recent recognition of the applicability of the E_{max} model to the relationship between the concentration and effect of beta-blockers has given great support to the development of slow release formulations. A great case for metoprolol CR and metoprolol 'Oros" has been made on the grounds that once daily administration of these formulations not only gives effective 24 hour beta-blockade but gives rise to a better safety profile in terms of $beta_1$-selectivity (Kendall et al 1991). These formulations maintain a plateau level of 300-400 nmol/L corresponding to maximal beta-blockade without achieving needlessly high peaks which might well give rise to $beta_2$-receptor blockade (Kendall et al 1991). Improved tolerability with these formulations of metoprolol in terms of lesser effects on airways, and reduced impairment of exercise tolerance has been demonstrated in relation to conventional atenolol (Dimenäs et al 1990, Kendall et al 1991).

The need for altered dosing schedules due to altered pharmacokinetics and/or pharmacodynamics in the elderly if they are the target population could easily be identified in phase II or III studies. The antihypertensive effect of amlodipine, a long acting calcium antagonist has been shown to be equivalent for young and elderly patients at a given

drug concentration (Abernethy et al 1990). The increased antihypertensive effect seen in the elderly was associated with an increased amlodipine concentration due to reduced clearance for a given dose.

Uccellini et al (1986) using simulations assessed the influence of intravenous infusion duration on the tissue drug concentration profile of drugs showing a classical two compartment pharmacokinetic disposition. They demonstrated that maximum tissue concentration is not greatly influenced by infusion duration but the time that tissue levels are maintained at a particular level (therapeutic or toxic) is dependent on both dose and duration of administration. Thus a proposal to shorten the infusion time of metronidazole in a bid to increase tumour levels (to increase radio-sensitization) (Rabin et al 1980) would probably not be successful.

A dosing strategy may have to take into account an equilibration delay between concentration at the effector site and the plasma concentration. An understanding of the nature of the delay may allow safer or more effective use of drugs. Disregard of the equilibration delay between plasma and the CNS, as was the case initially with midazolam, may result in fatal overdosing of patients since time to peak tissue concentration (and effect) lags behind peak plasma concentrations (Bührer et al 1990b). Diazepam is a safer agent than midazolam because the former equilibrates into the CNS faster than the latter (equilibration half-time 1.6 versus 4.8 minutes) (Bührer et al 1990b). The hysteresis can be overcome by administering the drug at a rate slower than the equilibration rate; for example midazolam is safe if infused relatively slowly. The CNS effects of anaesthetic doses of benzodiazepines were determined by using fast Fourier transformation and aperiodic analysis of the EEG (Bührer et al 1990a).

A pharmacokinetic-dynamic model incorporating an effect compartment has been successfully used with adaptive feed back control (measuring neuromuscular blockade) to determine atracurium administration (Olkkola & Schwilden 1989).

2.3.3.3. Metabolite Activity

Differences in the parameters of the pharmacodynamic model between oral and IV administration may indicate contributions from an active metabolite.

A study comparing the pharmacodynamic effects of intravenous and oral propafenone in healthy extensive metabolizers using effect compartment modelling demonstrated that 5-hydroxy-propafenone contributes to the antiarrhythmic effects (Haefeli et al 1990). Using pharmacokinetic-dynamic effect modelling for a drug with a large first pass effect, with two different routes of administration (IV and oral) generating different amounts of metabolite, obviated the need to administer the active metabolite directly.

2.3.3.4. Drug Combinations

Knowledge of pharmacokinetic-pharmacodynamic relationships of a drug alone and in combination with other drugs may provide insight into mechanisms of drug interactions. This knowledge could be extracted from data collected in Phase IV (Marketing support) studies (Kroboth et al 1991).

Lalonde et al (1990) studied the pharmacokinetics of oral labetalol and 4 of its stereoisomers as well as the beta-blocking effects in the presence and absence of the oxidative enzyme inhibitor, cimetidine. They showed that although cimetidine increased total labetalol concentrations and AUC it did not influence the pharmacodynamic effect measured because it had little influence on (R,R)-labetolol.

Kleinbloesem et al (1987) while studying the concentration-effect relationship of nifedipine showed that beta-blockers interacted with nifedipine at a kinetic and dynamic level, the extent of the interaction being dependent on dose and route of administration.

After reviewing the literature it is clear that the characterization of dose-concentration-effect relationships is necessary and is in fact central to the application of rational (safe and effective) therapeutics. Studying these relationships and their variation across populations will also assist in the safer and more efficacious utilization of medicines.

CHAPTER 3

METHODS

CHAPTER 3

METHODS

3.1. SUBJECTS

3.1.1. Ethical Considerations

The protocol was approved by the University of Durban-Westville's Faculty of Health Science Ethics Committee. Approval was also obtained from The South African Medicines Control Council because atenolol was not registered for intravenous administration in South Africa at the time of the study.

Informed, written consent was obtained from all participants before the study was initiated. Most participants were medical or pharmacy students.

3.1.2. Inclusions

Healthy volunteers (aged between 20 and 30 years) having normal blood pressure and belonging to the white (European) or black (African) population groups were recruited.

All volunteers had a full physical examination and were only included if considered to be in good health and physical condition. Additionally, blood chemistry, haematological studies and urinalysis were required to demonstrate no haematopoietic, hepatic or renal abnormalities.

3.1.3. Exclusions

The following exclusions were applied:

i)   Indians and people of mixed ancestry (coloureds);

ii)   Any history of asthma or allergy;

iii)   Highly trained athletes;

iv)   An abnormal ECG;

v)   History of cardiac disease.

3.1.4. Demographic Details

Using the student's t-test no significant differences between the two groups in terms of age, height, weight nor in pre-treatment values of systolic and diastolic blood pressure in the supine and erect position were found. Neither the workloads required to raise heart rate nor the pre-treatment resting and exercise heart rates were significantly different for the two groups (Table 3.1.).

Table 3.1. Demographic details (mean and range) for the black and white volunteer groups.

DEMOGRAPHIC CHARACTERISTICS	BLACKS		WHITES	
	Mean	Range	Mean	Range
Age (years)	23.1	20-27	21.3	20-30
Weight (kg)	67.8	48-80	72.1	67-79
Height (cm)	172	154-180	177	166-182
Supine Systolic BP (mm Hg)	111	98-130	111	103-118
Supine Diastolic BP (mm Hg)	66.5	53-90	66.1	60-73
Erect Systolic BP (mm Hg)	110	103-120	113	103-120
Erect Diastolic BP (mm Hg)	76.0	65-90	70.6	60-98
Resting Heart Rate (bpm)	69.0	59-80	69.8	57-83
Workload (W)	148	106-194	161	123-211
Exercise Heart Rate (bpm)	141	130-154	138	128-160

Demographic details of individual volunteers as well as means and standard deviations for the groups are presented in Appendix 1, Tables A1.1., A1.2., and A1.3.

3.2. EXPERIMENTAL PROCEDURE

3.2.1. Study Design

The study was placebo controlled, single blind and crossover in design.

The two phases of the study were separated by a washout period of at least one week but not more than six weeks.

Details of the order in which volunteers received the two treatments (placebo or atenolol) are shown in Appendix 1, Table A1.4.

3.2.2. Atenolol Administration

Atenolol (5 mg/10 ml) for intravenous administration (Tenormin Ampoules) and matching placebo were obtained from ICI South Africa (Pharmaceuticals) Limited. Using a Sage syringe pump, a constant rate intravenous infusion was given into a vein in the left hand over 7-8 minutes. The line was then immediately flushed with saline and the exact duration of the infusion was noted.

3.2.3. Plasma Sampling

An IV catheter (Jelco 18 gauge) was positioned in a right forearm cubital vein and kept patent for the first 12 hours of sampling by means of a slow infusion of normal saline (Sabax). Samples were drawn into a syringe via a three-way stopcock. Care was taken to flush out the saline before sampling. All samples taken after 12 hours were obtained with (Venoject) needles and vacuum tubes. The blood was immediately placed in chilled heparinised tubes which were kept on ice until plasma was separated at $4°$ C. The samples were stored at $-20°$ C until analyzed.

While the subjects were seated on a bicycle ergometer, samples were drawn as close as possible to the following times before and after the infusion was completed: 15-30 minutes before the infusion, 2, 5, 10, 15, 30, 45 minutes, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 30, 36 hours after the infusion.

3.3. PLASMA ANALYSIS

3.3.1. Atenolol Analysis

A reverse phase HPLC method based on one developed by Yee et al (1979) and adapted by the University of the Orange Free State (H Hundt - Personal Communication) was used for the measurement of atenolol concentrations in plasma.

3.3.1.1. Apparatus

A modular HPLC system consisting of the following Spectra Physics units, autosampler (SP8780xR), pump (SP8810), integrator (SP4290), coupled to a Shimadzu fluorescence spectrophotometer (RF535) was utilized. Initially a Brownlee C18 stainless steel column (Anatech) was used. A Nova-pak C18 radial pak cartridge column (Millipore) was found to give as good separation while halving retention times.

3.3.1.2. Reagents

The following HPLC grade or analar grade reagents were used: cyclohexane (Protea), n-butanol (Merck), Sodium hydroxide (Holpro), Sulphuric acid (Saarchem), Acetonitrile (Kleber), Methanol (Mallinckrodt), Acetic acid (BDH) and Hexane sulphonic acid (BDH).

Atenolol powder was obtained from ICI South Africa (Pharmaceuticals) Limited and the internal standard, nadolol, from Squibb Laboratories (Pty) Limited.

3.3.1.3. Chromatographic conditions

The excitation and emission wavelengths were set at 280 and 298 nm respectively and both excitation and emission slit widths at 10 nm.

The mobile phase was made up of 20% methanol, 20% aceto-nitrile and 60% of a 0.01 M hexane sulphonic acid solution. The solution was adjusted to pH 3.4 with acetic acid. The

flow rate was maintained at 1 ml/min and the system operated at ambient temperature.

3.3.1.4. Extraction procedure

Nadolol and atenolol stock solutions were made up in methanol. Appropriate dilutions of atenolol were made by weight to produce working standards in plasma.

A one ml plasma sample (standard or unknown) was placed in a centrifuge tube and 20 µl of nadolol (20µg/µl), the internal standard, was added. The plasma was subsequently alkalinised with 200 µl of 1 M sodium hydroxide. Atenolol and nadolol were then extracted into a 5 ml mixture of cyclohexane and n-butanol (55/45 v/v) by vortex mixing for one minute. The two phases were separated by centrifuging for 10 minutes at 1250 g.

The supernatant was transferred to another glass tube containing 40 µl of 0.1 N H_2SO_4 and vortex mixed for 1 minute. After further centrifugation as above, the organic layer was discarded and the H_2SO_4 layer was transferred to injection vials. The autosampler was loaded and the system was allowed to operate overnight.

A specimen chromatogram is shown in Figure 3.1. Average retention times for atenolol and nadolol were 7 and 14 minutes for the Brownlee column and 4 and 5.5 minutes respectively for the Nova-pak column. The limit of sensitivity was 10 ng/ml. A set of standards (10-1500 ng/ml) was processed with each batch of samples because there was some day to day variation in retention times.

A typical calibration curve is linear over the range of 10-1500 ng/ml with a regression coefficient of 0.9994 for the line, $y = 2.38x - 7.43$, where y is the peak height ratio of atenolol to internal standard and x is the concentration in ng/ml. Within day coefficients of variation (CV) ranged

from 10% at 20 ng/ml to 6% at 1500 ng/ml and inter-assay CV
from 13% at 10 ng/ml to 6.2% at 1282 ng/ml. (See Appendix
1, Table A1.5).

a)

b)
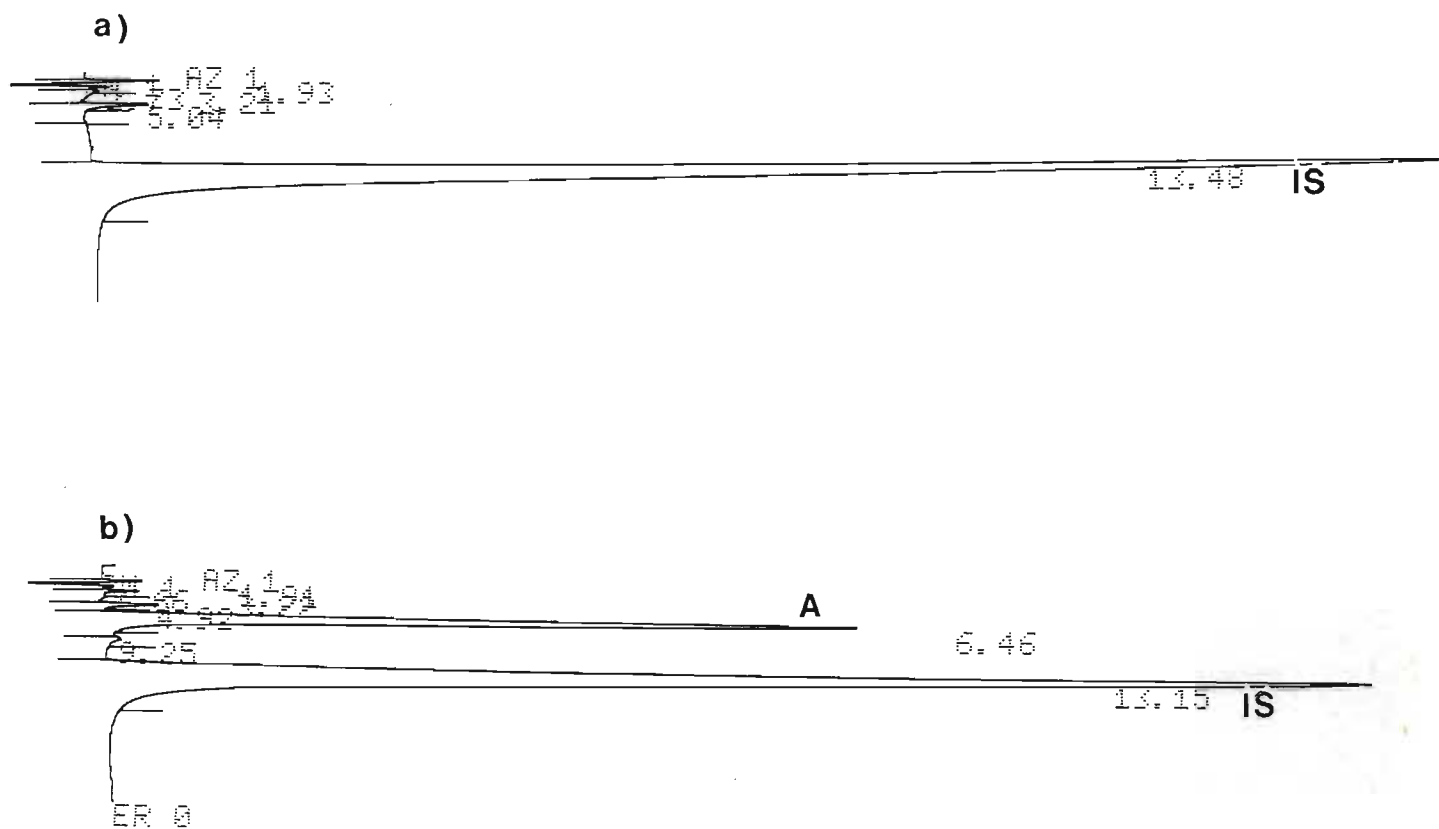
Figure 3.1. Specimen chromatograms using the Brownlee
column a) blank plasma with internal standard (IS);
b) volunteer sample containing atenolol (A) containing 676
ng/ml and IS.

3.3.2. Plasma Renin Activity (PRA)

A commercially available kit, Gammacoat [^{125}I] Plasma Renin Activity Radioimmunoassay Kit (Clinical Assays) obtained from Benmore Hospital Supplies was used. The PRA determination involved an initial incubation of plasma to generate angiotensin I which was then quantitated by radioimmunoassay. The assay kit sensitivity is quoted as 0.018 ng/tube. Percent recovery from spiked samples ranged from 99 to 117%. Intra-run precision ranged from CV% of 5.4 to 9.6 with inter-run CV% from 4.4 to 7.6.

Sodium and potassium levels in urine were measured by standard flame-photometry techniques in the laboratory of the Department of Clinical and Experimental Pharmacology, University of Natal Medical School.

3.4. EFFECT MEASUREMENTS

3.4.1. Blood Pressure Measurement

Blood pressure (BP) was measured with an aneroid manometer (Arteriosonde 1011) operating on the Doppler system. The microphone was always carefully positioned over the brachial artery of the left arm. Systolic blood pressure was taken at the onset of Korotkoff sounds and diastolic pressure as that at which they became inaudible (phase V). All measurements were performed by the same observer.

Supine blood pressure was measured after at least 3 minutes rest and erect blood pressure was taken 3 minutes after the volunteer stood up, prior to the exercise procedure.

Supine and erect blood pressure measurements were carried out prior to administration of atenolol and placebo and at approximately 0.3, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 30 and 36 hours after the infusions.

3.4.2. Exercise

Exercise tachycardia was chosen as the most reliable quantitative measurement of $beta_1$-receptor blockade (McDevitt 1977). This method was preferred to isoprenaline administration because it is physiological and safer for the volunteers (Johnsson & Regårdh 1976).

The volunteers were exercised for three minute periods on a Monark exercise bicycle at a constant load predetermined for a particular volunteer. The load had been chosen to increase the volunteers' heart rates to 140-150 beats/minute. The individual workloads and pre-treatment exercise heart rates are given in Appendix 1, Table A1.3. The exercise testing was carried out at ambient temperature which varied from 18-25° C. Exercise testing was performed 16 times over the 36 hours of the study subsequent to the BP measurements (See 3.4.1).

3.4.3. Heart Rate Measurement

Heart rate measurements were taken from ECG recordings on an Elema-Schönander Mingograph 81 (chart speed 10 mm/sec). The ECG was connected via an oscilloscope (Solartron Schlumberger) to a Hewlett Packard telemetry system (Transmitter 78100A, Receiver 78101A). Chest leads were used. Measurements were taken over 10 R-R intervals.

Resting heart rate was measured at the end of 3 minutes of supine rest whereas exercise heart rate was measured during the last 10-15 seconds of each 3 minute exercise period. These measurements were carried out prior to the placebo and atenolol infusions and repeated at approximately 0.3, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 30 and 36 hours after the end of the infusions.

For the pharmacokinetic-pharmacodynamic analysis the effect measurement was taken as the change in exercise heart rate after atenolol administration from that after placebo administration. It was obtained by subtracting the exercise heart rate at a particular time after atenolol treatment from the exercise heart rate at the equivalent time after placebo dosing.

3.5. DATA ANALYSIS

3.5.1. Statistical Analysis of Pharmacodynamic Data

3.5.1.1. Analysis of Variance

Analysis of variance (ANOVA) using the SAS programme (SAS/STAT USER'S GUIDE, Release 6.03) was used to analyze the effect time data at each point of measurement.

The following questions were asked:

i)   Did the drug affect heart rate, blood pressure or PRA at each time ?

ii) Was there any evidence of a racial difference in the effect of the drug on HR, BP or PRA?

The sources of variance were partitioned into between and within volunteers (split-plot design) and tests for differences were performed at each time point using the 'within person' error. Additionally a test for Race*Treatment interaction using the 'within person' error was carried out. A value of $p < 0.05$ was taken as significant at the 95% level.

3.5.1.2. Area under the Curve Analysis

Area under the Curve (AUC) was utilised as an alternative approach to the analysis of the effect-time data in an effort to obtain an overall assessment of the effect rather than looking at effect at specific times. This was thought to be necessary because the day to day intra-individual variation in blood pressure and heart rate dependent on extraneous factors appeared to affect the variation in measurements at discrete time points. Also any inter-individual differences in the time course of atenolol effect would also be expected to increase the inter-individual variation in effect at a particular time.

AUC was calculated for each individual for each effect measured (resting and exercise heart rate, systolic and diastolic blood pressure and plasma renin activity) from 0 to 12 hours after both placebo and atenolol administration.

The programme BIOPAK (Statistical Consultants, Inc., Lexington, Kentucky) was used to make the calculations. AUC was only calculated up to 12 hours because there were no measurements between 12 and 24 hours and measurements at 24, 30 and 36 hours were subject to increased variation as volunteers were not restricted in their activities. Thus the sparse 24, 30 and 36 hour measurements which are subject to increased variation would contribute a sizeable area.

The effect of atenolol in each individual was taken as the difference between the AUC after placebo and the AUC after atenolol for that particular effect. These differences for blacks and whites were compared using the unpaired Student's t-test with p<0.05 taken as a significant difference.

3.5.2. Pharmacokinetic Data Analysis

The pharmacokinetic parameters were estimated from the concentration time data. Parameters obtained in blacks and whites were compared using the Students t-test with p<0.05 considered a significant difference.

3.5.2.1. Model Independent Pharmacokinetic Analysis
3.5.2.1.1. Clearance (CL)

Clearance was estimated as follows:

$$CL = \frac{Dose_{IV}}{AUC}$$

where:

$$AUC = AUC(0 \rightarrow tn) + AUC(tn \rightarrow \infty)$$

AUC ($0 \rightarrow tn$) was calculated, using the trapezoidal rule (Gibaldi & Perrier 1982), from the start of the infusion to the last time (tn) at which a concentration (Cn) was measured. AUC ($tn \rightarrow \infty$) was calculated by dividing the last concentration measured (Cn) by the terminal elimination

rate constant (λ_z). The terminal elimination rate constant (λ_z) was obtained by linear regression analysis of the terminal log-linear decay phase (from 4 hours after the start of the infusion).

3.5.2.1.2. Half-life ($t_{\frac{1}{2}}$)

Mean residence time (MRT) is the statistical moment analogy to half-life and represents the time taken for 63.2% of the administered dose to be eliminated (Gibaldi & Perrier 1982). It is related to half life as follows:

$$t\frac{1}{2} = 0.693 \cdot MRT_{IV}$$

and:

$$MRT_{IV} = MRT_{INF} - \frac{T}{2}$$

where T is the duration of the infusion and

$$MRT_{INF} = \frac{AUMC}{AUC}$$

$$AUMC = AUMC(0 \to tn) + AUMC(tn \to \infty)$$

AUMC ($0 \to tn$) was obtained using the trapezoidal rule and the extrapolated AUMC as follows:

$$AUMC(Cn \to \infty) = \frac{Cn \cdot tn}{\lambda_z} + \frac{Cn}{\lambda_z^2}$$

(Rowland & Tozer 1989).

Terminal elimination half-life was calculated as follows:

$$t\tfrac{1}{2} = \frac{0.693}{\lambda_z}$$

Since atenolol is known to show multicompartment disposition characteristics the terminal elimination half-life is likely to be longer than that calculated from MRT above.

3.5.2.1.3. Volume of Distribution

Apparent Volume of Distribution at Steady State (V_{SS})

If a drug is given by a short term constant rate intravenous infusion then this parameter can be calculated as follows (Gibaldi & Perrier 1982):

$$V_{ss} = \frac{Dose_{INF} \cdot AUMC}{AUC^2} - \frac{Dose_{INF} \cdot T}{AUC \cdot 2}$$

It equates to the sum of the compartmental distribution volumes.

Area Volume of Distribution (V_d)

This parameter is calculated as follows:

$$V_d = \frac{Dose}{\lambda_z \cdot AUC}$$

Unlike V_{ss} this parameter is dependent on terminal elimination rate and can thus vary without a true variation in distribution space.

3.5.2.2. Model Dependent Pharmacokinetic Parameter Estimation

Curve fitting of models to data can be used for estimating various model dependent pharmacokinetic parameters. These parameters can in turn be used for predictions. The suitability of the models can be assessed to some extent by comparison of certain of the parameters with those derived by model independent methods.

Pharmacokinetic-pharmacodynamic modelling requires a good description of the concentration-time data for the prediction of concentrations at times when effects (pharmacodynamics) but not concentrations are measured. This is because it is seldom possible to measure concentrations and effects simultaneously.

Population pharmacokinetic modelling using NONMEM in addition to giving better parameter estimates when the number of samples per patient are sparse, can assess the contribution of physiological (age, weight etc.) and pathophysiological factors (disease states) to inter-subject variation in the pharmacokinetic parameters.

3.5.2.2.1. Pharmacokinetic Models

Since plasma-concentration-time data after intravenous atenolol administration has been reported to follow both a bi- and tri-exponential course (See 1.2.2.2.) both two and three compartment open models with zero-order input were fitted to the plasma concentration-time data for each volunteer (and for group data).

The standard equation for the two compartment open model is given below:

$$C = \frac{C_1}{\lambda_1}(1-e^{-\lambda_1 T}).(e^{-\lambda_1 t_{pi}}) + \frac{C_z}{\lambda_z T}.(1-e^{-\lambda_z T})(e^{\lambda_z t_{pi}})$$

For the two compartment model, the particular ELS regression and NONMEM subroutines chosen, generated parameters expressed in terms of clearance (CL), volume of the central compartment (V_1), intercompartmental clearance (Q_{12}) and volume of the peripheral compartment (V_2). The relevant microconstants were then calculated from these parameters.

The standard three compartment model equation is given below:

$$C = \frac{C_1}{\lambda_1 T}(1-e^{-\lambda_1 T})(e^{-\lambda_1 t_{pi}}) + \frac{C_2}{\lambda_2 T}(1-e^{-\lambda_2 T})(e^{-\lambda_2 t_{pi}})$$
$$+ \frac{C_z}{\lambda_z T}(1-e^{-\lambda_z T})(e^{-\lambda_z t_{pi}})$$

The parameters estimated were clearance (CL), volume of the central compartment (V_c), intercompartmental clearances (Q_{12} and Q_{13}) and volumes of the peripheral compartments (V_2 and V_3) from which the relevant microconstants were calculated.

3.5.2.2.2. ELS Pharmacokinetic Parameter Estimation for Individual Volunteers

The computer programme NONMEM (Double Precision NONMEM, Version III, level 1.0) was used for the estimation of all model dependent pharmacokinetic parameters. When data from a single person is analyzed with the NONMEM programme the analysis defaults to nonlinear extended least squares regression (ELS) (Beal & Sheiner 1979, Beal et al 1985).

The NONMEM PREDPP package (ADVAN 5, TRANS 1) was used (Beal et al 1985). A multiplicative statistical error routine was implemented for all pharmacokinetic as well as pharmacodynamic data fitting.

Concentration-time data for each individual was fitted to the 2 and 3 compartment models described above. For each individual, estimates of the various pharmacokinetic parameters were obtained together with standard errors of the estimates (SEE) and an estimate of the random intra-individual variance in the concentration measurement (σ_ϵ^2). By taking the square root and multiplying by 100 this value was expressed as a coefficient of variation. This estimate equates to error in the measurement, in the above case mainly assay error.

In this two stage analysis, the arithmetic mean of the individual estimates was taken as the group parameter estimate. Variation was calculated as follows:

$$CV\ (\%) = SD*100/mean$$

This method is analogous to the Standard Two Stage (STS) method described by Sheiner & Beal (1981, 1983) although in the present study variances were not estimated. Although seldom calculated, the population variances in the STS method have an upwards bias dependent on the number of samples per patient (Sheiner & Beal 1983).

3.5.2.2.3. Population Pharmacokinetic Parameter Estimation using NONMEM for Group Data

The computer programme NONMEM (Double Precision NONMEM, Version III, level 1.0) was used for the estimation of group (population) pharmacokinetic parameters.

The use of NONMEM as an alternative method of data analysis was implemented for the following reasons:

i)   NONMEM has been shown to be markedly superior to the STS method for the estimation of inter-individual random effect parameters (Sheiner & Beal 1980, 1981) particularly when the number of samples per individual differs as was the case with the present data.

ii) NONMEM is ideal for assessing the influence of fixed effects such as age, weight or possibly race in this case, on pharmacokinetic parameters (Driscoll et al 1989, Mungall et al 1985).

Two and 3 compartment models as described above were used for estimation of population pharmacokinetic parameters. Thereafter, the contribution of weight and race in explaining inter-individual variation in CL and V_c were investigated.

The same subroutines in NONMEM were utilised as were used in the ELS estimation (ADVAN5, TRANS1 from PREDPP). Subroutine Trans 1, expresses parameter values in terms of volume of the central compartment (V_c), clearance (CL), volumes of the second or third compartments (V_2 and V_3) and intercompartmental clearances (Q_{12} and Q_{13}), depending on the model.

Inter-individual variation in clearance and volume as well as residual intra-individual variability were modelled with proportional (heteroscedastic) error models.

NONMEM utilization gave estimates of:
1. population means of pharmacokinetic parameters;
2. variance of the inter-individual random effects of parameter estimates (ω^2);
3. variance of the residual intra-individual error (σ_ϵ^2);
4. correlation matrix of the estimates;
5. value of the minimum objective function (MOF), which is equal to minus twice the log-likelihood of the data.

3.5.2.2.4. Pharmacokinetic Model Choice

The most suitable pharmacokinetic model for each individual was chosen using the following criteria:

i) Minimum Objective Function (MOF); the smaller the MOF value the better the fit of the data.

ii) Akaike's Information Criterion (AIC)

$$AIC = MOF + 2p$$

where p is the number of parameters by which the models being compared differ. The lowest AIC was considered the best model.

iii) Chi squared test comparing the difference in minimum objective function (DOBF) relative to a tabled value with 1 or 2 degrees of freedom (the difference in

number of parameters between the models being compared).

iv) Additionally, correlations between parameters were assessed and plots of weighted residuals were examined.

The same criteria as above (i-iv) were used with NONMEM fitting of the 2 and 3 compartment models and subsequently to asses the influence of weight and race in building up models where one model was a restriction of the other. However, when evaluating two models neither of which is a restriction of the other, the likelihood ratio was used. A difference of at least 10 was considered a significant improvement (Ludden Personal Communication).

3.5.3. Pharmacokinetic-Pharmacodynamic Analysis

Only the influence of atenolol on exercise tachycardia was used as an effect (E) in this procedure. The inter- and intra-individual variation in resting heart rate, blood pressure and plasma renin activity made these effect measurements in individuals unsuitable for kinetic-dynamic analysis. These measurements appeared to be influenced, to a much greater extent than exercise tachycardia, by factors other than atenolol administration (See Chapter 1, Resting HR 1.1.2.1.2. and BP 1.1.2.2). Unfortunately the method of BP measurement was probably not accurate enough to allow meaningful evaluation in terms of pharmacodynamic modelling.

3.5.3.1. Pharmacodynamic Models

The following pharmacodynamic models were tested, firstly with effect data from each individual and secondly with all data combined.

i) Linear model with estimation of slope (S) only:

$$E = S.C$$

ii) Log-linear model with estimation of S and the constant (I):

$$E = S.logC+I$$

iii) The inhibitory E_{max} model with estimation of the maximum inhibitory effect attributable to the drug (E_{max}) and the concentration causing 50% inhibition of the maximum effect (IC_{50}):

$$E = \frac{E_{max}.C}{IC_{50}+C}$$

iv) The sigmoid E_{max} model with parameters as above but including the parameter (n) describing the slope:

$$E = \frac{E_{max}.C^{n}}{IC_{50}^{n}+C^{n}}$$

A few individuals appeared to have less of an effect at the first measurement than at subsequent points. An attempt was therefore made with the group data only, to assess the possibility of a delay in the onset of the reduction in exercise tachycardia. Accordingly, the following model was tested:

v) E_{max} model with an effect compartment:

$$E_t - \frac{E_{max} \cdot C_e(t)/K_p}{IC_{50} + C_e(t)/K_p}$$

Where C_e is the concentration in the effect compartment and K_p the partition coefficient between the effect and central compartments (Holford & Sheiner 1982).

3.5.3.2. Parameter Estimation

3.5.3.2.1. Individual Kinetic-Dynamic Parameter Estimation using ELS regression

Constraining the pharmacokinetic parameters (including variance) to those estimated from the best pharmacokinetic model in an individual, ELS regression was used to generate dynamic parameters relating effect to concentration with each of the effect models i-iv) for each subject in turn.

3.5.3.2.2. NONMEM Parameter Estimation for Group Data

The complete concentration-time-effect data set in all 14 volunteers was analyzed using the effect models i-iv) described above, in the NONMEM programme. An attempt was made to discern a possible lag time between atenolol concentration and inhibition of exercise tachycardia by fitting model v).

In addition, the possible influence of race on IC_{50} and E_{max} were assessed.

3.5.3.3. Pharmacodynamic Model Choice

The most suitable effect model (for each volunteer and for group data) was determined by using the same tests outlined in 3.5.2.2.4. above, for choosing pharmacokinetic models. Examination of the correlation matrices and plots of weighted residuals were particularly important in distinguishing between models in individuals.

CHAPTER 4

PHARMACODYNAMICS IN BLACK AND WHITE VOLUNTEERS

EXPERIMENTAL RESULTS AND DISCUSSION

CHAPTER 4

PHARMACODYNAMICS IN BLACK AND
WHITE VOLUNTEERS

EXPERIMENTAL RESULTS AND DISCUSSION

Results and discussion presented in this chapter relate to effect measurements only.

4.1. RESULTS

4.1.1. Effects on Heart Rate

4.1.1.1. Resting Heart Rate

The mean resting heart rate (RHR) measurements for all volunteers taken at intervals over 36 hours after placebo and atenolol administration are shown in Fig 4.1. RHR was significantly reduced after atenolol compared to placebo at most times measured from 0.5 to 36 hours after infusion (Table 4.1.). At 8, 24 and 36 hours post infusion the RHR although lower after atenolol treatment was on the borderline of statistical significance at the 5% level ($p=0.0522$, $p=0.0606$ and $p=0.0505$ respectively).

Although at 1 and 1.5 hours, RHR was significantly higher in blacks than in whites after both placebo and atenolol treatment (Fig 4.2) there was no significant racial difference in the RHR response to atenolol at any time of measurement (Fig 4.3.)(Table 4.1.). The mean maximum reduction in RHR due to atenolol was comparable in blacks and whites and followed a similar time course (Fig 4.3.) (Table 4.2.).

Factors other than treatment (atenolol or placebo) appeared to influence RHR at particular times. In whites and to a greater extent in blacks, RHR increased relative to baseline measurements during the first two hours after placebo administration, possibly due to frequent cycling (5 times in the first hour) (Fig 4.2.). A very similar response pattern was maintained in blacks after atenolol although at a somewhat reduced heart rate level (Fig 4.2.).

Table **4.1**. Mean resting heart rate (sem) after placebo and atenolol administration to all volunteers (n=16) and probability values for differences due to treatment, treatment interaction with race and race.

TIME (hours)	MEAN HEART RATE (sem) (beats/minute)		Probability Values (* $p<0.05$ taken as significant)		
	Placebo	Atenolol	Treatment	Treatment*Race	Race
0.0	68.0 (2.3)	70.5 (2.8)	0.2400	0.1800	0.8971
0.5	78.4 (2.3)	67.5 (5.1)	0.0230*	0.1191	0.0706
1.0	78.4 (2.3)	70.5 (2.9)	0.0440*	0.7070	0.0175*
1.5	72.0 (2.2)	66.7 (1.6)	0.0240*	0.8379	0.0171*
2.0	76.6 (2.0)	66.6 (2.0)	0.0002*	0.9264	0.3161
3.0	74.8 (2.0)	63.0 (2.1)	0.0001*	0.9295	0.1746
4.0	69.7 (2.4)	60.7 (2.0)	0.0011*	0.4746	0.1561
5.0	67.8 (2.3)	59.8 (1.8)	0.0014*	0.3274	0.6733
6.0	70.3 (2.3)	63.6 (1.9)	0.0301*	0.5705	0.4943
8.0	67.7 (1.6)	62.9 (2.2)	0.0522	1.0000	0.8521
10.0	64.7 (2.1)	58.1 (1.6)	0.0282*	0.2725	0.6354
12.0	66.9 (2.5)	61.4 (1.8)	0.0269*	0.2867	0.3593
24.0	66.7 (2.7)	62.3 (2.8)	0.0606	0.5936	0.7909
30.0	70.4 (2.1)	63.5 (1.2)	0.0089*	0.2451	0.3791
36.0	69.4 (2.4)	64.6 (1.8)	0.0505	0.7338	0.1783

Fig 4.1. Mean resting heart (RHR) after placebo and atenolol in all volunteers.

Resting heart rate (beats/minute)
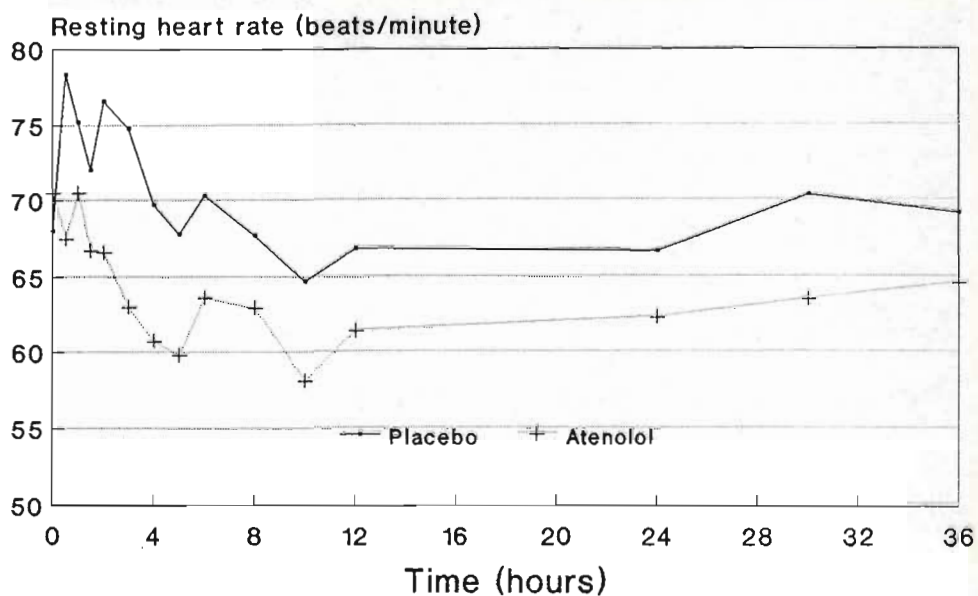
• Significant difference in treatment
from 0.5 to 30 hours (not at 8 and 24
hours).

Fig 4.2. Mean RHR in blacks and whites after placebo and atenolol.

Resting heart rate (beats/minute)
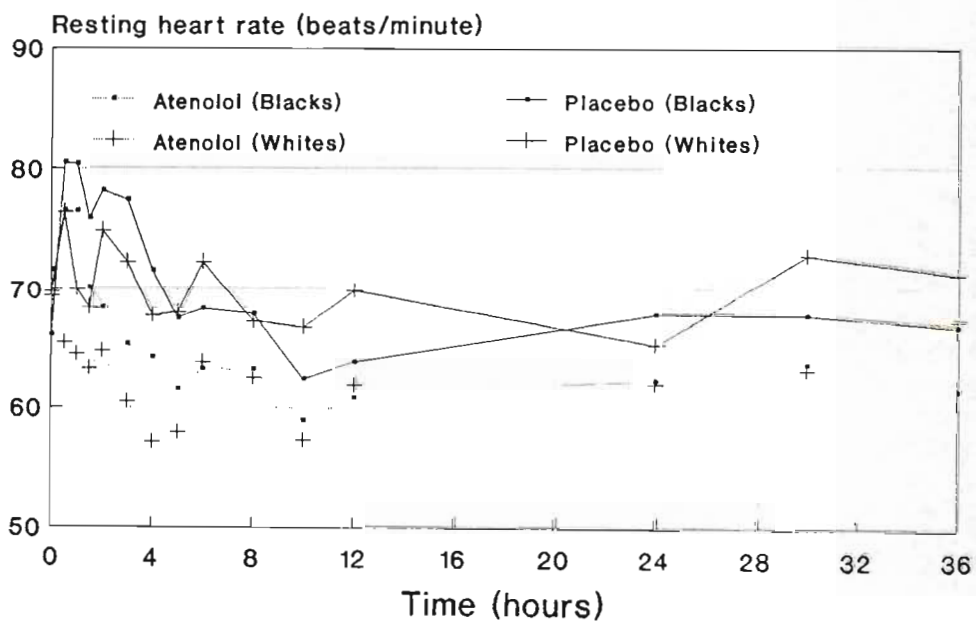
• Significant difference between races
at 1.0 and 1.5 hours.

Fig 4.3. Reduction in RHR in blacks and whites after atenolol administration (Placebo-atenolol).
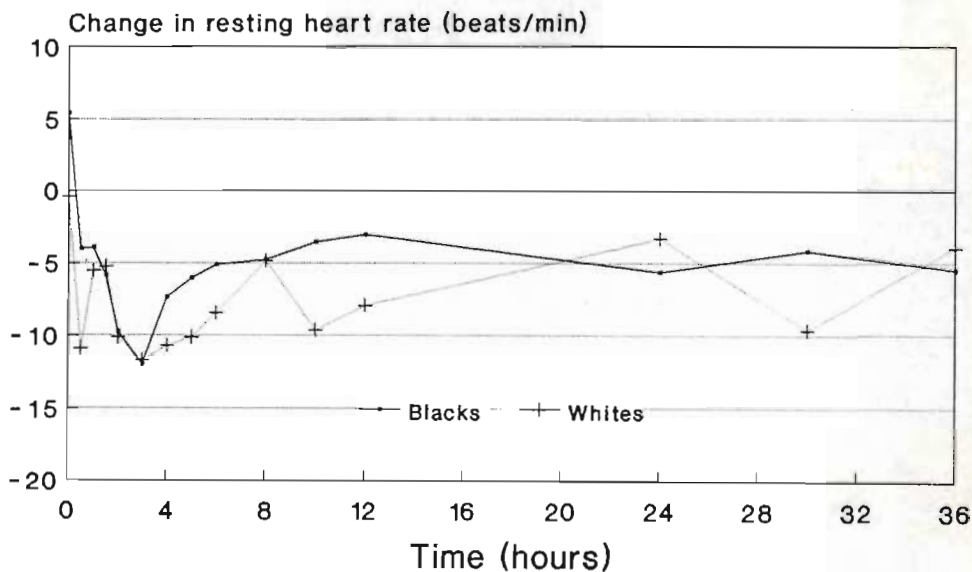
No significant differences due to
race in treatment response.

Fig 4.4. Change (Placebo-Atenolol) in AUC (0-12hrs) for RHR.
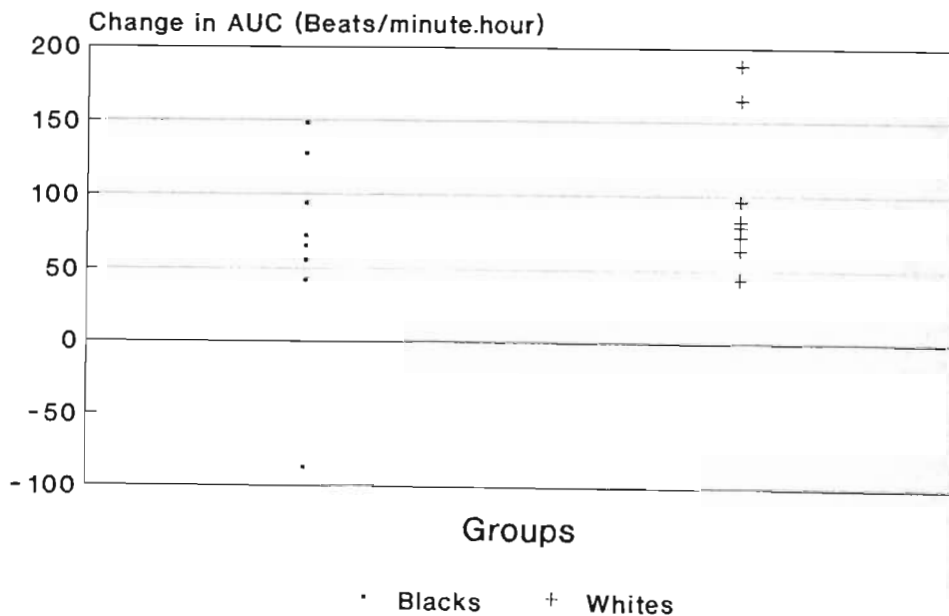
p‹0.3626

In whites, however, the increase in RHR above baseline seen with placebo in the first 1.5 hours was suppressed by atenolol. There was thus a short lived racial difference in RHR response in the first hour or two of the study with higher RHR observed in blacks after both placebo and atenolol (Table 4.1.). The lowest RHR in all volunteers occurred at 4-5 hours post treatment with another trough at 10 hours, irrespective of whether placebo or atenolol was given. These times coincided with periods when most volunteers were dozing. The serving of lunch between 5 and 6 hours after treatment (placebo and atenolol) appeared to correspond with a slight upswing in RHR in both groups of volunteers (Fig 4.2.).

In an attempt to analyze effects over a time period rather than at particular time points, resting heart rate area-under-the-curve (AUC) from 0 to 12 hours was calculated for each volunteer for both treatments. The overall individual response to atenolol was taken as the difference between AUC for placebo and AUC for atenolol. When these differences for blacks and whites were compared, no statistically significant difference was found (Fig. 4.4.).

The following results are given in Appendix 2:

Table A2.1. Resting heart rate in black and white individuals after placebo administration.

Table A2.2. Resting heart rate in black and white individuals after atenolol administration.

Table A2.3. Mean resting heart (beats/minute) after placebo and atenolol administration in the black and white groups (n=8 in each group).

Table A2.4. Area under the curve (AUC) for resting heart rate from 0 to 12 hours (beats/minute.hr) for placebo and atenolol and the difference between placebo and atenolol.

Table A2.29. Individual maximum changes in heart rate (E_{max}) and time to maximum (T_{max}) after atenolol.

Fig A2.1-A2.2. Resting heart rates in black individuals.

Fig A2.3-A2.4. Resting heart rates in white individuals.

Table 4.2. Maximum effects (E_{max}) taken as the difference between heart rates after placebo and atenolol and the time of maximum effects (T_{max}) in all volunteers and in blacks and whites separately.

	Resting Heart Rate		Exercise Heart Rate	
	E_{max} (bpm)	T_{max} (hrs)	E_{max} (bpm)	T_{max} (hrs)
ALL				
Mean	17.8	3.1	36.3	0.3
Median	18.0	3.0	37.5	0.3
CV%	35.0	43.7	17.6	42.4
Range	5-29	1.5-6.0	26-48	0.2-0.5
BLACKS				
Mean	15.6	2.9	36.9	0.4
Median	15.5	3.0	38.5	0.4
Range	5-26	1.5-4.0	26-44	0.2-0.5
WHITES				
Mean	19.9	3.2	35.6	0.3
Median	20.0	3.0	34.5	0.2
Range	11-29	1.5-6.0	27-48	0.2-0.5

4.1.1.2. Exercise Heart Rate

When compared to placebo, atenolol significantly reduced exercise heart rate (EHR) at all times measured from 0.2 up until 24 hours post infusion (Fig 4.5.)(Table 4.3.). The effect was maximal during the first half hour (Table 4.2.) and wore off with time until no significant difference was observed at 30 hours after the start of the infusion. Although baseline measurements (prior to treatment) were not different in blacks and whites, the experimental procedure appeared to increase the heart rate of blacks with repeated exercising to a peak of 10 -12 beats per minute above baseline between 1 and 2 hours following placebo treatment (Fig 4.6.). In whites the EHR after placebo was more or less stable for the duration of the study. At all times between 0.2 and 24 hours post-treatment (atenolol and placebo) the blacks had a mean exercise heart rate 5-10 beats higher than that of whites. This apparent racial difference in response to the exercise

Table 4.3. Mean exercise heart rate (sem) after placebo and atenolol administration to all volunteers (n=16) and probability values for differences due to treatment, treatment interaction with race and race. (# Values missing therefore statistical significance uncertain)

TIME (hours)	MEAN EXERCISE HEART RATE (sem) (beats/minute)		Probability Values (* p<0.05 taken as significant)		
	Placebo	Atenolol	Treatment	Treatment*Race	Race
0.0	137.9 (2.8)	140.8 (2.5)	0.2345	0.7110	0.3948
0.2#	139.9 (2.0)	107.1 (1.9)	0.0001*	0.8492	0.0191*
0.4#	143.5 (3.1)	112.0 (2.9)	0.0001*	0.2283	0.6016
0.5	144.2 (2.8)	110.9 (1.9)	0.0001*	0.8957	0.0802
0.8#	142.2 (3.5)	112.1 (2.3)	0.0001*	0.4016	0.0095*
1.0	145.1 (2.8)	112.4 (2.0)	0.0001*	0.5231	0.0233*
1.5	145.2 (3.3)	114.3 (2.0)	0.0001*	0.4022	0.0039*
2.0	147.5 (3.0)	116.1 (2.1)	0.0001*	0.9300	0.0243*
3.0	145.7 (2.4)	116.9 (2.2)	0.0001*	0.6301	0.0222*
4.0	145.7 (2.5)	116.8 (2.2)	0.0001*	0.7757	0.0248*
5.0	142.8 (2.5)	118.7 (2.0)	0.0001*	0.7736	0.0488*
6.0	144.9 (2.6)	122.2 (2.4)	0.0001*	0.6736	0.0911
8.0	141.9 (2.0)	123.1 (2.3)	0.0001*	0.3096	0.0795
10.0	141.8 (1.9)	125.2 (2.5)	0.0001*	0.4640	0.1754
12.0	144.1 (2.3)	129.1 (2.0)	0.0001*	0.3469	0.0208*
24.0	141.8 (2.4)	133.0 (2.3)	0.0005*	0.2179	0.0560
30.0	142.3 (2.4)	140.4 (2.4)	0.4900	0.7367	0.1669
36.0	146.1 (1.8)	143.5 (1.5)	0.0882	0.1875	0.2253

Fig 4.5. Mean exercise heart rate after placebo and atenolol in all volunteers.
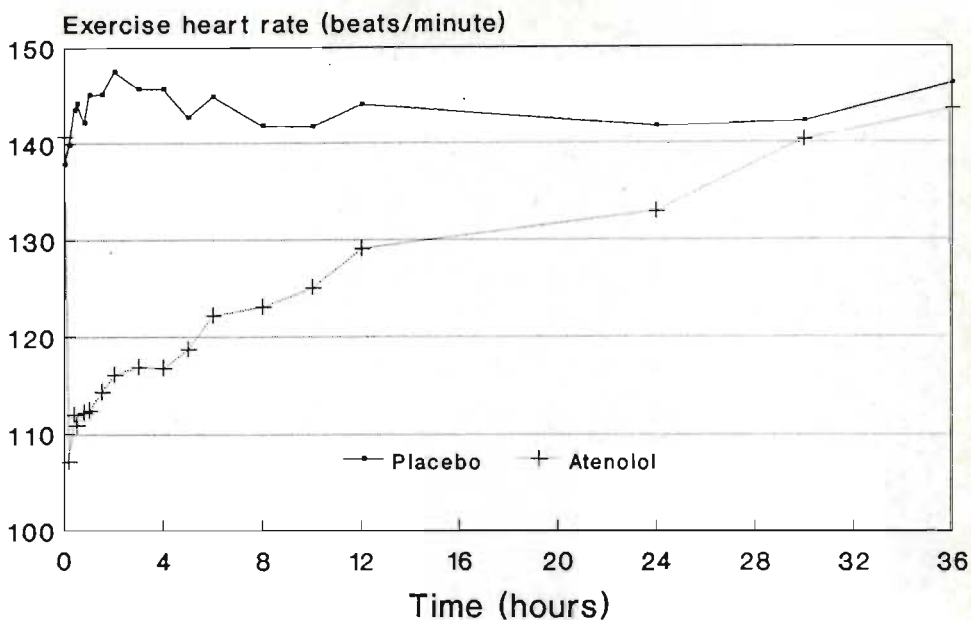
* Significant differences due to treatment from 0.2 to 24 hours.

Fig 4.6. Mean EHR for blacks and whites after placebo and atenolol.
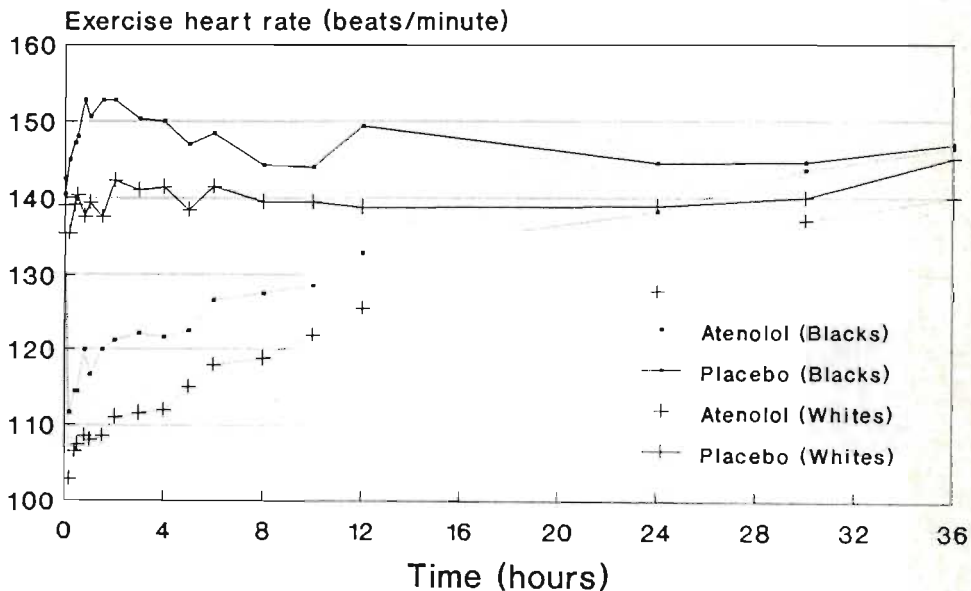
* Significantly higher EHR in blacks from 0.8 to 5 hours irrespective of treatment.

Fig 4.7. Reduction in EHR in blacks and whites by atenolol relative to placebo.
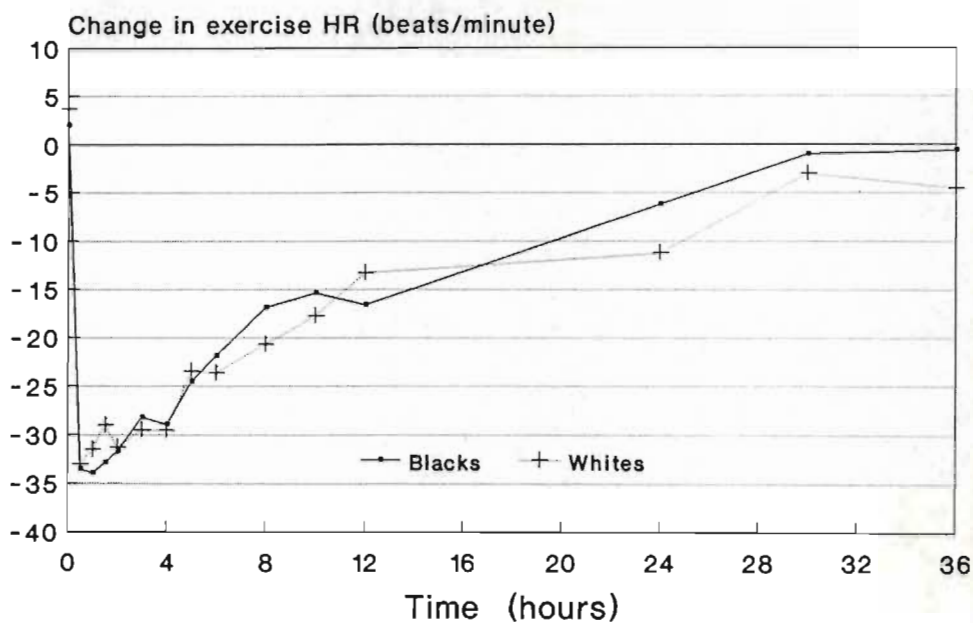
No significant differences in treatment
response due to race.

Fig 4.8. Change (Placebo-Atenolol) in AUC (0-12 hrs) for EHR.
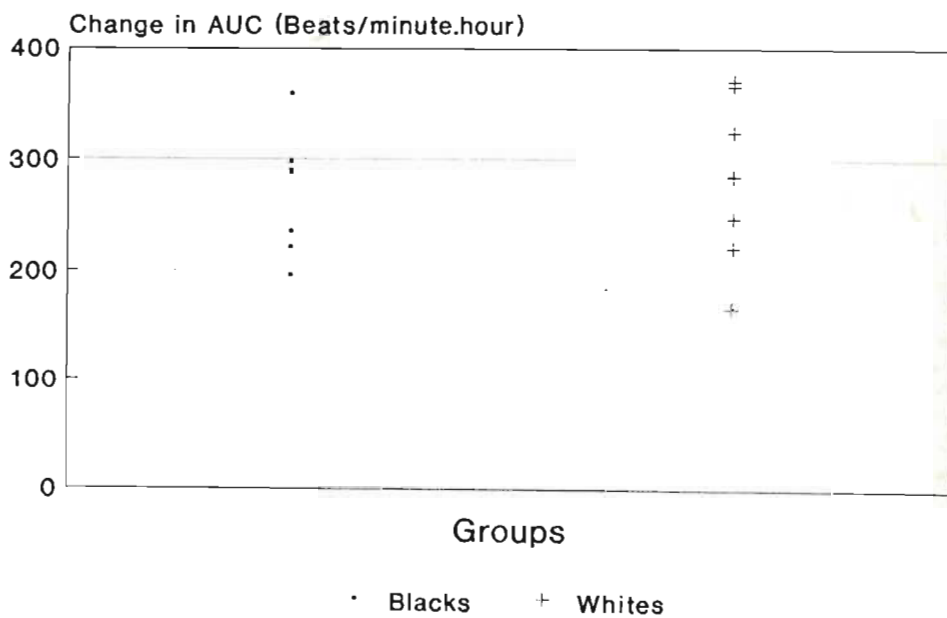
p‹0.5324

protocol achieved statistical significance from 0.5 to 5 hours post infusion (Table 4.3.). There was, however, no ethnic difference in the maximum magnitude of the reduction in EHR in response to atenolol taken as the difference between the EHR seen after placebo and that after atenolol administration nor in the time course of the effect (Fig 4.7.) (Table 4.2.).

When utilising the difference in EHR AUC (0 to 12 hours) after placebo and atenolol as a measure of the overall effect of atenolol, no significant difference between blacks and whites was observed (Fig 4.8.).

The following results are given in Appendix 2:

Table A2.5. Exercise heart rate in black and white individuals after placebo administration.

Table A2.6. Exercise heart rate in black and white individuals after atenolol administration.

Table A2.7. Mean exercise heart rate (beats/minute) after placebo and atenolol administration in the black and white groups (n=8 in each group).

Table A2.8. Area under the curve (AUC) for exercise heart rate from 0 to 12 hours (beats/minute.hr) for placebo and atenolol and the difference between placebo and atenolol.

Table A2.29. Individual maximum changes in heart rate (E_{max}) (bpm) and the time to maximum (T_{max}) after atenolol.

Fig A2.5-A2.6. Exercise heart rates in black individuals.

Fig A2.7-A2.8. Exercise heart rates in white individuals.

4.1.2. Blood Pressure Responses

4.1.2.1. Erect Blood Pressure

4.1.2.1.1. Erect Systolic Blood Pressure

Mean erect systolic blood pressure (ESBP) for all volunteers (n=16) was reduced by atenolol relative to placebo from 0.5 hours to 12 hours although the reduction was significant only from 1.5 to 8 hours post infusion (Fig 4.9.)(Table 4.4.).

There were no significant racial differences in overall ESBP responses at any time points measured (Fig 4.10.) although marked intra- and inter-individual variation was seen (See individual graphs in Appendix 2). When comparing the mean magnitude of effect of atenolol on ESBP in blacks and whites, the whites showed a greater mean response at all times up to 30 hours after administration although this was not statistically significant at any time point (Fig 4.11.) (Table 4.4.). Maximal effects were seen at about 3-4 hours in whites and at 5 hours in blacks (Table 4.5.) with mean effects disappearing on average more quickly in blacks (10-12 hours) than in whites (12 to 24 hours).

Using differences between placebo and atenolol AUC (0 to 12 hours) for ESBP as an indication of the response to atenolol there was no statistical difference between blacks and whites (Figure 4.12). One black (MN) and one white (NF) appeared to have an increased BP after atenolol relative to placebo values thus a negative overall response in terms of AUC differences between placebo and atenolol. Four whites had a greater response (difference in AUC) than the highest amongst the blacks.

The power to detect a difference between the two groups was very low because of the great inter-subject variation. To show a 20% difference in AUC change (unpaired, two-tailed with $\alpha=0.05$ and $\beta=0.02$) taking the whites as the reference group would require 59 volunteers per group.

Table 4.4. Mean erect systolic blood pressure (sem) after placebo and atenolol administration to all volunteers (n=16) and probability values for differences due to treatment, treatment interaction with race and race.

TIME (hours)	MEAN ERECT SYSTOLIC BP (sem) (mm Hg)		Probability Values (* p<0.05 taken as significant)		
	Placebo	Atenolol	Treatment	Treatment*Race	Race
0.0	112.8 (2.8)	111.3 (2.1)	0.5521	0.6908	0.9564
0.5	111.4 (1.9)	107.8 (2.1)	0.0732	0.3657	0.9736
1.0	108.1 (2.0)	104.9 (1.8)	0.1863	0.5659	0.7250
1.5	111.1 (2.1)	104.3 (2.3)	0.0049*	0.1603	0.8339
2.0	111.8 (1.8)	102.5 (2.3)	0.0026*	0.2550	0.3854
3.0	112.8 (1.9)	104.1 (2.4)	0.0023*	0.1414	0.8653
4.0	109.9 (2.5)	103.1 (2.5)	0.0036*	0.0794	0.6032
5.0	109.9 (2.2)	103.9 (2.3)	0.0190*	0.5089	0.9289
6.0#	112.7 (2.1)	107.8 (2.4)	0.0610	0.9903	0.9961
8.0	113.6 (1.8)	107.4 (2.1)	0.0199*	0.5059	0.8473
10.0	114.2 (2.2)	107.9 (2.5)	0.1352	0.7838	0.6463
12.0#	116.1 (1.6)	116.5 (2.6)	1.0000	0.1490	0.4088
24.0	110.1 (1.6)	110.5 (2.1)	0.8253	0.6825	0.8739
30.0	112.6 (2.1)	112.7 (2.5)	0.9551	0.3747	0.9292
36.0	116.0 (2.0)	116.9 (1.8)	0.5671	0.5671	0.4087

One value missing

Fig 4.9. Mean erect systolic BP in all volunteers after placebo and atenolol.
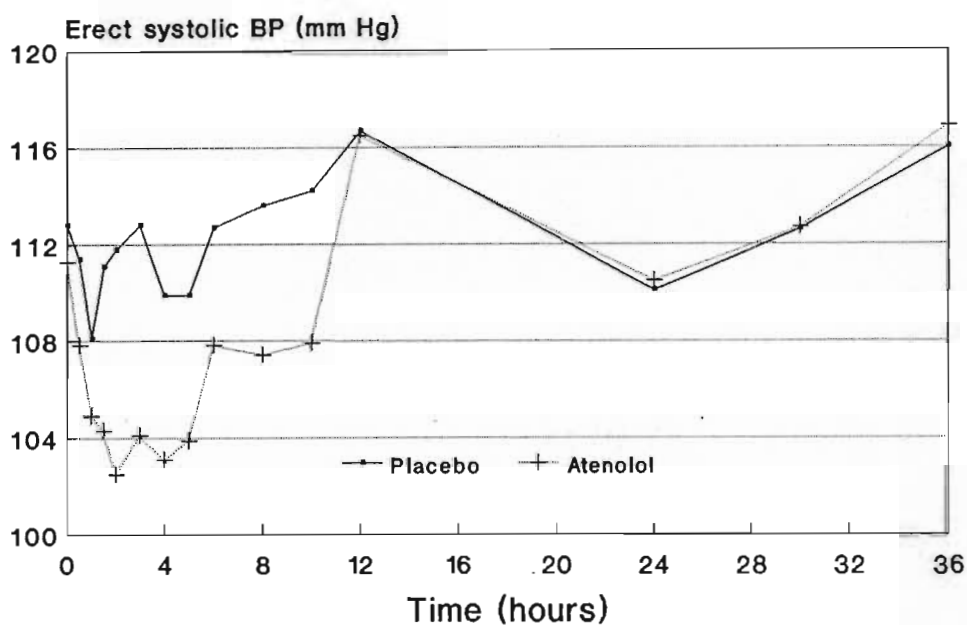
• Significant treatment differences from
1.5 to 8 hours.

Fig 4.10. Mean Erect systolic BP after placebo and atenolol in whites & blacks.
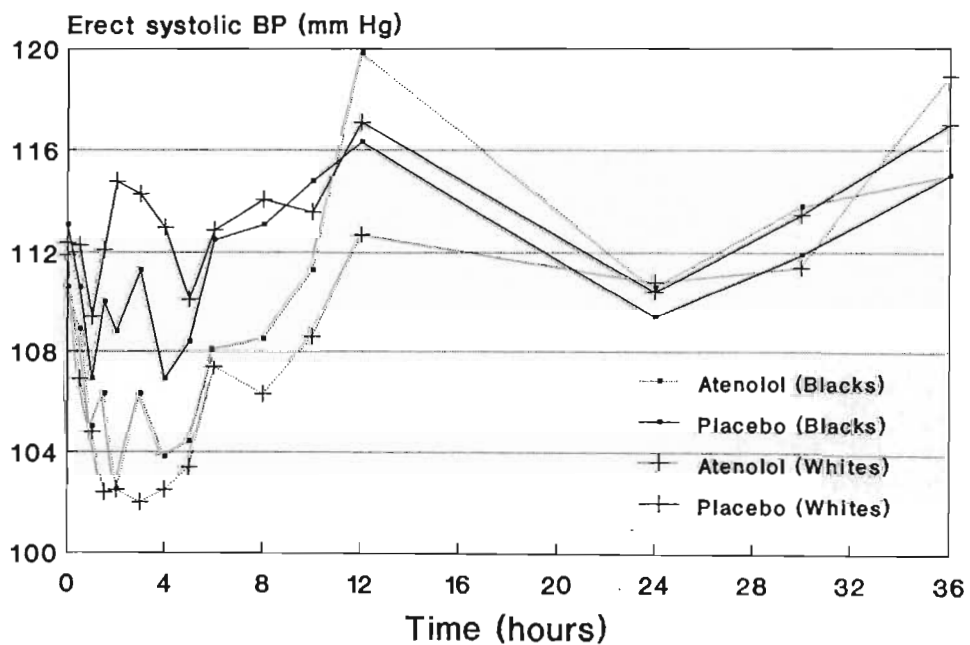
No significant differences between races

Fig 4.11. Change in mean erect systolic BP in blacks and whites after atenolol.
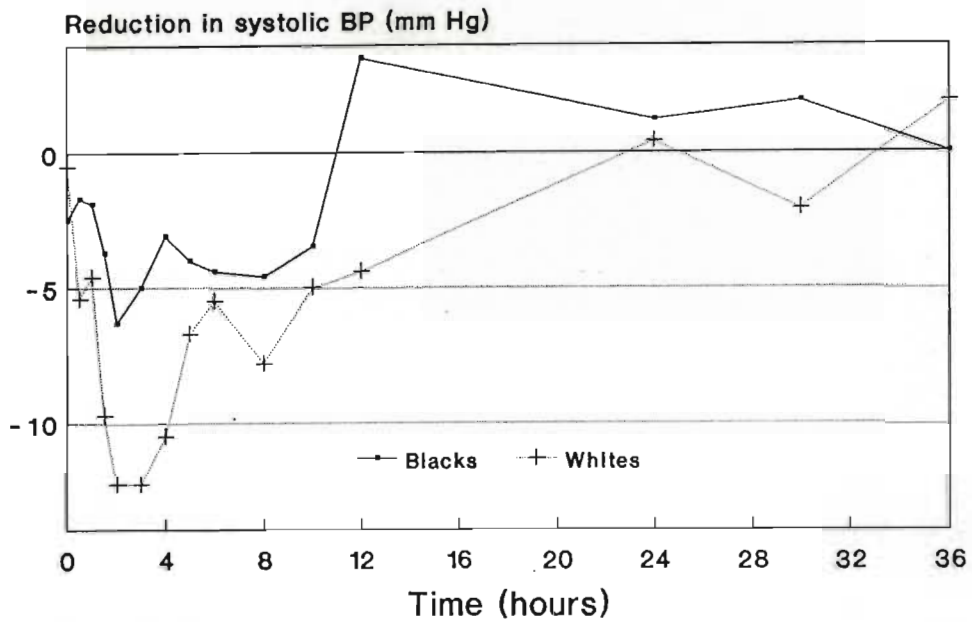
No significant differences in
treatment response between races.

Fig 4.12. Change (Placebo-Atenolol) in AUC (0-12 hrs) for Erect Systolic BP.

p<0.1906

111
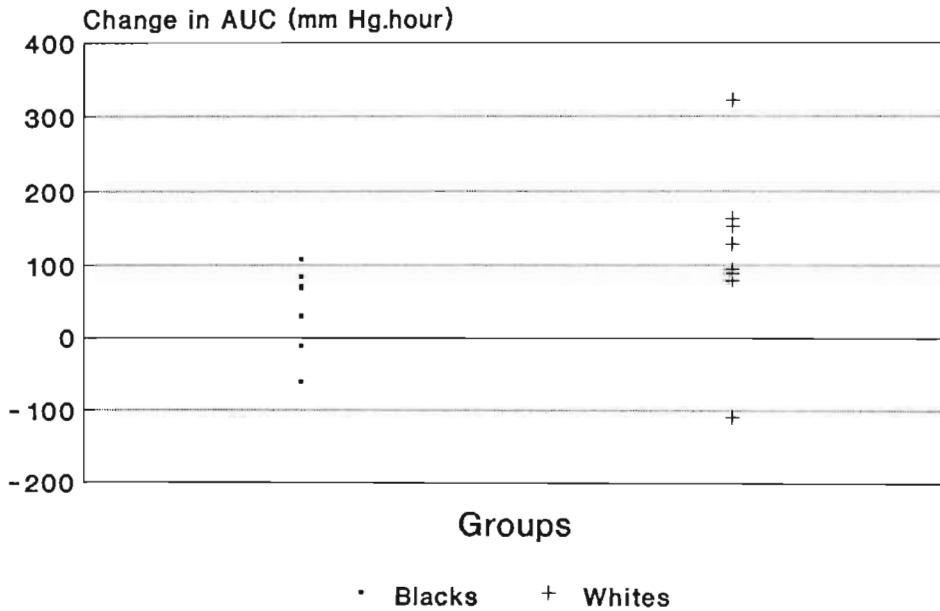
The following results are given in Appendix 2:

Table A2.9. Erect systolic blood pressure for black and white individuals after placebo administration.

Table A2.10. Erect systolic blood pressure in black and white individuals after atenolol administration.

Table A2.11. Mean erect systolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

Table A2.12. Area under the curve (AUC) for erect systolic blood pressure from 0 to 12 hours (mm Hg.hr) after placebo and atenolol and the difference between placebo and atenolol.

Table A2.30. Individual maximum changes in BP (E_{max}) (mm Hg) and the time to maximum (T_{max}) (hours) after atenolol.

Fig A2.9-A2.10. Erect blood pressures in black individuals.

Fig A2.11-A2.12. Erect blood pressures in white individuals.

Table 4.5. Maximum change in BP (E_{max}) (mm Hg) and time to maximum effects (T_{max}) (hours) after atenolol for erect and supine systolic and diastolic blood pressure in all volunteers and in blacks (B) and whites (W) considered separately.

	ERECT BP				SUPINE BP			
	SYSTOLIC		DIASTOLIC		SYSTOLIC		DIASTOLIC	
	E_{max}	T_{max}	E_{max}	T_{max}	E_{max}	T_{max}	E_{max}	T_{max}
ALL Mean	16	4.5	12.9	8.7	12.7	5.5	11.5	8.3
Median	16	4	15	8	10	6	10	6
Min	0	1.5	0	3	5	0.9	0	0.9
Max	30	10	25	24	23	12	20	24
BLACKS Mean	14	5.4	14.4	8.5	10.0	5.7	11.5	9
Median	15	5	15	8	10	5.5	10	8
Min	0	2	5	4	5	1.4	0	3
Max	20	8	25	12	15	12	20	24
WHITES Mean	18	3.6	11.5	8.9	15.4	5.2	11.5	7.6
Median	20	3	12.5	8	15	5	12.5	4.5
Min	0	1.5	0	3	5	0.9	4	0.9
Max	30	10	20	24	23	10	20	24
B vs W p<	.316	.373	.389	.903	.033	.716	#	.786

No statistically significant differences between blacks and whites.
Sample means identical.

4.1.2.1.2. Erect Diastolic Blood Pressure

When all volunteers were considered together atenolol was found to reduce mean erect diastolic blood pressure (EDBP) relative to placebo from 3 to 24 hours after administration(Table 4.6.)(Fig 4.13.). This reduction was only statistically significant at 8 hours after treatment when effects were maximal (Table 4.6.). Race did not significantly influence either EDBP (Fig 4.14.) or the effect of treatment on it at any time of measurement (Fig 4.15.)(Table 4.6.). Marked intra-individual variation in maximal effect (0-25 mm Hg) and time of maximum effect (3-24 hours) on EDBP was observed in both blacks and whites (Table 4.5). One white (JFO) showed no discernible reduction below placebo levels at any time after atenolol whilst two blacks showed minimal reductions (MN, ZN).

The difference between placebo and atenolol in AUC for EDBP (0 to 12 hours) was not significantly different between the black and white groups (Fig 4.16.).

The following results are given in Appendix 2:

Table A2.13. Erect diastolic blood pressure values in black and white individuals after placebo administration.

Table A2.14. Erect diastolic blood pressure values in black and white individuals after atenolol administration.

Table A2.15. Mean erect diastolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

Table A2.16. Area under the curve (AUC) for erect diastolic blood pressure from 0 to 12 hours (mm Hg.hr) for placebo and atenolol and the difference between placebo and atenolol.

Table A2.30. Individual maximum changes in BP (E_{max}) (mm Hg) and time to maximum (T_{max}) (hours) after atenolol.

Fig A2.9-A2.10. Erect blood pressures in black individuals.

Fig A2.11-A2.12. Erect blood pressures in white individuals.

Table **4.6.** Mean erect diastolic blood pressure (sem) after placebo and atenolol administration to all volunteers (n=16) and probability values for differences due to treatment, treatment interaction with race and race.

TIME (hours)	MEAN ERECT DIASTOLIC BP (sem) (mm Hg)		Probability Values (* p<0.05 taken as significant)		
	Placebo	Atenolol	Treatment	Treatment*Race	Race
0.0	70.5 (2.0)	74.0 (2.2)	0.0857	0.4918	0.1198
0.5	71.9 (2.2)	71.8 (1.9)	0.9552	0.2290	0.6266
1.0	71.7 (1.5)	69.6 (2.5)	0.3929	0.9373	0.6243
1.5	69.3 (2.0)	70.0 (2.4)	0.7094	0.8035	0.6045
2.0	68.4 (2.2)	69.0 (2.3)	0.8059	0.5256	0.8261
3.0	71.0 (1.8)	67.8 (2.1)	0.1779	0.3920	0.7162
4.0	71.8 (1.5)	69.8 (2.4)	0.4017	0.8735	0.7240
5.0	69.9 (1.9)	67.9 (2.3)	0.3285	0.1180	0.3633
6.0#	68.8 (1.6)	67.2 (1.9)	0.4288	0.8117	0.2617
8.0	73.4 (2.0)	67.6 (1.9)	0.0030*	0.6972	0.0527
10.0	74.8 (1.4)	71.8 (2.6)	0.2513	0.7693	0.1690
12.0#	73.8 (2.4)	69.4 (2.3)	0.1464	0.1592	0.5304
24.0	71.8 (1.3)	69.6 (1.9)	0.2241	0.2241	0.0830
30.0	67.5 (1.8)	70.3 (2.1)	0.1974	0.8562	0.4016
36.0	70.8 (2.2)	72.7 (2.0)	0.4224	0.2851	0.8261

One value missing

Fig 4.13. Mean erect diastolic BP after placebo and atenolol in all volunteers.

Erect diastolic BP (mm Hg)
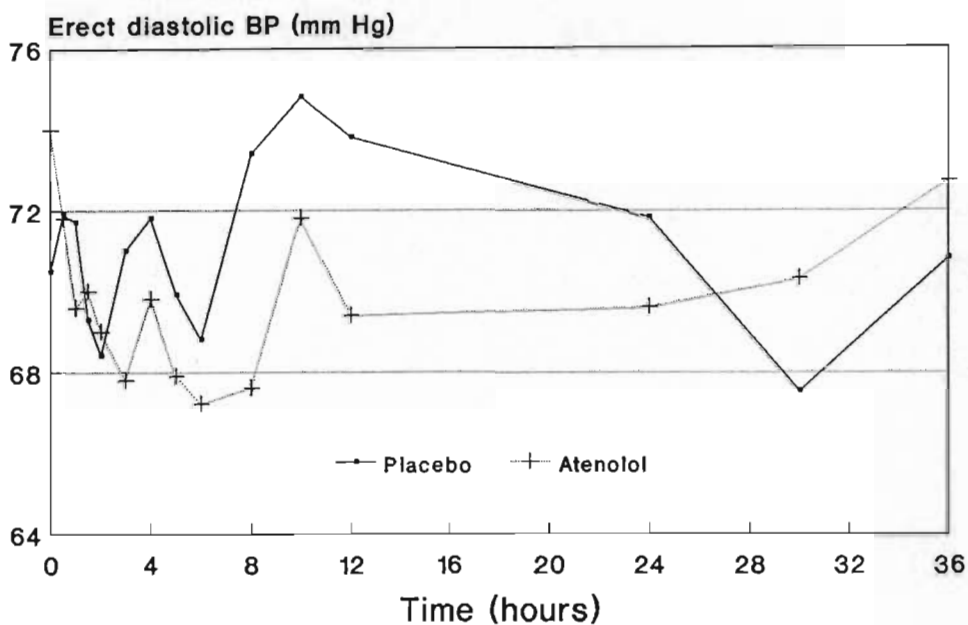
• Significant treatment difference at
8 hours only.

Fig 4.14. Mean erect diastolic BP after placebo and atenolol in blacks & whites.

Erect diastolic BP (mm Hg)
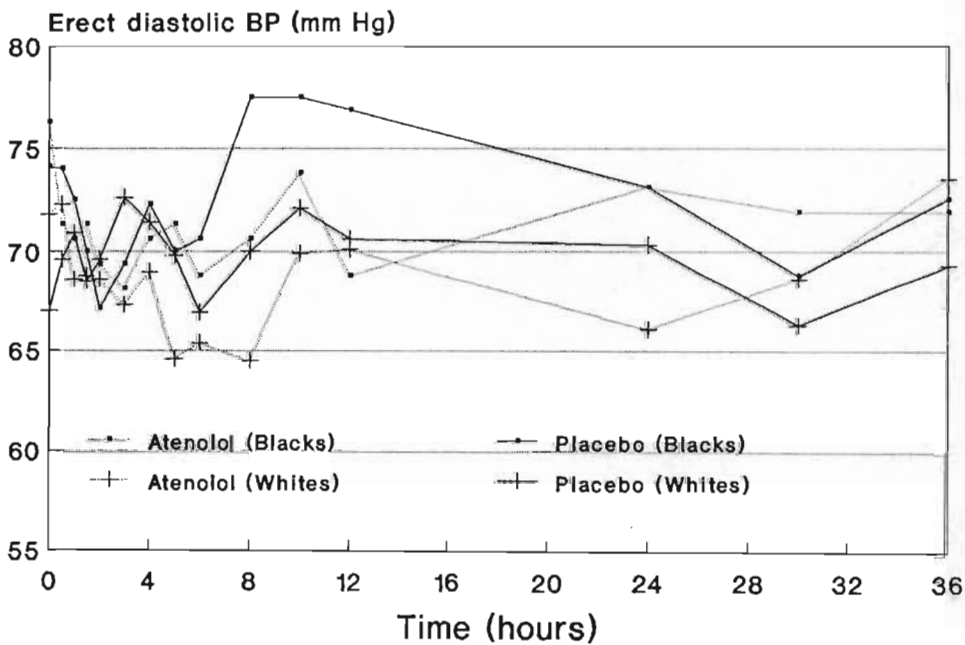
No significant racial differences

Fig 4.15. Reduction in erect diastolic BP in blacks and whites after atenolol.
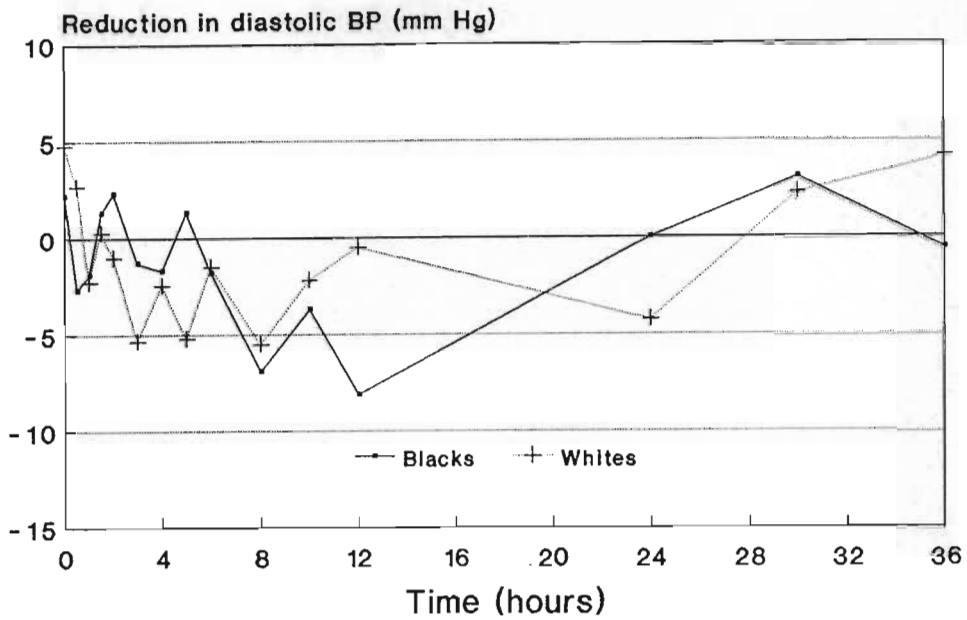
No significant racial differences in
treatment response.

Fig 4.16. Change (Placebo-Atenolol) in AUC (0-12 hrs) for Erect Diastolic BP.
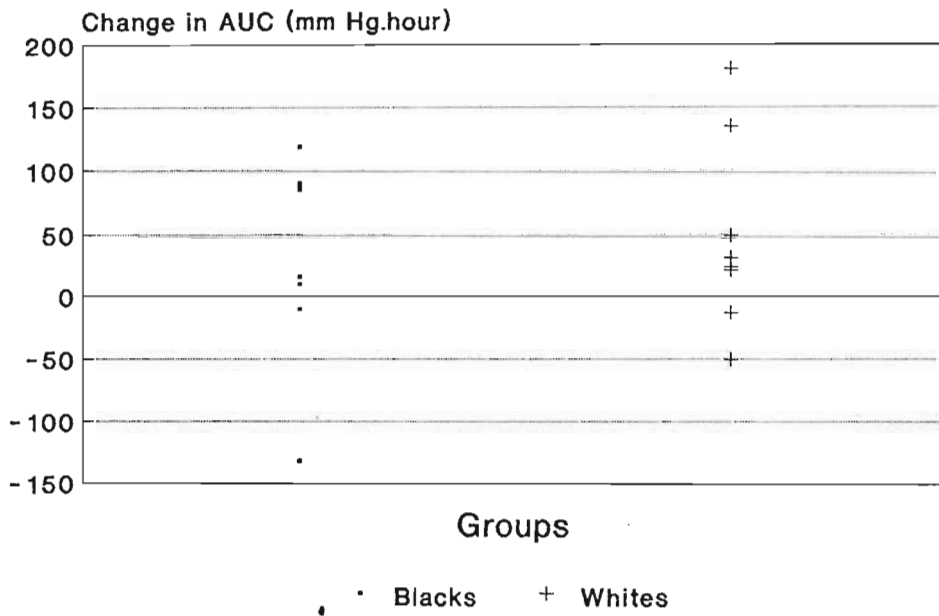
p<0.8570

4.1.2.2. Supine Blood Pressure

4.1.2.2.1. Supine Systolic Blood Pressure

Although it had little effect in the first hour after administration, atenolol significantly reduced supine systolic blood pressure (SSBP) compared with placebo at all time points measured between 1.4 and 10 hours post dosing except for the 5 hour measurement (Fig 4.17.)(Table 4.7.) when all volunteers were considered together. The mean maximal reduction of 10 and 15 mm Hg in blacks and whites respectively was seen at 5-6 hours (Table 4.5.) with a return to placebo values by 24 hours in most individuals. Mean supine systolic BP values after placebo and atenolol for blacks and whites considered separately are given in Fig 4.18. As with erect systolic BP the mean response to atenolol was less in blacks than in whites at most times measured but was statistically significantly different at only 4 and 10 hours after administration (Figure 4.19.)(Table 4.7.). Although there was marked inter-individual variation in the time course of this response all volunteers showed a reduction below placebo values at some point after atenolol administration.

Considering AUC (0-12 hours) differences (placebo minus atenolol) in individuals there was a significantly greater response in whites compared with blacks (Figure 4.20). Again NF proved to be an outlier within the white group showing a negative response to atenolol treatment ie. a relative increase in BP.

The following results are given in Appendix 2:

Table A2.17. Supine systolic blood pressure in black and white individuals after placebo administration.

Table A2.18. Supine systolic blood pressure in black and white individuals after atenolol administration.

Table A2.19. Mean supine systolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

Table A2.20. Area under the curve (AUC) for supine systolic blood pressure from 0 to 12 hours (mm Hg.hr) after placebo and atenolol and the difference between placebo and atenolol.

Table A2.30. Individual maximum changes in BP (E_{max}) (mm Hg) and time to maximum (T_{max}) (hours) after atenolol).

Fig A2.13-A2.14. Supine blood pressures in black individuals.

Fig A2.15-A2.16. Supine blood pressures in white individuals.

Table 4.7. Mean supine systolic blood pressure (sem) after placebo and atenolol administration to all volunteers (n=16) and probability values for differences due to treatment, treatment interaction with race and race.

TIME (hours)	MEAN SUPINE SYSTOLIC BP (sem) (mm Hg)		Probability Values (* p<0.05 taken as significant)		
	Placebo	Atenolol	Treatment	Treatment*Race	Race
0.0	108.4 (2.9)	112.5 (2.1)	0.1609	0.6718	0.8835
0.4	109.8 (2.0)	112.7 (2.2)	0.1747	0.0666	0.6139
0.9	109.4 (2.0)	106.9 (1.8)	0.3125	0.8951	0.8010
1.4	108.8 (2.1)	104.7 (2.2)	0.0428*	0.5967	0.9268
2.0	110.3 (1.5)	103.1 (2.1)	0.0015*	0.1396	0.8212
3.0	108.9 (2.1)	103.9 (2.2)	0.0218*	0.3403	0.6939
4.0	107.1 (1.9)	101.1 (1.8)	0.0003*	0.0191*	0.6219
5.0	105.8 (2.1)	105.4 (2.2)	0.8712	0.2896	0.8956
6.0	109.3 (2.6)	105.6 (2.4)	0.0061*	0.3343	0.7881
8.0	108.4 (1.9)	104.6 (2.1)	0.0238*	0.4914	0.5425
10.0	112.0 (2.4)	106.1 (2.3)	0.0028*	0.0060*	0.7756
12.0	112.9 (1.8)	110.3 (2.5)	0.1875	0.3125	0.7716
24.0	106.5 (1.3)	106.8 (2.0)	0.8851	0.6146	0.4285
30.0	110.3 (2.3)	107.6 (2.1)	0.0932	0.1915	0.8141
36.0	113.4 (1.8)	113.9 (2.3)	0.7783	0.2869	0.5522

Fig 4.17. Mean supine systolic BP after placebo and atenolol in all volunteers.
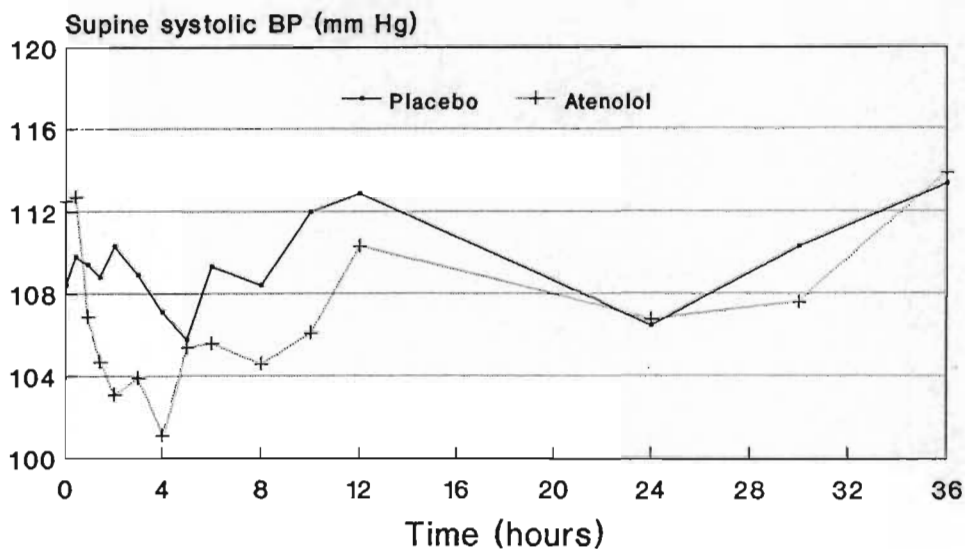
• Significant difference between placebo
and atenolol from 1.4 to 10 hours
(except at 5.0 hours).

Fig 4.18. Mean supine systolic BP in blacks and whites after placebo and atenolol.
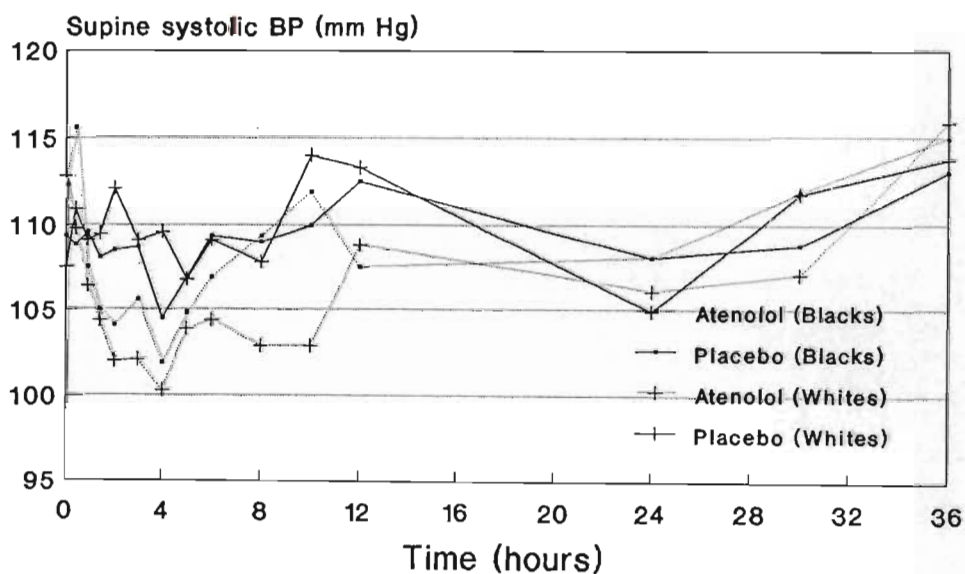
No significant racial differences in BP
responses.

Fig 4.19. Reduction in supine systolic BP in blacks & whites after atenolol.

Reduction in systolic BP (mm Hg)

Time (hours)
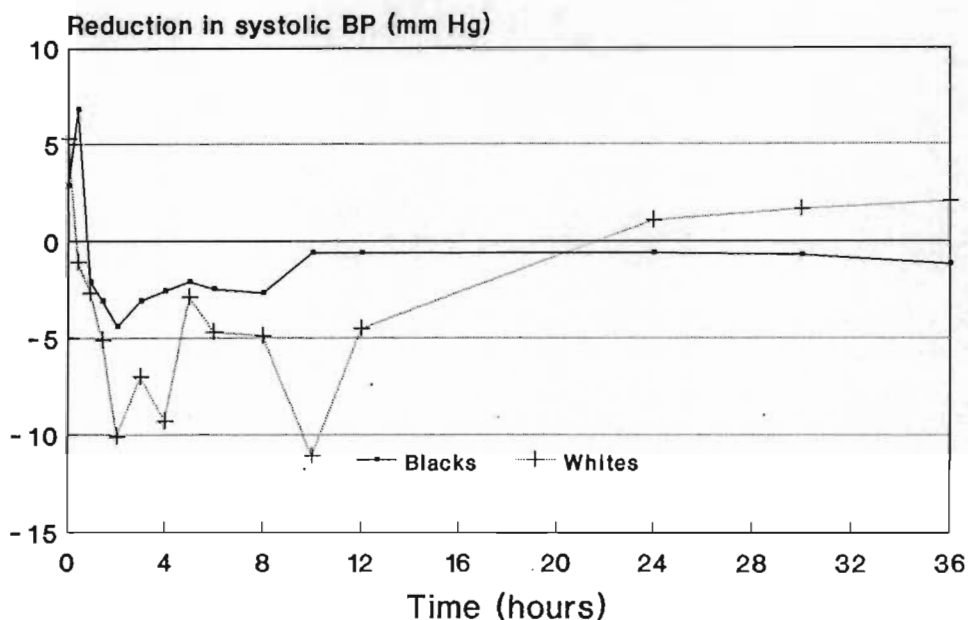
• Significant racial difference in
treatment response at 4 and 10 hours.

Fig 4.20. Change (Placebo-Atenolol) in AUC (0-12 hrs) for Supine Systolic BP.

Change in AUC (mm Hg.hour)

Groups

· Blacks   + Whites
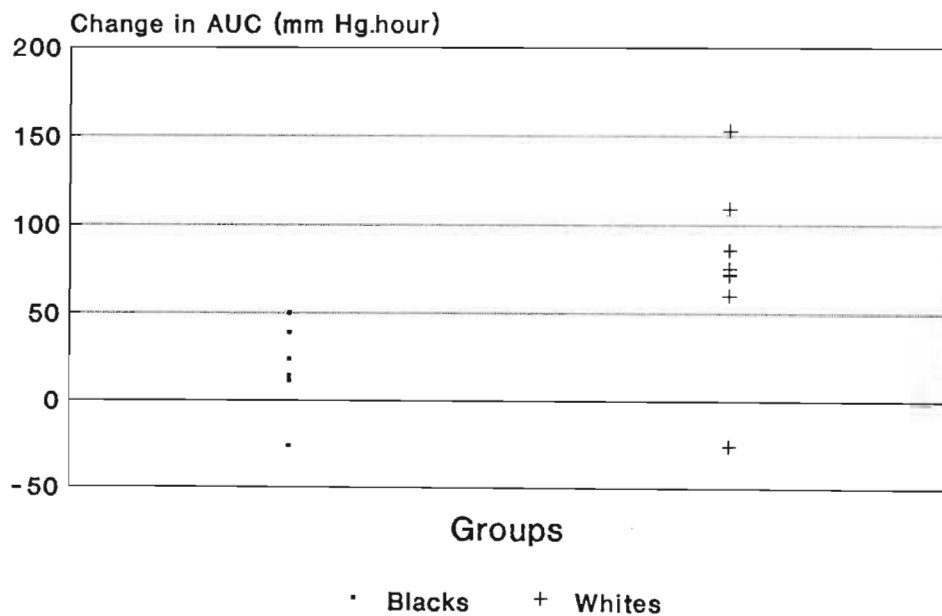
p<0.0102

4.1.2.2.2. Supine Diastolic Blood Pressure

Atenolol reduced mean supine diastolic blood pressure in most individuals from 6 to 30 hours after administration although this was only statistically significant at 6, 8 and 24 hours (Fig 4.21.)(Table 4.8.). The mean results for the separate race groups are given in Fig 4.22. Although the diastolic blood pressure showed great interindividual variation in both groups the mean maximum reduction seen with atenolol in blacks and whites was similar (12 mm Hg)(Table 4.5.). One black (MN) showed no reduction in supine diastolic BP at any point after atenolol administration.

The only apparent racial difference in response to atenolol treatment was at 12 hours after administration when whites showed a significantly greater effect. The relevance of these results is brought into question by the finding that baseline values of SDBP were also significantly influenced by an interaction between treatment and race (time 0 hours) before either atenolol or placebo infusions had begun (Fig 4.23).

Blacks and whites were found to be similar when SDBP AUC (0-12 hour) differences for placebo and atenolol were compared (Fig 4.24). One black (MN) showed an overall increase in SDBP after atenolol whilst 3 blacks and 2 whites showed minimal changes over the 12 hours.

The following results are given in Appendix 2:

Table A2.21. Supine diastolic blood pressure in black and white individuals after placebo administration.

Table A2.22. Supine diastolic blood pressure in black and white individuals after atenolol administration.

Table A2.23. Mean supine diastolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

Table A2.24. Area under the curve (AUC) for supine diastolic blood pressure from 0 to 12 hours (mm Hg.hr) after placebo and atenolol and the difference between placebo and atenolol.

Table A2.30. Individual maximum changes in BP (E_{max}) (mm Hg) and time to maximum (T_{max}) after atenolol.

Fig A2.13-A2.14. Supine blood pressures in black individuals.

Fig A2.15-A2.16. Supine blood pressures in white individuals.

Table 4.8. Mean supine diastolic blood pressure (sem) after placebo and atenolol administration to all volunteers (n=16) and probability values for differences due to treatment, treatment interaction with race and race.

TIME (hours)	MEAN SUPINE DIASTOLIC BP (sem) (mm Hg)		Probability Values (* p<0.05 taken as significant)		
	Placebo	Atenolol	Treatment	Treatment*Race	Race
0.0	65.1 (2.1)	65.1 (1.8)	1.0000	0.0310*	0.8847
0.4	59.7 (1.2)	60.0 (2.0)	0.8119	0.8119	0.9249
0.9	61.4 (1.9)	60.8 (2.3)	0.8199	0.8199	0.6604
1.4	60.4 (1.9)	61.1 (2.0)	0.7187	0.9520	0.9722
2.0	59.4 (1.5)	61.6 (2.1)	0.2076	0.2921	0.7059
3.0	60.8 (1.6)	58.7 (1.7)	0.3140	0.2626	0.9230
4.0	60.2 (1.6)	58.9 (1.6)	0.5747	0.9101	0.8067
5.0	60.5 (1.7)	60.9 (2.3)	0.7627	0.1260	0.8323
6.0	60.6 (1.5)	56.6 (2.1)	0.0047*	0.7575	0.2144
8.0	61.6 (1.6)	58.3 (1.6)	0.0408*	0.3869	0.1343
10.0	65.3 (1.5)	62.5 (1.8)	0.2562	0.5289	0.3999
12.0	63.8 (1.5)	62.0 (1.4)	0.3162	0.0492*	0.6234
24.0	61.6 (1.4)	57.9 (1.4)	0.0431*	0.3010	0.6385
30.0	59.7 (1.3)	58.2 (1.9)	0.3918	0.3918	0.1015
36.0	61.5 (1.9)	62.3 (1.8)	0.7594	0.9777	0.5659

Fig 4.21. Mean supine diastolic BP after placebo and atenolol in all volunteers.

Supine diastolic BP (mm Hg)
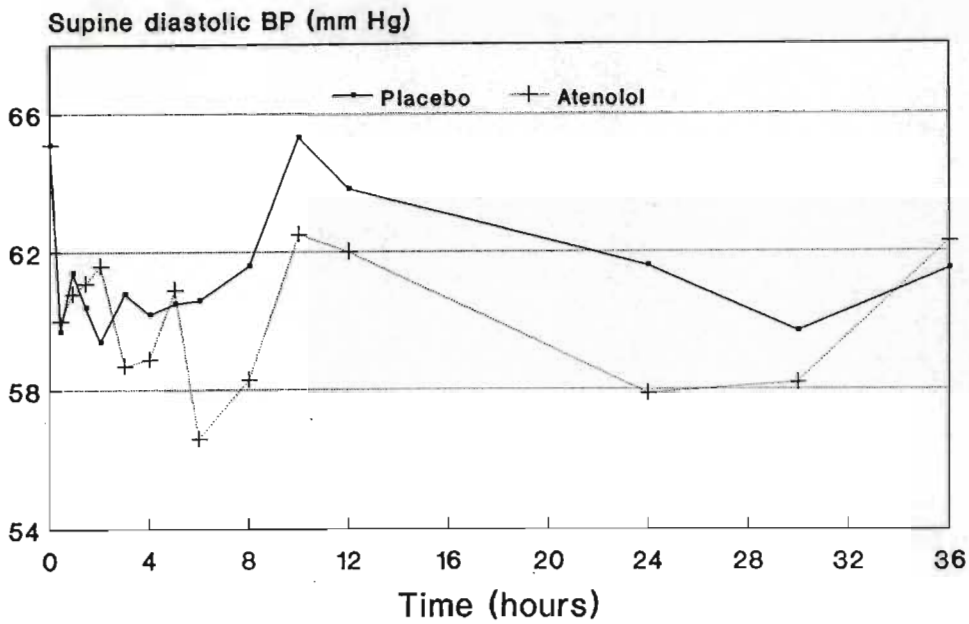
* Significant difference in treatment
at 6, 8 and 24 hours.

Fig 4.22. Mean supine diastolic BP after placebo and atenolol in blacks & whites.

Supine diastolic BP (mm Hg)
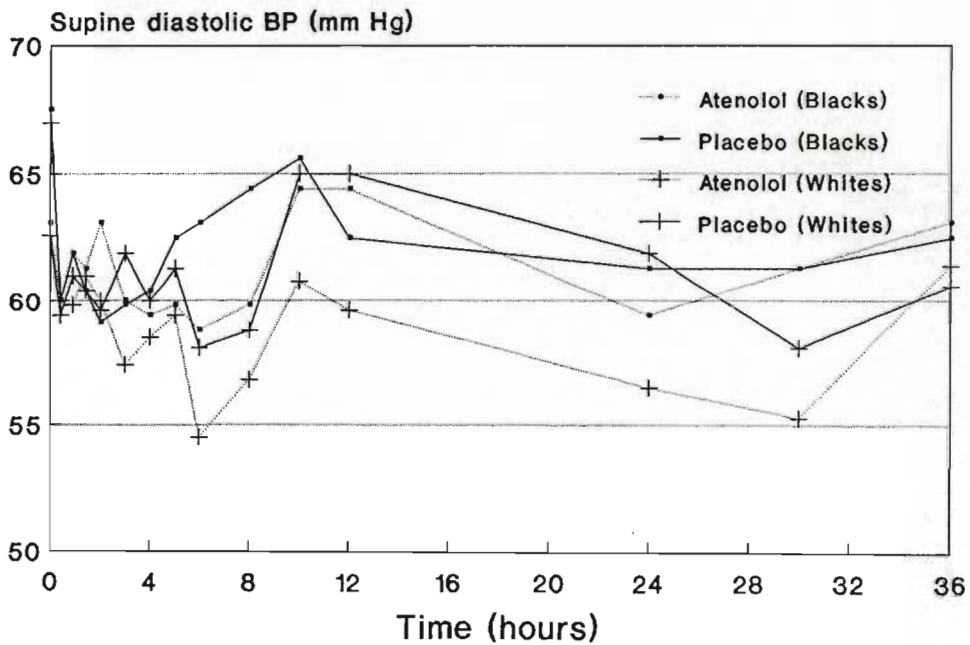
No significant differences between races

Fig 4.23. Reduction in supine diastolic BP after atenolol in blacks & whites.
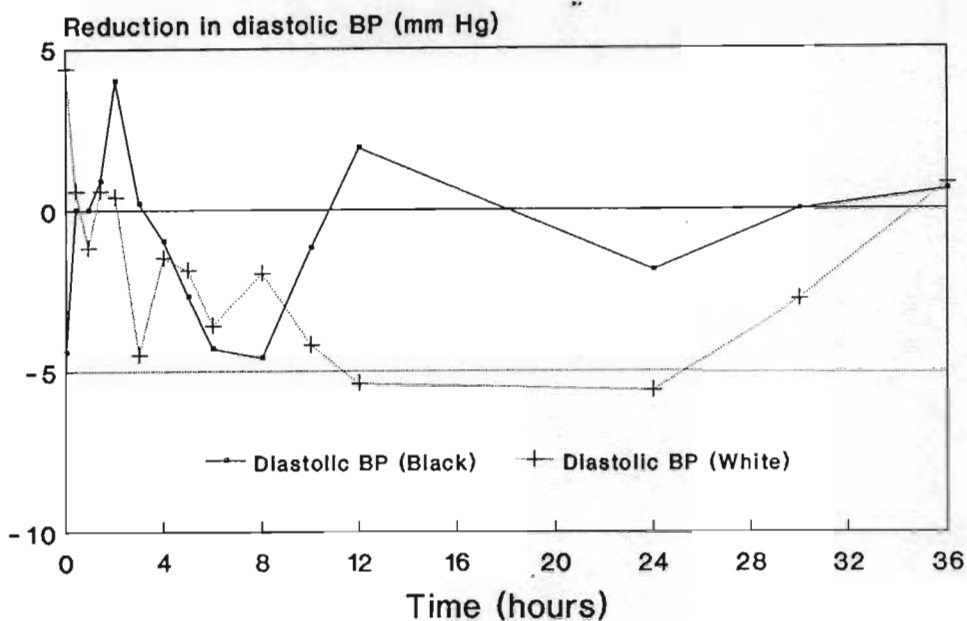
* Significant racial difference in treatment response at 12 hours.

Fig 4.24. Change (Placebo-Atenolol) in AUC (0-12 hrs) for Supine Diastolic BP.
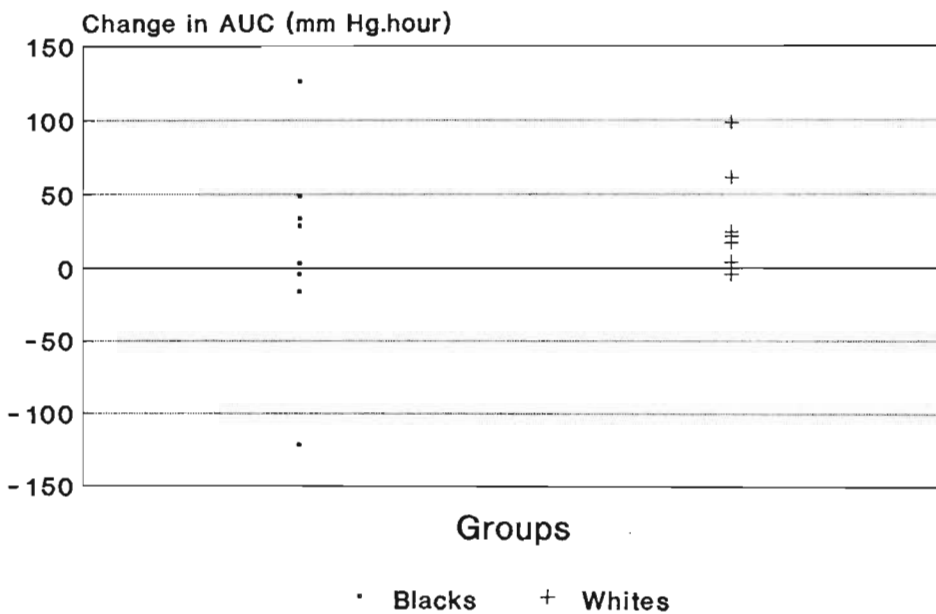
p<0.5226

4.1.3. Plasma Renin Activity

Plasma renin activity (PRA) was measured in only 10 of the volunteers (5 blacks and 5 whites). These results demonstrated great intra-subject variation after both placebo and atenolol administration which was clearly influenced by factors other than treatment (See individual graphs in Appendix 2). These factors include posture, exercise and sodium levels (Lijnen et al 1978). The protocol involved not only posture changes and exercise at variable times prior to plasma sampling but also the infusion of normal saline. In addition, the sodium content of the volunteers' diet was not controlled. Because PRA as an effect was clearly unsuitable for concentration-effect modelling further analyses were deemed not to be cost effective.

The PRA results following treatment will be discussed briefly but should be viewed with great circumspection because of the lack of control of factors mentioned above which are known to alter PRA.

When the 10 volunteers were considered as a group the average PRA prior to dosing (0 hours) was identical on placebo and atenolol days as were the values at 30 hours post dose (Fig 4.25)(Table 4.9.). At all other times, except 3 hours post dosing, the average values were always lower after atenolol than after placebo (Fig 4.25). However, the difference was only significant at 0.2, 0.3 and 6.0 hours because of inter- and intra-individual variation (Table 4.9.). At all times of measurement after placebo administration, except at 6 hours and 30 hours post dose, blacks had a lower average PRA activity than whites (Fig 4.26). At 0.2, 0.5 and 5 hours race significantly influenced overall PRA (Table 4.9.). When the average change in PRA after atenolol administration was assessed in the two race groups, the whites on the whole had a greater change than the blacks particularly in the first two hours

Table **4.9.** Mean plasma renin activity (sem) after placebo and atenolol administration to 10 volunteers and probability values for differences due to treatment, treatment interaction with race and race.

TIME (hours)	MEAN PLASMA RENIN ACTIVITY (sem) (ng/ml/hr)		Probability Values (* p<0.05 taken as significant)		
	Placebo	Atenolol	Treatment	Treatment*Race	Race
0.0	3.49 (0.72)	3.33 (0.78)	0.8572	0.1476	0.2538
0.1	3.22 (0.72)	3.06 (0.62)	0.8508	0.1423	0.0810
0.2	4.07 (0.91)	2.26 (0.50)	0.0359*	0.1678	0.0336*
0.3#	4.85 (0.93)	2.60 (0.57)	0.0449*	0.2187	0.3981
0.5#	4.17 (0.97)	2.72 (0.49)	0.3066	0.4495	0.0424*
0.8	3.94 (0.96)	2.26 (0.47)	0.0593	0.0344*	0.2072
1.0	3.35 (0.63)	2.20 (0.46)	0.1729	0.4361	0.2029
1.5	3.83 (0.93)	2.68 (0.66)	0.3689	0.1641	0.1748
2.0	3.62 (0.87)	2.45 (0.47)	0.1892	0.4350	0.1357
3.0	2.57 (0.48)	3.06 (0.80)	0.5934	0.8692	0.0670
4.0	2.50 (0.53)	1.66 (0.41)	0.2890	0.5513	0.2967
5.0	2.54 (0.55)	2.15 (0.52)	0.5554	0.4978	0.0484*
6.0	3.52 (0.68)	1.38 (0.21)	0.0273*	0.8645	0.8499
8.0	2.10 (0.51)	1.33 (0.22)	0.1926	0.2032	0.0951
10.0#	2.64 (0.61)	1.94 (0.43)	0.5360	0.4985	0.0821
12.0	1.97 (0.54)	1.73 (0.58)	0.7876	0.2792	0.3521
24.0#	1.83 (0.32)	1.70 (0.27)	0.4655	0.5494	0.0564
30.0#	2.29 (0.54)	2.31 (0.36)	0.7031	0.5586	0.6204

Statistical significance uncertain due to missing values

Fig 4.25. Mean PRA after placebo and atenolol in all volunteers.
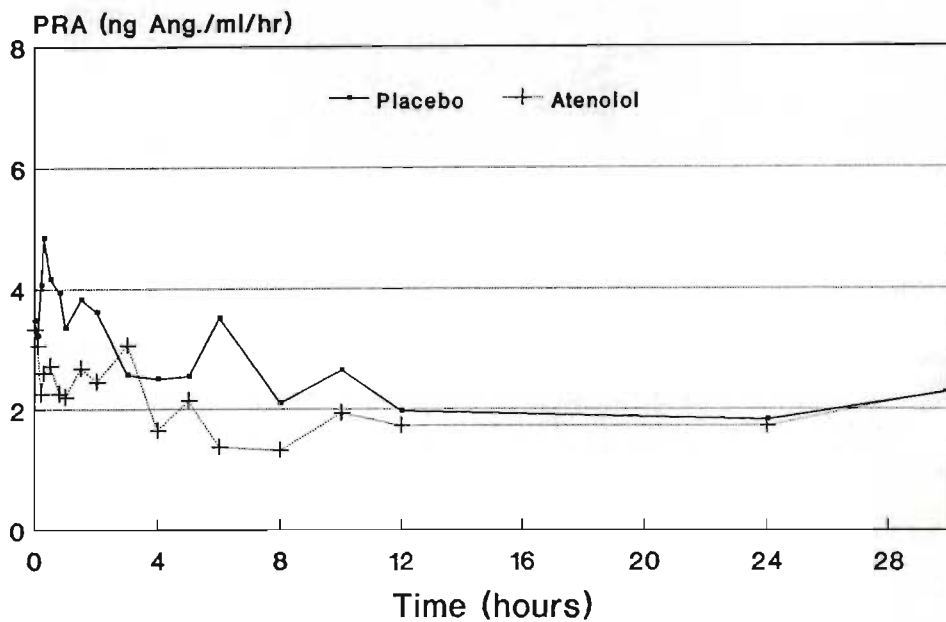
* Significant treatment effect at 0.2,
0.3 and 6 hours.

Fig 4.26. Mean PRA in blacks and whites after placebo and atenolol.
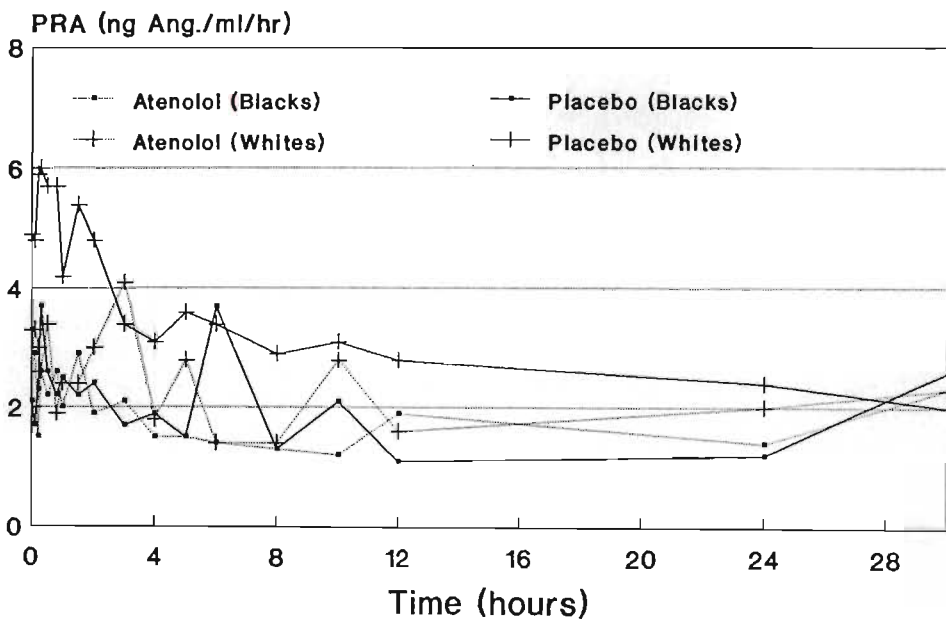
* Significant racial difference In PRA
at 0.3, 0.5 and 5 hours.

Fig 4.27. Reduction in mean PRA after atenolol in blacks and whites.

Reduction in PRA (ng Ang./ml/hr)

Time (hours)
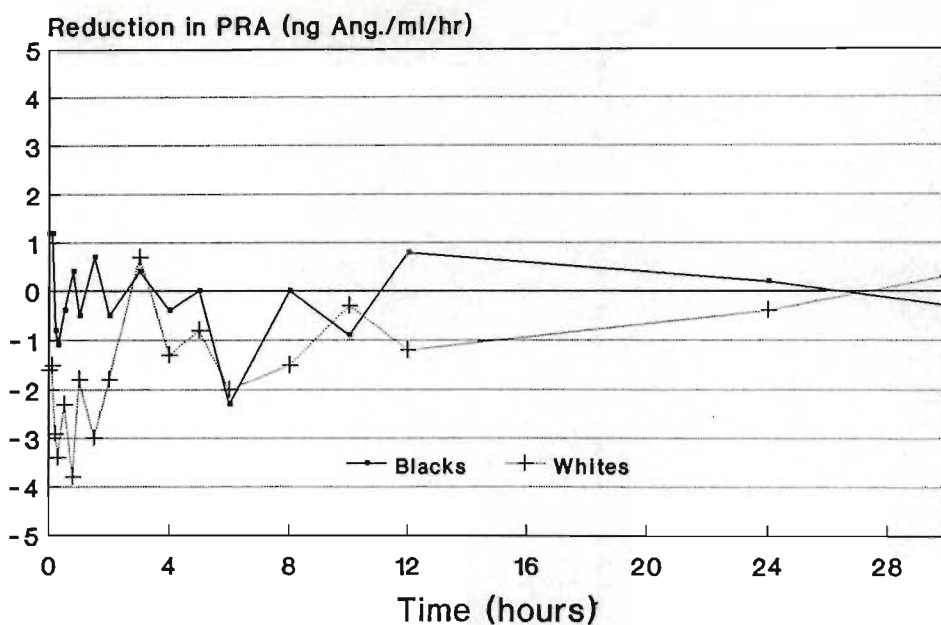
• Significant racial difference in
treatment response at 0.8 hours only.

Fig 4.28. Change (Placebo-Atenolol) in AUC (0-12 hrs) for PRA.

Change in AUC (ng Ang./ml)

Groups
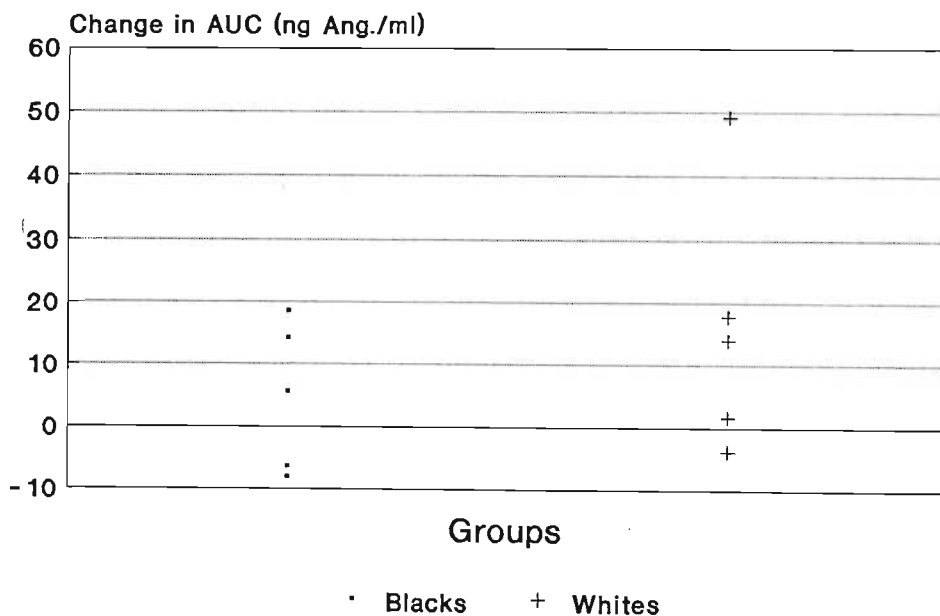
· Blacks   + Whites

p<0.3355

(Fig 4.27) but only at a single point, 0.8 hours, was race a significant factor in treatment response (Table 4.9.).

There was no statistically significant difference between blacks and whites in baseline PRA (mean of baseline both before placebo and atenolol) ($p < 0.2535$) although the mean in the blacks (2.7 ng Ang./ml/hr) was lower than that in whites (4.11 ng Ang./ml/hr). Taking the difference in AUC (0-12 hours) after placebo and atenolol as a measure of overall PRA response to atenolol there was no significant difference between blacks and whites (Fig 4.28.).

Because baseline PRA was measured prior to any exercising and within a few minutes of the initiation of the normal saline infusion it was considered a reasonable measure of basal PRA in the individual. Since the overall supine systolic BP response to atenolol (as measured by difference in AUC) was found to be significantly less in blacks than whites it seemed reasonable to test whether it might be related to baseline PRA. Although only 10 data points were available there did appear to be some relationship in these 10 individuals ($r^2 = 0.578$, $p < 0.0107$) (Fig 4.29.). There was no significant correlation between baseline PRA and either erect systolic BP, erect diastolic BP or supine diastolic BP responses over 12 hours (difference in AUC) (Table 4.10.).

A correlation between overall atenolol response (AUC 0-12 hour differences) for PRA and SSBP also showed a relationship ($r^2 = 0.552$, $p < 0.0138$) (Fig 4.30.) in the 10 individuals. There was however, no correlation between AUC differences in PRA and AUC differences in ESBP, EDBP or SDBP (Table 4.11.).

The 24 hour urinary sodium and potassium elimination was measured in all volunteers after both placebo and atenolol. The mean results are given in Table 4.12.

Fig 4.29. Correlation between baseline PRA and change (Placebo-Atenolol) in AUC (0-12 hrs) for supine systolic BP.

$r^2 = 0.578$ $p < 0.0107$

Y = 22.53X - 32.18
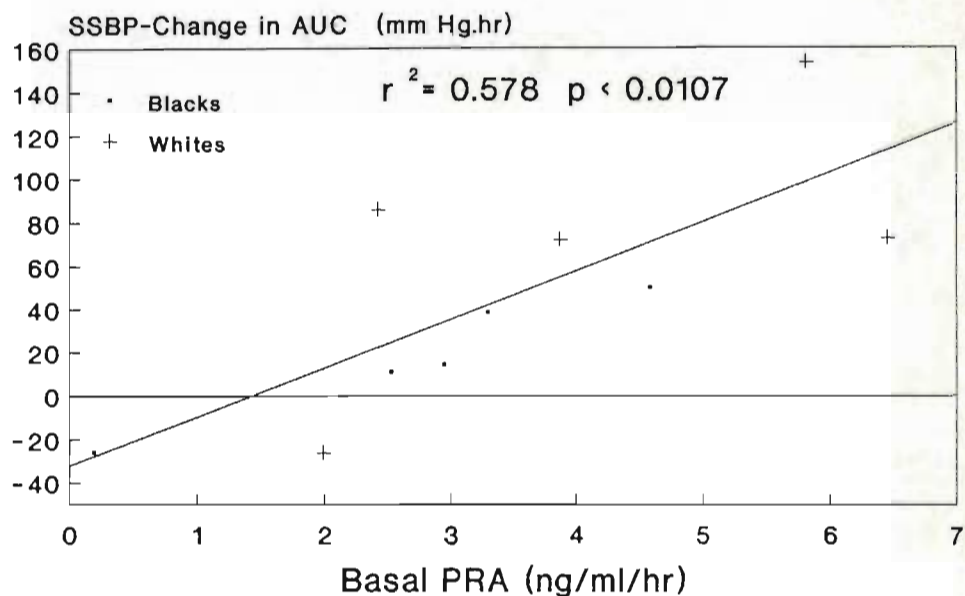
Fig 4.30. Correlation between changes in AUC (0-12 hrs)(Placebo-Atenolol) for PRA and Supine Systolic BP.

$r^2 = 0.552$ $p < 0.0138$

Y = 2.413X + 19.67
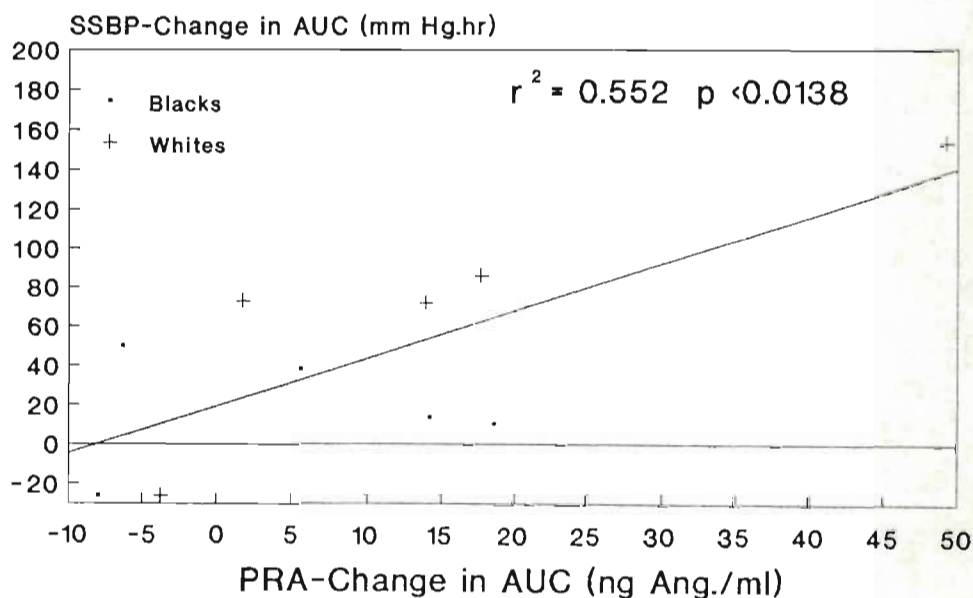
Table **4.10**. Correlation between baseline PRA and AUC (0-12 hours) differences between placebo and atenolol administration for erect and supine systolic and diastolic BP.

Correlation of PRA vs Change in AUC for:	Equation	r^2	p<
Erect Systolic BP	Y = 34.19X - 36.91	0.2736	0.1208
Erect Diastolic BP	Y = 18.96X - 23.02	0.1648	0.2444
Supine Systolic BP	Y = 22.53X - 32.18	0.5782	0.0107*
Supine Diastolic BP	Y = 16.50X - 29.57	0.2056	0.1881

* Significant correlation

Table **4.11**. Correlation between Change in PRA AUC (0-12 hours) after placebo and atenolol administration versus change in AUC (0-12 hours) after placebo and atenolol administration for erect and supine systolic and diastolic BP.

Correlation of PRA Change in AUC vs Change in AUC for:	Equation	r^2	p<
Erect Systolic BP	Y = 3.29X + 45.6	0.2109	0.1818
Erect Diastolic BP	Y = 1.31X + 28.0	0.0659	0.4741
Supine Systolic BP	Y = 2.41X + 19.7	0.5522	0.0138*
Supine Diastolic BP	Y = -20.7X + 24.5	0.0027	0.8865

* Significant correlation

Table 4.12. Twenty four hour urinary sodium and potassium elimination in blacks (B) and whites (W) and both groups together (All) after placebo (Pl) and atenolol (At).

GROUPS	24 HOUR URINARY ELIMINATION (mEq)			
	SODIUM		POTASSIUM	
	Placebo	Atenolol	Placebo	Atenolol
BLACKS n Mean SD CV (%)	6 300 64 21	6 368 50 14	6 53 17 32	6 53 16 30
WHITES n Mean SD CV (%)	7 259 125 48	7 329 92 28	6 73 36 49	6 84 33 39
B vs W p<	0.4799	0.3841	0.2234	0.0666
ALL n Mean SD CV (%)	13 278 100 36	12 348 73 21	13 64 29 45	12 69 30 43
Blacks At vs Pl p<	0.0698		#	
Whites At vs Pl p<	0.2832		0.5874	
All At vs Pl p<	0.0593		0.7018	

n = number of samples
# Sample means equal

There was no difference in 24 hour sodium elimination between blacks and whites after either placebo or atenolol or when both treatments were considered together. Although more sodium was eliminated after atenolol than after placebo in both groups this did not reach statistical significance. There was no treatment effect on potassium elimination in either blacks or whites or all subjects

considered together. Blacks on average eliminated less potassium per 24 hours after both placebo and atenolol treatments (53 mEq for both periods) than whites (73 and 84 mEq after placebo and atenolol respectively) although this did not reach statistical significance (p<0.2235 and 0.0666 respectively).

A correlation of the log of 24 hour sodium elimination with PRA measured at the end of the urine collection ie. twenty four hours after treatment (without regard to race or treatment) yielded the expected inverse relationship (r^2 = 0.4251, p < 0.0115) (Figure 4.31.).

The following results are given in Appendix 2:

Table A2.25. Plasma renin activity in black and white individuals after placebo administration.

Table A2.26. Plasma renin activity in black and white individuals after atenolol administration.

Table A2.27. Mean plasma renin activity (ng Ang/ml/hr) after placebo and atenolol administration in the black and white groups (n=5 in each group).

Table A2.28. Area under the curve (AUC) for PRA from 0-12 hours after placebo and atenolol and the difference between placebo and atenolol.

Table A2.31. Twenty four hour urinary elimination of sodium and potassium in black and white subjects after placebo and atenolol administration.

Fig A2.17. PRA in blacks after placebo and atenolol administration.

Fig A2.18. PRA in whites after placebo and atenolol administration.

Fig 4.31. Correlation between 24 hour urinary sodium elimination and PRA.

Y = -2.709log X + 8.481
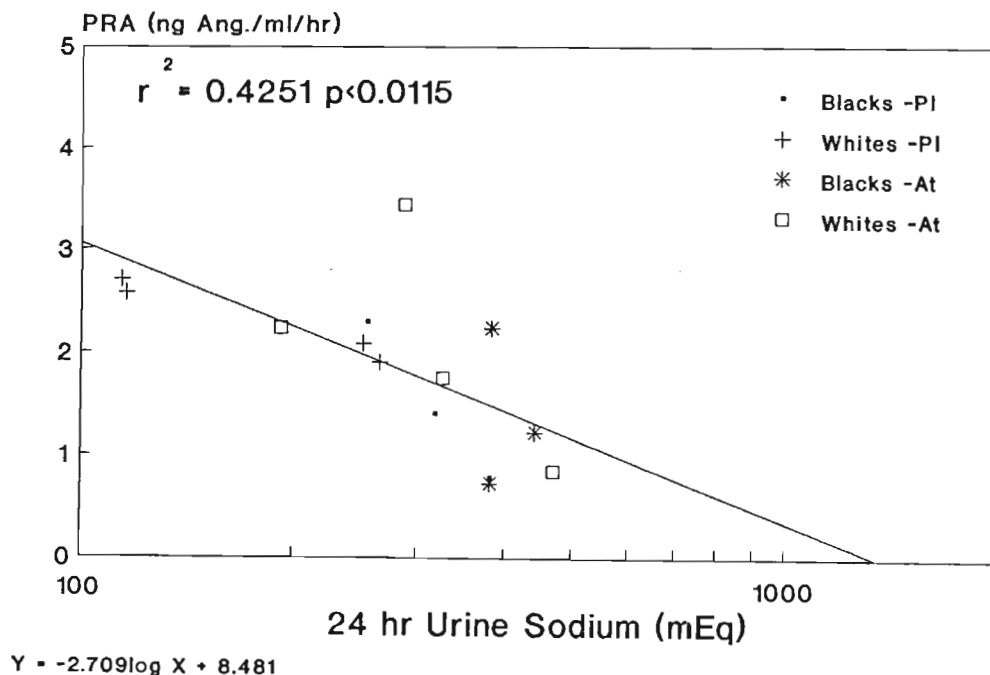
4.2. DISCUSSION

4.2.1. Effects on Heart Rate

As expected the influence of atenolol on mean resting heart rate was lower and less consistent than that on exercise heart rate. This is because there is a lower level of sympathetic activity at supine rest (Robinson et al 1966). The peak effect on EHR (25% reduction) occurred almost immediately (5-25 minutes after the end of the infusion) while maximal reduction in RHR (15%) was seen only on average at 3 hours (range 1.5 to 6.0) post dose (Fig 4.32).

The mean maximum fall of about 18 beats/minute in RHR was similar to that seen in other studies (14 to 20 beats/minute) in volunteers receiving comparable oral doses of atenolol ie. 100 mg (Fitzgerald et al 1978, Fuller & Vallance 1982, Maling et al 1979).

After IV atenolol maximum reductions in RHR have been reported to occur from 1-3 hours after the dose (Fitzgerald et al 1978). The peak reduction in RHR after oral atenolol is reported to be delayed by 1-2 hours relative to plasma concentrations. A similar delay in the time course of reduction of RHR has been observed with other beta-blockers. Myers & Thiessen (1980) showed that although orally administered metoprolol concentrations peaked at 1.5 hours, maximal reduction in RHR occurred at 3 hours. These researchers suggest that this can be explained by a delay in reaching the relevant receptors. This seems unlikely if the beta-receptors responsible for exercise heart rate increases are maximally blocked almost immediately. The effect on RHR may be an indirect response to other changes in the cardiovascular system in response to atenolol treatment.

Both blacks and whites showed an increase in RHR above baseline after placebo administration. This was possibly

the result of insufficient time being allowed for RHR to recover after exercise stimulation. Although no significant racial difference in response to atenolol was found the atenolol appeared to antagonise this rise above baseline more in the whites than the blacks. The rise above baseline RHR therefore appeared to have a greater sympathetic component in whites than in blacks.

The finding that there was no significant influence of race on the degree of reduction of resting heart rate by atenolol in young volunteers confirms the findings of Venter et al (1984b) with propranolol.

The almost immediate onset (0.3 hours after start of infusion) of the effect of atenolol on EHR in this study was similar to other studies with IV atenolol where maximal effects were measured at the first observation time after administration (Brown et al 1976, Shanks et al 1977).

Fig 4.32. Mean % Reduction in Exercise and Resting Heart Rate after Atenolol.

n=16
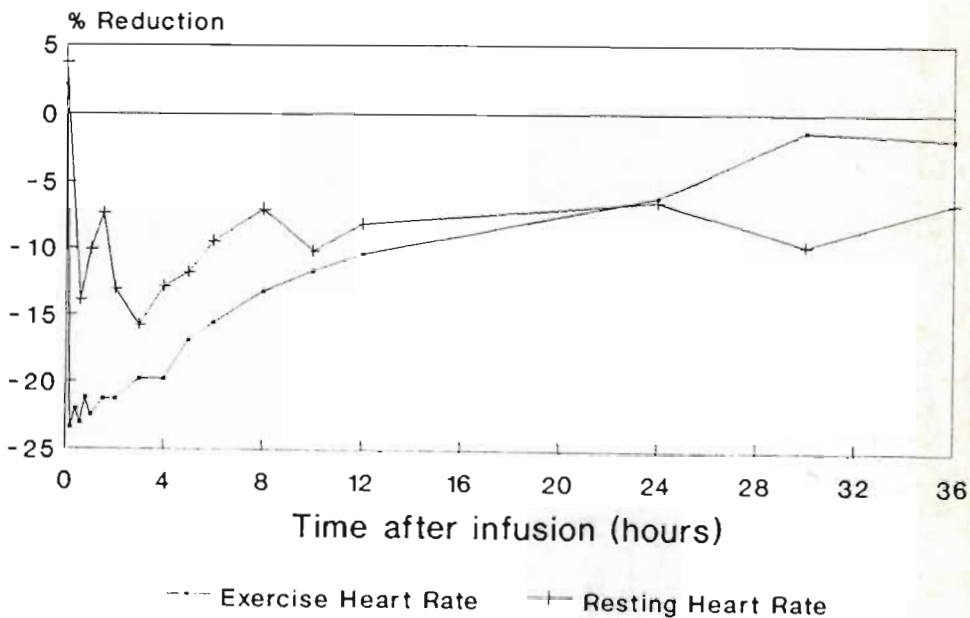
Although the average maximum reduction in this study (24%) (Fig 4.32.) was lower than the 30-32% observed by Shanks et al (1977) and Brown et al (1976) using the same dose, the initial heart rate in this study was also lower. It has been demonstrated that heart rate reduction by beta-blockade is greater at higher exercise levels (Leenen et al 1980).

In blacks, EHR after placebo administration showed an increase over baseline during the first 2 hours and remained 5 to 10 beats higher than baseline for the duration of the experiment. Whites on average showed relatively little change from baseline in EHR during the study period (Fig 4.33.). The diurnal variation and placebo effects on heart rate and blood pressure obviously require placebo control in drug efficacy studies. However, the apparent ethnic difference in 'placebo response' on EHR was unexpected. Had a placebo phase not been included in the experimental design it would have appeared that the EHR response to atenolol in blacks was less than that in whites (Fig 4.34). In fact the response to atenolol taken as the difference between HR after placebo and after atenolol is equivalent in blacks and whites with very similar maximal effects and time course. This was in contrast to a report (Venter & Joubert 1982) that penbutolol reduced exercise tachycardia less in blacks than in whites and that there was a shift to the right in the dose response curve for propranolol in blacks compared with whites (Venter & Joubert 1984a). In the latter study ethnic differences disappeared at higher exercise levels and higher doses.

It is interesting to speculate as to the reason for the significantly higher EHR, irrespective of placebo or atenolol treatment, observed in blacks compared with whites during the first 5 hours of the experiment. It appeared unlikely that the blacks were less fit than the whites because neither resting heart rates, nor workloads nor

Fig 4.33. Mean EHR in blacks and whites after placebo administration.
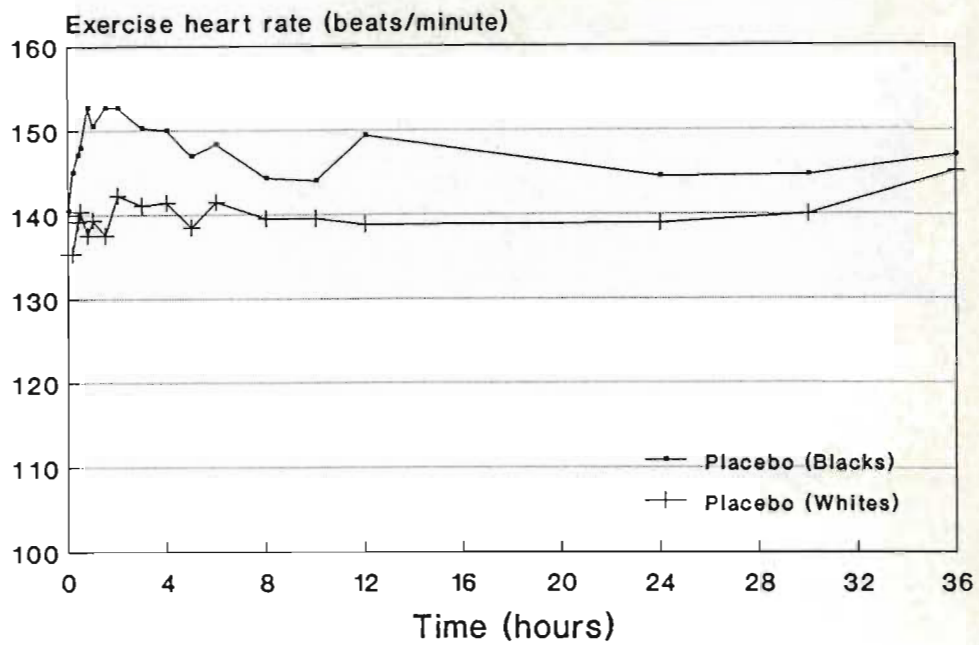
Fig 4.34. Mean EHR in blacks and whites after atenolol administration.
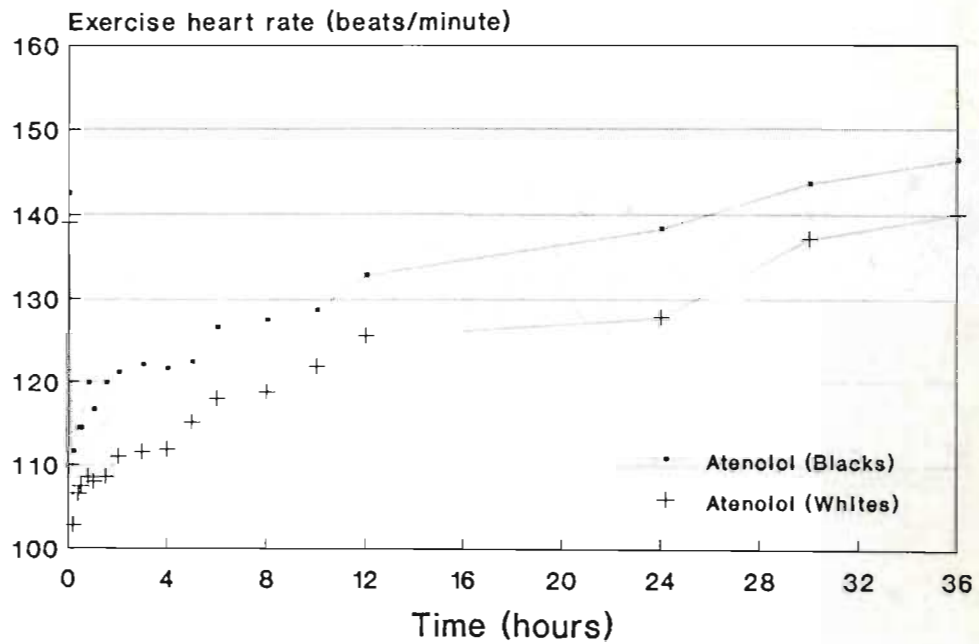
baseline exercise heart rates differed significantly between the two groups. On the other hand our results were not entirely incompatible with a difference in fitness since it has been shown that reduced heart rates in trained individuals are the result of increased vagal tone and not decreased sympathetic reactivity (Leenen et al 1980).

Lewis et al (1991) have reviewed cardiovascular characteristics which are reported to differ between blacks and whites. They cite a number of reports indicating an increased blood pressure response to physical and psychosocial stressors in black compared with white children as well as a faster heart rate in black newborns compared with whites. The present study demonstrated a similar phenomenon of increased reactivity of exercise heart rate (and to a lesser degree resting heart rate) to the stress of the study protocol in young blacks compared with whites. This ethnic difference did not appear to involve the sympathetic system as the differential was maintained after supra-maximal doses of atenolol. Venter et al (1984b) demonstrated a higher intrinsic heart rate and a greater vagal component to resting heart rate in young black volunteers compared with whites although they found no difference in the sympathetic component. These differences tended to disappear at higher levels of exercise (Venter & Joubert 1984a, Venter et al 1986). With mild exercise increase in heart rate is mainly due to vagal withdrawal while at maximal exercise (180-200 bpm) the sympathetic system is the major component (McDevitt 1977, Robinson et al 1966, Venter et al 1986). Erect bicycle ergometry involves sustained handgrip which may increase heart rate via vagal withdrawal even in the presence of propranolol, and independently of exercise (McDevitt 1977). The present study utilised sub-maximal exercise in the form of repeated erect bicycle ergometry. Ethnic differences in intrinsic heart rate and particularly vagal withdrawal might therefore have influenced absolute exercise heart rates without influencing the response to atenolol.

4.2.2. Blood Pressure Responses

This study confirmed that single IV doses of beta-blockers lower BP in normotensive volunteers (Fig 4.35. & 4.36.). Atenolol reduced erect and supine BP with maximal reductions of 16/13 mm Hg and 13/12 mm Hg respectively occurring between 4 and 8 hours after dosing. The onset and offset of atenolol's effect on diastolic BP lagged behind the effects on systolic BP.

The finding that onset of blood pressure reduction was delayed relative to the reduction in heart rate was in agreement with other studies of various beta-blockers given orally or IV which report delays of 1-6 hours (Collste et al 1980, Fagan et al 1982a, Man in't Veld & Schalekamp 1983, Myers & Thiessen 1980). Early studies which claimed no effects of IV beta-blockers used very low doses in some cases and for the most part did not follow effects for long enough (See Chapter 1, 1.1.2.2.1.1.).

Similarly results in this study were comparable with other studies in normotensive and hypertensive subjects in terms of maximal BP reduction and time course with the most consistent reduction being in supine systolic BP. (See Chapter 1,1.1.2.2.1.). Fitzgerald et al (1978) showed an almost identical time course of BP reduction with 10 mg IV and 200 mg of oral atenolol, the effect on heart rate and systolic BP occurring earlier (1 to 3 hours) than effects on diastolic BP (from 3 hours onwards). In a study of a single oral 100 mg dose of atenolol in normotensive volunteers, maximal reduction of about 15 mm Hg in systolic BP was seen at 7 hours while diastolic BP was maximally reduced (10 mm Hg) between 5 and 8 hours (Maling et al 1979). Similarly single 100 mg doses of atenolol in hypertensive patients reduced BP 17/11 mm Hg at 6 and 10 hours post dose (Leonetti et al 1980).

Fig 4.35. Mean % Reduction in Erect
Systolic and Diastolic BP after Atenolol
administration.

— Erect systolic BP   ⁻⁺⁻ Erect diastolic BP
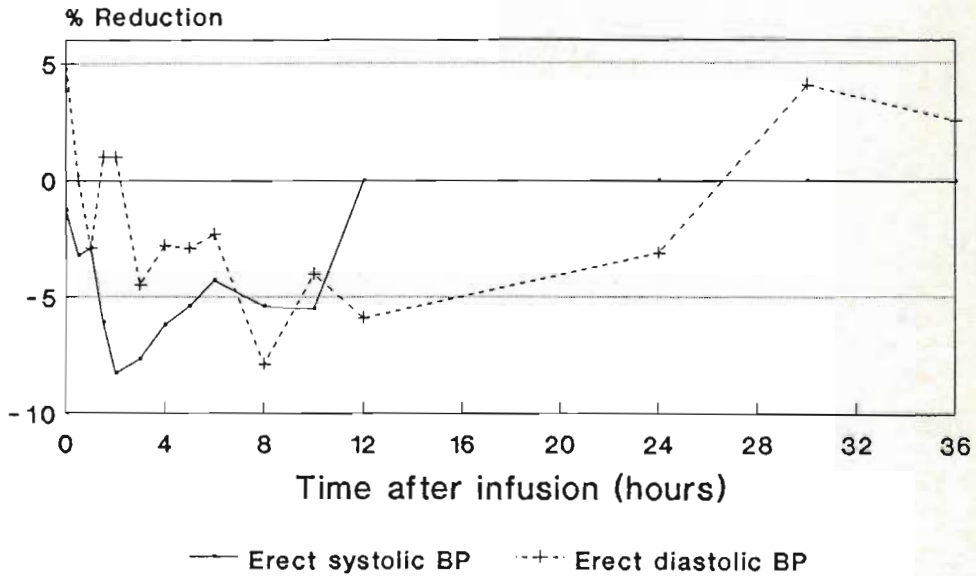
n=16

Fig 4.36. Mean % Reduction in Supine
Systolic and Diastolic BP after Atenolol
administration.

— Supine systolic BP   ⁻⁺⁻ Supine diastolic BP
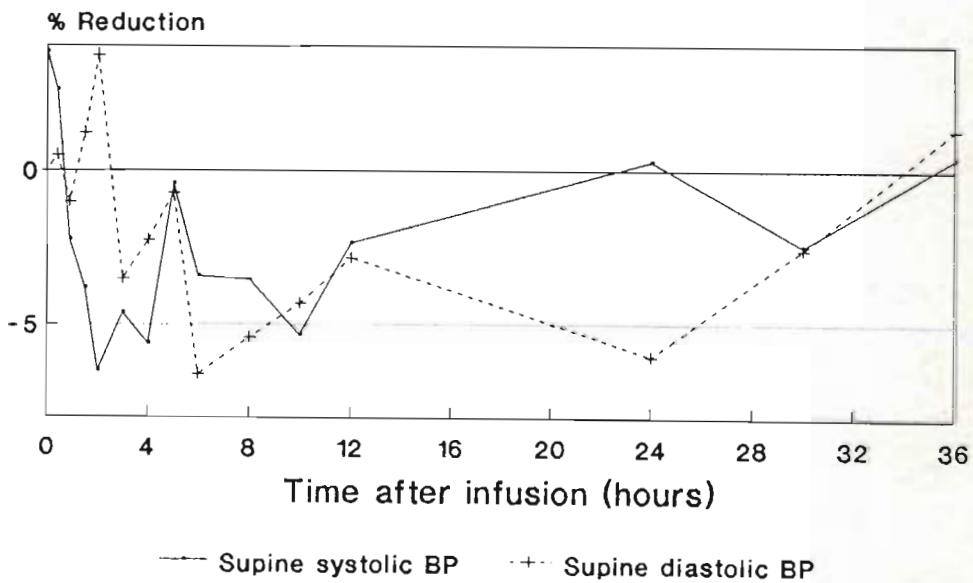
n=16

In the present study there was minimal evidence of ethnic differences in blood pressure response after a single IV dose of atenolol to healthy normotensive young men except for the effect on supine systolic BP. Although erect systolic BP response (difference in AUC) tended to be less in blacks it did not reach statistical significance. However any inter-subject variation in effect and time course would make it difficult to detect subtle differences between blacks and whites with only 8 subjects in each group. In fact in the present study the effect of atenolol on BP (particularly diastolic BP) showed great inter-subject variation in terms of both magnitude and time course. One black (MN) and one white (NF) showed increases in BP after atenolol. Others have also reported inter-individual differences in the time course and magnitude of blood pressure reduction by single doses of beta-blockers with effects on diastolic BP being most variable (Collste et al 1980).

The greater reduction in supine systolic BP in whites may appear surprising in view of there being no ethnic difference in atenolol's effect on either EHR or RHR. However, as the blood pressure and exercise heart rate responses differ in time course one should probably not expect a parallel between these two responses.

Whether this racial difference in the effect of atenolol on resting systolic BP in normotensives is in any way relevant to or predictive of the reduced response of black hypertensives to beta-blockers is a matter of conjecture. The first point to consider is whether single dose studies are predictive of long term hypotensive responses. The second point is whether extrapolation from normotensive to hypertensive subjects is valid.

Some studies in hypertensive patients claim similar responses in BP after single doses and continued therapy (Leonetti et al 1980, Leenen et al 1982, Myers & Thiessen

1980) while others claim no relationship (Collste et al 1980).

A study of short-term and long-term haemodynamic and blood pressure responses to single and multiple dose beta-blockade comparing a beta-blocker with ISA and one without in matched hypertensive blacks and whites may cast some light on these issues. Continuous ambulatory BP monitoring techniques could facilitate these comparisons.

To state categorically that black hypertensives do not respond while white hypertensive patients do respond to monotherapy with beta-blockers is incorrect. It is probably more accurate to say that more whites respond adequately than blacks to this form of therapy. There are blacks who show a good response while there are some whites who show a poor response. The inter-individual variability in the magnitude of the response in the two ethnic/race groups would provide useful information for predicting the probability of an adequate response.

A dose ranging study using NONMEM analysis of BP reduction in reasonably matched black and white hypertensives, similar to a recently published study comparing two beta-blockers, atenolol and betaxolol (Sambol & Sheiner 1990), might give some insight into the intra- and inter-subject variation in response. In the above mentioned study a graded dose response to atenolol (25, 50 and 100 mg) was demonstrated for supine diastolic blood pressure measured 24 hours after dosing. The maximal reduction in supine diastolic BP was 13 mm Hg (95% confidence interval 10 to 15 mm Hg) with an interindividual variability (coefficient of variation) of 31% (95% confidence intervals of 0% to 47%).

4.2.3. Effects on Plasma Renin Activity

Baseline PRA values were within the limits reported for normotensive subjects between 20 and 30 years of age on an ad libitum sodium diet (Lijnen et al 1978). Measurements of PRA after both placebo and atenolol administration were inconsistent and showed great intra- and inter-subject variation.

PRA is known to show diurnal variations as well as changes in response to sodium levels, posture, stress and exercise. Although the placebo period of measurement controlled for diurnal variation the other factors were not standardized in the present study. There was no control of dietary sodium in the subjects and normal saline was infused during the first 12 hours. Relatively high sodium intake would be expected to suppress basal PRA while the change in position from recumbency to being seated on the bicycle as well as the previous exercise sessions would have had the opposite effect. The stress involved when blood sampling proved difficult might also have contributed to the intra-individual variation.

Beta$_1$-selective blockers such as atenolol and metoprolol (Amery et al 1977b, Lijnen et al 1978, Lijnen et al 1979) as well as nonselective blockers such as propranolol (Traub et al 1980) without ISA have been reported to lower basal PRA while those with ISA do not (Bühler et al 1975b, Traub et al 1980). In the present study although there was a general trend for atenolol to lower PRA relative to placebo the only statistically significant reduction was observed within the first hour. The small number of subjects and inter- and intra-individual variation probably accounted for the lack of significance.

Blacks on average tended to have lower PRA after both placebo and atenolol when compared with whites. However, the differences were not significant probably because of the small numbers. The relative differences are similar to

those found between normotensive black and white Americans (Hildreth & Saunders 1991). As expected the PRA measured 24 hours after treatment was correlated inversely with the amount of sodium eliminated in the previous 24 hours (Lijnen et al 1978). There was insufficient data to test whether the correlation was different between races and between treatments.

Although not significant in the present study the reduced potassium elimination by blacks compared with whites (in normotensive and hypertensive people) is widely recognized (Kuminyika & Adams-Campbell 1991, M'Buyamba-Kabangu 1986, Touyz et al 1987). Atenolol did not appear to influence potassium elimination as found by other investigators (Colantonio et al 1991). The non-significant increase in sodium natriuresis after atenolol administration noted in the present study, might be ascribed to atenolol. Similar small increases in sodium elimination after short-term atenolol administration in hypertensive patients have been reported (Colantonio et al 1991).

There appeared to be a significant correlation between:
i)   reduction in systolic BP by atenolol (AUC differences) and baseline PRA; and
ii) reduction in systolic BP and reduction in PRA by atenolol (AUC differences).
Thus it would appear that baseline PRA may predict the response of systolic BP to atenolol ie. the higher the PRA the greater the overall reduction in systolic BP in response to single doses of atenolol. In addition the 12 hour reduction in systolic BP and the reduction in PRA produced by atenolol, paralleled one another. There were too few subjects in each group to investigate whether or not the correlation differed between blacks and whites.

A number of studies in hypertensive patients have shown a relationship between blood pressure reduction by beta-blockers and basal PRA values (Volpe et al 1983, Von Bahr

et al 1976, Weber et al 1980) while others have shown no relationship (Salvetti et al 1977). Hollifield et al (1976), using propranolol, showed a positive correlation between fall in BP and fall in PRA in a group including high, medium and low renin patients. Others however, have shown little (Leonetti et al 1975) or no relationship (Pedersen et al 1981) between BP changes and PRA changes with continuous propranolol therapy in hypertensive patients.

The relative importance of the renin-angiotensin-aldosterone system (RAAS) in the various subsets of patients with hypertension has been extensively debated over the past 20 years or more (Bühler et al 1972, Bühler et al 1975, Fagard 1978). Much emphasis has been placed by certain investigators on renin profiling in order to select appropriate antihypertensive medication (mainly diuretics versus beta-blockers but more recently also ACE-inhibitors and calcium antagonists). However, others maintain that renin-profiling is not helpful in determining the extent of BP reduction to be expected with diuretics or beta-blockers. Some of the discrepancies are undoubtedly due to methodological problems in the assay methods, lack of standardization of sampling conditions (Amery et al 1977b) and poor study design. PRA is often regarded as a discontinuous variable eg. division of patients into groups above or below certain values. The conclusions in some studies are even frankly erroneous. For example, Holland & Fairchild (1982), in a study assessing the antihypertensive efficacy of hydrochlorothiazide (HCTZ) and metoprolol in black hypertensives with normal and low renin, concluded that the response to HCTZ was equivalent in low and normal renin groups. To obtain an adequate (equivalent) response however, required on average 90 mg HCTZ in those patients with normal renin while the low renin group required only 71 mg. Renin status was thus predictive of response to HCTZ.

The present study tends to support the idea of a relationship between PRA and BP lowering effects in normal individuals although the number of subjects was too small to assess whether the relationships were different in the two race groups.

Carefully controlled studies utilizing NONMEM analysis of antihypertensive drug treatment effects might be able to relate response variability to factors such as PRA and other components of the RAAS across a continuum of values. This might assist in elucidating mechanisms of action of drugs as well as physiological mechanisms controlling BP.

4.3. CONCLUSION

The effects of atenolol in reducing heart rate and blood pressure which were observed in this study were in broad agreement with those found by most other investigators.

The apparent racial difference in exercise heart rate with repeated bicycle ergometry clearly demonstrated the necessity for crossover placebo control in any study of drug effects on haemodynamics, particularly at sub-maximal exercise.

In young normotensive volunteers the reduction in exercise tachycardia in response to beta-blockade showed no ethnic differences. Since inhibition of exercise tachycardia is considered a good measure of $beta_1$-blockade, the ethnic difference in blood pressure response which has been reported in hypertensive patients is probably not a function of any genetic difference in $beta_1$-receptors. Obviously caution is necessary in extrapolating results to hypertensive patients where the disease state may affect receptor activity.

The predictive significance of the reduced response in supine systolic blood pressure in young normotensive blacks compared with whites is uncertain. Further single dose and long term studies of BP responses to beta-blockers (with and without ISA) in matched hypertensive blacks and whites using continuous ambulatory BP monitoring may assist in elucidation of ethnic differences. NONMEM analysis of effects may assist in elucidating factors responsible for variation within and between ethnic groups.

PRA appears to be predictive of systolic BP reduction by single dose beta-blockade in normotensive volunteers.

CHAPTER 5

PHARMACOKINETICS IN BLACK AND WHITE VOLUNTEERS

EXPERIMENTAL RESULTS AND DISCUSSION

CHAPTER 5

PHARMACOKINETICS IN BLACK AND WHITE VOLUNTEERS
EXPERIMENTAL RESULTS AND DISCUSSION

5.1. RESULTS

Plasma concentration time data from only 14 of the 16 volunteers was used in the pharmacokinetic analysis because the plasma samples for two volunteers (HA and AK) were damaged during storage.

5.1.1. Model Independent Analysis

Clearance (CL), half-life ($t\frac{1}{2}$) (terminal and 0.693.MRT), area volume of distribution (V_d) and apparent volume of distribution at steady state (V_{SS}) were calculated for 14 volunteers (7 black and 7 white) by model independent methods as discussed in Chapter 3 (3.5.2.1.). The individual results are presented in Table 5.1.

For all volunteers, the mean CL, $t\frac{1}{2}$ (terminal), $t\frac{1}{2}$ (0.693.MRT), V_d and V_{SS} values were 17.4±3.2 L/hr, 6.4±2.0 hrs, 5.2±1.6 hrs, 155.6±41.1 and 126.1±28.8 L respectively. The greatest variation (32%) was seen in $t\frac{1}{2}$ (terminal) with the least variation in CL (18%). The weight normalised mean value of CL was 0.26±0.05 L/hr/kg, while V_d and V_{SS} were 2.31±0.77 and 1.87±0.53 L/kg respectively (Table 5.2.). Weight normalization marginally increased the variation in CL (19%) and increased it more markedly in V_d (33%) and V_{SS} (28%).

Using the Student's t-test, no statistically significant differences between blacks and whites were found for any of the above parameters whether they were normalised for weight (Table 5.2.) or not (Fig. 5.1-5.4.).

148

Table 5.1. Parameters ($t\frac{1}{2}$ (terminal), CL, $t\frac{1}{2}$ (0.693.MRT), V_d and V_{SS}) for black (B) and white (W) volunteers calculated by model independent methods.

Subject	$t\frac{1}{2}$ (hr) terminal	CL (L/hr)	$^1t\frac{1}{2}$ (hr) 0.693.MRT	V_d (L)	V_{SS} (L)
MN (B)	7.1	18.0	5.2	185	136
CM (B)	5.8	15.3	5.1	129	112
VL (B)	3.5	20.5	3.1	105	90
AP (B)	9.5	15.0	7.4	206	161
ZN (B)	8.9	15.7	6.8	202	153
DS (B)	5.7	13.5	4.7	112	92
NM (B)	8.7	16.4	7.1	205	168
Mean SD CV (%)	7.0 2.17 31	16.3 2.29 14	5.6 1.54 28	163 46.1 28	130 32.5 25
NV (W)	7.7	17.0	5.9	189	145
BB (W)	4.3	15.5	3.9	96	88
ACA(W)	8.3	13.1	7.4	156	139
NF (W)	4.5	24.0	3.6	155	130
JFI(W)	6.7	19.9	5.4	194	154
JFO(W)	5.4	17.8	4.0	138	103
ACL(W)	3.4	22.1	3.0	107	94
Mean SD CV (%)	5.8 1.85 32	18.5 3.79 20	4.7 1.55 33	148 37.4 25	122 26.4 22
ALL Mean Median SD sem CV (%)	6.4 6.3 2.04 0.55 32	17.4 16.7 3.2 0.86 18	5.2 5.2 1.56 0.42 30	155.6 155.5 41.1 11.0 26	126.1 133.0 28.8 7.70 23

$^1t\frac{1}{2}$ (terminal) > $t\frac{1}{2}$ (0.693.MRT) because atenolol shows multicompartment disposition.

Fig 5.1. Model independent CL values in blacks and whites.

Groups

· Blacks   + Whites

p<0.2234
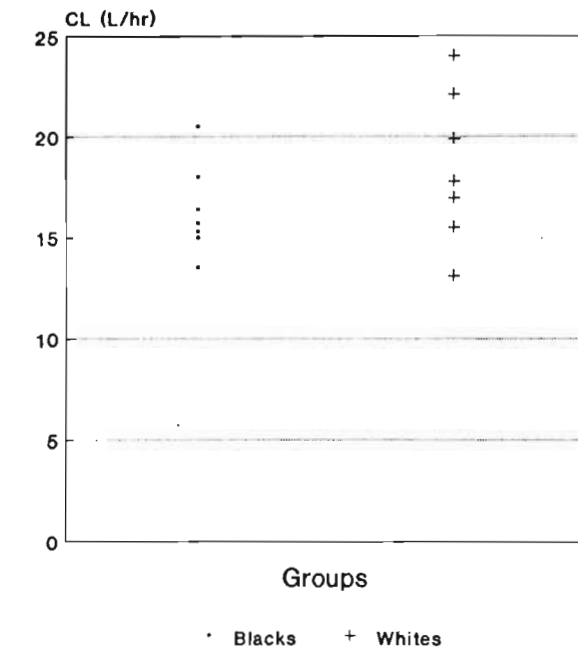
Fig 5.2. Model independent terminal half-lives in blacks and whites.

Groups

· Blacks   + Whites

p<0.2604
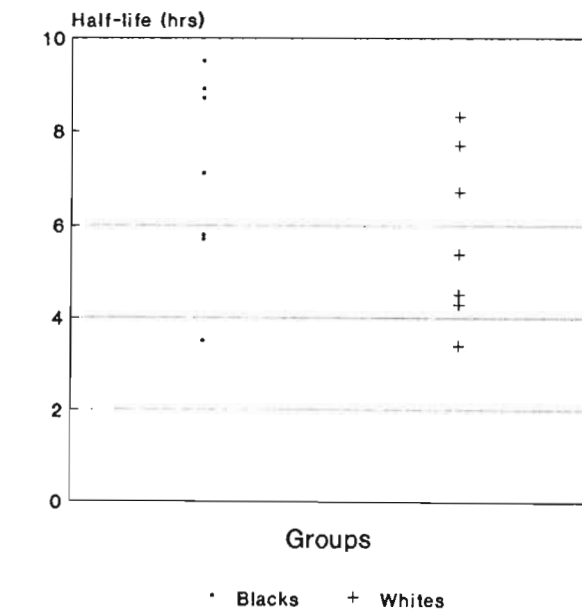
Fig 5.3. Model independent
Vss in blacks and whites.
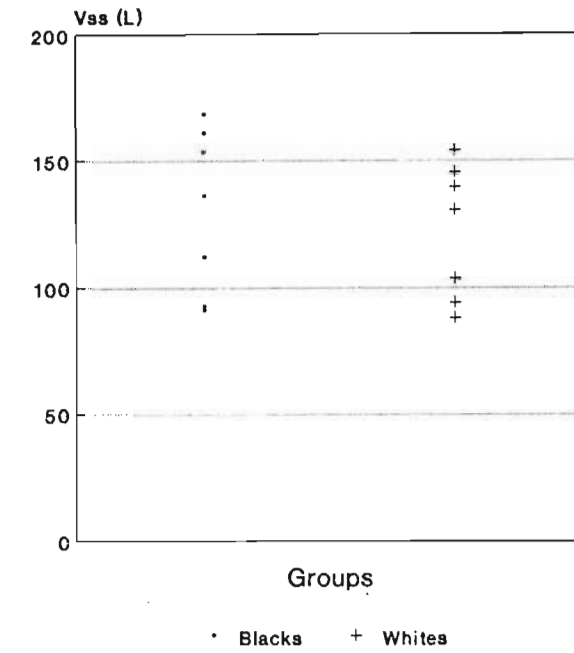
p‹0.6045

Fig 5.4. Model independent
half-lives (0.693.MRT) in blacks
and whites.
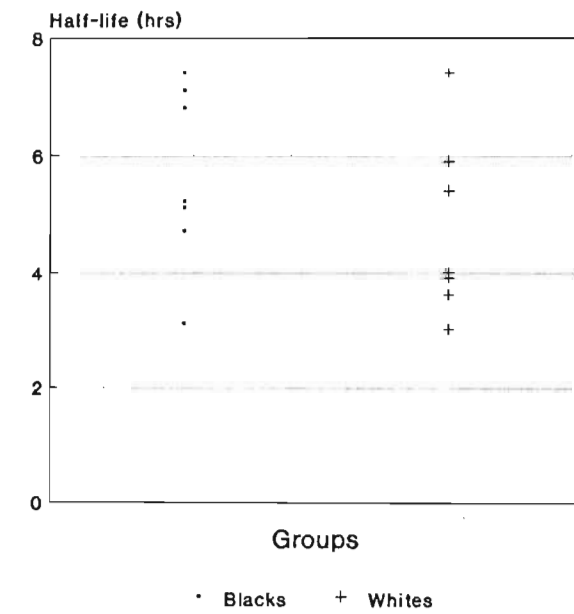
p‹0.3061

Table 5.2. Weight normalised values of CL, V_d and V_{SS} by model independent methods for individual black and white volunteers.

Subject (Race)	CL (L/hr/kg)	V_d (L/kg)	V_{SS} (L/kg)
MN (B)	0.26	2.6	1.94
CM (B)	0.24	2.0	1.77
VL (B)	0.29	1.5	1.30
AP (B)	0.23	3.3	2.55
ZN (B)	0.32	4.2	3.20
DS (B)	0.20	1.6	1.36
NM (B)	0.21	2.6	2.10
Mean	0.25	2.5	2.03
SD	0.04	0.97	0.67
CV (%)	16	39	33
NV (W)	0.23	2.6	1.99
BB (W)	0.22	1.4	1.23
ACA (W)	0.19	2.2	1.99
NF (W)	0.34	2.2	1.86
JFI (W)	0.26	2.5	2.00
JFO (W)	0.27	2.1	1.54
ACL (W)	0.32	1.5	1.34
Mean	0.26	2.1	1.56
SD	0.05	0.46	0.45
CV (%)	19	22	29
ALL Mean	0.26	2.31	1.87
Median	0.25	2.20	1.90
SD	0.05	0.77	0.53
SEM	0.01	0.21	0.14
CV (%)	19	33	28
B vs W p<	0.6697	0.2665	0.2740

Mean values for terminal elimination rate constant (λ_z), area under the curve ($AUC_{0-\infty}$) and mean residence time (MRT_{IV}) in blacks and whites are given in Table 5.3. There were no significant racial differences in any of these intermediate parameters.

Table 5.3. Mean values of λ_z, $AUC_{0\to\infty}$ and MRT_{IV} for blacks (B) and whites (W).

	λ_z (hr^{-1})	$AUC_{0\to\infty}$ $(ug/L.hr)$	MRT_{IV} (hr)
BLACKS Mean SD CV (%)	0.109 0.040 37	3110 407 13	8.12 2.24 28
WHITES Mean SD CV (%)	0.133 0.020 15	2810 594 21	6.86 2.20 32
B vs W p<	0.3324	0.2900	0.3100

The following can be found in Appendix 3:

Table A3.1. Atenolol plasma concentration (ng/ml) versus time (hours after start of infusion) data for black volunteers.

Table A3.2. Atenolol plasma concentration (ng/ml) versus time (hours after start of infusion) data for white volunteers.

Table A3.3. Intermediate model independent pharmacokinetic parameters.

Figure A3.1-3.14. Individual plasma concentration-time plots a) with concentration on a linear scale and b) concentration on a log scale.

5.1.2. Model Dependent Analysis

5.1.2.1. Extended Least Squares (ELS) Parameter Estimation

The concentration-time data for each of the 14 volunteers was individually fitted to both a two and a three compartment model by ELS regression. The estimated parameters for each individual for the respective models are given in Tables 5.4 and 5.6.

The utilization of a two compartment model for curve fitting of the plasma concentration-time data produced average clearance and volume estimates which were similar to those obtained by model independent methods. For all subjects, an average volume of 36.3±6.7 L was obtained for the central compartment (V_c) with 89.8±26.0 L for the average peripheral volume (V_2). Adding these two average volumes together gave a total of 126.1 L which was identical to the average V_{SS} obtained using model independent analysis above. The average CL of 17.2±3.6 L/hr was also very similar to that obtained by model independent means viz. 17.4±3.2 L/hr.

No statistically significant differences were found when these parameters were compared between blacks and whites (Table 5.4.)(Fig 5.5. and 5.6.). The weight normalised parameters (V_c, CL and V_2) from the two compartment fit given in Table 5.5 also showed no significant differences between the two ethnic groups. Mean CL was marginally smaller in blacks than whites (0.25 versus 0.26 L/hr/kg) although the variation was greater in whites than in blacks (25 versus 14%). Mean V_c on the other hand was marginally smaller in blacks than whites (0.53 and 0.54 L/kg respectively) showing 26% variation in blacks and 17% variation in whites. Mean V_2 was smaller in whites than blacks (1.25 versus 1.38 L/kg) but coefficients of variation were similar (30 and 32 % respectively).

Table 5.4. Pharmacokinetic parameters (V_c, CL, V_2) and microconstants (k_{10}, k_{12} and k_{21}) for individual black (B) and white (W) volunteers obtained by two compartment ELS analysis.

Subject	V_c (L)	CL (L/hr)	V_2 (L)	k_{10} (hr^{-1})	k_{12} (hr^{-1})	k_{21} (hr^{-1})
MN (B)	35.6	17.5	99.2	0.49	1.37	0.49
CM (B)	33.8	15.6	80.7	0.46	1.64	0.68
VL (B)	23.8	20.2	65.4	0.85	3.19	1.16
AP (B)	44.5	14.8	117.0	0.33	0.91	0.34
ZN (B)	33.9	14.0	92.1	0.41	0.65	0.24
DS (B)	28.3	14.1	52.3	0.50	1.47	0.80
NM (B)	40.5	16.1	121.0	0.40	1.65	0.55
Mean	34.3	16.0	89.7	0.49	1.55	0.61
SD	7.0	2.2	25.5	0.17	0.81	0.31
CV (%)	20	14	28	35	52	51
NV (W)	34.5	16.4	123.0	0.47	1.64	0.46
BB (W)	33.3	15.2	50.2	0.45	2.18	1.45
ACA(W)	42.6	11.3	115.0	0.27	1.24	0.46
NF (W)	43.1	24.4	84.8	0.57	2.16	1.10
JFI(W)	42.6	19.8	117.0	0.46	1.52	0.55
JFO(W)	43.4	18.4	72.0	0.42	0.92	0.55
ACL(W)	27.7	22.4	67.2	0.81	3.72	1.53
Mean	38.2	18.3	89.9	0.49	1.91	0.87
SD	6.3	4.4	28.6	0.17	0.92	0.48
CV (%)	16	24	32	35	48	55
Mean	36.3	17.2	89.8	0.49	1.73	0.74
Median	35.0	16.3	88.4	0.46	1.58	0.55
SD	6.7	3.6	26.0	0.16	0.85	0.41
CV (%)	18	21	29	33	49	55
B vs W p<	.3022	.2575	.9884	.9875	.4826	.2445

Fig 5.5. Central compartment volumes (Vc) from ELS 2 compartment fitting.
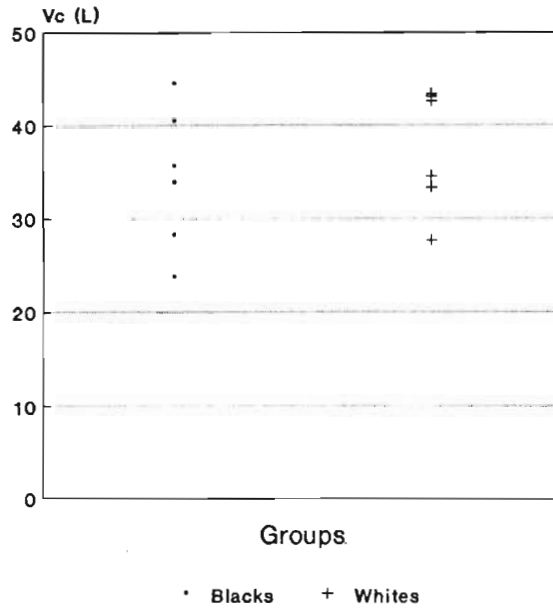
p‹0.3022

Fig 5.6. ELS 2 compartment CL in blacks and whites.
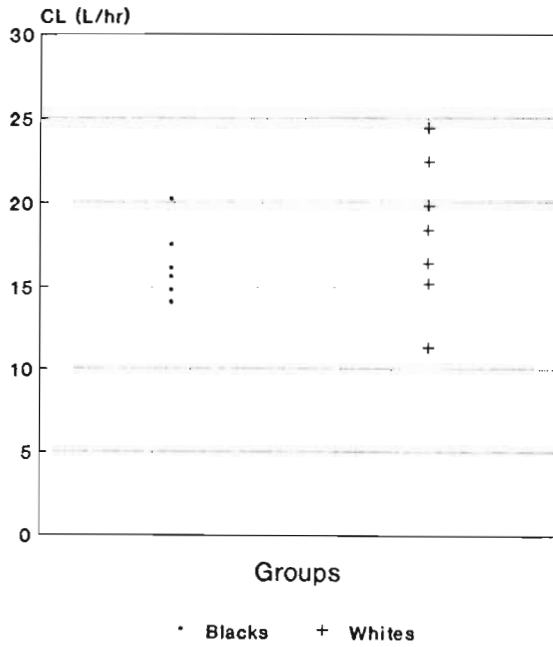
p‹0.2575

Table 5.5. Weight normalised values for V_c, CL and V_2 obtained from ELS two compartment modelling in black and white volunteers.

SUBJECTS	V_c (L/kg)	CL (L/hr/kg)	V_2 (L/kg)
BLACKS			
MN	0.51	0.25	1.42
CM	0.54	0.25	1.28
VL	0.34	0.29	0.93
AP	0.71	0.23	1.86
ZN	0.71	0.29	1.92
DS	0.42	0.21	0.77
NM	0.51	0.20	1.51
Mean	0.53	0.25	1.38
SD	0.138	0.036	0.433
CV (%)	26	14	32
WHITES			
NV	0.47	0.22	1.68
BB	0.47	0.21	0.71
ACA	0.61	0.16	1.64
NF	0.62	0.35	1.21
JFI	0.55	0.26	1.52
JFO	0.65	0.27	1.07
ACL	0.45	0.30	1.10
Mean	0.54	0.26	1.25
SD	0.094	0.066	0.372
CV (%)	17	25	30
ALL			
Mean	0.54	0.25	1.33
SD	0.109	0.049	0.384
CV (%)	20	20	29
B vs W p<	0.9469	0.7288	0.5581

Curve fitting of a 3 compartment kinetic model presented problems in certain individuals. This was probably the result of insufficient samples having been collected from 12 hours onwards, together with an increase in assay error in the samples close to the limit of sensitivity of the assay (10 ng/ml).

Table 5.6. Pharmacokinetic Parameters (V_c, CL, V_2) and microconstants (k_{10}, k_{12}, k_{21}, k_{13}, k_{31}) for individual blacks and whites estimated by three compartment model ELS analysis.

Subject	V_c (L)	CL (L/hr)	V_2 (L)	k_{10} (hr^{-1})	k_{12} (hr^{-1})	k_{21} (hr^{-1})	k_{13} (hr^{-1})	k_{31} (hr^{-1})
MN (B)	25.3	22.5	64.4	0.89	3.70	1.45	0.0016	0.0023
CM (B)	33.3	15.8	78.3	0.47	1.71	0.73	0.0013	0.0001
VL (B)	[1]Minimization routine terminated due to rounding errors.							
AP (B)	39.6	19.1	74.9	0.48	1.23	0.65	0.0001	0.0014
ZN (B)	21.4	18.4	55.0	0.86	3.44	1.34	0.0017	0.0019
DS (B)[1]	21.7	0.26[2]	34.2	0.01	2.97	1.88	0.8802	0.0102
NM (B)	29.6	20.1	86.0	0.70	2.88	0.99	0.0020	0.0017
NV (W)	23.8	21.0	79.0	0.88	4.37	1.32	0.0017	0.0011
BB (W)	32.7	15.5	48.1	0.47	2.36	1.60	0.0004	0.0002
ACA(W)	37.0	13.7	64.0	0.37	1.94	1.12	0.1410	0.0054
NF (W)	42.6	24.6	83.4	0.58	2.23	1.14	0.0006	0.0001
JFI(W)	36.8	22.3	88.3	0.61	2.36	0.98	0.0195	0.0010
JFO(W)	38.5	19.7	56.1	0.51	1.70	1.17	0.0242	0.0013
ACL(W)	26.6	22.7	63.1	0.85	4.02	1.70	0.0285	0.0017
[3] Mean	32.3	19.6	70.1	0.64	2.66	1.18	0.0186	0.0015
Median	33.0	19.9	69.7	0.69	2.36	1.15	0.0017	0.0014
SD	6.9	3.3	13.3	0.19	1.01	0.32	0.0399	0.0014
CV(%)	21	17	19	30	38	27	215	93

[1] All attempts at curve fitting unsuccessful, rounding errors dominating.
[2] Unrealistic parameter estimates.
[3] VL and DS excluded.

It was impossible to fit the 3 compartment model to the data from volunteer VL due to the minimization routine terminating with rounding errors. A 3 compartment model is probably a model misspecification in this individual (Boeckmann et al 1990). For volunteer DS on the other hand, 3 compartment curve fitting attempts, although successful in terms of MOF, resulted in unrealistically low CL values, no matter what the initial parameter estimates (Table 5.6).

Average values of V_c, CL and V_2 obtained from 3 compartment model curve fitting, together with calculated 3 compartment microconstants, for the remaining 12 individuals are presented in Table 5.6. To make a comparison between the average parameters from this model and the model independent and two compartment model dependent analysis is probably not meaningful because of the exclusion of 2 subjects from the 3 compartment analysis. Similarly, no comparison between blacks and whites in terms of 3 compartment parameters was attempted.

The major purpose in undertaking three compartment modelling was to obtain the best fit individual pharmacokinetic parameters for use in effect modelling to be discussed in Chapter 6. To achieve this, 2 and 3 compartment models were compared in each individual using a number of criteria including MOF, AIC, chi-squared test (Table 5.7.) (See Chapter 3, 3.5.2.2.4.). There was little difference between the 2 and 3 compartment model in 4 volunteers (CM, BB, NF, ACL) and therefore the simplest model (2 compartment) was chosen (Table 5.7.). In 8 volunteers (MN, AP, ZN, NM, NV, ACA, JFI, JFO) the 3 compartment model was clearly better (Table 5.7.). The parameters generated from the 2 compartment fit were utilised for individual effect modelling in subjects VL and DS because 3 compartment curve fitting was considered unsuccessful.

Table 5.7. Tests for choice between a 2 compartment model (2BCM) and a 3 compartment model (3BCM) including Minimum Objective Function (MOF), Akaike's Information Criterion (AIC) and Chi square probability of difference in Objective Function (DOBF) together with the intra-subject variation (σ_ϵ).

Subject	Model	MOF	AIC	Chi Square Probability (DOBF)	σ_ϵ (CV%)
MN	2BCM	147	147		21
	3BCM#	124*	128*	$p<0.005$	11
CM	2BCM#	119	119*		7
	3BCM	118	122	$p<0.6$	7
VL	2BCM#	101			9
	3BCM	Curve fit unsuccessful[1]			–
AP	2BCM	124	124		9
	3BCM#	112*	116*	$p<0.005$	10
ZN	2BCM	155	155		24
	3BCM#	141*	145*	$p<0.005$	16
DS	2BCM#	133*	–		13
	3BCM	112[2]	–	–	6
NM	2BCM	129	129		15
	3BCM#	98*	104*	$p<0.0005$	6
NV	2BCM	147	147		22
	3BCM#	123*	127*	$p<0.0005$	11
BB	2BCM#	110	110*		5
	3BCM	106*	110	$p<0.1$	5
ACA	2BCM	135	135		14
	3BCM#	116*	120*	$p<0.0005$	8
NF	2BCM#	111	111*		9
	3BCM	110	114	$p<0.6$	9
JFI	2BCM	120	120		13
	3BCM#	99*	103*	$p<0.0005$	7
JFO	2BCM	121	121		17
	3BCM#	115*	119*	$p<0.05$	13
ACL	2BCM#	84	84*		6
	3BCM	82*	86	$p<0.3$	6

\# Final Model Choice
* Intermediate Choice of Model
[1] All attempts at curve fitting a 3 compartment model unsuccessful due to rounding errors.
[2] Although the 3 compartment model appeared better (MOF & AIC), CL was unrealistic.

5.1.2.2. NONMEM Parameter Estimation

All concentration time data for the 14 volunteers was subjected concurrently to NONMEM analysis. Firstly, the two and three compartment models were compared in order to select the most appropriate pharmacokinetic model. Subsequently the influence of weight on the variability of V_c and CL and lastly the effect of race on CL were investigated in a stepwise fashion as described below.

Step 1. Both an open two compartment model and an open 3 compartment model, expressed in terms of parameters, V_c, CL, peripheral volumes (V_2 and V_3) and intercompartmental clearances (Q_{12} and Q_{13}), were fitted to the data. Both pharmacokinetic models assumed that all volunteers had the same values for the respective parameters irrespective of weight or race and that differences were due to random inter- and intra-subject variation. Iterative estimates of the parameters with residual inter-individual variance (ω^2) and residual intra-subject error variance (σ_ϵ^2) are presented in Table 5.8.

Table 5.8. NONMEM parameter estimates with inter-individual parameter variances (ω^2) as well as residual intra-subject variance (σ_ϵ^2) and MOF values for 2 and 3 compartment pharmacokinetic models.

	2 Compartment		3 Compartment	
	Parameter	Inter-individual variance (ω^2)	Parameter	Inter-individual variance (ω^2)
V_c	36.5 L	0.0112	28.0 L	0.0567
CL	15.4 L/hr	0.0497	13.6 L/hr	0.0728
V_2	101 L	0.1140	53.9 L	0.0479
Q_{12}	**58 L/hr**	0.0204	92.8 L/hr	1.37^{-15}
V_3	–	–	69.7 L	0.2560
Q_{13}	–	–	11.5 L/hr	0.0723
σ_ϵ^2	0.0329		0.00934	
MOF	1967.3		1781.8	

The 3 compartment model was clearly superior to the 2 compartment model using the criteria of MOF (1781.8 versus 1967.3), and the Chi-squared test with 2 degrees of freedom (DOBF = 175.5, p<0.0005).

The residual inter-subject variance of Q_{12} in the 3 compartment estimation yielded a negligibly small value (1.37^{-15}) and was therefore removed. Because this removal caused no alteration in the MOF or any of the parameter estimates the exclusion of this term was applied throughout further analyses.

Step 2. Using the three compartment model (with ω^2_{Q12} removed) as the reduced model (Model 1, Table 5.9) linear functions incorporating weight (WT) as follows were tested:

   i) V_c only, (V_c = P1*WT+P2) (Model 2, Table 5.9);

   ii) CL only, (CL = P1*WT+P2) (Model 3, Table 5.9);

   iii) WT in V_c and CL simultaneously (Model 4, Table 5.9).

When comparing Model 2 with Model 1, a difference in Minimum Objective Function (DOBF) of 3.2 indicated only a marginal improvement (0.05<p<0.10). Model 3 compared with Model 1 yielded a DOBF of 4.2 (p<0.05) suggesting that weight could account for some variability in CL (p<0.05). Inter-individual variation in CL, however, increased from 27 to 138%. Incorporating weight into both CL and V_c simultaneously (Model 4, Table 5.9) was unsuccessful in that the minimization routine could not converge (requiring in excess of 4000 iterations). Model 3 thus appeared the best of the weight adjusted models tested. Estimates of parameters, inter-individual variation, as well as MOF and intra-individual variation are given in Table 5.9.

Step 3. The next step in model building was to assess whether race together with weight might contribute to the inter-individual variability in CL.

Table 5.9. Parameter estimations for Models 1 to 4 assessing the influence of weight on V_c and CL separately and together and Model 5 with race and weight in CL.

Parameter	Model 1*	Model 2	Model 3	Model 4#	Model 5
V_c (L)	28.0	0.383*WT+1.86	28.0	0.435*WT+0.107	27.8
CL (L/hr)	13.6	13.7	0.169*WT+2.59	0.199*WT+0.0146	(0.21*WT-1.64)*1.27(Blacks)
V_2 (L)	53.9	55.3	54.2	65.9	53.3
Q_{12} (L/hr)	92.8	91.4	92.7	84.5	92.6
V_3 (L)	69.7	70.4	67.7	121	64.2
Q_{13} (L/hr)	11.5	11.5	11.0	8.01	11.4
ω_{Vc}	23.8%	273.5%	23.6%	4712%	23.6%
ω_{Cl}	27.0%	26.7%	138.2%	21817%	26.6%
ω_{V2}	21.9%	23.7%	21.1%	25.2%	21.3%
ω_{V3}	50.6%	51.1%	56.5%	very small	49.5%
ω_{Q13}	26.9%	28.1%	27.1%	54.9%	25.2%
σ_ϵ	9.7%	9.8%	9.7%	10.6%	9.6%
MOF	1781.8	1778.6	1777.6	1781.3	1772.9

* ω^2_{Q12} removed.
# Unsuccessful in converging.

Accordingly, the following linear model (Model 5, Table 5.9.) was tested:

$$CL = (P1*WT+P2)*(P3)$$

where P3 is some estimated value in blacks and 1 in whites. A DOBF of 4.5 relative to the reduced model of only weight in CL (Model 3) showed that differentiating CL by race made a small but significant contribution to the definition of the model (1 degree of freedom, $p<0.0250$). From model 5 it appeared that in the present study the black volunteers had a weight adjusted CL 1.27 times faster than the whites.

Because Model 5 appeared to give the best description of the concentration-time data by virtue of having the lowest MOF it was used in subsequent pharmacokinetic-dynamic modelling in Chapter 6.

However, the finding that blacks had a faster weight adjusted CL than whites was in contradiction to results from both two stage assessments viz. model independent and 2 compartment ELS regression. The possibility that the above finding might be an artefact arising from the NONMEM model building procedure was therefore considered in the following step.

Step 4. Scrutiny of Model 5 output of the NONMEM minimization routine, revealed that parameters 1 and 2 (P1 and P2) were highly inversely correlated (-0.948). Some inverse correlation was even evident between P1 and P2 in Model 2 (-0.800). This signified that the two parameters were poorly distinguished. Therefore a simpler model (Model 6) of weight related to CL was investigated:

$$CL = P1*WT.$$

Results are presented in Table 5.10, indicating little advantage of Model 6 over Model 1. Using the maximum log-likelihood ratio, Model 6 was 6.4 times more likely than Model 1 which was not considered a significant improvement.

In a similar manner the influence of race on CL was considered (Model 7, Table 5.10.):

$$CL = P1 * P2$$

where P2 is an estimated value for blacks and 1 for whites. From the results in Table 5.10. it is evident that the factor of 1.06 for blacks relative to 1 in whites is inconsequential. The two models gave almost identical MOF values.

Thus in the final analysis, neither weight nor race substantially influenced the inter-individual variability of the clearance of atenolol as assessed by NONMEM analysis.

Table 5.10. Parameter estimations of simpler models assessing the influence of weight and race on CL.

Parameter	Model 1	Model 6	Model 7
V_c (L)	28.0	28.0	27.9
CL (L/hr)	13.6	0.207*WT	13.1*1.06(B)
V_2 (L)	53.9	54.2	53.8
Q_{12} (L/hr)	92.8	92.7	92.8
V_3 (L)	69.7	68.1	69.7
Q_{13} (L/hr)	11.5	11.0	11.6
ω_{Vc}	23.8%	23.5%	23.8%
ω_{Cl}	27.0%	25.9%	27.6%
ω_{V2}	21.9%	20.5%	22.1%
ω_{V3}	50.6%	57.8%	48.4%
ω_{Q13}	26.9%	27.6%	25.7%
σ_ϵ	9.7%	9.7%	9.6%
MOF	1781.8	1778.1	1781.5

5.1.2.3. NONMEM versus Two Stage Analysis

Since NONMEM assumes a logarithmic error model, estimates generated from NONMEM proper should be compared to geometric means (Sheiner & Beal 1981) obtained from individual ELS estimations or moment analysis and not arithmetic means as given in the results tables. Correction for geometric means however, only marginally reduced values from those in the results tables.

Two compartment NONMEM estimates on the whole concurred with two stage estimates obtained by both ELS regression and model independent analysis of individual data although CL was lower at 15.4 L/hr.

The 3 compartment NONMEM CL estimate of 13.6 L/hr was lower than the geometric mean found with both 3 compartment ELS regression (19.3 L/hr) or moment analysis (17.2 L/hr) in individuals. It is probably not valid to compare the NONMEM values (obtained from data for 14 volunteers) with the mean of the 3 compartment ELS regression because of the exclusion of two volunteers in the ELS analysis. Moment analysis however, included all the same volunteer data as NONMEM. The higher CL obtained from moment analysis compared with the 3 compartment NONMEM estimate, is possibly the result of poor characterization of the terminal slope in most of the individuals because of few samples and levels close to the limit of detection. NONMEM by pooling the data from all individuals would be expected to give a more reliable (unbiased) definition of this terminal elimination phase using all available data.

The average V_{SS} of 126 L obtained from both two stage methods ie. moment analysis and ELS regression was intermediate between that of 94.5 L from two compartment NONMEM analysis and 151.6 L derived from the 3 compartment NONMEM analysis.

5.2. DISCUSSION

5.2.1. Model Independent Pharmacokinetics

The model independent pharmacokinetic parameters (CL, V_{SS} and $t\frac{1}{2}$) of atenolol in healthy young blacks and whites showed no significant racial differences. This is not surprising because the elimination of atenolol is almost exclusively via the renal route and all volunteers were healthy young males with normal serum creatinine values. Atenolol clearance is correlated with renal function (Kirch et al 1981, Wan et al 1979) with a strong correlation between GFR and plasma clearance (k_{el} = 0.024 + 0.00056 GFR, r = 0.82)(Kirch et al 1981). Thus impaired renal function and age (probably a result of deteriorating renal function) are known to influence the clearance and half-life of atenolol (Barber et al 1981, Rigby et al 1985). Phenotype would therefore be unlikely to affect the disposition kinetics as is the case with the beta-blockers metoprolol, bufarolol, timolol and bopindolol, which undergo extensive oxidation (Lennard et al 1986). The disposition of atenolol has been shown to be unrelated to debrisoquine phenotype (Lennard et al 1986, Lewis et al 1985).

The mean terminal elimination $t\frac{1}{2}$ of 6.4 hrs is in reasonable agreement with other IV atenolol studies in healthy volunteers where values range from 5.33 hrs (Wan et al 1979) to 6 and 7 hrs (Brown et al 1976, Mason et al 1979, McAinsh et al 1980a). Terminal elimination half-lives after oral dosing in subjects with normal renal function are reported to range from 4.8 hrs to 9.2 hours (Kunka et al 1989, McAinsh et al 1980b, Rigby et al 1985, Riva et al 1980) depending to some extent on the dose administered and the age of the subjects. An average half-life of 11.1 hours has been reported in a group of hypertensive patients over 60 years of age (Dimenäs et al 1990). Some studies in hypertensive subjects appear to indicate a somewhat longer half-life at steady state (11.5 hours) than after a single dose (7.2 hours)(Dixon et al 1990).

The average atenolol MRT_{IV} of 450 minutes found in the present study is in the same range as the 517 minutes calculated from the data of Mason et al (1979) (Hinderling et al 1984).

The mean clearance of 17.4 L/hr found in this study was somewhat higher than has been previously reported in healthy young adults. Reported clearances have ranged from 6 L/hr (Brown et al 1976, Reeves et al 1978b) through 9 L/hr (Kirch et al 1981) to 11-12 L/hr (Mason et al 1979, Rubin et al 1982). The mean weight normalised V_{ss} of 1.9 L/kg was also 58% higher than the 1.2 L/kg found by Kirch et al (1981). The large CL and V_{ss} were the consequence of a relatively small $AUC_{0-\infty}$ which was 30-40% lower than in another study where the same dose was used (Mason et al 1979).

The variation between studies, of published values of pharmacokinetic parameters of beta-blockers, using apparently specific assay methods, has been highlighted by Hinderling et al (1984). Comparing two studies in each case, these authors showed a 38% difference in V_{ss} of propranolol, a 141% difference in renal clearance of timolol and an 86% difference in non-renal clearance of oxprenolol. The reasons for the discrepancies are not readily apparent.

Various possibilities in accounting for the differences between the present findings and published studies have been considered.

Although the specificity of the assay methods were not in question, none of the above mentioned studies used the same method of atenolol measurement as was used in the present study. Also, most unfortunately, the plasma samples were stored for 30 months prior to analysis and some degree of degradation could have occurred. Although an early report

claimed atenolol was unstable when stored at $-20°$ C (Yee et al 1979) a more recent report has shown atenolol to be stable under these storage conditions (Lewis et al 1985). All samples were, however, stored for the same length of time, under identical conditions. Therefore the comparison between blacks and whites would not be invalidated by the possibility of some degree of deterioration.

One white volunteer (NV) had a respiratory tract infection on the day of atenolol administration. Inflammation (respiratory tract infections) has been shown to reduce plasma levels and AUC of atenolol by about 40% while increasing renal clearance (Kirch et al 1983). This might explain a relatively rapid clearance of 17 L/hr found in this one individual but not in the others.

Another point of difference between the present study and the atenolol kinetic studies mentioned above was that none of them included exercise in their procedure.

There is relatively little information available on the effects of exercise on the pharmacokinetics of drugs in general and on the beta-blockers in particular, despite the fact that many studies have assessed the effect of beta-blockers on exercise haemodynamics. Exercise causes profound haemodynamic changes including increased cardiac output and redistribution of blood flow away from the splanchnic area and the kidneys towards the skeletal muscle and skin (Van Baak 1990).

Increased distribution of drugs to skeletal muscle and skin and adipose tissue with exercise might increase the volume of distribution of some drugs. Van Baak (1990) cites conflicting evidence on distribution of beta-blockers during exercise. Rapid increases in plasma concentrations of oxprenolol, propranolol and acebutolol have been found when sampling was done during exercising while no change in

distribution was seen in different studies of propranolol and atenolol.

Frank et al (1990) in a study of the effect of exercise on the kinetics of IV propranolol in 14 healthy volunteers, showed a large difference in the degree and direction of changes in individuals with exercise. Although the differences were not significant, exercise, on average, decreased total propranolol plasma clearance and increased average volume of distribution, relative to the sedentary study phase (Frank et al 1990). A reduction in clearance of high extraction ratio drugs like propranolol would be expected when blood is diverted away from the liver as occurs with exercise.

Exercise would not be expected to markedly alter atenolol clearance because the drug is eliminated via the kidneys. In a study using orally administered atenolol, a reduction of 8% in renal clearance was demonstrated, possibly the result of reduced renal blood flow (Mason et al 1980). The above mentioned study differed from the present one in that the volunteers were exercised (Bruce protocol) at 4, 8 and 24 hours post dosing when distribution would have been expected to be complete. In the present study exercising was most frequent during the initial distribution phase (8 periods of 3 minutes of exercise between 0-2 hours post dose). The exercise might therefore have increased the initial distribution volume (demonstrated to be large in the model dependent analysis discussed below). This would in turn contribute to a larger V_{ss}.

5.2.2. Model Dependent Pharmacokinetics
5.2.2.1. ELS Estimations
The average parameters obtained from two compartment ELS fitting of individual volunteer data sets was in agreement with the parameters obtained from model independent methods. This was not surprising when it is considered that

the atenolol concentrations from 4 hours onwards were used in calculating the terminal slope and would have biased results in the direction of two compartment modelling. Thus the model independent values confirmed that the two compartment model provided an adequate description of the concentration time data.

As with model independent kinetics, the two compartment ELS modelling produced no evidence of any ethnic differences in atenolol disposition.

As expected, the three compartment model appeared to give a better fit in those volunteers where more concentrations from 24 to 36 hours were available. However, the relatively poor definition of this terminal phase in most individuals (24-36 hours) due to lack of samples or levels close to or below the assay sensitivity casts some doubt on the relevance of the ELS generated 3 compartment pharmacokinetic parameters in individual subjects.

For comparative purposes, the published study by Mason et al (1979) in which an IV atenolol infusion was administered to 12 healthy volunteers is probably the most informative. These investigators used NONLIN to curve fit both two and three compartment models, finding the three compartment model more suitable in eleven of the 12 volunteers. Their findings differ from ours in that they measured much higher levels in the first hour after the infusion, accounting for the much smaller initial distribution compartment of 13 L (range 3 to 26 L) compared with 32 L (range 21 to 40 L) found in the present study. Despite their subjects not being exercised and their sampling time only extending to 24 hours, the reported parameters and microconstants showed much greater inter-individual variation than was noted in the present study. The possibility that the exercising immediately prior to administration and during the early distribution phase might have influenced the present

results cannot be discounted. This has been discussed in 5.2.1. above.

As much as the present study differs from that of Mason et al (1979), other studies involving similar IV doses of atenolol differ in the opposite direction. Brown et al (1976) after administration of 50 mg of atenolol (IV) to 4 volunteers, obtained a V_c of 17.5 L, a V_d of only 51 L and a clearance of only 5 L/hr. The last two parameters are half of those found in the study discussed above (Mason et al 1979) but in agreement with a study by Wan et al (1979).

5.2.2.2. NONMEM Estimations

Concurrent analysis of concentration-time data from all 14 volunteers by means of NONMEM, clearly showed that the 3 compartment pharmacokinetic model was more appropriate than the 2 compartment model for the group as a whole. Most other investigators who have administered an IV dose of 50 mg or more, have also found a 3 compartment model appropriate for describing atenolol concentration-time data (Brown et al 1976, Mason et al 1979, Wan et al 1979).

The 3 compartment NONMEM estimate of 28 L (0.4 L/kg) for the central volume of distribution although lower than the 32 L obtained from the 2 stage ELS regression estimates remained much larger than most previously published values. Only one study, in children, reported a comparable V_c of 0.33±0.06 after 0.1 mg/kg of IV atenolol (Buck et al 1989). Mason et al (1979) using NONLIN 3 compartment curve fitting in 12 volunteers, reported wide ranging values from 3.27 to 22.3 L (mean 12.8±5.72). Exercise as a possible reason for differences from published values in the initial distribution space have been discussed in the previous sections (5.2.1. and 5.2.2.).

In support of the reliability of the NONMEM generated CL value of 13.6 L/hr (See 5.1.2.3.) is its similarity to the 11-12 L/hr reported for young healthy volunteers after IV administration in two different studies (Mason et al 1979, Rubin et al 1982). Apparent oral CL in young people (23-33 years) with normal renal function is reportedly about 22 L/hr (Rigby et al 1985). Assuming 50% bioavailability in the above study, would give an estimated CL corrected for F, of approximately 11 L/hr, again reasonably consistent with the NONMEM estimation in the present study.

The significance of the results of modelling for factors contributing to inter-individual variability in V_c and CL in the present study is debatable. Modelling for a weight adjustment in CL while improving the MOF significantly at the 5% level, increased the inter-individual CV for CL from 27 to 138%. A subsequent adjustment for race and weight in CL further improved the MOF but reduced interindividual variability back to 26.6%. Surprisingly, this analysis yielded a factor indicating that blacks had a weight adjusted CL 1.27 times that of whites. This was contrary to results from both moment analysis and ELS regression where blacks on average appeared to have a slightly slower clearance. This discrepancy might be the result of different statistical assumptions in the different methods but is most probably an artifact generated in the NONMEM model building. The latter appears to be the case because further NONMEM modelling of weight and race used separately as scaling factors did not improve the estimates or fit (Table 5.10.).

The influence of renal function (probably the most important factor) on the CL of atenolol could not be evaluated because neither serum creatinine values nor creatinine clearance values were available. If a real difference in CL between the blacks and whites in the present study existed, it would be most unlikely the result

of a true ethnic difference which could be extrapolated to other groups of blacks and whites. It would almost certainly be the result of differences in renal function within the group studied. Defining population variability of CL of atenolol should always take renal function into account. The lack of creatinine clearance values in the present study was a serious oversight.

5.3. CONCLUSION

Moment analysis produced estimates of half-life and MRT_{IV} which were comparable to literature values. CL, V_d and V_{SS} were however, larger than literature values, possibly the result of the exercising protocol. There were no significant differences between blacks and whites in any of the parameters obtained from model independent methods.

ELS regression analysis using a two compartment pharmacokinetic model exhibited no evidence of kinetic differences between the blacks and whites in the present study. The mean parameters obtained from two compartment modelling with ELS regression and NONMEM were consistent with mean values from moment analysis.

Although 3 compartment ELS modelling in individuals was not particularly successful, NONMEM analysis appeared to yield reliable parameter estimates. The estimate of CL (13 L/hr) was lower than the other methods used, being only marginally larger than two published reports of 11-12 L/hr (Mason et al 1979, Rubin et al 1982). Attempts to ascribe inter-individual variation in V_c and CL to weight or race contributed nothing of scientific interest.

CHAPTER 6
PHARMACOKINETIC-DYNAMIC MODELLING
EXPERIMENTAL RESULTS AND DISCUSSION

CHAPTER 6
PHARMACOKINETIC–DYNAMIC MODELLING
EXPERIMENTAL RESULTS AND DISCUSSION

6.1. RESULTS

The atenolol induced decrease in exercise heart rate (EHR) was the only effect measurement considered suitable for pharmacokinetic–dynamic modelling. The BP, resting heart rate and PRA measurements were thought to have too much baseline noise to give meaningful results in relating atenolol concentration to effect.

6.1.1. ELS Analysis of Data for Individuals

The pharmacokinetic parameters were constrained to the values obtained from the best fit derived previously for each individual (See Chapter 5, 5.1.2.1.). Thereafter, ELS regression was used to relate concentration to the change in EHR. The linear, log-linear, E_{max} and Sigmoid E_{max} models were tested with the data from each individual. A direct relationship between concentration and effect was assumed because change in exercise tachycardia appeared maximal at either the first or second measurement after the termination of the atenolol infusion.

Curve fitting of the pharmacodynamic data in individuals proved somewhat problematic. This was the result of a fundamental flaw in the study design. Namely, that many measurements were carried out during the first 6 hours but few measurements of either concentration or effect were done at the critical time between 12 and 30 hours when effect changes were maximal.

The DOBF, AIC and chi-squared tests, although suitable for differentiating between the E_{max} and sigmoid E_{max}, models were not appropriate for making a selection between the linear, log linear and E_{max} models because the models are not nested.

Although the maximum log-likelihood ratio could be used, the following were also considered in making a choice:

i)   Successful termination without rounding errors dominating;

ii) Exclusion of the model, if any of the parameter estimates neared boundaries which were obviously unreasonable eg. $E_{max} >$ 70 bpm; $IC_{50} >$ 1000 ng/ml; or slope, $0.1 > n > 5.0$;

iii) Exclusion of the model if a correlation between any 2 of the parameters describing the model was greater than ±0.9 (to ensure parameter differentiation);

iv) inspection of the scatter plots of weighted residuals against predicted values, for the absence of a pattern;

v)   relatively low standard errors of the estimates (SEE);

vi) low random intra-individual variation (σ_ϵ) (measurement error or model misspecification) expressed as a coefficient of variation.

For all individuals, the MOF values for each of the models where the minimization routine terminated without rounding errors dominating, is given in Table 6.1. overleaf. The best model overall is indicated by an asterisk (*), with footnotes indicating why some models were rejected. Details, including parameter estimates, are available in Appendix 4 (Tables A4.1-4.4.).

In all subjects, the linear model was the least suitable by virtue of having by far the largest MOF value as well as the largest variation in random intra-individual error, the latter indicating model misspecification. The plot of weighted residuals versus predicted values showed a pattern (similar to that in Fig.6.4. for NONMEM group data analysis) again indicating model misspecification.

When comparing the log-linear to the E_{max} model, in only two volunteers was the former superior to the latter as judged

by a maximum log likelihood ratio of greater than 10 (>1000 and 27 times more likely for VL and NF respectively). In one subject (CM) the log-likelihood ratio of 9 in favour of the log-linear over the E_{max} model indicated a marginal advantage in favour of the former. In 8 of the 14 subjects, curve fitting to the log-linear model resulted in the ELS minimization routine terminating with rounding errors dominating. These results were therefore considered unreliable (Boeckmann et al 1990).

Table 6.1. Individual MOF values for the various effect models tested in blacks (B) and whites (W).

	Linear Model	Log-linear Model	E_{max} Model	Sigmoid E_{max} Model
MN (B)	195.4	#	176.4*	175.8[1,2]
CM (B)	254.5	181.2	185.6*	177.1[1,2]
VL (B)	#	156.2*	198.9	189.5[1,2]
AP (B)	225.2	185.9[2]	186.3*	185.8[2]
ZN (B)	222.7	#	208.6[2]	195.8*
DS (B)	269.2	#	228.1*	224.8[1,2]
NM (B)	226.8	178.0[2]	179.2*	179.0[2]
NV (W)	230.6	#	193.2*	193.02
BB (W)	295.0	#	178.8*	172.1[2]
ACA (W)	221.3	#	201.9*	201.2[2]
NF (W)	293.6	187.9*	194.5	182.0[1,2]
JFI (W)[3]	184.2	#	177.7[2]	137.3[1,2]
JFO (W)	311.2	#	251.2*	251.2
ACL (W)	269.4	155.1[2]	163.7*	157.0[1]

* Most suitable model overall.
\# Minimization routine terminated due to rounding errors dominating.
[1] Estimate of parameter near boundary and therefore probably uninterpretable.
[2] Parameters correlated, therefore poorly distinguished.
[3] No suitable model.

In the remaining individuals (AP, NM and ACL) a correlation between the slope and intercept parameters led to rejection of the model. (See Appendix 4, Table A4.2. and 4.3. for full details.)

Plots of the average EHR against time (Chapter 4, Fig.4.5 and 4.6.) indicated an initial relatively small decline in effect in the first hour, followed by a plateau phase lasting about 3-5 hours after atenolol administration. Thereafter a more rapid decline occurred. This corresponds to the typical plateau effect seen with beta-blockade on reduction of exercise tachycardia (See Chapter 1, 1.3.3.1.2.). Thus either an E_{max} or a sigmoid E_{max} model appeared reasonable possibilities.

When the sigmoid E_{max} model was fitted to the data, significant correlation between 2 or more of the parameters was observed in 11 of the 14 volunteers. This demonstrated that the data was insufficient to obtain reasonably well defined estimates of all parameters describing this model. In one of the 3 remaining volunteers (ZN) a DOBF of 12.8 in favour of the sigmoid E_{max} model when compared to the E_{max} model, indicated a significantly better fit (one degree of freedom, $p < 0.0005$). In another (VL) the IC_{50} estimate was on a boundary of 1000 ng/ml leading to rejection of the sigmoid E_{max} model. In the last individual (JFO) the MOF was identical for both sigmoid and E_{max} models, the choice thus being the simpler E_{max} model. In subject JFI none of the models tested appeared to adequately describe the data.

In summary: the sigmoid E_{max} model proved best in one subject; in two subjects the log-linear model appeared most appropriate; the data from one subject proved impossible to fit to any of the models; and the E_{max} model was chosen for the remainder.

Estimates of E_{max} and IC_{50} (with standard errors of estimates, SEE) for all individuals together with intra-individual variability in measurement are given in Table 6.2. An asterisk marks those subjects where the E_{max} and sigmoid E_{max} models were considered unsuitable. These values were not included in subsequent comparisons or calculations of means.

When the E_{max} and IC_{50} values (excluding VL, NF and JFI) were compared between blacks and whites, no significant differences were found (Fig 6.1. and 6.2.). The E_{max} and IC_{50} mean values with standard deviation for the 11 subjects were 32.9±5.73 bpm and 49.5±38.9 ng/ml. The mean E_{max} values in blacks and whites were very similar (33.7±3.43 and 32.0±8.08 bpm respectively) while the mean IC_{50} in the blacks (n=6) was 62.5±40.6 compared with 34.0±34.2 ng/ml in the whites (n=5) although the difference was not significant.

In subjects where a two compartment pharmacokinetic model was applied, low IC_{50} values (Fig. 6.3.) with particularly large errors of the estimates were found (Appendix 4, Table A4.3 and A4.4.). The value of the IC_{50} became dependent on the pharmacokinetic model chosen. The limitation in defining the IC_{50} estimates below 10 ng/ml lay in the inability to accurately measure low atenolol concentrations compounded by the paucity of samples. Failure to define a slow elimination phase thus distorted the pharmacodynamic results.

Table 6.2. Individual parameter estimates with SEE in brackets, and random measurement error (σ_ϵ) for the E_{max} or sigmoid E_{max} models.

	E_{max} (bpm)	IC_{50} (ng/ml)	n	σ_ϵ CV %
MN (B)	37.4 (3.6)	124.0 (38.2)	–	33
CM (B)	34.7 (2.0)	18.9 (5.1)	–	23
VL (B)*	24.8 (3.4)	2.2 (4.5)	–	17
AP (B)	28.4 (3.1)	27.4 (5.7)	–	36
ZN (B)	34.9 (7.8)	95.4 (9.3)	1.86	30
DS (B)	30.8 (3.6)	47.4 (17.8)	–	54
NM (B)	36.2 (2.7)	61.6 (8.9)	–	19
NV (W)	35.5 (2.5)	45.6 (13.1)	–	30
BB (W)	34.3 (2.5)	5.4 (3.0)	–	19
ACA (W)	35.5 (2.2)	86.0 (23.6)	–	39
NF (W)*	36.7 (3.5)	4.7 (2.8)	–	29
JFI (W)*	42.7 (8.3)	252 (121)	–	51
JFO (W)	36.9 (1.8)	30.8 (3.0)	–	26
ACL (W)	17.6 (3.0)	2.3 (2.5)	–	55

*Both E_{max} and sigmoid E_{max} unsuitable in describing data.

Fig 6.1. Emax values in blacks and whites.

p<0.6351
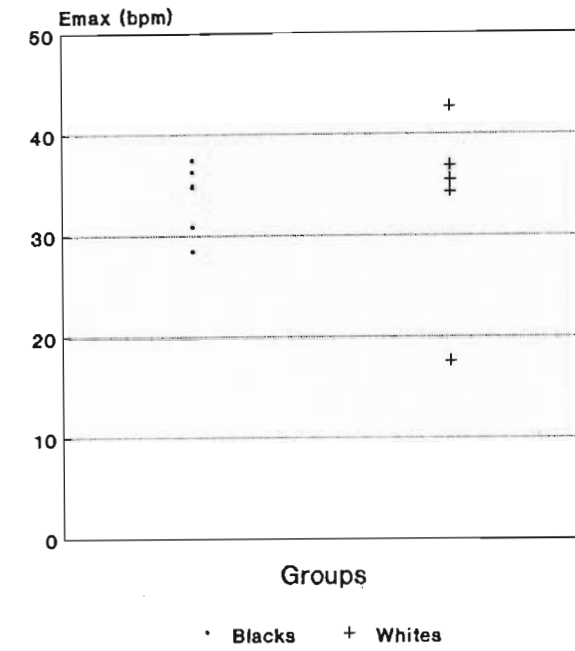
Fig 6.2. IC50 values in blacks and whites.

p<0.2463
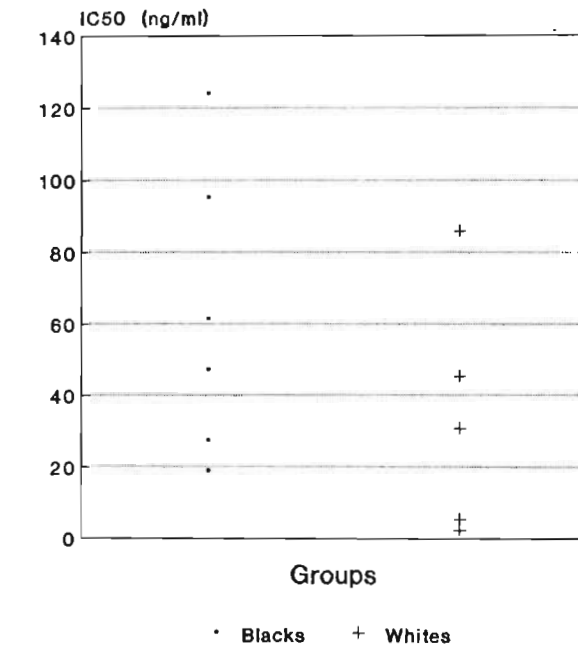
Fig 6.3. IC50 values in relation to two and three compartment kinetics.
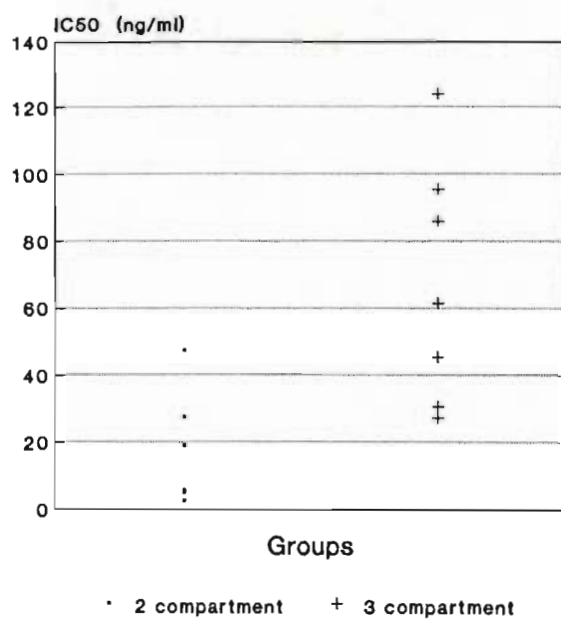
6.1.2. NONMEM Analysis of Group Data

The data set of atenolol induced changes in exercise tachycardia for all 14 volunteers was subjected to NONMEM analysis. With the pharmacokinetic parameters constrained to the values obtained with Model 5 in Chapter 5 (5.1.2.1.), curve fitting of the effect data to the linear, log-linear, E_{max} and sigmoid E_{max} models was effected. The assumption at this point was that race would not influence inter-individual variation in parameter estimates. The parameter estimates with standard errors of the estimates (SEE), inter-individual parameter variation (ω) and intra-individual random variation (σ_e) for each of the four models are presented in Table 6.3. overleaf.

The linear model not only had the largest MOF and intra-individual variation of all 4 models, but the plot of weighted residuals versus predicted values clearly indicated model misspecification (Figure 6.4.). As a result this model was rejected.

The log-linear model was considered inappropriate because although the minimization routine appeared to terminate successfully, an error message resulted (R matrix algorithmically non-positive semidefinite but nonsingular). The reliability of final estimates were therefore in doubt. The model is possibly misspecified (Boeckmann et al 1990). This is supported by a diamond pattern (Figure 6.5.) displayed by the plot of weighted residuals against predicted values. When comparing the log-linear model to the E_{max} model, a DOBF of 111.8 in favour of the E_{max} model demonstrated that it described the data considerably better than the log-linear model (Table 6.3.).

Table 6.3. NONMEM generated effect model parameters with standard errors of the estimate (SEE), MOF and inter-individual parameter variation (ω) together with random intra-subject variation (σ_ϵ).

MODEL	PARAMETER (SEE)	ω (CV %)	MOF	σ_ϵ (CV %)
LINEAR*	S=0.0814 (0.0192)	102	3415.1	157
LOG-LINEAR**	S=18.1 (0.434)	23	2967.7	64
	I=-29.8 (0.403)	50		
E_{max}	E_{max}=37.0 (1.83)(bpm)	12	2855.9	19
	IC_{50}=36.5 (7.2)(ng/ml)	121		
SIGMOID E_{max}	E_{max}=43.8 (2.74)(bpm)	8	2843.0	16
	IC50=32.1 (9.6)(ng/ml)	120		
	n=0.738 (0.0746)	#		

* Plot of weighted residuals versus predictions indicated that this model was inappropriate.

** Although minimization routine terminated successfully, error message: R matrix algorithmically non-positive semidefinite but nonsingular.

Including inter-individual variation on slope did not alter MOF (2843.1) but increased σ_ϵ (22%) and an inverse correlation between E_{max} and IC_{50} (-0.918) became evident.

Figure 6.4. A plot of weighted residuals (WRES) versus predicted values (PRED) from NONMEM analysis using a linear pharmacodynamic model.

186

Figure 6.5. A plot of weighted residuals (WRES) versus
predicted values (PRED) from NONMEM analysis using a log-
linear pharmacodynamic model.

Figure 6.6. A plot of weighted residuals (WRES) versus predicted values (PRED) from NONMEM analysis using an E_{max} pharmacodynamic model.
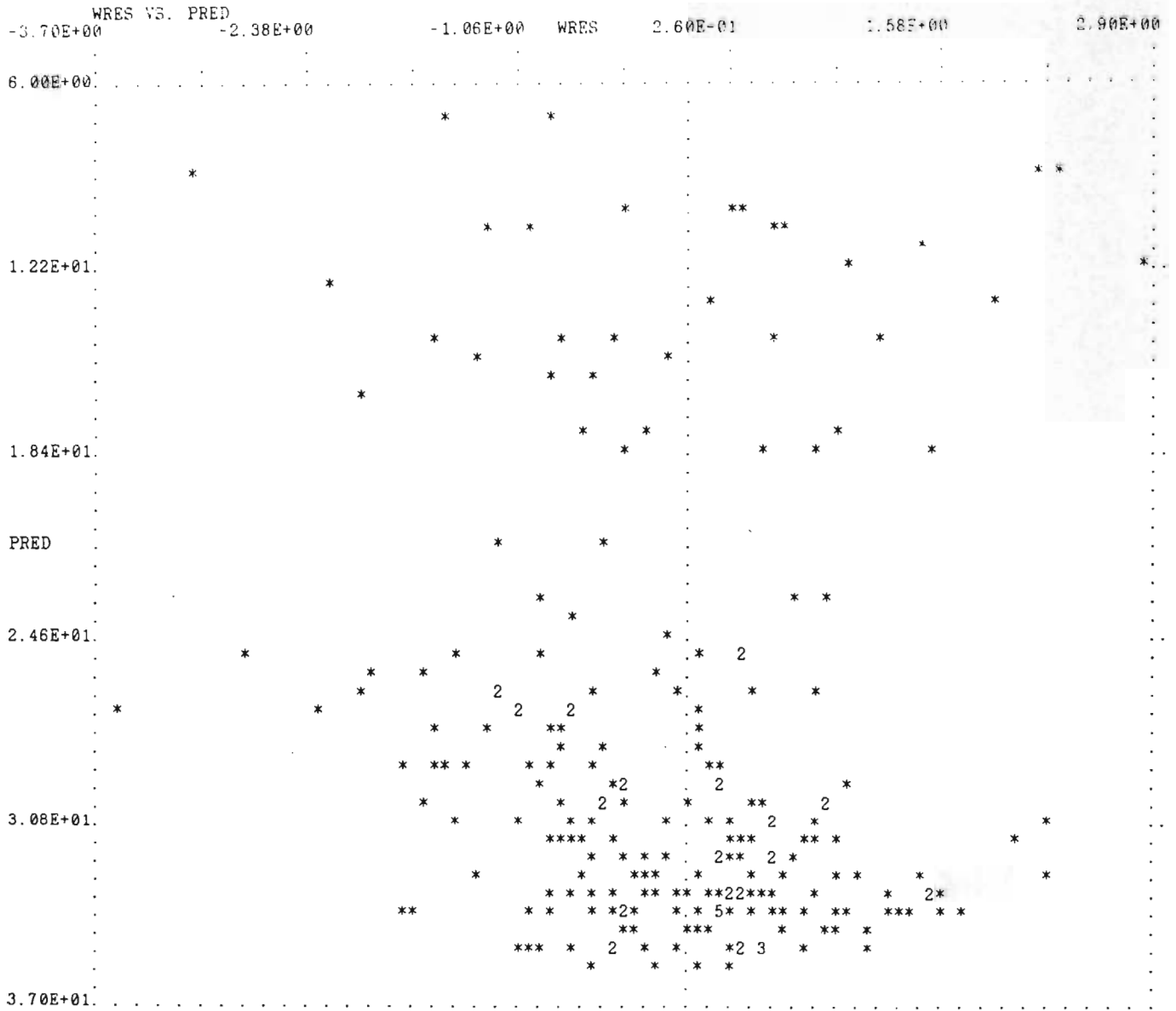
Figure 6.7. A plot of weighted residuals (WRES) versus predicted values (PRED) from NONMEM analysis using a sigmoid E_{max} model.
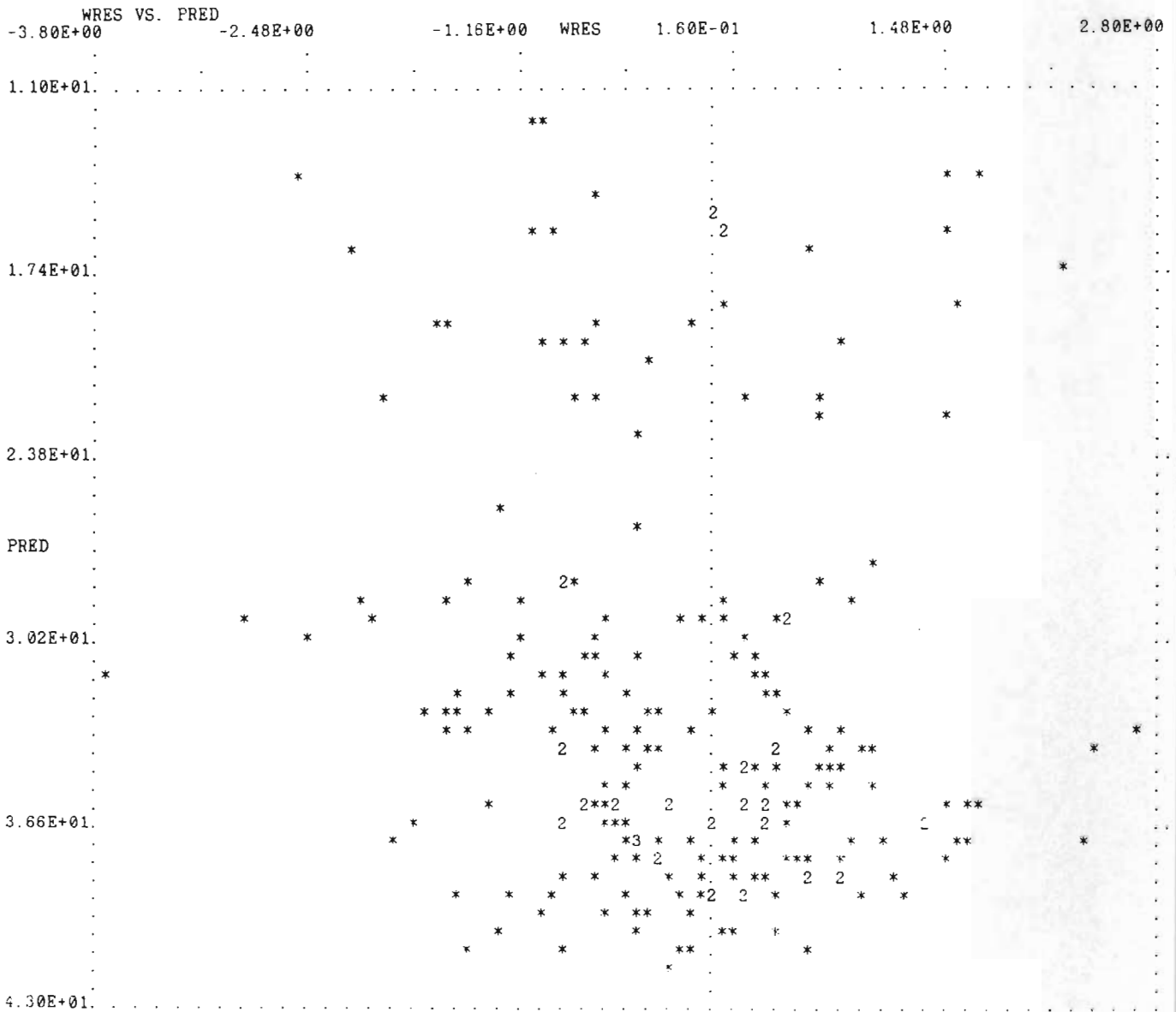
The sigmoid E_{max} model when compared to the E_{max} model produced a DOBF of 12.9 in favour of the former, indicating a significant improvement in data fitting (one degree of freedom, $p<0.0005$) (Table 6.3.). The inter-individual variability in parameter estimates was very similar although with the sigmoid E_{max} model intra-individual variability was marginally better at 16% compared with 19% for the E_{max} model (Table 6.3). Plots of the weighted residuals versus predicted values for these two models are given in Figures 6.6. and 6.7. Although both plots showed a random distribution of points with little to choose between the two, they were both better than the plots from the linear and log-linear models which demonstrated distinct patterns.

NONMEM analysis thus demonstrated that the sigmoid E_{max} model best represented the data as a whole. The E_{max}, IC_{50} and slope (n) estimates were 43.8 ± 2.7 bpm, 32.1 ± 9.6 ng/ml and 0.738 ± 0.074 respectively.

An attempt to fit the sigmoid E_{max} model including inter-individual variance on the slope parameter did not alter the MOF but increased intra-individual variation and caused E_{max} and IC_{50} estimates to become inversely correlated.

Although there was little evidence of disequilibration between inhibition of exercise tachycardia and atenolol plasma concentration, an effort was made, by means of NONMEM, to fit the whole data set to the sigmoid E_{max} model with an effect compartment. Unfortunately, the minimization procedure was unsuccessful for reasons which are not clear at present.

The final step was to assess whether race influenced the E_{max} and IC_{50} values for inhibition of exercise tachycardia with the sigmoid E_{max} model. Each of the following models was therefore tested:

i) E_{max} = P1*P2

ii) IC_{50} = P1*P2

     with P2 in each case being some estimated value in blacks and 1 in whites.

The results are presented in Table 6.4.

Table 6.4. Parameters (SEE) obtained by NONMEM analysis of the sigmoid E_{max} model and then separately incorporating a factor for the influence of race on E_{max} and IC_{50}.

	Sigmoid E_{max}	$E_{max}=$ P1*P2(B)	$IC_{50}=$ P1*P2(B)
E_{max} (bpm)	43.8 (2.74)	42.6*1.05(B) (3.11)	43.7 (2.64)
IC_{50} (ng/ml)	32.1 (9.55)	32.3 (9.67)	35.4*0.848(B) (13.0)
n	0.738 (0.075)	0.741 (0.073)	0.742 (0.069)
MOF	2843.0	2841.0	2841.4
σ_e (CV%)	16	16	16

Including a factor for race, had little influence on the fit of the data, with only small changes seen in either MOF values or parameter estimates (Table 6.4.) Relative to the plain sigmoid E_{max} model, both models with race resulted in increased inter-individual variation of the parameter estimates, E_{max} (from 8 to 13%) and IC_{50} (from 120 to 180%). Inclusion of race increased the standard error of the IC_{50} estimate from 30 to 37%. The E_{max} value in blacks was higher (1.05 times) and the IC_{50} lower (0.848 times) than that of the whites in the present study. These differences were not regarded as significant as they did not explain inter-individual variability.

6.2. DISCUSSION

6.2.2. ELS Estimation in Individuals

As a result of the inappropriate timing of blood samples and heart rate measurements the characterization in individuals, of the relationship between change in EHR and atenolol concentration was not satisfactory. Firstly, model selection was difficult in some volunteers and secondly, the group mean of parameters particularly IC_{50} is probably questionable. Group variability was also likely to be biased upwards because of contributions from not only inter-individual biological sources but also from parameter estimation (Sheiner & Beal 1980a).

The identification of a suitable pharmacodynamic model was a greater problem in those individuals where atenolol concentrations displayed two compartment pharmacokinetic disposition. This was thought to have resulted from the limitation imposed by sensitivity of the atenolol assay and lack of samples after 12 hours.

Nevertheless, in the majority of subjects (11 of 14) a maximum effect was reasonably well defined. The average of 32.9±5.7 bpm (in 11 subjects) was comparable to the mean E_{max} of 36.3 bpm obtained from visual inspection of the data in 16 volunteers (Chapter 4, 4.1.1.2.). As already discussed (Chapter 4, 4.2.1.) this was lower than that demonstrated by some other investigators with the same dose of atenolol (Shanks et al 1977, Brown et al 1976) but was possibly the result of either a lower level of exercise (Leenen et al 1980) or lower atenolol concentrations than those found by Brown et al (1976).

The estimation of a reliable IC_{50} value for the group using a two stage analysis with only 2 to 3 data points per subject was much more difficult. After excluding 3 volunteers because of the unsuitability of the E_{max} model the reliability of results became even more suspect. The

major reason for employing NONMEM was to try to improve the reliability of this estimate. This will be discussed below.

Similar difficulties have been encountered by others when attempting to define the concentration response curve for the influence of (-)-propranolol on exercise tachycardia in individuals (Clifton et al 1990). These authors found that curve fitting by iterative least-squares regression, showed the E_{max} or sigmoid E_{max} models to adequately describe the decrease in heart rate in only 8 of 11 subjects, the linear model in 2 subjects while none of the models appeared suitable in another subject.

In the present study, using two stage analysis, the maximal effect was no different between blacks and whites and IC_{50} showed no significant ethnic differences but large inter-individual variation. This corroborates the findings in Chapter 4, 4.1.1.2. when no racial differences in change in EHR after atenolol were found in the study groups.

6.2.2. NONMEM Estimations

Because of the shortcomings in the design of the study, difficulties were experienced firstly, in selecting an appropriate model and secondly in obtaining reliable parameter estimations particularly IC_{50}, in individual subjects. It is in precisely this situation (few samples available from an individual) when the strength of NONMEM as an alternative approach in analyzing the data is manifested (Sheiner & Beal 1980a, Grasela et al 1986). NONMEM's estimates from pharmacokinetic data analysis have been demonstrated to be at least as good as the standard two stage method (STS) for mean parameters and for residual variability but better for inter-individual variability (Sheiner & Beal 1981). With experimental data from relatively few individuals the latter estimates are however, not acceptable as population values as they are unlikely to be representative of the population as a whole.

The selection of the E_{max} and sigmoid E_{max} models as more appropriate than the linear or log-linear models posed no difficulty. When comparing the E_{max} and sigmoid E_{max} model the latter gave a significantly better description of the data based on MOF. However, the physiological relevance of the value of the slope parameter viz. 0.738±0.074 being less than one in the present study is debatable.

The slope reflects the mechanism of action of a drug as well as its binding to the receptor (Ross & Gilman 1985). Values usually range between 1 and 3 unless there is an all or nothing response (Rowland & Tozer 1989). The relatively shallow slope might be the consequence of timing of measurements rather than a true difference from unity in the slope parameter. The effect might have returned to baseline before a measurement was actually made. It has also been suggested that the in vivo effect on suppression of heart rate may only be discernable when it is 10 to 20% different from baseline. This is due to variation in baseline EHR in response to internal and external stimuli (Rowland & Tozer 1989). This would also tend to make the slope appear less steep as well as difficult to characterise. Therefore it did not seem worthwhile to attach any great significance to the actual value of the slope parameter. A value of 1.3±0.5 has been reported for the slope of the sigmoid E_{max} model as applied to the effect of (-)-propranolol on exercise tachycardia (Clifton et al 1990).

The E_{max} estimate from NONMEM analysis using the sigmoid E_{max} of 43.8±2.7 bpm appears to be on the high side relative to visual assessment where a mean value of 36.3 was obtained (Chapter 4, Table 4.2) as well as the STS method above (32.5 bpm) and even compared to the NONMEM fit using the E_{max} model (37.0±1.83). With hindsight it might have been better to fix the E_{max} value instead of estimating it when fitting the sigmoid E_{max} model.

The NONMEM sigmoid E_{max} model estimate of IC_{50} of 32.1 ± 9.6 ng/ml is much lower than the IC_{50} values of 180 and 300 ng/ml quoted by Wellstein et al (1985b). These values were obtained by re-evaluating the data of Shanks et al (1977) and McAinsh et al (1977) respectively, using fairly complicated calculations involving the time course of clinical effects after oral dosing.

The IC_{50} value would be expected to vary according to the amount of agonist present at the receptors. With exercise tachycardia the endogenous agonist concentration is obviously unknown but would be expected to be related to the degree of exercise. Utilising NONMEM, it should be possible to relate the E_{max} value to baseline tachycardia as an indirect measure of agonist concentration although this was not done in the present study.

Race (black versus white) did not appear to significantly influence the value of either the E_{max} or IC_{50} of atenolol with respect to inhibition of exercise tachycardia. This confirms the observations made in Chapter 4.(4.1.2) where neither the treatment effect on EHR at discrete time points nor the EHR change in AUC with atenolol demonstrated any racial differences.

This apparent lack of any black-white difference in inhibition of exercise tachycardia while a reduced overall effect on supine systolic BP in blacks was noted, should be viewed in relation to a series of recent studies investigating ethnic differences in response to beta-blockade between Chinese and Caucasians.

In response to the perception that substantially lower doses of propranolol are prescribed in China compared to those used in Europe and the USA, a series of experiments in normotensive young men have been conducted. Zhou et al (1989) demonstrated a two fold greater sensitivity to the

negative chronotropic effects of propranolol and a ten fold greater sensitivity to the BP lowering effects of propranolol in the supine position, in Chinese compared to American white men. No difference in lymphocyte beta-receptor density or affinity was found between the two groups. However, the Chinese subjects although having lower blood levels of propranolol, had a 45 percent higher free fraction of propranolol which may have contributed to the increased effect although it did not fully explain it. This ethnic difference in plasma protein binding of propranolol (and some other drugs) was found to be due to reduced levels of α_1-acid glycoprotein in Chinese subjects (Zhou et al 1990).

Because most beta-blockers including propranolol are administered as racemates, another possible explanation for the greater effect at lower total propranolol concentrations in Chinese was that there might be a difference in stereoselective disposition of propranolol between Chinese and Caucasians (Zhou & Wood 1990a). This was found not to be the case because, although plasma concentrations of both (-)- and (+)-propranolol were lower in the Chinese than the white subjects the proportion of the two isomers did not differ.

Since differences in propranolol disposition do not explain the marked ethnic difference in the hypotensive response, a pharmacodynamic explanation for the altered sensitivity in Chinese subjects is currently being sought. A recent abstract (Zhou & Wood 1990b) has reported a significantly greater reduction in plasma renin activity (after exercise) in Chinese compared to Caucasian subjects in response to propranolol. The mean blood pressure reduction in this study correlated with the reduction in plasma renin activity ($r=0.6760$, $p<0.001$.)

Zhou et al (1989) found that the ethnic difference in response to propranolol, between Chinese and Caucasians was 10 fold on supine BP, fourfold on erect BP but only twofold on inhibition of exercise tachycardia. This suggests an amplification of the ethnic difference at a level of BP control either removed from or not involving the chronotropic beta-receptors. Altered effects are probably related to components of the renin-angiotensin-aldosterone system as this latest study suggests (Zhou & Wood 1990b). Clifton et al (1990) have reported significantly greater potency of propranolol in reducing exercise heart rate compared with its effects on left ventricualr systolic function. Concentration-response curves for the various effects of beta-blockers in an individual are clearly different and could be expected to vary independently across populations (Zhou et al 1989) and possibly with different disease states.

From the results in the present study, it would seem that in normotensive subjects, black-white differences in beta-blocker responses are not as dramatic as white-Chinese differences. The black-white differences may however, be accentuated in hypertensive subjects. Hypertensive subjects differ from normotensive subjects in having increased peripheral vascular resistance. A very interesting recent publication has demonstrated that the apparent abnormality in ß-receptor mediated arterial vasodilatation (inability to respond to volume expansion) in patients with hypertension can be corrected by low sodium intake (Naslund et al 1990). Although this study involves the vasodilatory beta$_2$-receptor the role of sodium in receptor regulation points to the involvement of the renin-angiotensin yet again.

Thus careful assessment of the concentration-response relationship of beta-blockers using supine BP (where ethnic differences appear greatest) in reasonably matched

hypertensive black and white subjects should prove worthwhile. Provided baseline noise is minimised, it should be feasible to model for the delay in BP responses using effect compartment modelling as has been done for the slowly developing effect of ergotamine on peripheral arteries (Tfelt-Hansen & Paalzow 1985). This would be particularly useful if response or lack of it could be related to physiological variables (eg. PRA, sodium handling) across a spectrum of values. This could assist in identifying physiological variables predictive of response in order to individualise antihypertensive treatment in a cost-effective manner.

6.3. CONCLUSION

Due to methodological problems in the sampling design of the study, curve fitting of inhibition of EHR data in response to atenolol was particularly problematic in individuals. The simultaneous use of data from all volunteers in the programme NONMEM, proved more satisfactory in obtaining IC_{50} values.

Pharmacokinetic-dynamic modelling corroborated the findings in Chapter 4, that race did not significantly influence the reduction in exercise tachycardia induced by atenolol in normotensive young men.

Assessment of the BP response differences between hypertensive blacks and whites in a rigorous experimental protocol in order to define the dose-concentration-response relationship with effect compartment modelling should yield interesting results. In addition response variation could be related to physiological variables possibly predictive of response.

REFERENCES

Abernethy DR, Gutkowska J, Winterbottom LM. Effects of amlodipine, a long acting dihydropyridine calcium antagonist in aging hypertension: Pharmacodynamics in relation to disposition. Clin Pharmacol Ther 1990; 48:76-86

Abila B, Wilson JF, Marshall RW and Richens A. The tremorolytic action of B-adrenoceptor blockers in essential, physiological and isoprenaline induced tremor is mediated by B-adrenoceptors located in a deep peripheral compartment. Br J Clin Pharmacol 1985; 20:369-376

Åblad B, Borg KO, Johnsson G, Regårdh C-G and Sölvell L. Combined pharmacokinetic and pharmacodynamic studies on alprenolol and 4-∝hydroxyalprenolol in man. Life Sci 1974; 14:693-704

Abson CP, Levy LM and Eyherabide G. Once-Daily atenolol in hypertensive Zimbabwean Blacks. S Afr Med J 1981; 60:47-48

Achong MR, Piafsky KM and Ogilvie RI. Duration of cardiac effects of timolol and propranolol. Clin Pharmacol Ther 1976; 19(2):148-152

Aderounmu AF. The relative importance of genetic and environmental factors in hypertension in black subjects. Clin Exp Hypertens 1981; 3(4):597-621

Ahlquist RP. A study of adrenotropic receptors. Amer J Physiol 1948; 153:586-599

Alderman EL, Davies RO, Crowley JJ. Dose response effectiveness of propranolol for the treatment of angina pectoris. Circulation 1975; 51:964-975

Amery A, Lijnen P, Fagard R, Reybrouck T. Atenolol and plasma renin concentration in hypertensive patients. Postgrad Med J 1977a; 53(Supp3):116-119

Amery A, de Plaen J-F, Lijnen P, McAinsh J and Reybrouck T.Relationship between blood level of atenolol and pharmacologic effect. Clin Pharmacol Ther 1977b; 21(6): 691-699

Ariëns EJ, Simonis AM and Van Rossum JM. Drug-receptor interaction: interaction of one or more drugs with one receptor system. In: Ariëns EJ ed. Molecular Pharmacology New York: Academic Press 1964: 119-269

Arnold JMO, McDevitt DG. Reflex vagal withdrawal and the haemodynamic response to intravenous isoproterenol in the presence of beta-antagonists. Clin Pharmacol Ther 1986; 40(2):199-208

Ausems ME, Hug CC, Stanski D and Burm AG. Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. Anesthesiology 1986; 65:362-373

Ausems ME, Vuyk J, Hug CC and Stanski D. Comparison of a computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 1988; 68:851-861

Baber NS, Dawes DM. B-adrenoreceptor blocking drugs and diuretics in hypertension. Br J Clin Pharmacol 1979; 7:404-405

Barber HE, Hawksworth GM, Petrie JC, Rigby JW, Robb OJ, Scott AK. Pharmacokinetics of atenolol and propranolol in young and elderly subjects. Br J Clin Pharmacol 1981; 11:118-119

Beal SL, Sheiner LB. NONMEM USERS GUIDE. Division of Clinical Pharmacology, University of California, San Francisco. 1979

Beal SL, Boeckmann AJ, Sheiner LB. NONMEM USERS GUIDE Part VI. Division of Clinical Pharmacology, University of California, San Francisco. 1985

Bengtsson C, Johnsson G and Regardh CG. Plasma levels and effects of metoprolol on blood pressure and heart rate in hypertensive patients after an acute dose and between two doses during long term treatment. Clin Pharmacol Ther 1975; 17:400-408

Birkenhäger WH, de Leeuw DW, Webster A et al. Therapeutic effects of beta-adrenoreceptor blocking agents. Ergeb Inn Med Kinderheilkd 1977; 39:117-134

Black JW, Stephenson JS. Pharmacology of a new adrenergic beta-receptor blocking compound (Nethalide). Lancet 1962; 2:311-314

Black JW, Crowther AF, Shanks RG, Smith LH, Dornhorst AC. A new adrenergic beta-receptor antagonist. Lancet 1964; 1:1080-1081

Boeckmann AJ, Sheiner LB, Beal SL. NONMEM USERS GUIDE, Part V. Introductory Guide. Division of Clinical Pharmacology, University of California, San Francisco. 1990

Bourne HR, Roberts JM. Drug receptors and pharmacodynamics. In: Katzung BG, ed. Basic Clinical Pharmacology. 3rd Edition. Norwalk, Connecticut:Appleton & Lange, 1987:9-22

Breckenridge A. Which beta Blocker? Brit Med J 1983; 286:1085-1088

Brockmeier D, Hajdu P, Henke W, Mutschler E, Palm D et al. Penbutolol:Pharmacokinetics, effect on exercise tachycardia and in vitro inhibition of radioligand binding. Eur J Clin Pharmacol 1988; 35:613-623

Brown HC, Carruthers SG, Johnston GD, Kelly JC, McAinsh J, McDevitt DG, Shanks RG. Clinical pharmacologic observations on atenolol a beta-adrenoceptor blocker. Clin Pharmacol Ther 1976; 20: 524-534

Brown JE, McLeod AA, Shand DG. Evidence for cardiac B_2-adrenoceptors in Man. Clin Pharmacol Ther 1983; 33(4):424-428

Buck ML, Wiest D, Gillette PC, Trippel D, Krull and O'Neal W. Pharmacokinetics and pharmacodynamics of atenolol in children. Clin Pharmacol Ther 1989; 46(6):629-633

Bühler FR, Laragh JH, Baer L, Vaughan ED, Brunner HR. Propranolol inhibition of renin secretion : A specific approach to diagnosis and treatment of renin dependent hypertensive disease. N Engl J Med 1972; 287: 1209-1214

Bühler FR, Burkart F, Lutold BR, Kung M, Marbet G and Pfisterer M. Antihypertensive beta-blocking action as related to renin and age : a pharmacologic tool to identify pathologic mechanisms in essential hypertension. Am J Cardiol 1975; 36:635-669

Bühler FR, Marbet G, Patel U and Burkart F. Renin-suppressive potency of various beta adrenergic blocking agents at supine rest and during upright exercise. Clin Sci Mol Med 1975b; 48:615-645

Bühler FR, Hulthen L, Kiowski W and Bolli P. Greater antihypertensive efficacy of the calcium channel inhibitor verapamil in older and low renin patients. Clin Sci 1982; 63:439s-442s

Bührer M, Maitre PO, Hung O, Stanski DR. Electro-encephalographic effects of benzodiazepines. I. Choosing an electroencephalographic parameter to measure the effect of midazolam on the central nervous system. Clin Pharmacol Ther 1990a; 48:544-554

Bührer M, Maitre PO, Crevoisier C, Stanski DR. Electro-encephalographic effects of benzodiazepines. II. Pharmacodynamic modeling of the electroencephalographic effects of midazolam and diazepam. Clin Pharmacol Ther 1990b; 48:555-567

Carruthers SG, Twum-Barima Y. Measurement of partial agonist activity of pindolol. Clin Pharmacol Ther 1981; 30(5):581-586

Chidsey C, Pine M, Favrot L, Smith S, Leonetti G, Morselli P and Zanchetti A. The use of drug concentration measurements in studies of the therapeutic response of propranolol. Postgrad Med J 1976; 52(Suppl 4): 26-32.

Chrysant SG, Danisa K, Kem DC et al. Racial differences in pressure, volume and renin interrelationships in essential hypertension. Hypertension 1979; 1:136-141

Clifton GD, Pennell AT, Harrison MR. Pharmacodynamics of propranolol on left ventricular function: Assessment by doppler echocardiography. Clin Pharmacol Ther 1990; 48:431-438

Coelho JB, Dvornik D, Mullane JF, Kaufman J, Simon J, Krantz KD, Lee TY, Perdue HS and Weidler D. Dynamics of propranolol dosing schedules. Clin Pharmacol Ther 1983; 34(4):440-447

Colantonio D, Casale R, Desiate P, Giandomenico G, Bucci V et al. Short-term effects of atenolol and nifedipine on atrial natriuretic peptide, plasma renin activity and plasma aldosterone in patients with essential hypertension. J Clin Pharmacol 1991; 31:238-242

Colburn WA. Simultaneous pharmacokinetics and pharmacodynamic modeling. J Pharmacokinet Biopharm 1981; 9(3):367-387

Colburn WA. Pharmacokinetic/dynamic modeling. What it is! J Pharmacokinet Biopharm 1987; 15(5):545-555

Collste P, Haglund K and Von Bahr C. Plasma levels and effects of metoprolol after single and multiple oral doses. Clin Pharmacol Ther 1980; 27(4):441-449

Coltart DJ, Shand DG. Plasma propranolol levels in the quantitative assessment of beta-adrenergic blockade in man. BMJ 1970; 3:731-734

Coltart DJ, Gibson D, Shand DG. Plasma propranolol levels associated with suppression of ventricular ectopic beats. BMJ 1971; 1:490-491

Connell JMC. Essential hypertension-rational pharmacotherapy. Trends Pharmacol Sci 1986; 412-418

Conway FJ, Fitzgerald JD, McAinsh J, Rowland DJ, Simpson WT. Human pharmacokinetics and pharmacodynamic studies on atenolol a new cardioselective B-adrenoceptor blocking drug. Br J Clin Pharmacol 1976; 3:267-272

Corbo M, Wang PR, Li JK-J, Chien YW. Effect of propranolol on the myocardial contractility of normotensive and spontaneously hypertensive rabbits : relationship of pharmacokinetics and pharmacodynamics. J Pharmacokinet Biopharm 1989; 17(5):551-570

Cruikshank JM. The clinical importance of cardioselectivity and lipophilicity. Am Heart J 1980; 100:160-178

Cruikshank JK and Beevers DG. Epidemiology of hypertension: blood pressure in blacks and whites. Clin Sci 1982; 62:1-6

Cubberley R. Labetalol as monotherapy in hypertensive black patients. J Clin Hypertens 1985; 4:304-314

Dahlström BE, Paalzow LK, Segre G and Agren AJ. Relationship between morphine pharmacokinetics and analgesia. J Pharmacokinet Biopharm 1978; 6(1):41-53

Dale HH. On some physiological actions of ergot. J Physiol 1906; 34:163-206

Dayer P, Leemann T, Marmy A and Rosenthaler J. Interindividual variation of B-adrenoreceptor blocking drugs, plasma concentrations and effect : Influence of genetic status on behaviour of atenolol, bopindolol and metoprolol. Eur J Clin Pharmacol 1985; 28:149-153

Deering AH, Harron DWG, Riddell JG, Shanks RG. Effect of acute administration of propranolol and atenolol on baroreflex function in normal man. Eur J Clin Pharmacol 1988; 35:607-612

Dillon N, Sydney C, Kelly J and O'Malley K. Age and beta adrenoceptor mediated function. Clin Pharmacol Ther 1980; 27(6):769-772

Dimenäs ES, Dahlöf CG, Heibel B, Moore RG, Olofsson BK, Westergren GE, Lücker PW. Subjective symptoms and pharmacokinetics/dynamics of metoprolol CR in elderly subjects - a comparison with atenolol. Eur J Clin Pharmacol 1990; 38:571-578

Distler A, Klim JH, Cordes V, Philipp T and Wolff HP. Sympathetic responsiveness and antihypertensive effects of beta-receptor blockade in essential hypertension. Am J Med 1978; 64:446-457

Dixon MS, Thomas P, Sheridan DJ. A randomized double-blind study of bisoprolol versus atenolol in mild to moderate essential hypertension. Eur J Clin Pharmacol 1990; 38:21-24

Dornhorst AC, Robinson BF. Clinical pharmacology of a beta-adrenergic blocking agent (Nethalide). Lancet 1962; 2:314-316

Douglas-Jones AP, Cruikshank JM. Once daily dosing with atenolol in mild to moderate hypertension. BMJ 1976; 1:990-991

Drayer DE. Pharmacodynamic and pharmacokinetic differences between drug enantiomers in humans : An overview. Clin Pharmacol Ther 1986; 40(2):125-131

Driscoll MS, Ludden TM, Casto DT, Littlefield LC. Evaluation of theophylline pharmacokinetics in a paediatric population using mixed effects models. J Pharmacokinet Biopharm 1989; 17:141-168

Duchin KL, Vukovich RA, Dennick LG, Groel JT and Willard DA. Effects of nadolol ß-blockade on blood pressure in hypertension. Clin Pharmacol Ther 1980; 27:57-63

Esler M, Zweifler A, Randall O and DeQuattro V. Patho-physiologic and pharmacokinetic determinants of the antihypertensive response to propranolol. Clin Pharmacol Ther 1977; 22(3):299-308

Ezra D, Abdelrahim M, Esposito R, Dubois A and Peck CC. Simultaneous pharmacokinetic-pharmacodynamic modeling of cimetidine in man. Clin Pharmacol Ther 1985; 37(2):194

Fagan TC, Gourley L, Lee J, Sawyer P, Corneux C, Blackley D, Walle T, Walle UK and Gaffney T. Hypotensive and haemodynamic effects of single oral and intravenous doses of propranolol. Clin Pharmacol Ther 1982a; 31(2):223

Fagan TC, Walle T, Walle UK, Hurwitz R, Conradi E, Privitera P, Webb J, Gaffney T. Time course of antihypertensive effects of oral propranolol. Clin Pharmacol Ther 1982b; 31(2):224

Fagard R. Thesis: Studies on the renin-angiotensin-aldosterone system. Katholieke Universiteit-Leuven, Leuven. 1978

Fitzgerald JD, Rubin R, Smedstad KG, Roberts R and McAinsh J. Studies on the pharmacokinetics and pharmacodynamics of atenolol in man. Eur J Clin Pharmacol 1978; 13:81-89

Flamenbaum W, Weber M, McMahon F et al. Monotherapy with labetalol compared with propranolol: differential effects by race. J Clin Hypertens 1985; 1:1-13

Forrester W, Lewis RP, Weissler AM and Wilke TA. The onset and magnitude of the contractile response to commonly used glycosides in normal subjects. Circulation 1974; 49:517-521

Frank S, Somani SM, Kohnle M. Effect of exercise on propranolol pharmacokinetics. Eur J Clin Pharmacol 1990; 39:391-394

Frohlich ED, Tarazi RC, Dustan HP, Page IH. The paradox of beta-adrenergic blockade in hypertension. Circulation 1968; 37:417-423

Fujimura A, Kumagai Y, Sugimoto K, Nakashima H, et al. Circadian influence on effect of propranolol on exercise-induced tachycardia in healthy subjects. Eur J Clin Pharmacol 1990; 38:133-137

Fuller RW, Vallance PJT. Atenolol reduces blood pressure and FEV_1 in normal subjects. Br J Clin Pharmacol 1982; 14:445-446

Fuseau E and Sheiner LB. Simultaneous modeling of pharmacokinetics and pharmacodynamics with a non-parametric pharmacodynamic model. Clin Pharmacol Ther 1984; 35:733-741

Galeazzi RL, Benet LZ, Sheiner LB. Relationship between the pharmacokinetics and pharmacodynamics of procainamide. Clin Pharmacol Ther 1976; 20(3):278-289

Gengo F, Huntoon L, Fagan S. Simultaneous pharmacodynamics of multiple actions of metoprolol. Clin Pharmacol Ther 1985; 37(2):198

Gengo FM, Ermer JC, Carey C, Kalonares GC, McHugh WB. The relationship between serum concentrations and central nervous system actions of metoprolol. J Neurol Neurosurg Psych 1985a; 48:101-106

Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York:Marcel Dekker, Inc. 1982

Gibson DG. Pharmacodynamic properties of beta-adrenergic receptor blocking drugs in man. Drugs 1974; 7:8-38

Giles TD, Sander GE, Kaneish A, Quiroz AC. Time-dependent antihypertensive effect of carteolol - a beta-adrenoceptor antagonist with partial agonist activity. Clin Pharmacol Ther 1984; 35:301-306

Giudicelli JF, Richer C, Chauvin M, Idrissi N and Berdeau A. Comparative B-adrenoreceptor blocking effects and pharmacokinetics of penbutolol and propranolol in man. Br J Clin Pharmacol 1977; 4:135-140

Grasela TH, Antal JA, Townsend RJ, Smith RB. An evaluation of population pharmacokinetics in therapeutic trials. Part 1. Comparison of methodologies. Clin Pharmacol Ther 1986; 39:605-612

Grell GAC, Forrester TE, Alleyne GAO. Comparison of the effectiveness of a beta-blocker (atenolol) and a diuretic (chlorthalidone) in black hypertensive patients. South Med J 1984; 77(12):1524-1528

Gugler R, Krist R, Raszinski H, Höffgen K and Bodem G, Comparative pharmacodynamics and plasma levels of B-adrenoreceptor blocking drugs. Br J Clin Pharmacol 1980; 10:337-343

Guyton. Textbook of Medical Physiology. WB Saunders, Philadelphia 1986; 150-164

Haefeli EW, Vozeh S, Ha H-R, Follath F. Comparison of the pharmacodynamic effects of intravenous and oral propafenone. Clin Pharmacol Ther 1990; 48:245-254

Hager WD, Pieniaszek HJ, Perrier D, Mayersohn M and Goldberger RN. Assessment of beta blockade with propranolol. Clin Pharmacol Ther 1981; 30(3):283-290

Hall WD, Kong W. Hypertension in blacks: nonpharmacologic and pharmacologic therapy. In: Cardiovascular diseases in blacks. Ed. Saunders E. F A Davis Company, Philadelphia 1991; 157-169

Hansson L, Zweifler AJ, Julius S, Ellis CN. Propranolol therapy in essential hypertension observations on predictability of therapeutic response. Int J Clin Pharmacol Ther Toxicol 1974; 10:78-89.

Harron DWG, Balnave K, Kinney CD, Wilson R, Russel CJ, Shanks RG. Effects on exercise tachycardia during forty eight hours of a series of doses of atenolol, sotalol and metoprolol. Clin Pharmacol Ther; 1981; 29(3):295-302

Harry JD. The demonstration of atenolol as a beta-adrenoceptor blocking drug in man. Postgrad Med J 1977; 53(Suppl3):65-69

Harry JD, Knapp MF, Linden RJ, Stoker JB, Newcombe C. Effects of 4 beta-adrenoceptor blocking drugs on blood pressure and exercise heart rate in hypertension. Eur J Clin Pharmacol 1979; 10(2):131-141.

Hespel P, Lijnen P, Vanhees L, Fagard R and Amery A. B-Adrenoceptors and the regulation of blood pressure and plasma renin during exercise. J Appl Physiol 1986; 60(1) 108-113

Hildreth C, Saunders E. Hypertension in blacks: Clinical overview. In: Cardiovascular Disease in Blacks. Ed: Saunders E. FA Davis Company, Philadelphia. 1991: 85-114

Hinderling PH, Schmidlin O and Seydel JK. Quantitative relationships between structure and pharmacokinetics of beta-adrenoceptor blocking agents in man. J Pharmacokinet Biopharm 1984; 12(3):263-287

Hitzenberger G. Plasma concentration and antihypertensive effect of B-receptor blockers. Cardiology 1979; 64 (Suppl 1): 14-19

Holford NHG, Sheiner LB. Understanding the dose-effect relationship. Clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet 1981; 6:429-453

Holford NHG, Coates PE, Guentert TW, Riegelman S, Sheiner LB. The effect of quinidine and its metabolites on the electro-cardiogram and systolic time intervals: concentration-effect relationships. Br J Clin Pharmacol 1981; 11:187-195

Holford NHG, Sheiner LB. Kinetics of pharmacologic response. Pharmacol Ther 1982; 16:143-166

Holland OB, Fairchild C. Renin classification for diuretic and beta-blocker treatment of black hypertensive patients. J Chronic Dis 1982; 35(3):179-182

Hollifield JW, Sherman K, Zwagg RV and Shand DG. Proposed mechanism of propranolol's antihypertensive effect in essential hypertension. N Eng J Med 1976; 295:68-73

Hollifield JW, Sherman K, Staton P. Age, race and sex as a determinant of successful antihypertensive therapy. Prev Med 1978; 7:88

Holtzman JL, Finley D, Johnson B, Berry DA and Sirgo A. The effects of single-dose atenolol, labetalol and propranolol on cardiac and vascular function. Clin Pharmacol Ther 1986; 40(3):268-273

Hull CJ, Van Beem H, McLeod K, Sibbald A and Watson MJ. A pharmacodynamic model for pancuronium. Br J Anaesth 1978; 50:1113-1123

Hull CJ. Pharmacokinetics and pharmacodynamics. Br J Anaesth 1979; 51:579-594

Humphreys GS and Delvin DG. Ineffectiveness of propranolol in hypertensive Jamaicans. BMJ 1968; 2:601-603

Hypertension Detection and Follow up Program Cooperative Group. Five year findings of the hypertension detection and follow up program 1. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979a; 242(23):2562-2571

Hypertension Detection and Follow Up Program Cooperative Group. Five year findings of the hypertension detection and follow up program. II. Mortality by race, sex and age. JAMA 1979b; 242(23):2572-2577

Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics in patients with chronic pain. Clin Pharmacol Ther 1987; 41:392-401

Inturrisi CE, Portenoy RK, Max MB, Colburn WA, Foley KM. Pharmacokinetic-pharmacodynamic relationships of methadone infusions in patients with cancer pain. Clin Pharmacol Ther 1990; 47:565-577

Ishizaki T, Oyama Y, Suganuma T, Sasaki T, Nakaya H, Shibuya T and Sato T. A dose ranging study of atenolol in hypertension: fall in BP and plasma renin activity, B-blockade and steady state pharmacokinetics. Br J Clin Pharmacol 1983; 16:17-25

Iyun AO, Lennard MS, Tucker GT and Woods HF. Metoprolol and debrisoquin metabolism in Nigerians : Lack of evidence for polymorphic oxidation. Clin Pharmacol Ther 1986; 40(4): 387-394

Jennings GL, Bobik A, Fagan ET, Korner PI. Pindolol pharmacokinetics in relation to time course of inhibition of exercise tachycardia. Br J Clin Pharmacol 1979; 7:245-256

Johnsson G, Regårdh CG. Clinical Pharmacokinetics of B-adrenoceptor blocking drugs. Clin Pharmacokinet 1976; 1:233-263

Jose AD. Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man. Am J Cardiol 1966; 18:476-478

Joubert PH, Venter CP and Wellstein A. Ethnic differences in response to beta-blockade : Fact or Artefact? A study with bisoprolol and propranolol. Eur J Clin Pharmacol 1988 34:363-368

Jun HW, Hayes SL, Vallner JJ, Honigberg IL, Rojos AE, Stewart JJ. Plasma level profiles and clinical response of Penbutolol after 3 different single oral doses in man. J Clin Pharmacol 1979; 415-423

Kaila T, Huupponen R, Karhuvaara S, Havula P, Scheinin M, Iisalo E. ß-blocking effects of timolol at low plasma concentrations. Clin Pharmacol Ther 1991; 49:53-58

Kaplan NM. The present and future use of beta-blockers. Drugs 1983;25:1-4

Kelman AW, Whiting B. Modelling of drug response in individual subjects. J Pharmacokinet Biopharm 1980a; 8:115-130

Kelman AW, Sumner DJ, Lonsdale M, Lawrence JR and Whiting B. Comparative pharmacokinetics and pharmacodynamics of cardiac glycosides. Br J Clin Pharmacol 1980b; 10:135-143

Kendall MJ, Maxwell RJ, Sandberg A, Westergren G. Controlled release metoprolol. Clinical pharmacokinetic and therapeutic implications. Clin Pharmacokinet 1991; 21:319-330

Kirch W, Köhler H, Mutschler E and Schäfer M. Pharmacokinetics of atenolol in relation to renal function. Eur J Clin Pharmacol 1981; 19:65-71

Kirch W and Görg KG. Clinical Pharmacokinetics of Atenolol - A review. Eur J Drug Metab Pharmacokinet 1982; 7(2):81-91

Kirch W, Spahn H, Ohnhaus EE, Köhler H, Heinz U, Mütschler E. The influence of inflammatory disease on the clinical pharmacokinetics of atenolol and metoprolol. Biopharm Drug Dispos 1983; 4:73-80

Klein C, Gerber JG, Gal J and Nies AS. Beta-adrenergic receptors in the elderly are not less sensitive to timolol. Clin Pharmacol Ther 1986; 40(2):161-164

Kleinboesem CH, Van Brummelen P, Van Harten J, Danhof M and Breimer DD. Nifedipine : Influence of renal function on pharmacokinetic/haemodynamic relationship. Clin Pharmacol Ther 1985; 37:563-574

Kleinbloesem CH, Van Brummelen P and Bremmer DD. Nifedipine-relationship between pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 1987; 12:12-29

Kostis JB, Lacy CR, Krieger SD and Cosgrove NM. Atenolol, nadolol and pindolol in angina pectoris on effort : Effect of pharmacokinetics. Am Heart J 1984; 108(4) 1131-136

Krediet AJ, Dunning AJ and Offerhaus I. Relationship of propranolol pharmacokinetics to antihypertensive effect and B-adrenergic blockade in the treatment of hypertension. Eur J Clin Pharmacol 1980; 18:391-394

Kroboth PD, Schmith VD, Smith RB. Pharmacodynamic modelling. Application to new drug development. Clin Pharmacokinet 1991; 20:91-98

Kumanyika S, Adams-Campbell L. Obesity, diet and psychosocial factors contributing to cardiovascular disease in blacks. In: Cardiovascular Disease in Blacks. Ed: Saunders E. FA Davis Company, Philadelphia. 1991; 47-73

Kunka RL, Wong YY, Andersen RL, Haack DG. Steady state fluctuation and variability of betaxolol and atenolol plasma levels. Ther Drug Monit 1989; 11:523-527

Lalonde RL, Straka RJ, Pieper JA, Botorff MB, Mirvis DM. Propranolol pharmacodynamic modeling using unbound and total concentrations in healthy volunteers. J Pharmacokinet Biopharm 1987; 15(6):569-582

Lalonde RL, O'Rear TL, Wainer IW, Drda KD, Herring VL, Botorff MI. Labetalol pharmacokinetics and pharmacodyanmics:evidence of stereoselective disposition. Clin Pharmacol Ther 1990; 48:510-519

Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown TG. Differentiation of receptor systems activated by sympathomimetic amines. Nature 1967; 214: 597-598

Langer SZ. Presynaptic receptors and their role in the regulation of transmitter release. Br J Pharmacol 1977; 60:481-487

Laragh JH, Baer L, Brunner HR, Bühler FR, Sealey JE and Vaughan ED. Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. Am J Med 1972; 52:633-647

Laragh JH. Vasoconstriction-volume for analysis for understanding and treating hypertension : The use of renin and aldosterone profiles. Am J Med 1973; 55:261-272

Laragh JH. Two forms of vasoconstriction in systemic hypertension. Am J Cardiol 1987; 60:82G-93G

Leenen FHH, Coenen CHM, Zonderland M, Maas AHJ. Effects of cardioselective and nonselective beta-blockade on dynamic exercise performance in mildly hypertensive men. Clin Pharmacol Ther 1980; 28;12-21

Leenen FHH, Boer P, Dorhout Mees EJ. Antihypertensive effect of propranolol at rest and during exercise and degree of beta-blockade.Clin Pharmacol Ther 1982; 43(2):242

Lennard MS, Tucker CT and Woods HF. The polymorphic oxidation of B-adrenoreceptor antagonists. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1986; 11:1-17

Lehtonen A, Kanto J and Kleimola T. Plasma concentrations of propranolol in patients with essential hypertension. Eur J Clin Pharmacol 1977; 11:155-157

Leonetti G, Mayer G, Morganti A et al. Hypotensive and renin-suppressing activities of propranolol in hypertensive patients. Clin Sc Mol Med 1975; 48:491-499

Leonetti G, Terzoli L, Bianchini C, Sala C and Zanchetti A. Time-course of the anti-hypertensive action of atenolol : Comparison of response to first dose and to maintained oral administration. Eur J Clin Pharmacol 1980; 18:365-374

Leopold G, Ungethüm W, Papst J, Simane Z, Buhring KU and Wiemann H. Pharmacodynamic profile of bisoprolol a new B_1-selective adrenoceptor antagonist. Br J Clin Pharmacol 1986; 22:293-300

Levesque H, Richard MO, Fresel J, Gancel A, Moore N, Courtois H. Evolution of atenolol kinetics when hypothyroidism is corrected. Eur J Clin Pharmacol 1990; 38:185-188

Lewis CE, Raczynski JM, Oberman A, Cutter GR. Risk factors and natural history of coronary heart disease in blacks. In: Cardiovascular Diseases in Blacks. Ed. Saunders E. F A Davis Company, Philadelphia. 1991; 29-45

Lewis RV, Lennard MS, Jackson PR, Tucker GT, Ramsay LE and Woods HF. Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol 1985; 19:329-333

Lijnen P, Amery AK, Fagard RH, Reybrouck TM. Relative significance of plasma renin activity and concentration in physiologic and pathophysiologic conditions. Angiology 1978; 29:354-366

Lijnen PJ, Amery AK, Fagard RH, Reybrouck TM, Moerman EJ and De Schaepdryver AF. The effects of B-adrenoceptor blockade on renin, angiotensin, aldosterone and catecholamines at rest and during exercise. Br J Clin Pharmacol 1979; 7:175-181

Lowenthal DT, Saris SD, Packer J, Haratz A, Conry K. Mechanisms of action and clinical pharmacology of beta-adrenergic blocking drugs. Am J Med 1984; 77(4A):119-127.

Maling TJB, Ferrara A, Mucklow JC, Reid JL, Hamilton CA and Dollery CT. Blood pressure and plasma noradrenaline during single high dose beta adrenoceptor blockade. Eur J Clin Pharmacol 1979; 15:375-379

Mancia G, Ferrari A, Pomidossi G et al. Twenty-four-hour blood pressure variability in untreated hypertension and during antihypertensive treatment by once daily nadolol. Am Heart J 1984; 108(4): 1078-1083

Man in't Veld AJ, Schalekamp MA. Effects of 10 different beta-adrenoceptor antagonists on haemodynamics, plasma renin activity, plasma norepinephrine in hypertension : The key role of vascular resistance changes in relation to partial antagonist activity. J Cardiovasc Pharmacol 1983; 5(Suppl 1):s30-s45

Marshall AJ, Barritt DW, Harry JD. Dose response and frequency of administration of atenolol in essential hypertension - once daily treatment with beta-blockade. Postgrad Med J 1977; 53(suppl 3):168-172.

Mason WD, Winer N. Pharmacokinetics of oxprenolol in normal subjects. Clin Pharmacol Ther 1976; 20(2):401-412

Mason WD, Winer N, Kochak G, Cohen I, Bell R. Kinetics and absolute bioavailability of atenolol. Clin Pharmacol Ther 1979; 25(4):408-415

Mason WD, Kochak G, Winer N, Cohen I. Effect of exercise on renal clearance of atenolol. J Pharm Sci 1980; 69:344-345

M'Buyamba-Kabangu JR. THESIS: Blood pressure and hypertension in African Blacks. Katholieke Universiteit Leuven 1986

M'Buyamba-Kabangu JR, Lepira B, Fagard R, Lijnen P, Ditu M, Tshiani KA, Amery A. Relative potency of a beta-blocking and a calcium entry blocking agent as antihypertensive drugs in black patients. Eur J Clin Pharmacol 1986; 29:523-527

McAinsh J. Clinical pharmacokinetics of Atenolol. Postgrad Med J 1977; 53(Supp 3):74-78

McAinsh J, Barber NS, Smith R and Young J. Pharmacokinetics and pharmacodynamic studies with long-acting propranolol. Br J Clin Pharmacol 1978; 6:115-121

McAinsh J, Holmes BF, Smith S, Hood D and Warren D. Atenolol kinetics in renal failure. Clin Pharmacol Ther 1980; 28(3): 302-309

McAinsh J, Simpson WT, Holmes BF, Young J and Ellis SH. Bioavailability of atenolol formulations. Biopharm Drug Dispos 1980; 1:323-332

McDevitt DG, Shand DW. Plasma concentration and time-course of beta-blockade due to propanolol. Clin Pharmacol Ther 1975; 18:708-713

McDevitt DG, Frisk-Holmberg M, Hollifield JW and Shand DW. Plasma binding and the affinity of propranolol for a beta-receptor in man. Clin Pharmacol Ther 1976; 20(2):152-157

McDevitt DG. The assessment of B-adrenoceptor blocking drugs in man. Br J Clin Pharmacol 1977; 4:413-425

McDevitt DG. Adrenoceptor blocking drugs : clinical pharmacology and therapeutic use. Drugs 1979; 17:267-288

Melander A, Stenbury P, Liedholm H, Schirsten B and Watkin-Boll. Food induced reduction in bioavailability of atenolol. Eur J Clin Pharmacol 1979; 16:327-330

Meredith PA, Kelman AW, Elliott HL, Reid JL. Pharmacokinetic and pharmacodynamic modelling of trimazosin and its major metabolite. J Pharmacokinet Biopharm 1983; 11(4):323-335

Moran NC, Perkins ME. Adrenergic blockade of the mammalian heart by a dichloroanalogue of isoproterenol. J Pharmacol Exp Ther 1958; 124:223-237

Moser M, Guyther JR, Finnerty et al. Report of the joint national committee on detection evaluation and treatment off high blood pressure. JAMA 1977; 237:255-261

Moser M, Lunn J. Comparative effects of pindolol and hydrochlorothiazide in Black hypertensive patients. Angiology 1981; 32:561-566

Moser M. Stepped-care treatment of hypertension. The rationale for an empirical approach. Postgrad Med J 1983; 73(1) 199-210

Mullane JF, Kaufman J, Dvornik D and Coelho J. Propranolol dosage, plasma concentration, and beta blockade. Clin Pharmacol Ther 1982; 32(6)692-700

Müller FO, Hundt HKL, Bromley PA, Torres J and Vanderbeke O. Single and divided doses of Penbutolol. Clin Pharmacol Ther 1979; 25(5):528-535

Mungall DR, Ludden TM, Marshall J, Hawkins DW, Talbert RL, Crawford MH. Population pharmacokinetics of racemic warfarin in adult patients. J Pharmacokinet Biopharm 1985; 13:213-227

Myers MG, Lewis GRJ, Steiner J and Dollery CT (1976). Atenolol in hypertension. Clin Pharmacol Ther 1976; 19(5):502-507

Myers MG, Thiessen JJ. Metoprolol kinetics and dose response in hypotensive patients. Clin Pharmacol Ther 1980; 27(6):756-762

Naslund T, Silberstein DJ, Merrell WJ, Nadeau JH, Wood AJJ. Low sodium intake corrects abnormality in ß-receptor mediated arterial vasodilatation in patients with hypertension: Correlation with ß-receptor function in vitro. Clin Pharm Ther 1990; 48:87-95

Nies AS, Shand DG. Clinical pharmacology of propranolol. Circulation 1975; 52:6-15

Ochs HR, Greenblatt DJ, Arendt RM, Schäfer-Korting and Mutschler E. Single dose kinetics of oral propranolol, metoprolol, atenolol and sotalol : Relation to lipophilicity. Arzneimmittelforschung 1985; 35:1580-1582

O'Connor PC, Arnold JMO, Brown AN, Francis RJ, Finch MB, Galloway DB, Harron DWG, McDevitt DG and Shanks RG. Human pharmacokinetic and pharmacodynamic studies on RO 31-1118, a new ß-adrenoceptor antagonist. Br J Clin Pharmacokinet 1985; 19:319-327

Okubo S, Matsuoka, Yamada H, Handa K, Kusama S. Effect of intravenous administration of pindolol on haemodynamics: comparison of normotensive and hypertensive groups. Current Therapeutic Research 1981; 30(6):929-936.

Olanoff LS, Walle T, Cowart TD, Walle UK, Oexmann MJ and Conradi EC. Food Effects on propranolol systemic and oral clearance; Support for a blood flow hypothesis. Clin Pharmacol Ther 1986; 40(4):408-414

Oli JM. Open clinical trial of Timolol in Nigerians with Hypertension. Current Therapeutic Research 1982; 31(5)93-98

Olkkola KT, Schwilden H. Use of a pharmacokinetic-dynamic model for automatic feedback control of atracurium. Eur J Clin Pharmacol 1989; 36(Suppl):A183

Oosterhuis B, Braat MCP, Roos CM, Wemer J and Van Boxtel CJ. Pharmacokinetic-pharmacodynamic modeling of terbutaline bronchodilation in asthma. Clin Pharmacol Ther 1986; 40:469-475

Oosterhuis B, Van Boxtel CJ. Kinetics of drug effects in man. Ther Drug Monit 1988; 10:121-132

Opie LH. Basis for cardiovascular therapy with beta-blocking agents. Am J Cardiol 1983; 52:2D-9D.

Paterson JW and Dollery CT. Effect of propranolol in mild hypertension. Lancet 1966; 2:1148-1450

Paalzow LK. Integrated pharmacokinetic-dynamic modeling of drugs action on the CNS. Drug Metab Rev 1984; 15(1+2):383-400

Peck C, Sheiner LB and Nichols AL. The problem of choosing weights in nonlinear regression analysis of pharmacokinetic data. Drug Metab Rev 1984; 15 (1+2):133-148

Pedersen EB, Kornerup HJ, Pedersen OL, Andreasen F and Bjerregaard P. Correlation between propanolol in plasma and urine, renin-aldosterone system and blood pressure in essential hypertension. Eur J Clin Pharmacol 1981; 20:251-258

Perucca E, Pickles H, Richens A. Effect of atenolol, metoprolol and propranolol on isoproterenol-induced tremor and tachycardia in normal subjects. Clin Pharmacol Ther 1981; 29(4):425-433

Pimenta J, Pereira CB. Effects of atenolol in patients with reciprocating supraventricular tachycardia. Clin Cardiol 1986; 9:191-195

Pine M, Favrot L, Smith S, McDonald K and Chidsey CA. Correlation of plasma propranolol concentration with therapeutic response in patients with angina pectoris. Circulation 1975; 52:886-893

Powell CE, Slater IH. Blocking of inhibitory adrenergic receptors by a dichloro-analogue of isoproterenol. J Pharmacol Exp Ther 1958; 122:480-

Prichard BNC. Hypotensive action of pronethalol. BMJ 1964a; 1:1227-1228

Prichard BNC, Gillam PMS. Use of propranolol (Inderal) in treatment of hypotension. BMJ 1964b; 2:725-727

Prichard BNC. The treatment of hypertension by beta adrenergic blocking drugs. Angiologica 1966; 3:318-329.

Prichard BNC and Gillam PMS. Propranolol in hypertension. Am J Cardiol 1966; 18:387-391

Prichard BNC and Gillam PMS. Treatment of hypertension with propranolol. BMJ 1969; 1:7-15

Prichard BNC. Beta adrenergic receptor blocking drugs in angina pectoris. Drugs 1974; 7:55-84.

Prichard BNC. Beta-adrenoceptor-blocking agents in the management of hypertension. Cardiology 1979; 64(suppl 1):44-87

Quarterman CP, Kendall MJ and Welling PG. Plasma levels and negative chronotropic effect of metoprolol following single doses of a conventional and sustained-release formulation. Eur J Clin Pharmacol 1979; 15:97-103

Rabin HR, Urtasun C, Partington D et al. High dose metronidazole: pharmacokinetics and bioavailability using an IV preparation and application of its use as a radiosensitizer. Cancer Treat Rev 1980; 64:1087-1095

Rasmussen S, Rasmussen K. Influence of metoprolol alone and in combination with a thiazide diuretic on blood pressure, plasma volume, extracellular volume and glomerular filtration rate in essential hypertension. Eur J Clin Pharmacol 1979; 15:305-310

Reeves PR, Barnfield DJ, Longshaw S, McIntosh DAD and Winrow MJ. Disposition and metabolism of atenolol in animals. Xenobiotica 1978a; 8(5):305-311

Reeves PR, McAinsh J, McIntosh DAD and Winrow MJ. Metabolism of atenolol in man. Xenobiotica 1978b; 8(5):313-320

Regårdh CG. Pharmacokinetic aspects of some beta-adrenoceptor blocking drugs. Acta Med Scand 1982; 212(S665):49-60

Rescigno A, Beck JS. The use and abuse of models. J Pharmacokinet Biopharm 1987; 15:327-345

Richardson DW, Freund J, Gear AS, Mauck HP and Preston LW. Effect of propranolol on elevated arterial blood pressure. Circulation 1968; 37:534-542

Riddell JG, Harron DWG and Shanks RG. Clinical pharmacokinetics of beta-adrenoceptor antagonists - An update. Clin Pharmacokinet 1987; 12:305-320

Rigby JW, Scott AK, Hawksworth GM, Petrie JC. A comparison of the pharmacokinetics of atenolol, metoprolol, oxprenolol and propranolol in elderly hypertensive and young healthy subjects. Br J Clin Pharmacol 1985; 20:327-331

Ritschel WA. Compilation of Pharmacokinetic parameters of B-adrenergic blocking agents. Drug Intelligence and Clinical Pharmacy 1980; 14:746-755

Riva E, Farina PL, Sega R, Tononi G, Bastain W, McAinsh J. Pharmacokinetics of atenolol in hypertensive subjects with and without co-administration of chlorthalidone. Eur J Clin Pharmacol 1980; 17:333-337

Robertson JIS. State-of-the-art review: Beta blockade and the treatment of hypertension. Drugs 1983; 25(Suppl 2):5-11.

Robinson BF, Epstein ES, Beiser GD and Braunwald E. Control of heart rate by the autonomic nervous system. Circ Res 1966; 19:400-411

Rosendorff C. Drug therapy of hypertension. In: Hypertension and rheumatic heart disease in black South Africans. Eds. Milne FJ, Sareli P. Helm Publishing Company, Johannesburg 1988; 27-28

Ross E, Gilman AG. Pharmacodynamics: mechanisms of drug action and the relationship between concentration and effect. In: The Pharmacological Basis of Therapeutics. Eds: Gilman AG, Goodman LS, Rall TW, Murad F. Macmillan Publishing Company, New York. 1985: 181-214

Routledge PA and Shand DG. Clinical pharmacokinetics of propranolol. Clin Pharmacokinet 1979; 4:73-90

Rowland M, Tozer P. Clinical Pharmacokinetics:Concepts and Applications. 2nd ed. Philadelphia:Lea & Fabiger. 1989

Rubin PC, Scott PJW, McLean K, Pearson A. Ross D and Reid JL. Atenolol disposition in young and elderly subjects. Br J Clin Pharmacol 1982; 13:235-237

Rutledge DR, Cardozo L, Steinberg JD. Racial differences in drug response : isoproterenol on heart rate in healthy males. Pharm Res 1989; 6(2):182-185

Rutledge DR, Wallace A, Melchior, Touchette M. Racial differences in baseline cyclic adenosine monophosphate concentrations per million T-lymphocytes and protein concentration. Ther Drug Monit 1990; 12:541-546

Salako LA, Falase AO, Aderounmu AF. Comparative beta-adrenoceptor blocking effects and pharmacokinetics of propranolol and pindolol in hypertensive Africans. Clin Sci 1979; 57:393s-396s

Salvetti A, Sassano P, Poli L, Pedrinelli R and Arzilli F. The effect of beta-adrenergic blockade on patterns of urinary sodium excretion, blood pressure and plasma renin activity in patients with essential and renovascular hypertension. Eur J Clin Inv 1977; 7:331-336

Sambol NC, Sheiner LB. Population dose versus response of betaxolol and atenolol: A comparison of potency and variability. Clin Pharmacol Ther 1990; 49:24-31

Sandler G, Clayton GA. Clinical evaluation of practolol, a new cardioselective beta-blocking agent in angina pectoris. BMJ 1970; 2:399-402

Seedat YK, Reddy J. Propranolol in the South African non-white hypertensive patient. S Afr Med 1971; 45:284-285

Seedat YK, Stewart-Wynne E. Clinical experiences with prindolol (VISKEN) in the therapy of hypertension. S Afr Med J 1972; 46:1524-1526.

Seedat YK. Treatment of hypertension with the aid of beta adrenergic blocking agents. S Afr Med J 1975; 49:846-848

Seedat YK. Race, environment and blood pressure:the South African experience. J Hypertens 1983; 1(1):7-12

Seedat YK. Trial of atenolol and chlorthalidone for hypertension in black South Africans. BMJ 1980; 281:1241-1243

Segre G. Kinetics of interactions between drugs and biological systems. Il Farmaco 1968; 23:907-918

Serlin MJ, Orme LE, Baber NS, Sibeon RG, Laws E and Breckenridge A. Propranolol in the control of blood pressure: a dose response study. Clin Pharmacol Ther 1980; 27:586-592

Shand DG. State-of-the-art: comparative pharmacology of the beta-adrenoceptor blocking drugs. Drugs 1983; 25(Suppl 2):92-99.

Shanks RG, Kelly JG, Carruthers SG and McDevitt DG. Correlation of exercise heart rate with blood levels of atenolol after oral and intravenous administration. Postgrad Med J 1977; 53(Suppl3):70-73

Shanks CA, Avram MJ, Fragen RJ and O'Hara D. Pharmacokinetics and pharmacodynamics of vecuronium administered by bolus and infusion during halothane or balanced anaesthesia. Clin Pharmacol Ther 1987; 42(4):459-464

Sheiner LB, Rosenberg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J pharmacokinet Biopharm 1977; 5:445-479

Sheiner LB, Stanski D, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine.Clin Pharmacol Ther 1979; 25(3):358-371

Sheiner LB, Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters. I. Michaelis-Menten model: routine clinical pharmacokinetic data. J Pharmacokinet Biopharm 1980; 8:553-571

Sheiner LB, Beal SL. Analysis of nonexperimental data. In Drug Absorption and Disposition. Ed. Albert KS. American Pharmaceutical Association, Washington. 1980a: 31-49

Sheiner LB, Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters. II. Biexponential model and experimental pharmacokinetic data. J Pharmacokinetic Biopharm 1981; 9:635-651

Sheiner LB, Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters. III. Monoexponential model. Routine clinical pharmacokinetic data. J Pharmacokinet Biopharm 1983; 11:303-319

Sheiner LB, Beal SL. Pharmacokinetic parameter estimates from several least squares procedures: superiority of extended least squares. J Pharmacokinet Biopharm 1985; 13:185-201

Sheiner LB. Commentary to pharmacokinetic/pharmacodynamic modeling:What it is! J Pharmacokinet Biopharm 1987; 15(5):553-555

Shepherd AMM, Kwan CM, Brodie CL, Jamieson MJ. Determination of α-adrenergic blocking potency. Clin Pharmacol Ther 1991; 49:69-77

Shinebourne E, Fleming J and Hamer J. Effects of beta-adrenergic blockade during exercise in hypertensive and ischaemic heart disease. Lancet 1967; 2:1217-1220

Simpson FO. Beta-adrenergic receptor blocking drugs in hypertension. Drugs 1974; 7:85-105.

Singh BN, Williams FM, Whitlock RM, Collett J and Chew C. Plasma timolol levels and systolic time intervals. Clin Pharmacol Ther 1980; 28:159-166

Smolen VF. Theoretical and computational basis for drug bioavailability determinations using pharmacological data I. General considerations and procedures. J Pharmacokinet Biopharm 1976; 4:337-353

Stanski DR, Hudson RJ, Homer TD, Saidman LJ, Meathe E. Pharmacodynamic modeling of thiopental anesthesia. J Pharmacokinet Biopharm 1984; 12:223-240

Stein M, Kilfeather S, O'Malley K. Racial differences in alpha-2 (AAR) and beta-2 adrenoceptor (BAR) function. Br J Clin Pharmacol 1987; 24:251P-252P

Steinberg SF and Bilezikian JP. Total and free propranolol levels in sensitive and resistant patients. Clin Pharmacol Ther 1983; 33(2):163-171

Stokes GS, Weber MA and Thornell IR. Beta-blockers and plasma renin activity in hypertension. BMJ 1974; 1:60-62

Stoll RW, Cavanaugh JH and MacLeod CM. Beta blocking effect of single oral doses of carteolol. Clin Pharmacol Ther 1981; 30(5):605-610

Svendsen TL, Hartling O, Trap Jensen J. Immediate haemodynamic effects of different adrenergic receptor blocking drugs in healthy volunteers. A comparison between propranolol, practolol, pindolol and ICI 189,406. Eur J Clin Pharmacol 1979; 15:223-228

Svendsen TL, Hartling O, Trap-Jensen J, McNair A, Bliddal T. Adrenergic beta-receptor blockade: Haemodynamic importance of intrinsic sympathomimetic activity at rest. Clin Pharmacol Ther 1981; 29:711-718

Svendsen TL, Trap-Jensen J, Carlsen JE, McNair A. Immediate central haemodynamic effects of five different beta-adrenoceptor blocking agents, acebutolol, atenolol, pindolol, practolol and propranolol in patients with ischaemic heart disease. Am Heart J 1985; 109 (5):1145-1150.

Tallarida RJ. Receptor theories and quantitative effect versus dose-concentration relationship. Drug Metab Rev 1984; 15:345-363

Tarazi RC, Dustan HP. Beta-adrenergic blockade in hypotension. Am J Cardiol 1972; 29:633-640

Tfelt-Hanssen P, Paalzow LK. Intramuscular ergotamine: Plasma levels and dynamic activity. Clin Pharmacol Ther 1985: 37:29-35

Thadani U. Beta blockers in hypertension. Am J Cardiol 1983; 52(9):10D-15D

Thibonnier M, Holford NHG, Upton RA, Blumer CD and Williams RL. Pharmacokinetic-pharmacodynamic analysis of unbound disopyramide directly measured in serial plasma samples in man. J Pharmacokinet Biopharm 1984; 12(6):559-573

Touyz RM, Milne FJ, Seftel HC, Reinach SG. Magnesium, calcium, sodium and potassium status in normotensive and hypertensive Johannesburg residents. S Afr Med J 1987; 72:377-381

Traub YM, Rabinov M, Rosenfeld J and Treuherz S. Elevation of serum potassium during beta-blockade: absence of relationship to the renin-aldosterone system. Clin Pharmacol Ther 1980;28(6):765-768

Uccellini DA, Raymond K, Morgan DJ. Influence of intravenous infusion duration on the tissue drug concentration profile. J Pharmacokinet Biopharm 1986; 14:323-334

Ulrych M. Frohlich ED, Dustan HP, Page IH. Immediate haemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive man. Circulation 1968; 37:411-415

Unadkat JD, Bartha F, Sheiner LB. Simultaneous modeling of pharmacokinetics and pharmacodynamics with nonparametric kinetic and dynamic models. Clin Pharmacol Ther 1986; 40(1) 86-93

Van Baak MA. Influence of exercise on the pharmacokinetics of drugs. Clin Pharmacokinet 1990; 19:32-43

Van den Brink G, Baer P, Van Asten P, Dorhout Mees EJ and Geyskes GG. One and three doses of propranolol a day in hypertension. Clin Pharmacol Ther 1980; 27(1):9-15

Van Rossum JM, Burgers JPT. Quantitative relationships between dynamics and kinetics of drugs:A systems approach. Drug Metab Rev 1984; 15(1+2):365-382

Van Zwieten PA, Timmerman PB. Comparison between the acute haemodynamic effects and brain penetration of atenolol and metoprolol. J Cardiovasc Pharmacol 1979; 1:85-96

Vaughan Williams EM, Hassan MO, Floras JS, Sleight P, Jones JV. Adaptation of hypertensives to treatment with cardioselective and non-selective beta-blockers. Absence of correlation between bradycardia and blood pressure control and reduction in slope of the QT/RR relation. Br Heart J 1980; 44:473-487

Venter CP, Joubert PH. Ethnic differences in beta-1-adrenoceptor sensitivity. S Afr Med J 1982; 62(27):849-850

Venter CP, Joubert PH. Ethnic differences in response to B_1-adrenoceptor blockade by propranolol. J Cardiovasc Pharmacol 1984a; 6:361-364

Venter CP, Joubert PH, Strydom WJ. Ethnic differences in response to pharmacological denervation of the heart. IRCS Med Sci 1984b; 12:963-964

Venter CP, Daya S, Joubert PH, Strydom WJ. Ethnic differences in human lymphocyte cyclic AMP production after isoprenaline stimulation and propranolol blockade. Br J Clin Pharmacol 1985; 19:197-190

Venter CP, Joubert PH, Van Reenen OR. Ethnic differences in the relative contributions of intrinsic heart rate and the autonomic nervous system to the generation of heart rate during exercise. IRCS Med Sc 1986; 14:944-945

Vestal RE, Wood AJJ and Shand DG. Reduced ß-adrenoceptor sensitivity in the elderly. Clin Pharmacol Ther 1979; 26:181-186

Veterans Administration Cooperative Study Group on Antihypertensive Agents. Propranolol in the treatment of essential hypertension. JAMA 1977; 237:2303-2310

Veterans Administration co-operative Study Group on Antihypertensive Agents. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. I. Results of short term titration with emphasis on racial differences in response. JAMA 1982a; 248(16):1996-2003

Veterans Administration Cooperative Study Group on Antihypertensive Agents. Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension II. Results of long term therapy. JAMA 1982b; 248(16):2004-2011

Veterans Administration Cooperative Study Group on Antihypertensive agents. Efficacy of nadolol alone and combined with bendroflumethiazide and hydralazine for systemic hypertension. Am J Cardiol 1983; 52:1230-1237

Volpe M, Trimarco B, Ricciardell, Cuocolo A, Veniero AM, De Luca N and Condorelli M. Predictability of antihypertensive efficacy of selective β_1-blockers. Clin Pharmacol Ther 1983; 34(6):758-763

Von Bahr C, Collste P, Frisk-Holmberg M, Haglund K, Jorfelt L, Orme M, Östman J and Sjögvist F. Plasma levels and effects of metoprolol on blood pressure adrenergic beta receptor blockade and plasma renin activity in essential hypertension. Clin Pharmacol Ther 1976; 20:130-137

Wadworth AN, Murdoch D, Brogden RN. Atenolol. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. Drugs 1991; 42:468-510

Wan SH, Koda RT and Maronde RF. Pharmacokinetics, pharmacology of atenolol and effect of renal disease. Br J Clin Pharmacol 1979; 7:569-574

Weber MA, Priest RT, Ricci BA et al. Low-dose diuretic and beta-adrenoceptor blockers in essential hypertension. Clin Pharmacol Ther 1980; 28:149-158

Weiner N. Drugs that inhibit adrenergic nerves and block adrenergic receptors. The Pharmacological Basis of Therapeutics. New York:MacMillan Publishing Company, 1985; 181-214

Wellstein A, Palm D, Pitschner HF and Belz GG. Receptor binding of propranolol is the missing link between plasma concentration kinetics and the effect-time course in man. Eur J Clin Pharmacol 1985a; 29:131-147

Wellstein A, Palm D, Belz GG and Pitschner HF. Receptor binding characteristics and pharmacokinetic properties as a tool for the prediction of clinical effects of beta blockers. Arzneimmitelforschung 1985b; 35:2-6

Whiting B, Holford NHG and Sheiner LB. Quantitative analysis of the disopyramide concentration-effect relationship. Br J Clin Pharmacol 1980; 9:67-75

Wieselgren I, Lundborg P, Sandberg A, Olofsson B and Bergstrand R. Pharmacokinetic and pharmacodynamic evaluation of metoprolol controlled release (CR) 50mg in young subjects. Eur J Clin Pharmacol 1989; 36(Supp):A161

Wilson TW, Firor WB, Johnson GE, Holmes GI, Tsianco MC, Huber PB and Davies RO. Timolol and propranolol: bioavailability, plasma concentrations and beta blockade. Clin Pharmacol Ther 1982; 32(6):676-685

Wong L, Nation RL, Chiou WL and Mehta PK. Plasma concentrations of propranolol and 4 hydroxypropranolol during chronic oral propranolol therapy. Br J Clin Pharmacol 1979; 8:163-167

Wood AJJ, Carr K, Vestal RE, Belcher S, Wilkinson GR and Shand DG. Direct measurement of propranolol bioavailability during accumulation to steady state. Br J Clin Pharmacol 1978; 6:345-350

Wood AJ. Pharmacologic differences between beta-blockers. Am Heart J 1984; 108(4):1070-1076

Woods KL, Linton SP, Kendall MJ, Faragher EB and Grieve RJ. Exercise responses of healthy subjects in the evaluation of cardioselectivity of B-blockers. Eur J Clin Pharmacol 1979; 15:229-233

Yee Y-G, Rubin P, Blaschke TF. Atenolol determination by HPLC and fluorescence detection. J Chromatogr 1979; 171:357-362

Zacest R, Koch-Weser J. Relation of propranolol levels to ß-blockade during oral therapy. Pharmacology 1972; 7:178-184

Zahler R, Wachtel P, Jatlow P and Byck R. Kinetics of drug effect by distributed lags analysis: an application to cocaine. Clin Pharmacol Ther 1982; 31(6):775-782

Zhou H-H, Koshakji RP, Silberstein DJ, Wilkinson GR, Wood JJ. Racial differences in drug response. Altered sensitivity to and clearance of propranolol in men of Chinese descent as compared with American whites. N Eng J Med 1989; 320:565-570

Zhou H-H, Wood JJ. Differences in stereoselective disposition of propranolol do not explain sensitivity differences between white and Chinese subjects: Correlation between the clearance of (-)- and (+)-propranolol. Clin Pharmacol Ther 1990a; 47:719-723

Zhou H-H, Wood JJ. Propranolol suppressed exercise induced rise in renin more in Chinese than Caucasians. Clin Pharm Ther 1990b; 47:141

Zhou H-H, Adedoyin A, Wilkinson GR. Differences in plasma binding of drugs between Caucasians and Chinese subjects. Clin Pharmacol Ther 1990; 48:10-17

APPENDIX 1
Appendix to Chapter 3

Table A1.1. Details of age, weight, height and pretreatment supine and erect blood pressure and resting heart rate (RHR) of black volunteers.

	Age (yrs)	Weight (kg)	Height (cm)	Supine BP* (mm Hg)	Erect BP* (mm Hg)	RHR* (bpm)
MN	25	70	180	130/90	120/90	61
CM	27	63	170	122/65	118/85	80
VL	21	70	173	120/68	110/75	59
AP	21	63	175	103/68	103/80	62
ZN	24	48	154	100/53	103/65	77
DS	23	68	173	98/63	103/65	64
NM	24	80	175	110/65	115/75	73
AK	20	80	175	105/60	105/73	76
Mean	23.1	67.8	172	111/60	110/76	69
SD	2.4	10.3	7.8	12/9	7/9	8.4
SEM	0.8	3.7	2.7	4/3	3/3	3.0
CV%	10.4	15.2	4.5	10/15	6/12	12.2

Table A1.2. Details of age, weight, height and pretreatment erect and supine blood pressure and resting heart rate (RHR) for white volunteers.

	Age (yrs)	Weight (kg)	Height (cm)	Supine BP* (mm Hg)	Erect BP* (mm Hg)	RHR* (bpm)
NV	22	73	177	105/60	118/68	78
HA	23	79	173	110/63	110/68	75
BB	21	71	178	115/73	120/78	61
ACA	21	70	180	118/73	115/78	57
NF	23	70	166	116/71	116/77	83
JFI	20	77	180	118/63	120/63	79
JFO	20	67	182	103/63	103/73	63
ACL	20	70	181	103/63	103/60	62
Mean	21.3	72.1	177.0	111/66	113/71	69.8
SD	1.3	4.0	5.3	6/5	7/7	10.0
SEM	0.5	1.4	1.9	2/2	3/3	3.5
CV%	6.1	5.5	2.8	5/8	6/10	14.3

* Mean of 2 baseline readings

Table A1.3. Workloads and pretreatment exercise heart rates (EHR) for blacks and whites.

BLACKS	Workload (W)	EHR* (bpm)	WHITES	Workload (W)	EHR* (bpm)
MN	141	137	NV	211	138
CM	123	154	HA	176	145
VL	194	130	BB	176	133
AP	123	133	ACA	176	128
ZN	106	147	NF	141	160
DS	176	142	JFI	159	129
NM	159	139	JFO	123	137
AK	159	149	ACL	123	130
Mean SD SEM CV%	148 29.8 10.5 20.1	141 8.2 2.9 5.8	Mean SD SEM CV%	161 30.4 10.7 18.9	138 10.7 3.8 7.8

*Mean of two baseline readings

Table A1.4. Order in which volunteers received placebo (P) and atenolol treatment (A).

BLACKS	Phase 1	Phase 2	WHITES	Phase 1	Phase 2
MN	P	A	NV	P	A
CM	A	P	HA	A	P
VL	P	A	BB	P	A
AP	A	P	ACA	A	P
ZN	P	A	NF	P	A
DS	A	P	JFI	A	P
NM	P	A	JFO	P	A
AK	A	P	ACL	A	P

Table A1.5. Inter-assay coefficients of variation (%) for seeded control samples analysed over a 3 day period.

Concentration	10	39	161	321	1282
Day 1	11.2 12.1	43.9 39.1	161 161	334 318	1315 1257
Day 2	10.7 12.3	43.9 43.8	176 166	338 –	1402 1305
Day 3	9.2 9.2	40.7 36.0	159 154	– –	1195 1242
Mean SD CV%	10.8 1.36 12.6	41.2 3.2 7.8	162.8 7.7 4.6	330 10.6 3.1	1282 80 6.2

APPENDIX 2
Appendix to Chapter 4

Table A2.1. Resting heart rate values in black and white individuals after placebo administration.

| TIME (hours) | RESTING HEART RATE AFTER PLACEBO (beats/minute) | | | | | | | | | | | | | | | |
| | BLACKS | | | | | | | | WHITES | | | | | | | |
	MN	CM	VL	AP	ZN	PB	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	64	83	55	63	69	60	70	66	83	73	66	56	82	74	64	60
0.3	N/A	78	N/A	77	90	N/A	N/A	N/A	84	N/A	68	N/A	N/A	64	N/A	69
0.5	82	82	79	76	78	83	74	90	87	72	68	68	99	75	80	62
1.0	65	75	84	72	87	94	78	88	83	64	67	57	77	71	70	71
1.5	82	65	75	76	73	77	76	83	80	60	69	58	70	75	54	79
2.0	80	73	69	76	73	80	77	98	86	77	73	65	79	65	80	74
3.0	75	73	76	72	75	77	87	84	87	75	76	65	69	59	65	82
4.0	57	69	59	68	74	86	67	93	80	69	60	63	67	68	69	66
5.0	65	64	53	73	66	59	75	86	78	61	57	71	64	67	66	81
6.0	57	80	55	69	65	65	75	81	81	64	72	60	65	75	83	78
8.0	72	71	56	68	69	65	62	81	73	64	67	57	67	68	74	69
10.0	60	68	59	55	56	63	73	66	88	62	57	68	57	74	63	66
12.0	60	75	57	54	65	67	61	72	72	64	63	63	58	96	76	67
24.6	60	67	56	71	66	59	66	99	79	62	64	50	72	69	66	61
30.0	60	77	72	72	67	60	62	73	78	83	74	61	85	69	60	73
36.0	56	77	70	66	71	57	60	79	75	63	92	65	69	79	60	68

A6

Table A2.2. Resting heart rate in black and white individuals after atenolol administration.

TIME (hours)	RESTING HEART RATE AFTER ATENOLOL (beats/minute)															
	BLACKS								WHITES							
	MN	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	57	81	58	60	84	66	81	86	75	72	55	65	84	80	65	59
0.3	74	79	78	N/A	N/A	N/A	80	99	68	N/A	64	64	72	N/A	66	63
0.5	70	68	79	68	74	78	76	99	72	76	N/A	62	63	76	53	58
1.0	60	65	82	68	81	82	75	99	64	69	77	57	65	63	57	64
1.5	69	60	70	66	73	72	68	83	67	62	66	58	62	64	69	58
2.0	60	58	66	68	72	74	66	84	74	57	66	59	56	67	64	75
3.0	49	60	74	54	69	63	71	83	65	57	62	56	58	56	67	64
4.0	48	52	68	65	63	67	74	77	58	57	58	57	54	58	54	61
5.0	48	52	64	64	60	62	73	70	69	56	56	55	58	58	49	63
6.0	57	53	63	58	63	76	66	70	64	56	63	58	65	75	54	76
8.0	52	74	63	69	63	63	51	71	72	54	55	52	65	77	54	72
10.0	63	54	76	54	54	57	53	61	55	55	54	54	56	68	53	63
12.0	48	55	69	54	57	68	63	73	66	58	55	57	59	71	67	63
24.0	69	56	57	62	65	54	50	86	77	49	48	52	61	79	68	63
30.0	62	63	68	57	62	63	61	74	70	57	57	65	66	69	61	61
36.0	60	63	57	60	54	61	61	77	70	63	70	72	59	81	60	65

Table A2.3. Mean resting heart rate (beats/minute) after placebo and atenolol administration in the black and white groups (n=8 in each group).

TIME (hours)	AVERAGE RESTING HEART RATE (beats/minute)			
	BLACKS		WHITES	
	Placebo	Atenolol	Placebo	Atenolol
0.0	66.2	71.6	69.8	69.4
0.5	80.5	76.5	76.4	57.5
1.0	80.4	76.5	70.0	64.5
1.5	75.9	70.1	68.5	63.3
2.0	78.2	68.5	74.9	64.8
3.0	77.4	65.4	72.3	60.6
4.0	71.6	64.3	67.8	57.1
5.0	67.6	61.6	68.1	58.0
6.0	68.4	63.3	72.3	63.9
8.0	68.0	63.3	67.4	62.6
10.0	62.5	59.0	66.9	57.3
12.0	63.9	60.9	69.9	62.0
24.0	68.0	62.4	65.4	62.1
30.0	67.9	63.8	72.9	63.3
36.0	67.0	61.6	71.4	67.5

Table A2.4. Area under the Curve (AUC) for resting heart rate from 0 to 12 hours (beats/minute.hr) after placebo and atenolol and the difference between placebo and atenolol.

Subjects	AUC (0-12 hours)(bpm.hr)		
Blacks	Placebo	Atenolol	Difference
MN	797.00	669.55	127.45
CM	864.40	716.20	148.20
VL	742.00	828.85	-86.85
AP	802.80	737.00	65.80
ZN	822.40	766.50	55.90
DS	844.50	802.00	42.50
NM	861.75	767.75	94.00
AK	971.00	898.30	72.70
Whites			
NV	970.40	782.45	187.95
HA	791.00	694.25	96.75
BB	785.45	712.45	73.00
ACA	756.25	673.20	83.05
NF	806.25	726.65	79.60
JFI	861.60	817.25	44.35
JFO	852.50	687.80	164.70
ACL	861.45	797.15	64.30

Table A2.5. Exercise heart rate in black and white individuals after placebo administration.

| TIME (hours) | EXERCISE HEART RATE AFTER PLACEBO (beats/minute) | | | | | | | | | | | | | | | |
| | BLACKS | | | | | | | | WHITES | | | | | | | |
	NM	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	146	151	134	129	142	146	136	140	138	140	136	125	161	124	133	126
0.2	N/A	155	137	140	149	154	140	140	139	138	133	133	145	129	134	132
0.4	N/A	N/A	140	145	147	159	142	150	N/A	N/A	141	N/A	160	129	129	137
0.5	148	146	138	142	149	163	152	146	138	144	152	141	164	123	132	129
0.8	N/A	N/A	143	138	150	165	146	150	N/A	N/A	N/A	139	N/A	125	131	135
1.0	141	152	144	152	152	168	144	152	135	146	144	143	162	129	130	128
1.5	146	150	144	155	155	169	152	151	140	142	144	139	162	115	131	128
2.0	144	150	143	150	155	173	150	157	142	144	147	147	166	125	134	133
3.0	140	150	137	149	155	162	154	155	136	146	144	140	161	133	136	133
4.0	140	153	136	151	152	159	158	151	140	147	144	133	159	129	148	131
5.0	136	152	135	155	150	153	140	155	140	140	143	130	160	133	128	134
6.0	140	154	133	155	153	155	140	157	140	146	147	131	165	137	133	133
8.0	140	152	132	151	144	140	140	155	139	142	143	133	156	135	136	132
10.0	140	149	137	150	138	146	142	150	140	140	144	128	155	138	128	143
12.0	148	160	136	158	151	146	146	150	137	140	144	138	155	136	128	132
24.0	132	152	136	140	143	150	140	163	140	144	146	129	154	134	139	126
30.0	136	147	135	148	141	155	151	144	136	152	140	145	159	127	132	129
36.0	132	160	133	148	149	149	151	154	142	142	142	146	154	142	147	146

Table A2.6. Exercise heart rate in black and white individuals after atenolol administration.

TIME (hours)	EXERCISE HEART RATE AFTER ATENOLOL (beats/minute)															
	BLACKS								WHITES							
	NM	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	130	160	125	136	152	138	142	157	138	150	129	131	158	133	140	134
0.2	111	111	99	112	111	116	113	120	98	111	96	101	113	100	103	100
0.4	N/A	N/A	100	115	113	121	115	124	N/A	115	N/A	N/A	N/A	105	100	N/A
0.5	109	115	103	110	115	121	116	126	104	120	105	101	116	107	101	105
0.8	112	N/A	106	113	116	126	115	128	N/A	N/A	105	105	116	109	102	105
1.0	110	115	106	115	115	127	115	130	105	115	108	103	116	108	103	107
1.5	118	114	110	121	121	129	116	130	106	115	109	105	116	107	104	107
2.0	117	118	109	122	124	129	117	133	108	120	109	107	120	108	103	113
3.0	118	116	111	124	119	136	120	133	108	120	108	110	122	106	108	111
4.0	115	116	111	126	122	132	118	133	109	120	108	111	121	103	108	115
5.0	119	116	110	126	122	133	123	130	109	123	111	112	123	115	106	121
6.0	127	118	112	132	125	143	124	131	112	124	115	111	131	115	110	125
8.0	128	128	113	130	124	142	119	135	114	127	117	110	130	117	112	123
10.0	125	128	115	131	128	145	118	139	116	122	119	114	140	122	111	130
12.0	125	135	122	136	129	138	130	147	124	125	125	116	140	127	119	128
24.0	140	144	126	136	141	142	129	148	127	123	124	117	142	133	128	128
30.0	148	134	132	136	140	161	144	154	133	132	130	141	149	132	130	150
36.0	145	151	135	152	149	144	140	155	140	136	135	141	148	138	143	144

A12

Table A2.7. Mean exercise heart rate (beats/minute) after placebo and atenolol administration in the black and white groups (n=8 in each group).

TIME (hours)	AVERAGE EXERCISE HEART RATE (beats/minute)			
	BLACKS		WHITES	
	Placebo	Atenolol	Placebo	Atenolol
0.0	140.5	142.5	135.4	139.1
0.2	145.0	111.6	135.4	102.8
0.4	147.2	114.7	139.2	106.7
0.5	148.0	114.4	140.4	107.4
0.8	150.6	116.6	132.5	107.0
1.0	150.6	116.6	139.6	108.1
1.5	152.8	119.9	137.6	108.6
2.0	152.8	121.1	142.3	111.0
3.0	150.3	122.1	141.1	111.6
4.0	150.0	121.6	141.4	111.9
5.0	147.0	122.4	138.5	115.0
6.0	148.4	126.5	141.5	117.9
8.0	144.3	127.4	139.5	121.8
10.0	144.0	128.6	139.5	118.8
12.0	149.4	132.8	138.8	125.5
24.0	144.5	138.3	139.0	127.8
30.0	144.6	143.6	140.0	137.1
36.0	147.0	146.4	145.0	140.0

A13

Table A2.8. Area under the curve (AUC) for exercise heart rate from 0 to 12 hours (beats/minute.hr) after placebo and atenolol and the difference between placebo and atenolol.

Subjects	AUC (0-12 hours)(bpm.hr)		
Blacks	Placebo	Atenolol	Difference
MN	1696.00	1460.20	235.80
CM	1823.75	1464.75	359.00
VL	1636.30	1346.25	290.05
AP	1816.25	1527.75	288.50
ZN	1781.80	1483.60	298.20
DS	1840.65	1644.05	196.60
NM	1740.70	1443.00	297.70
AK	1834.15	1613.25	220.90
Whites			
NV	1668.75	1344.40	324.35
HA	1714.10	1467.45	246.65
BB	1730.70	1365.20	365.50
ACA	1612.10	1327.20	284.90
NF	1909.30	1538.95	370.35
JFI	1592.30	1371.50	220.80
JFO	1597.60	1312.60	285.00
ACL	1607.15	1440.35	166.80

Table A2.9. Erect systolic blood pressure for black and white individuals after placebo administration.

| TIME (hours) | ERECT SYSTOLIC BP AFTER PLACEBO (mm Hg) | | | | | | | | | | | | | | | |
| | BLACKS | | | | | | | | WHITES | | | | | | | |
	MN	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	120	115	140	105	100	105	115	105	118	120	125	106	110	120	95	105
0.5	120	110	125	110	100	100	110	110	120	118	115	105	110	120	110	100
1.0	110	110	110	110	100	90	120	105	110	110	120	105	100	120	110	100
1.5	120	105	120	110	95	100	115	115	110	120	120	107	105	125	105	105
2.0	120	110	105	110	100	100	115	110	118	125	120	110	110	120	105	110
3.0	120	110	125	105	105	100	115	110	110	125	105	114	110	120	110	120
4.0	115	105	125	100	90	105	115	100	115	100	120	114	115	120	120	100
5.0	120	115	122	110	95	100	110	95	110	100	120	106	115	115	105	110
6.0	120	110	125	110	95	105	115	120	100	105	120	113	115	120	120	110
8.0	110	115	125	120	100	110	120	105	110	118	120	105	110	120	120	110
10.0	120	118	140	115	100	110	110	105	120	110	115	109	110	120	110	115
12.0	120	115	125	110	110	120	120	110	110	118	120	119	110	130	110	120
24.0	115	115	115	105	95	100	120	110	110	105	110	111	110	110	120	110
30.0	120	115	130	100	100	100	120	110	110	118	120	115	110	110	115	110
36.0	130	105	125	110	100	110	120	120	120	110	120	111	115	125	120	115

Table A2.10. Erect systolic blood pressure in black and white individuals after atenolol administration.

TIME (hours)	ERECT SYSTOLIC BP AFTER ATENOLOL (mm Hg)															
	BLACKS								WHITES							
	MN	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	120	120	120	100	105	100	115	105	118	100	115	110	122	120	110	100
0.5	125	115	110	105	100	95	115	105	105	105	110	100	120	110	110	95
1.0	115	105	105	110	90	100	110	105	100	105	105	100	118	110	95	105
1.5	120	105	115	105	85	105	110	105	105	100	105	85	114	110	100	100
2.0	120	105	110	100	90	100	105	90	105	95	100	90	120	110	100	100
3.0	125	110	110	105	90	95	115	100	105	100	100	90	116	105	100	100
4.0	120	110	115	100	85	95	110	95	100	95	105	95	120	105	100	100
5.0	120	105	105	105	85	105	110	100	100	105	107	90	120	110	100	95
6.0	120	110	120	105	90	110	110	100	110	90	N/A	105	122	110	110	105
8.0	118	100	120	105	105	115	100	105	100	100	117	95	118	115	105	100
10.0	130	120	115	105	105	110	100	105	105	100	117	100	122	120	110	95
12.0	130	118	140	110	115	120	120	105	110	105	N/A	105	124	120	120	105
24.0	120	105	120	100	100	110	115	115	110	100	116	100	112	125	120	100
30.0	130	120	120	95	105	110	120	110	105	95	121	120	120	115	110	105
36.0	125	110	120	120	105	105	120	115	125	120	122	115	124	120	120	105

Table A2.11. Mean erect systolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

TIME (hours)	ERECT SYSTOLIC BLOOD PRESSURE (mm Hg)			
	BLACKS		WHITES	
	Placebo	Atenolol	Placebo	Atenolol
0.0	113.1	110.6	112.4	111.9
0.5	110.6	108.9	112.3	106.9
1.0	106.9	105.0	109.4	104.8
1.5	110.0	106.3	112.1	102.4
2.0	108.8	102.5	114.8	102.5
3.0	111.3	106.3	114.3	102.0
4.0	106.9	103.8	113.0	102.5
5.0	108.4	104.4	110.1	103.4
6.0	112.5	108.1	112.9	107.4
8.0	113.1	108.5	114.1	106.3
10.0	114.8	111.3	113.6	108.6
12.0	116.3	119.8	117.1	112.7
24.0	109.4	110.6	110.4	110.8
30.0	111.9	113.8	113.5	111.4
36.0	115.0	115.0	117.0	118.9

Table A2.12. Area under the curve (AUC) for erect systolic blood pressure from 0 to 12 hours(mm Hg.hr) for placebo and atenolol and the difference between placebo and atenolol.

Subjects	AUC (0-12 hours)(mm Hg.hr)		
Blacks	Placebo	Atenolol	Difference
MN	1410.00	1471.00	61.00
CM	1349.75	1319.25	30.50
VL	1505.75	1397.50	108.25
AP	1333.75	1262.50	71.25
ZN	1190.00	1161.25	28.75
DS	1268.75	1280.00	-11.25
NM	1380.00	1295.00	85.00
AK	1288.75	1221.25	67.50
Whites			
NV	1343.00	1253.25	89.75
HA	1354.25	1191.25	163.00
BB	1413.75	1092.25	321.50
ACA	1318.00	1165.00	153.00
NF	1330.00	1439.50	-109.50
JFI	1447.50	1352.50	95.00
JFO	1350.00	1270.00	80.00
ACL	1326.25	1197.50	128.75

Table A2.13. Erect diastolic blood pressure in black and white individuals after placebo administration.

| TIME (hours) | ERECT DIASTOLIC BP AFTER PLACEBO (mm Hg) | | | | | | | | | | | | | | | |
| | BLACKS | | | | | | | | WHITES | | | | | | | |
	MN	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	78	80	80	80	65	60	75	75	65	65	80	71	70	60	65	60
0.5	78	80	65	85	65	70	80	70	80	75	75	67	70	60	70	60
1.0	70	80	70	80	60	65	80	75	65	80	75	67	70	70	70	70
1.5	70	70	80	75	50	60	80	75	65	80	70	63	70	65	70	65
2.0	62	75	60	75	55	60	80	70	75	85	65	67	75	55	70	65
3.0	70	75	75	70	60	60	80	65	65	85	75	66	80	70	70	70
4.0	68	75	75	75	60	75	80	70	75	70	75	66	80	70	75	60
5.0	80	80	80	75	55	60	65	65	70	70	75	63	75	70	70	65
6.0	80	70	75	70	55	70	70	75	70	70	70	60	70	70	65	60
8.0	80	80	85	80	65	70	80	80	75	85	70	60	75	60	70	65
10.0	80	80	80	80	65	80	80	75	75	80	70	67	75	70	70	70
12.0	80	65	75	80	60	95	80	80	70	80	75	60	80	65	70	65
24.0	80	75	80	75	60	70	70	75	65	75	70	67	75	70	70	70
30.0	75	70	65	80	55	65	70	70	70	70	70	60	75	55	70	60
36.0	75	70	75	80	55	75	70	80	70	75	70	54	80	55	75	75

Table A2.14. Erect diastolic blood pressure in black and white individuals after atenolol administration.

TIME (hours)	ERECT DIASTOLIC BP AFTER ATENOLOL (mm Hg)															
	BLACKS								WHITES							
	MN	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	90	90	70	80	65	70	75	70	70	70	75	70	84	65	80	60
0.5	90	85	65	60	60	70	75	65	75	75	70	70	78	60	80	70
1.0	90	80	65	80	50	65	70	65	65	70	65	60	84	60	75	70
1.5	85	75	65	75	55	70	80	65	65	80	65	60	80	60	70	70
2.0	90	70	70	70	55	60	75	65	65	70	65	65	84	55	75	70
3.0	85	70	60	75	60	65	70	60	75	70	65	60	78	55	75	60
4.0	90	80	60	65	55	75	80	60	60	70	70	65	82	65	75	65
5.0	90	80	65	70	55	75	75	60	60	60	72	60	70	60	70	65
6.0	75	80	75	65	55	75	65	60	65	60	N/A	60	78	65	65	65
8.0	85	70	75	70	60	70	60	75	70	65	66	60	70	55	70	60
10.0	95	80	70	70	65	80	60	70	85	65	72	60	72	70	80	55
12.0	85	50	80	65	70	70	60	70	70	70	N/A	65	76	70	80	60
24.0	80	70	75	70	55	70	85	80	70	65	59	65	65	70	70	65
30.0	85	75	75	70	55	60	75	80	75	60	62	75	72	65	75	65
36.0	85	70	80	60	60	65	75	80	75	85	75	65	78	70	70	70

Table A2.15. Mean erect diastolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

TIME (hours)	ERECT DIASTOLIC BLOOD PRESSURE (mm Hg)			
	BLACKS		WHITES	
	Placebo	Atenolol	Placebo	Atenolol
0.0	74.1	76.3	67.0	71.8
0.5	74.0	71.3	69.6	72.3
1.0	72.5	70.6	70.9	68.6
1.5	70.0	71.3	68.5	68.8
2.0	67.1	69.4	69.6	68.6
3.0	69.4	68.1	72.6	67.3
4.0	72.3	70.6	71.4	69.0
5.0	70.0	71.3	69.8	64.6
6.0	70.6	68.8	66.9	65.4
8.0	77.5	70.6	70.0	64.5
10.0	77.5	73.8	72.1	69.9
12.0	76.9	68.8	70.6	70.1
24.0	73.1	73.1	70.3	66.1
30.0	68.8	71.9	66.3	68.6
36.0	72.5	71.9	69.3	73.5

Table A2.16. Area under the curve (AUC) for erect diastolic blood pressure from 0 to 12 hours (mm hg.hr) for atenolol and placebo and the difference between atenolol and placebo.

Subjects	AUC (0-12 hours)(mm Hg.hr)		
Blacks	Placebo	Atenolol	Difference
MN	913.00	1045.00	-132.00
CM	911.25	895.00	16.25
VL	920.00	835.00	85.00
AP	921.25	832.50	88.75
ZN	722.50	712.50	10.00
DS	852.50	862.50	-10.00
NM	928.75	810.00	118.75
AK	883.75	793.75	90.00
Whites			
NV	862.50	841.25	21.25
HA	937.50	802.50	135.00
BB	863.75	683.50	180.25
ACA	765.50	741.25	24.25
NF	898.75	912.00	-13.25
JFI	793.75	745.00	48.75
JFO	836.25	886.25	-50.00
ACL	781.25	750.00	31.25

Table A2.17. Supine systolic blood pressure in black and white individuals after placebo administration.

TIME (hours)	SUPINE SYSTOLIC BP AFTER PLACEBO (mm Hg)															
	BLACKS								WHITES							
	MN	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	140	110	120	100	95	100	110	100	100	105	120	105	110	120	95	105
0.4	120	105	120	105	95	100	120	105	118	110	110	109	100	120	110	110
0.9	120	102	120	110	95	105	115	110	114	105	110	114	95	120	110	105
1.4	120	100	120	110	95	95	115	110	110	110	115	106	110	120	105	100
2.0	118	105	110	110	100	100	115	110	105	110	120	112	110	120	110	110
3.0	120	105	120	110	100	100	115	100	100	110	115	118	110	120	100	100
4.0	118	100	118	100	95	100	105	100	110	105	115	107	110	115	110	105
5.0	118	105	120	105	100	90	110	90	100	110	105	109	110	110	105	105
6.0	120	105	125	120	95	95	110	105	100	90	120	108	115	120	110	110
8.0	120	110	122	110	95	100	110	105	110	105	110	107	105	120	105	100
10.0	120	110	130	110	95	105	110	100	110	110	120	112	110	130	105	115
12.0	120	105	125	110	105	110	120	105	110	110	120	116	110	125	110	105
24.0	120	105	110	105	100	110	110	105	100	100	110	104	105	105	105	110
30.0	120	105	125	105	90	100	120	105	110	110	115	124	105	110	110	110
36.0	125	105	125	110	100	110	120	110	110	110	110	115	115	120	120	110

Table A2.18. Supine systolic blood pressure in black and white individuals after atenolol administration.

| TIME (hours) | SUPINE SYSTOLIC BP AFTER ATENOLOL (mm Hg) | | | | | | | | | | | | | | | |
| | BLACKS | | | | | | | | WHITES | | | | | | | |
	NM	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	120	133	120	105	105	95	110	110	110	115	110	115	122	115	110	105
0.4	130	120	125	110	100	110	120	110	110	118	105	105	120	110	110	100
0.9	120	100	120	105	100	100	110	105	100	108	105	100	118	110	100	110
1.4	120	105	115	105	85	105	110	95	105	110	110	90	110	105	105	100
2.0	120	100	110	108	90	100	110	95	100	100	100	90	116	110	100	100
3.0	125	100	115	110	90	95	110	100	100	100	100	95	112	105	105	100
4.0	120	100	110	105	90	90	105	95	100	100	99	95	108	105	95	100
5.0	120	105	110	105	90	105	120	100	105	100	113	90	108	115	100	100
6.0	120	105	120	110	90	95	110	105	105	90	115	100	110	115	100	100
8.0	115	100	120	105	100	100	110	100	95	95	115	95	108	115	100	100
10.0	130	110	120	105	100	95	110	105	95	95	107	105	106	110	100	105
12.0	125	110	130	105	110	100	110	105	110	100	120	100	120	120	100	100
24.0	120	110	120	105	100	95	105	105	105	95	108	95	110	115	110	110
30.0	120	105	125	105	95	100	110	105	100	100	117	110	110	110	110	100
36.0	130	105	125	105	100	100	120	110	120	115	122	110	120	120	110	110

Table A2.19. Mean supine systolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

| TIME (hours) | SUPINE SYSTOLIC BLOOD PRESSURE (mm Hg) | | | |
| | BLACKS | | WHITES | |
	Placebo	Atenolol	Placebo	Atenolol
0.0	109.4	112.3	107.5	112.8
0.4	108.8	115.6	110.9	109.8
0.9	109.6	107.5	109.1	106.4
1.4	108.1	105.0	109.5	104.4
2.0	108.5	104.1	112.1	102.0
3.0	108.7	105.6	109.1	102.1
4.0	104.5	101.9	109.6	100.3
5.0	106.9	104.8	106.8	103.9
6.0	109.4	106.9	109.1	104.4
8.0	109.0	106.3	107.8	102.9
10.0	110.0	109.4	114.0	102.9
12.0	112.5	111.9	113.3	108.8
24.0	108.1	107.5	104.9	106.0
30.0	108.8	108.1	111.8	107.1
36.0	113.1	111.9	113.8	115.9

Table A2.20. Area under the curve (AUC) for supine systolic blood pressure from 0 to 12 hours (mm hg.hr) for placebo and atenolol and the difference between placebo and atenolol.

Subjects	AUC (0-12 hours)(mm Hg.hr)		
Blacks	Placebo	Atenolol	Difference
MN	1438.40	1464.50	-26.10
CM	1271.75	1260.85	10.90
VL	1466.50	1416.50	50.00
AP	1315.75	1277.15	38.60
ZN	1164.00	1149.75	14.25
DS	1202.25	1178.75	23.50
NM	1343.75	1329.50	14.25
AK	1233.25	1219.75	13.50
Whites			
NV	1284.60	1211.75	72.85
HA	1271.50	1185.60	85.90
BB	1382.75	1310.75	72.00
ACA	1324.95	1171.75	153.20
NF	1305.50	1331.70	-26.20
JFI	1450.00	1340.75	109.25
JFO	1279.25	1203.50	75.75
ACL	1276.00	1216.00	60.00

Table A2.21. Supine diastolic blood pressure in black and white individuals after placebo administration.

TIME (hours)	SUPINE DIASTOLIC BP AFTER PLACEBO (mm Hg)															
	BLACKS								WHITES							
	NM	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	90	65	75	65	55	65	65	60	60	65	70	61	65	55	60	65
0.4	70	65	50	65	50	60	60	60	60	60	60	55	60	60	60	60
0.9	60	60	80	65	45	60	60	65	68	60	65	50	60	60	65	60
1.4	68	50	70	55	45	60	70	65	58	55	65	55	70	60	55	65
2.0	58	60	60	60	45	60	70	60	55	70	60	52	65	60	60	55
3.0	58	60	65	60	50	60	70	55	60	75	65	55	65	60	55	60
4.0	58	60	75	60	50	60	60	60	70	55	65	50	65	60	55	60
5.0	58	70	65	65	45	60	60	55	60	55	65	55	65	70	65	55
6.0	70	70	65	70	50	55	60	65	55	55	60	50	65	55	60	65
8.0	70	70	70	70	50	60	60	65	55	60	60	50	65	60	60	60
10.0	65	70	70	75	55	65	65	60	60	70	70	55	70	70	65	60
12.0	70	55	65	70	55	60	60	65	60	65	70	55	70	70	70	60
24.0	60	60	60	65	50	70	60	65	55	60	70	55	60	65	70	60
30.0	60	65	65	65	50	60	60	65	55	60	55	50	65	60	60	60
36.0	75	65	65	55	50	65	65	60	60	55	60	50	70	55	75	60

Table A2.22. Supine diastolic blood pressure in black and white individuals after atenolol administration.

TIME (hours)	SUPINE DIASTOLIC BP AFTER ATENOLOL (mm Hg)															
	BLACKS								WHITES							
	MN	CM	VL	AP	ZN	DS	NM	AK	NV	HA	BB	ACA	NF	JFI	JFO	ACL
0.0	75	65	60	70	50	60	65	60	60	60	75	70	76	70	65	60
0.4	75	70	45	55	45	60	65	65	55	55	65	55	65	60	65	60
0.9	75	70	55	75	40	60	65	55	50	60	60	55	68	60	65	60
1.4	70	60	55	70	40	65	70	60	55	65	60	50	68	65	65	60
2.0	80	60	60	65	45	60	75	60	50	60	60	55	70	60	65	60
3.0	75	60	55	65	45	60	60	60	60	55	60	50	64	55	60	55
4.0	75	60	55	60	45	60	65	55	60	60	54	55	64	60	60	55
5.0	75	70	60	65	40	65	70	55	55	55	66	50	64	70	60	55
6.0	70	70	55	65	40	55	55	60	50	50	50	50	66	60	50	60
8.0	75	58	55	65	50	60	60	55	60	50	57	50	62	60	55	60
10.0	80	70	60	55	55	60	70	65	65	50	65	55	66	60	65	60
12.0	75	70	65	60	60	60	60	65	55	55	57	60	70	60	60	60
24.0	70	60	60	60	45	60	60	60	55	50	55	55	62	60	55	60
30.0	75	70	55	60	45	60	65	60	50	50	52	55	60	55	60	60
36.0	75	60	70	55	50	60	70	65	60	70	53	60	58	70	60	60

Table A2.23. Mean supine diastolic blood pressure (mm Hg) after placebo and atenolol administration in the black and white groups (n=8 in each group).

| TIME (hours) | SUPINE DIASTOLIC BLOOD PRESSURE (mm Hg) | | | |
| | BLACKS | | WHITES | |
	Placebo	Atenolol	Placebo	Atenolol
0.0	67.5	63.1	62.6	67.0
0.4	60.0	60.0	59.4	60.0
0.9	61.9	61.9	61.0	59.8
1.4	60.4	61.3	60.4	61.0
2.0	59.1	63.1	59.6	60.0
3.0	59.8	60.0	61.9	57.4
4.0	60.4	59.4	60.0	58.5
5.0	62.5	59.8	61.3	59.4
6.0	63.1	58.8	58.1	54.5
8.0	64.4	59.8	58.8	56.8
10.0	65.6	64.4	65.0	60.8
12.0	62.5	64.4	65.0	59.6
24.0	61.3	59.4	61.9	56.5
30.0	61.3	61.3	58.1	55.3
36.0	62.5	63.1	60.6	61.4

Table A2.24. Area under the curve (AUC) for supine diastolic blood pressure from 0 to 12 hours (mm hg.hr) for placebo and atenolol and the difference between placebo and atenolol.

Subjects	AUC (0-12 hours)(mm Hg.hr)		
Blacks	Placebo	Atenolol	Difference
MN	782.30	903.75	-121.45
CM	777.75	781.50	-4.00
VL	811.50	685.50	126.00
AP	803.00	754.25	48.50
ZN	601.75	568.25	33.50
DS	723.50	720.25	3.25
NM	754.50	770.75	-16.25
AK	743.25	714.75	28.50
Whites			
NV	711.40	687.00	24.40
HA	748.75	650.50	98.25
BB	772.25	711.25	61.00
ACA	633.80	637.75	-3.95
NF	793.00	788.85	4.15
JFI	751.50	729.75	21.75
JFO	734.75	717.50	17.25
ACL	722.25	705.00	17.25

Table A2.25. Plasma renin activity in black and white individuals after placebo administration.

TIME (hours)	PLASMA RENIN ACTIVITY AFTER PLACEBO (ng/ml/hr)									
	BLACKS					WHITES				
	MN	CM	VL	AP	ZN	NV	HA	BB	ACA	NF
0.0	0.11	3.23	0.70	3.91	2.56	7.03	3.48	5.01	6.62	2.28
0.1	0.84	2.68	1.04	2.31	1.55	4.98	4.48	4.23	8.21	1.92
0.2	0.67	3.45	0.95	1.89	4.30	4.82	6.54	5.17	10.26	2.64
0.3	4.37	6.90	0.57	2.81	3.55	3.57	8.46	5.28	10.33	2.48
0.5	1.09	5.44	0.99	2.50	3.01	5.91	3.10	7.35	10.51	1.83
0.8	1.07	3.81	0.62	2.14	3.37	4.68	3.46	7.43	10.61	2.22
1.0	3.06	4.27	0.51	1.77	2.77	3.42	3.64	4.43	7.92	1.66
1.5	1.72	2.74	0.60	3.05	3.12	4.62	4.58	5.10	11.06	1.65
2.0	0.65	3.10	0.56	3.84	3.86	3.23	2.67	5.83	10.08	2.27
3.0	0.77	2.18	0.79	1.98	2.86	2.62	2.49	4.72	5.47	1.75
4.0	0.78	2.23	0.37	1.42	4.80	1.89	2.43	4.01	5.40	1.71
5.0	0.95	2.39	0.83	1.04	2.21	2.69	6.17	4.64	3.24	1.31
6.0	0.56	5.05	0.80	7.82	4.07	2.87	4.17	4.36	3.72	1.72
8.0	0.87	2.42	0.51	0.66	1.90	1.77	5.58	2.07	3.95	1.13
10.0	0.91	N/A	0.59	4.88	1.91	1.83	2.04	1.72	4.37	5.60
12.0	0.64	2.48	0.23	0.60	1.67	1.99	3.76	1.72	5.76	0.78
24.0	0.36	N/A	0.78	1.40	2.29	3.13	2.08	2.57	2.70	1.90
30.0	0.30	N/A	5.48	1.87	2.91	1.44	N/A	2.17	2.52	1.68

Table A2.26. Plasma renin activity in black and white individuals after atenolol administration.

TIME (hours)	PLASMA RENIN ACTIVITY AFTER ATENOLOL (ng/ml/hr)									
	BLACKS					WHITES				
	MN	CM	VL	AP	ZN	NV	HA	BB	ACA	NF
0.0	0.27	1.80	8.45	2.67	3.31	5.87	1.36	2.73	5.00	1.70
0.1	0.76	2.25	7.75	1.10	2.30	3.28	2.72	3.92	4.03	2.35
0.2	0.14	1.52	0.99	2.48	2.57	2.54	1.14	1.63	5.11	4.62
0.3	N/A	1.68	1.07	1.70	5.91	3.09	2.27	1.42	4.87	1.26
0.5	0.59	0.85	3.27	3.68	2.33	N/A	2.51	1.87	4.47	4.77
0.8	0.35	3.15	0.78	4.97	3.58	2.98	1.17	1.32	2.94	1.16
1.0	0.39	2.04	0.66	1.95	4.81	2.45	1.43	1.13	2.93	4.18
1.5	7.43	0.73	2.01	2.81	1.83	1.53	0.84	4.43	1.41	4.03
2.0	0.52	0.65	1.94	4.71	1.75	3.03	2.46	5.04	2.45	1.90
3.0	1.28	1.48	1.27	3.22	3.02	9.56	2.23	4.80	1.92	1.79
4.0	0.56	0.84	0.64	4.33	1.40	1.93	0.93	0.80	1.60	3.66
5.0	2.92	1.17	0.87	0.86	1.81	1.08	2.10	6.11	1.09	3.44
6.0	2.16	1.34	0.53	1.17	1.66	1.13	2.20	0.54	0.89	2.22
8.0	1.53	1.17	1.57	1.05	0.88	1.20	2.08	0.68	0.31	2.72
10.0	1.61	2.18	0.51	1.29	0.59	2.62	4.76	1.51	1.71	2.38
12.0	0.43	1.75	0.72	5.81	0.65	0.82	1.60	4.34	0.46	0.68
24.0	N/A	1.40	0.73	1.22	2.23	1.54	1.75	3.44	2.23	0.85
30.0	N/A	1.38	2.24	2.13	3.63	N/A	N/A	3.71	1.48	1.65

Table A2.27. Mean plasma renin activity (ng/ml/hr) after placebo and atenolol administration in the black and white groups (n=5 in each group).

TIME (hours)	PLASMA RENIN ACTIVITY (ng/ml/hr)			
	BLACKS		WHITES	
	Placebo	Atenolol	Placebo	Atenolol
0.0	2.1	3.3	4.9	3.3
0.1	1.7	2.9	4.8	3.3
0.2	2.3	1.5	5.9	3.0
0.3	3.7	2.6#	6.0	2.6
0.5	2.6	2.2	5.7	3.4#
0.8	2.2	2.6	5.7	1.9
1.0	2.5	2.0	4.2	2.4
1.5	2.2	2.9	5.4	2.4
2.0	2.4	1.9	4.8	3.0
3.0	1.7	2.1	3.4	4.1
4.0	1.9	1.5	3.1	1.8
5.0	1.5	1.5	3.6	2.8
6.0	3.7	1.4	3.4	1.4
8.0	1.3	1.3	2.9	1.4
10.0	2.1#	1.2	3.1	2.8#
12.0	1.1	1.9	2.8	1.6
24.0	1.2#	1.4#	2.4	2.0
30.0	2.6#	2.3#	2.0#	2.3#

Missing values

Table A2.28. Area under the curve (AUC) from 0 to 12 hours for PRA (ng Ang./ml) after placebo and atenolol and the difference in AUC between placebo and atenolol.

Subjects	AUC (0-12 Hours) (ng Ang./ml)		
Blacks	Placebo	Atenolol	Difference
MN	11.31	19.33	-8.02
CM	35.91	17.24	18.67
VL	7.24	13.62	-6.38
AP	34.80	29.18	5.62
ZN	33.53	19.24	14.29
Whites			
NV	31.14	29.47	1.67
HA	46.10	28.32	17.78
BB	43.36	29.33	14.03
ACA	66.96	17.76	49.20
NF	26.65	30.46	-3.81

Table A2.29. Individual maximum changes (E_{max}) in heart rate and the time to maximum effects (T_{max}) for atenolol.

	Resting Heart Rate		Exercise Heart Rate	
	E_{max} (bpm)	T_{max} (hr)	E_{max} (bpm)	T_{max} (hr)
BLACKS				
MN	26	3.0	39	0.5
CM	10	4.0	44	0.2
VL	5	1.5	40	0.4
AP	18	3.0	30	0.4
ZN	11	4.0	38	0.2
DS	23	4.0	42	0.5
NM	11	2.0	36	0.5
AK	14	2.0	26	0.4
WHITES				
NV	22	3.0	41	0.2
HA	20	2.0	27	0.2
BB	20	3.0	37	0.2
ACA	16	5.0	40	0.5
NF	23	2.0	48	0.5
JFI	11	1.5	29	0.2
JFO	29	6.0	31	0.2
ACL	18	3.0	32	0.2

Table A2.30. Individual maximum BP changes (E_{max}) (mm Hg) and time to maximum (T_{max}) (hours) effects after atenolol.

	ERECT BP				SUPINE BP			
	Systolic		Diastolic		Systolic		Diastolic	
	E_{max}	T_{max}	E_{max}	T_{max}	E_{max}	T_{max}	E_{max}	T_{max}
BLACKS								
MN	0	–	5	6.0	5	8.0	0	–
CM	15	8.0	15	12.0	10	8.0	12	8.0
VL	17	5.0	15	4.0	10	5.0	20	4.0
AP	15	8.0	15	12.0	10	6.0	20	10.0
ZN	15	3.0	5	8.0	10	1.4	10	6.0
DS	10	4.0	25	12.0	10	4.0	10	24.0
NM	20	8.0	20	8.0	10	12.0	10	3.0
AK	20	2.0	15	6.0	15	1.4	10	8.0
WHITES								
NV	15	10.0	15	4.0	15	0.9	18	0.9
HA	30	2.0	20	8.0	15	10.0	20	3.0
BB	20	2.0	10	3.0	20	2.0	15	4.0
ACA	24	3.0	7	10.0	23	3.0	5	5.0
NF	0	–	10	24.0	5	6.0	4	10.0
JFI	15	1.5	15	3.0	20	10.0	10	10.0
JFO	20	4.0	0	–	15	4.0	15	24.0
ACL	20	3.0	15	10.0	10	6.0	5	4.0

Table A2.31. Twenty four hour urinary elimination of sodium and potassium in black and white subjects after placebo and atenolol administration.

SUBJECTS	24 HOUR URINARY EXCRETION (mEq)			
	Placebo		Atenolol	
	Sodium	Potassium	Sodium	Potassium
BLACKS				
MN	87*	20*	–	–
CM	–	–	–	–
VL	381	74	381	46
AP	318	39	442	83
ZN	254	30	383	37
DS	233	51	289	55
NM	366	66	360	54
AK	250	58	350	43
Mean	300	53	368	53
Median	286	55	371	50
SD	64	17	50	16
CV (%)	21	32	14	30
WHITES				
NV	–	–	–	–
HA	251	72	326	68
BB	116	31	287	85
ACA	114	83	192	50
NF	265	42	470	67
JFI	229	49	327	89
JFO	436	117	–	–
ACL	401	120	370	146
Mean	259	73	329	84
Median	251	72	327	77
SD	125	36	92	33
CV (%)	48	49	28	39
B vs W p<	0.4799	0.2234	0.3841	0.0666
ALL				
Mean	278	64	348	69
Median	254	58	355	61
SD	100	29	73	30
CV (%)	36	45	21	43
At vs Pl p<	0.0593	0.7018		

* Excluded from statistical analysis–Urine volume unrealistically low.
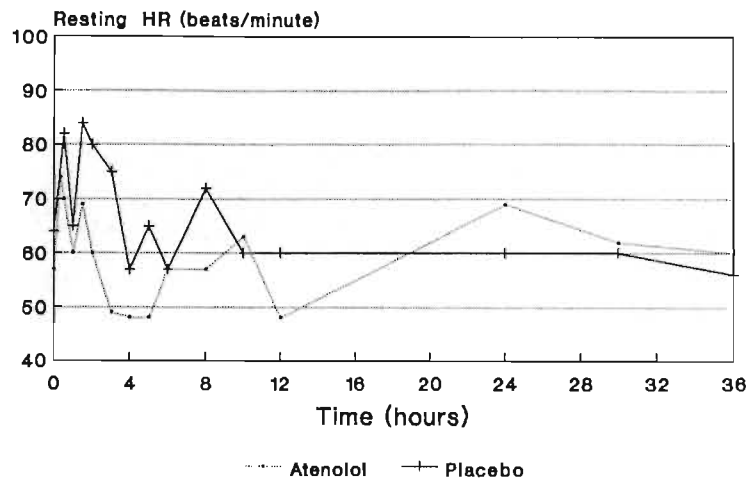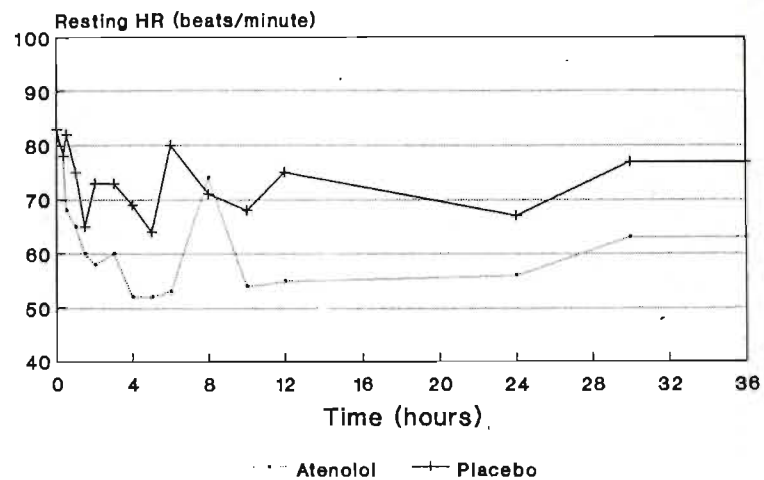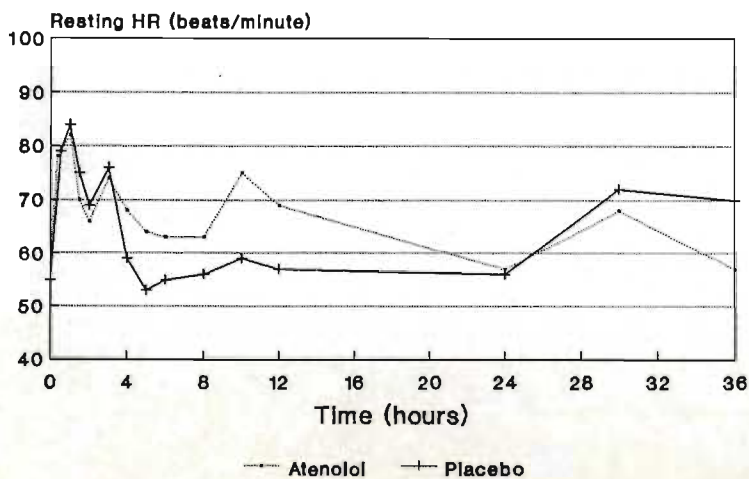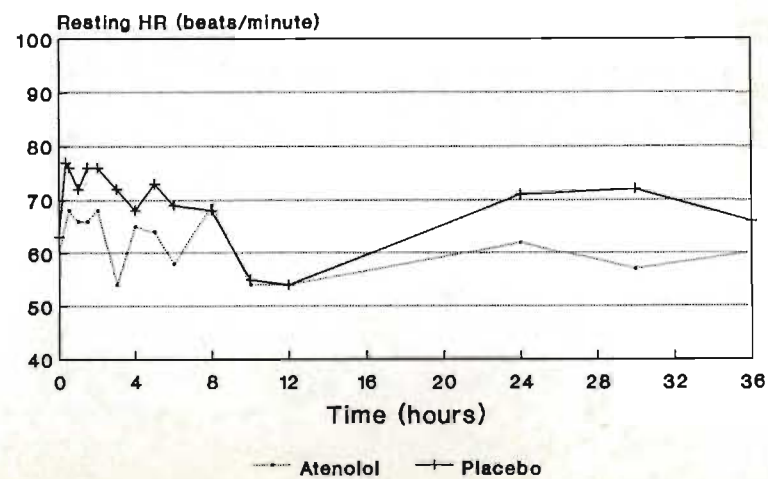
Fig A2.1. Resting heart rates in black individuals.
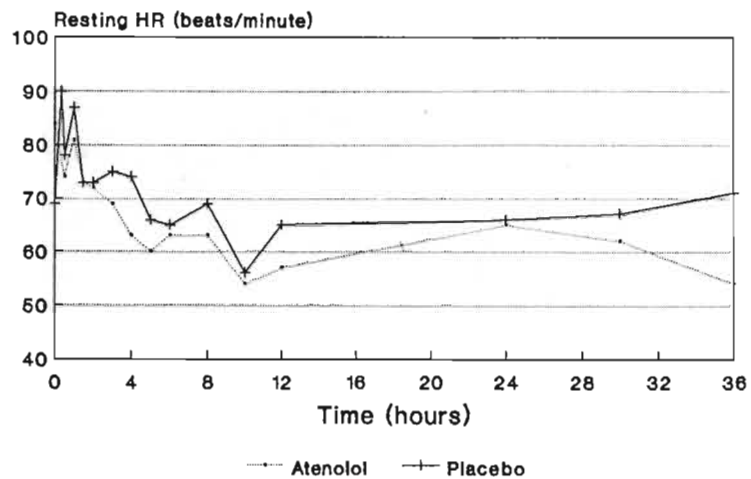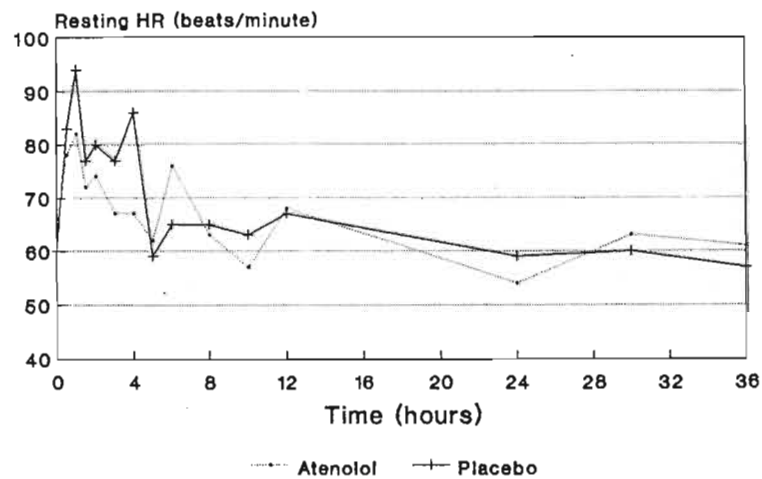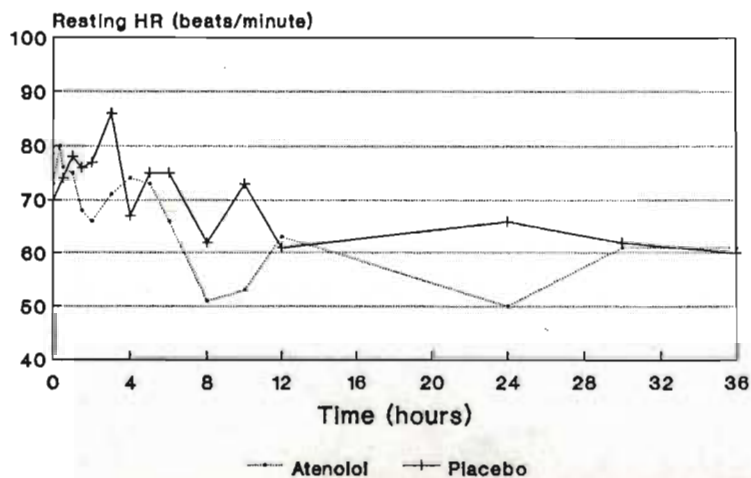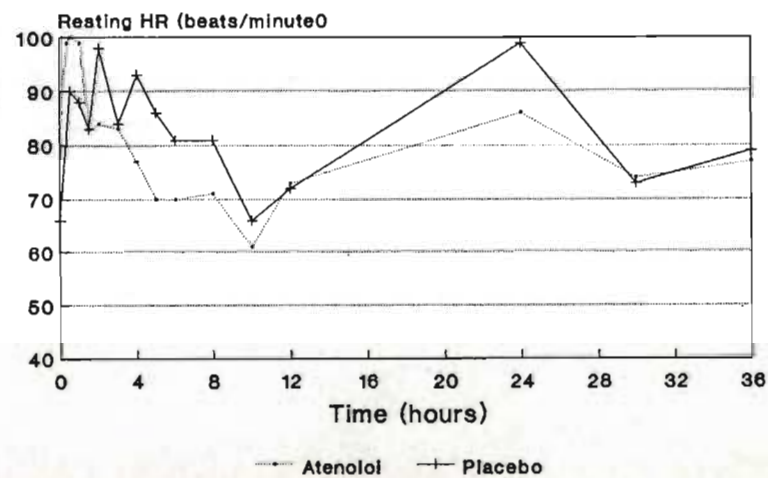
Fig A2.2. Resting heart rates in black individuals.
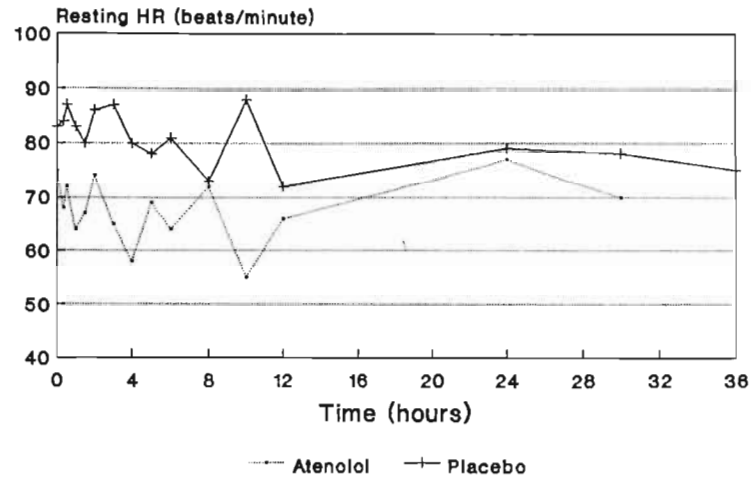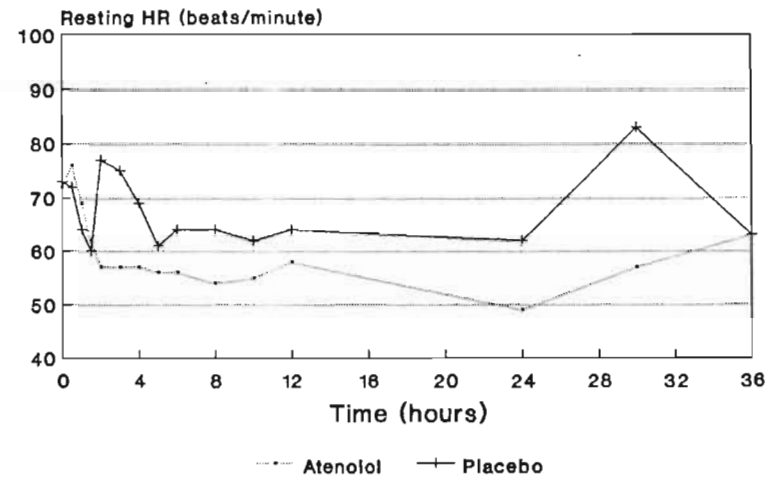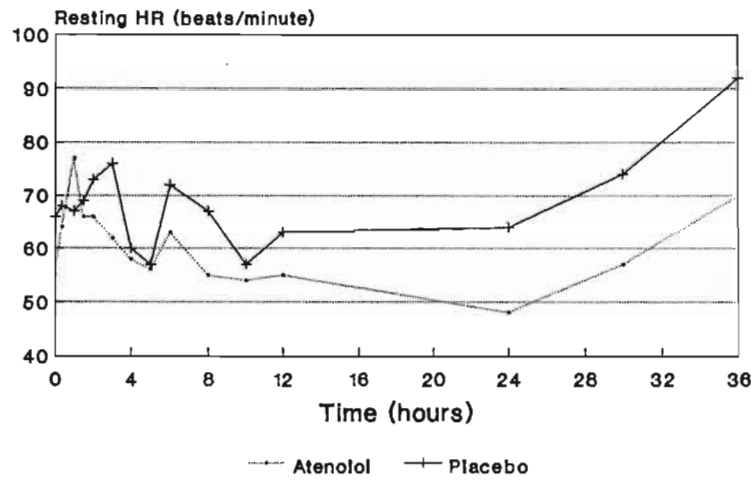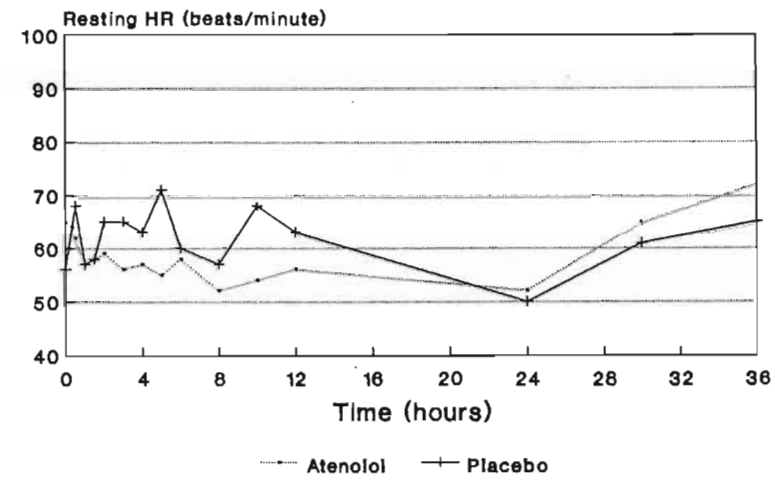
Fig A2.3. Resting heart rates in white individuals.

NF

Resting HR (beats/minute)

Time (hours)

···· Atenolol   ─┼─ Placebo

JFI

Resting HR (beats/minute)

Time (hours)

···· Atenolol   ─┼─ Placebo

JFO

Resting HR (beats/minute)

Time (hours)

···· Atenolol   ─┼─ Placebo

ACL

Resting HR (beats/minute)

Time (hours)

···· Atenolol   ─┼─ Placebo
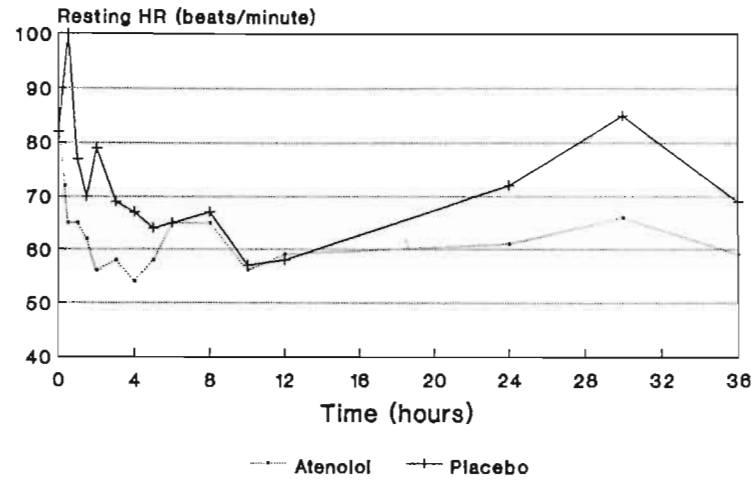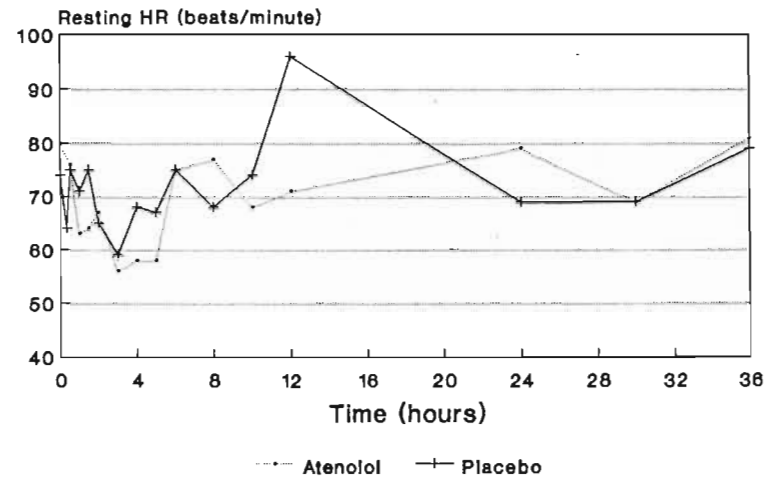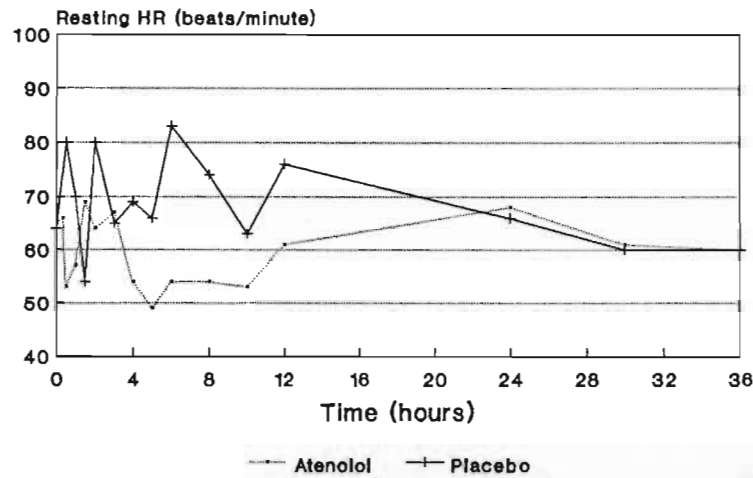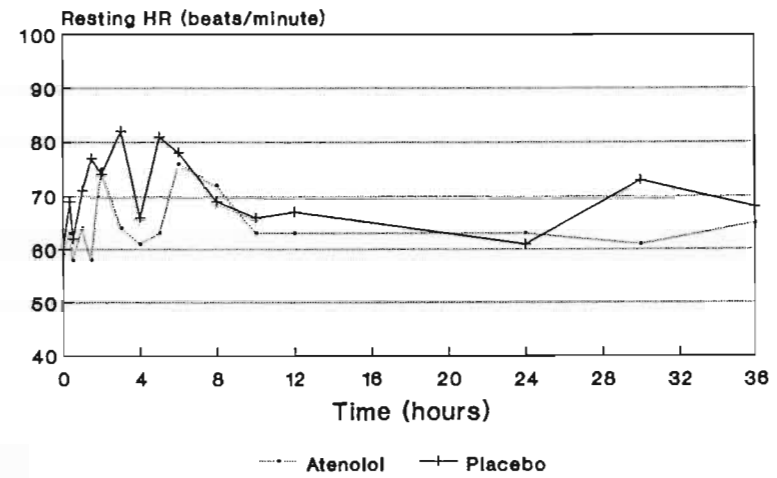
Fig A2.4. Resting heart rates in white individuals.
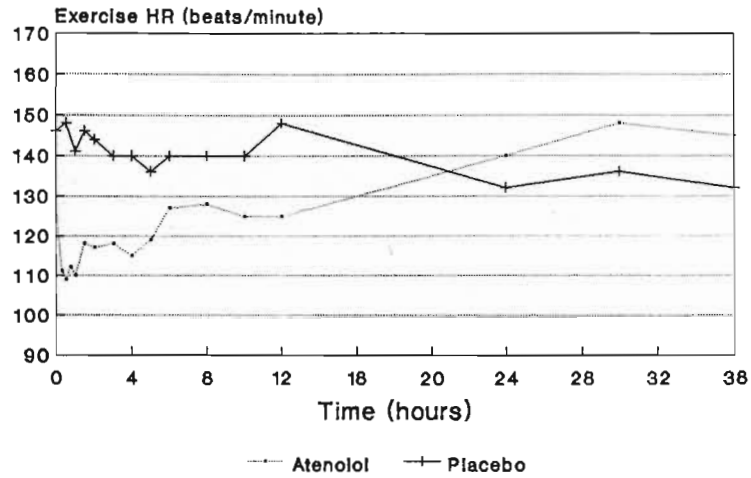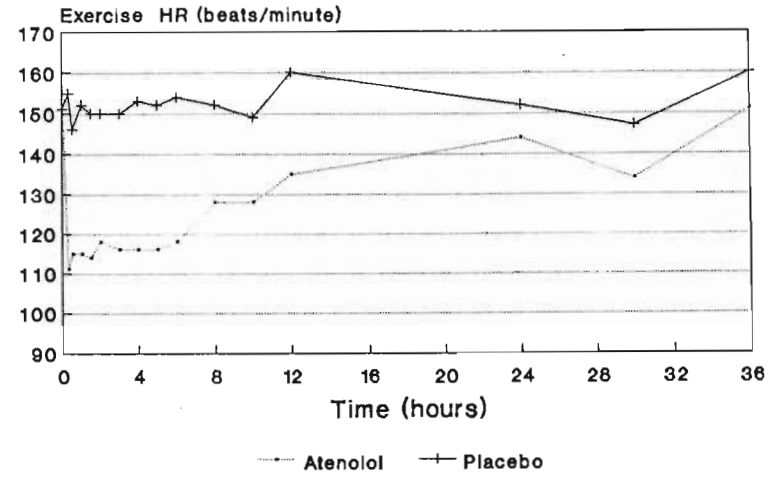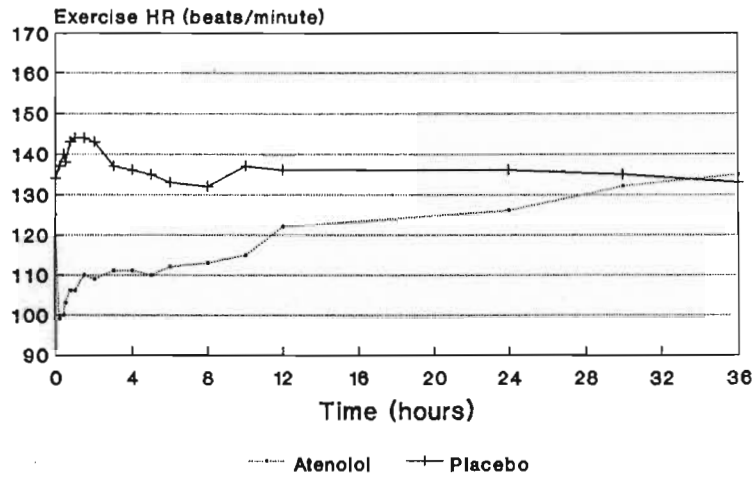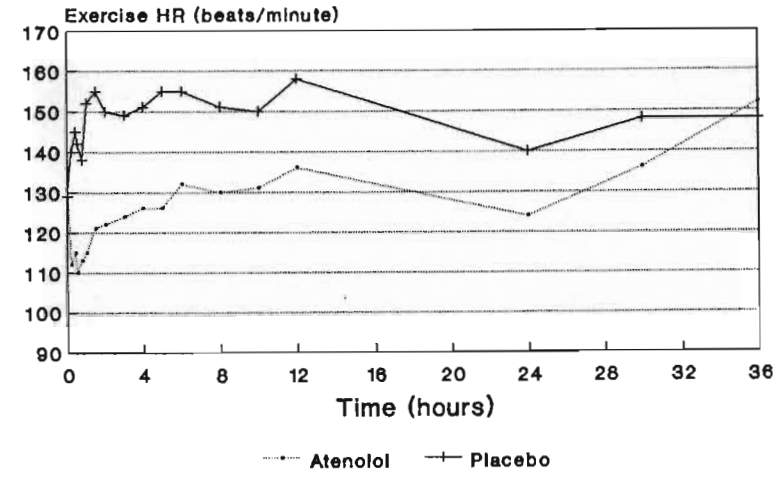
Fig A2.5. Exercise heart rates in black individuals.

Fig A2.6. Exercise heart rates in black individuals.

NV

Exercise HR (beats/minute)

Time (hours)

······· Atenolol ——+—— Placebo

HA

Exercise HR (beats/minute)

Time (hours)

······· Atenolol ——+—— Placebo

BB

Exercise HR (beats/minute)

Time (hours)

······· Atenolol ——+—— Placebo

ACA

Exercise HR (beats/minute0

Time (hours)

······· Atenolol ——+—— Placebo
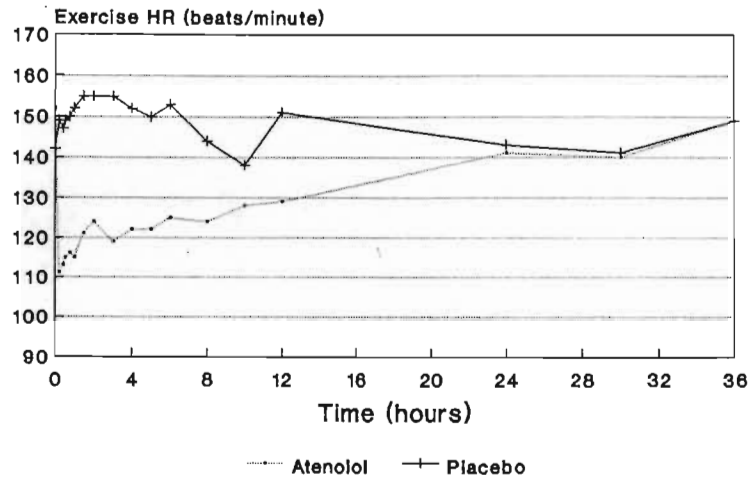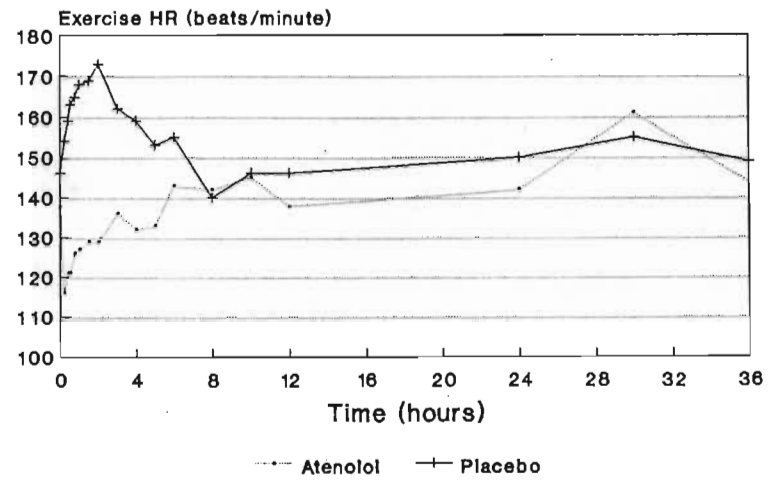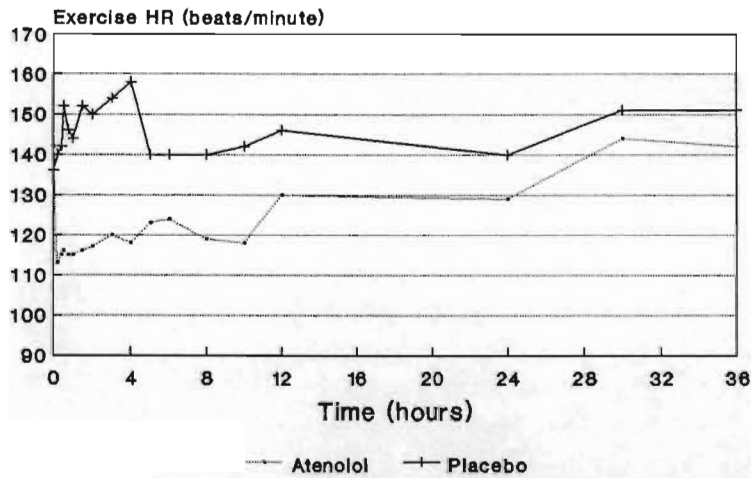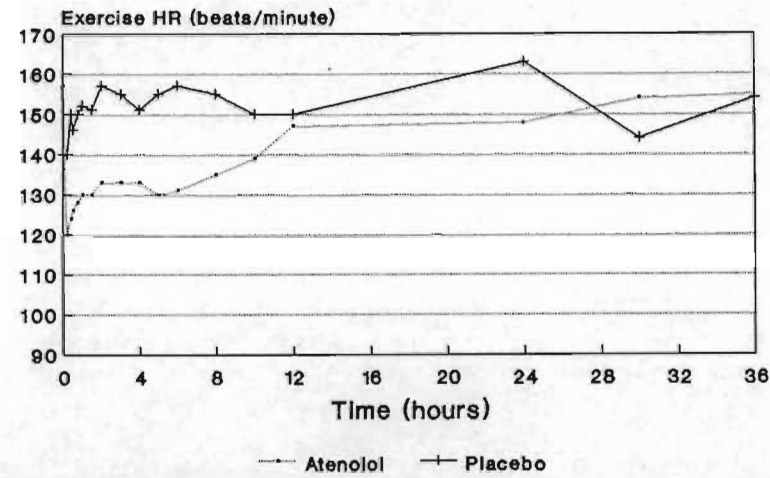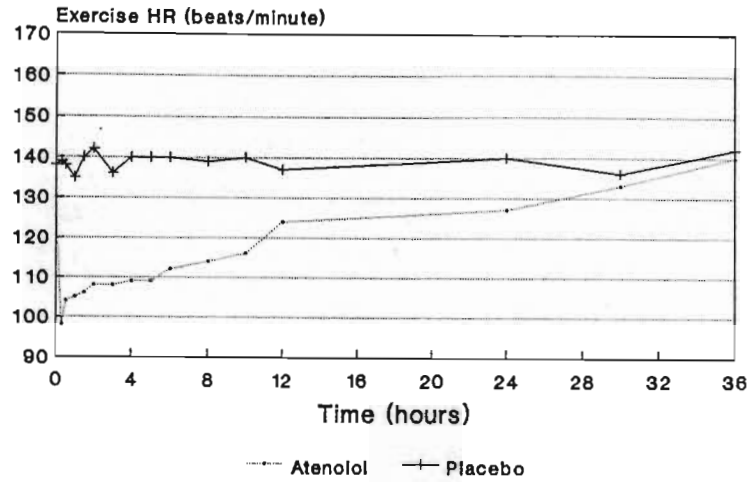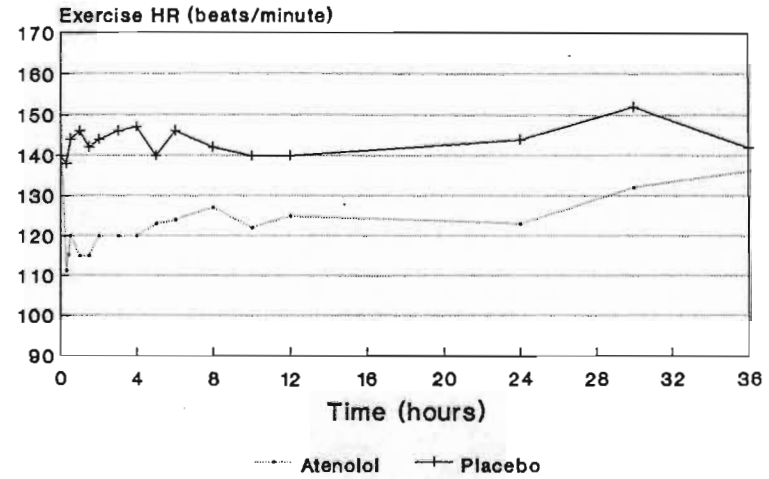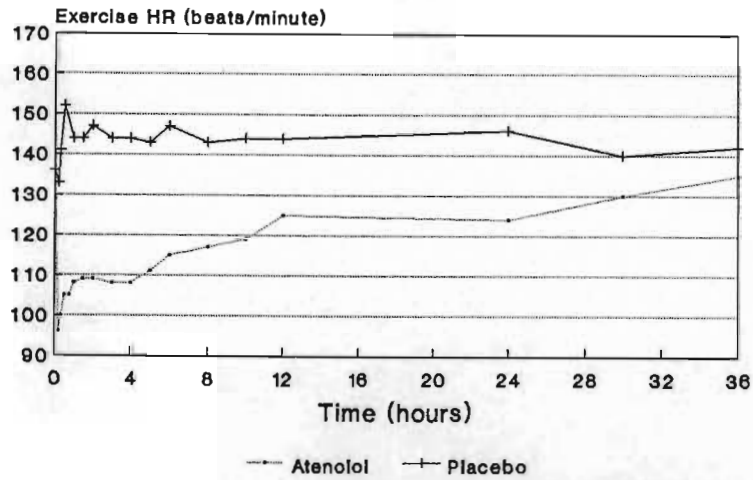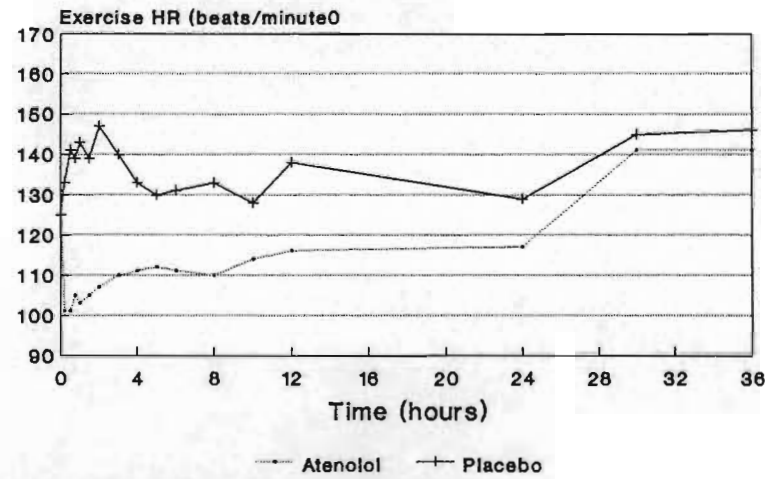
Fig A2.7. Exercise heart rates in white individuals.

Fig A2.8. Exercise heart rates in white individuals.

MN

Erect BP (mm Hg)

Time (hours)

....•.... At Systolic BP   ---+--- At Diastolic BP
---*--- Pl Systolic BP   ---□--- Pl Diastolic BP

CM

Erect BP (mm Hg)

Time (Hours)

....•.... AT Systolic BP   ---+--- AT Diastolic BP
---*--- PL Systolic BP   ---□--- PL Diastolic BP

VL

Erect BP

Time (hours)

....•.... AT Systolic BP   ---+--- AT Diastolic BP
---*--- Pl Systolic BP   ---□--- PL Diastolic BP

AP

Erect BP (mm Hg)

Time (hours)
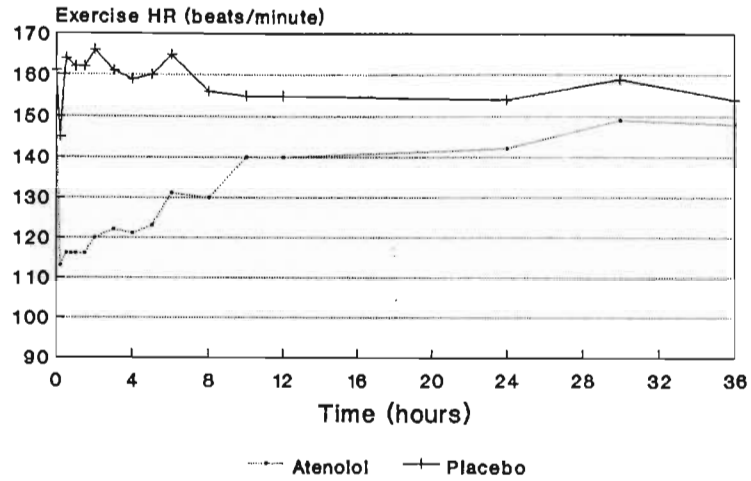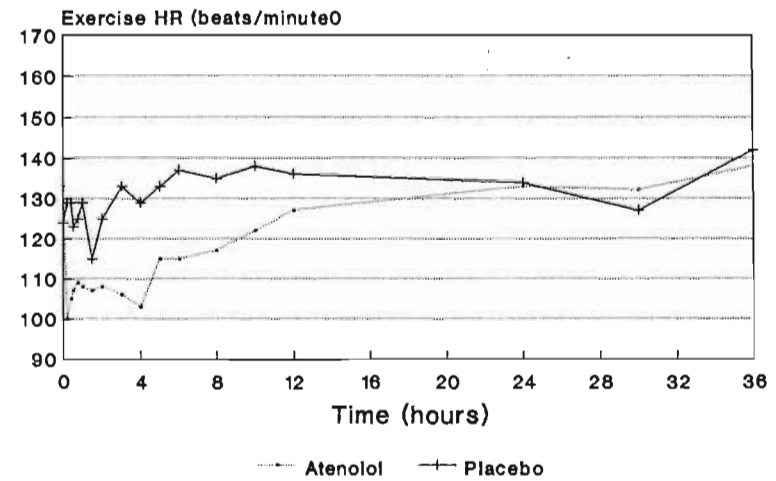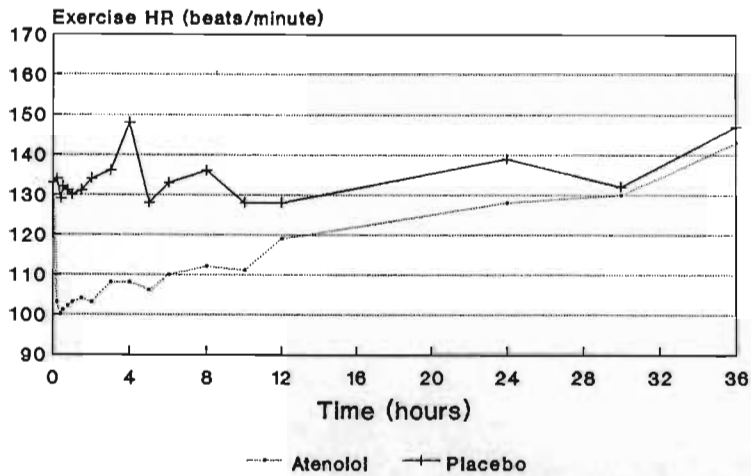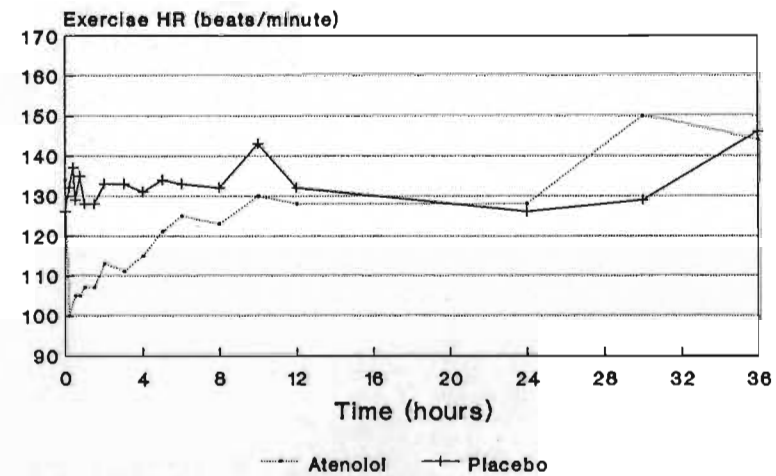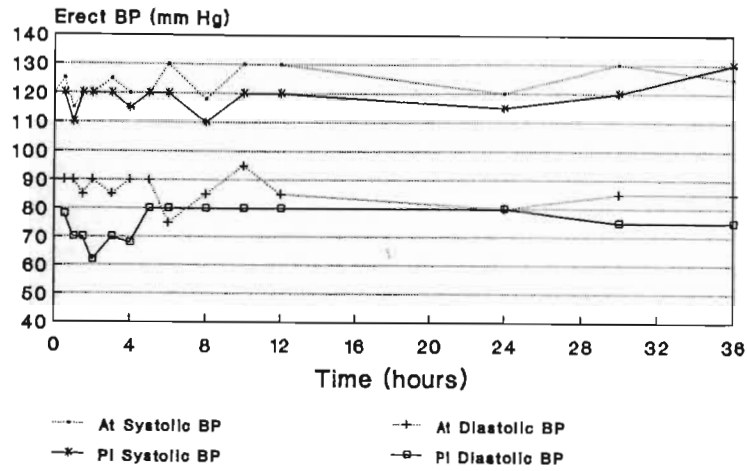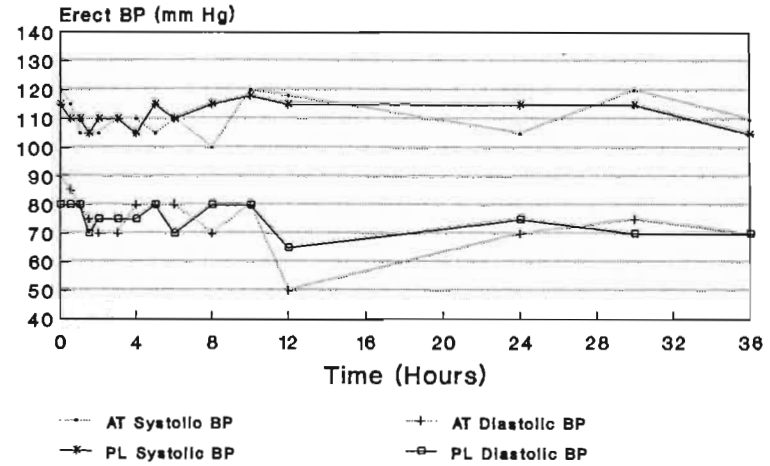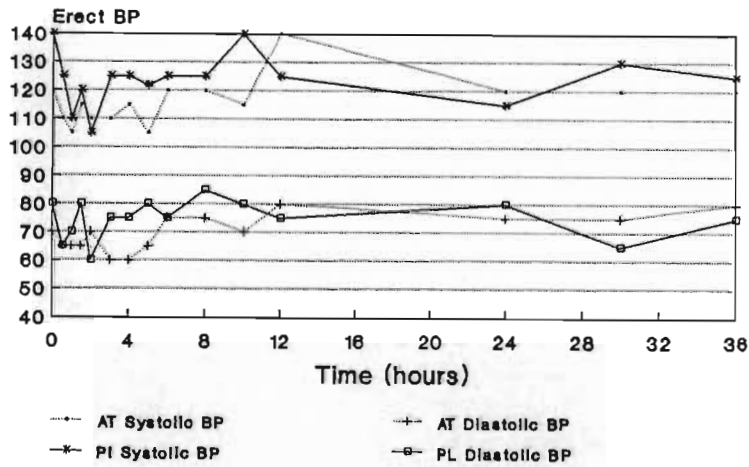
....•.... AT Systolic BP   ---+--- AT Diastolic BP
---*--- Pl Systolic BP   ---□--- PL Diastolic BP
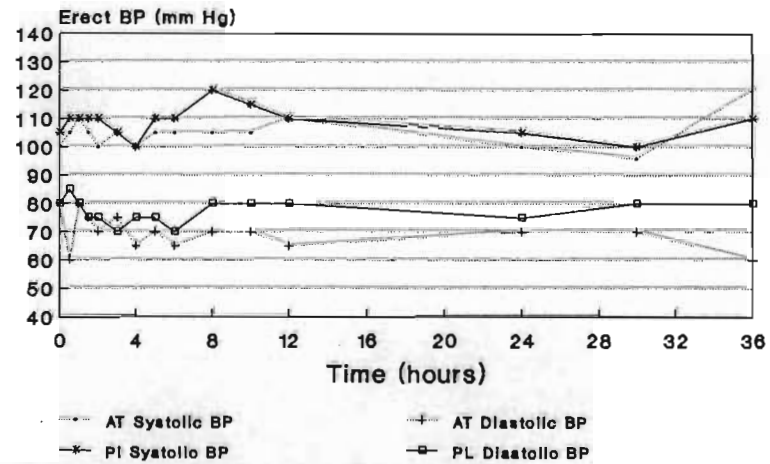
Fig A2.9. Erect blood pressures in black individuals.
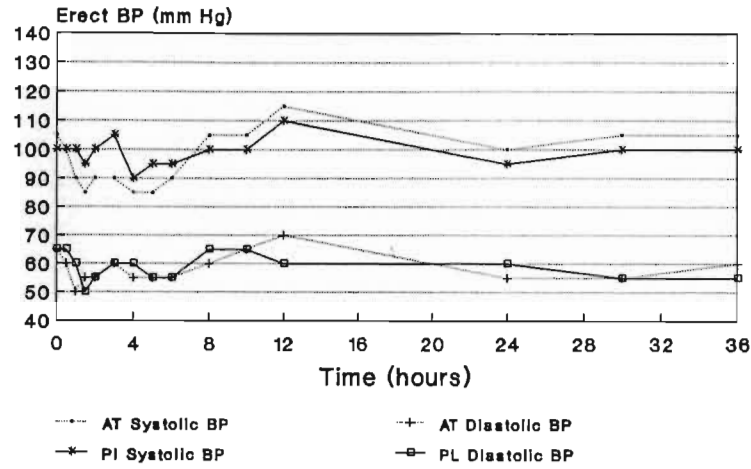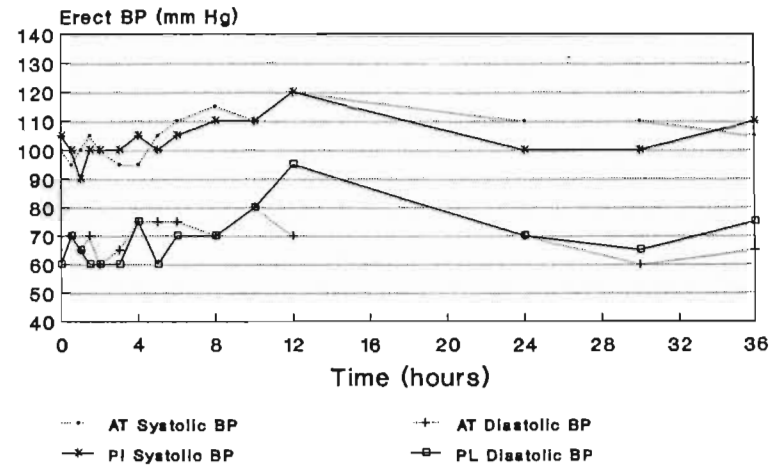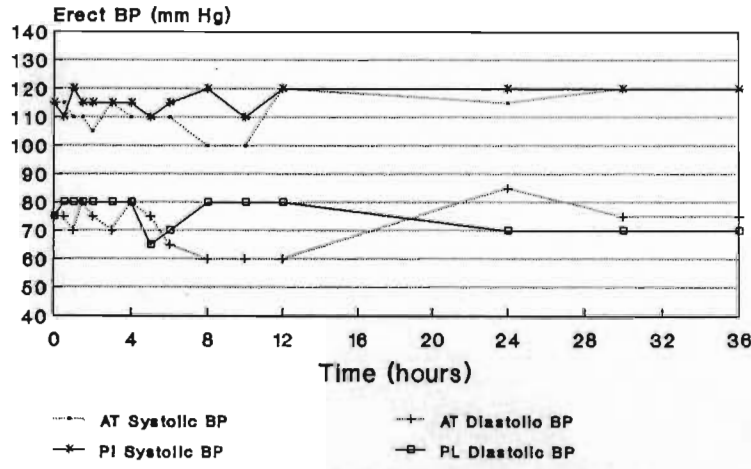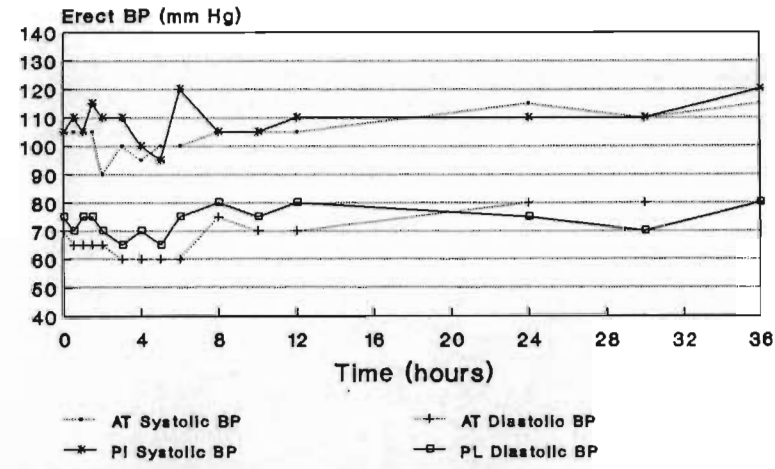
Fig A2.10. Erect blood pressures in black individuals.
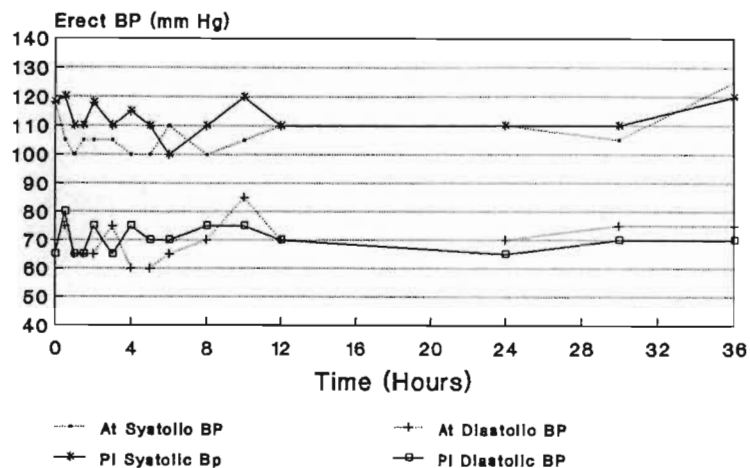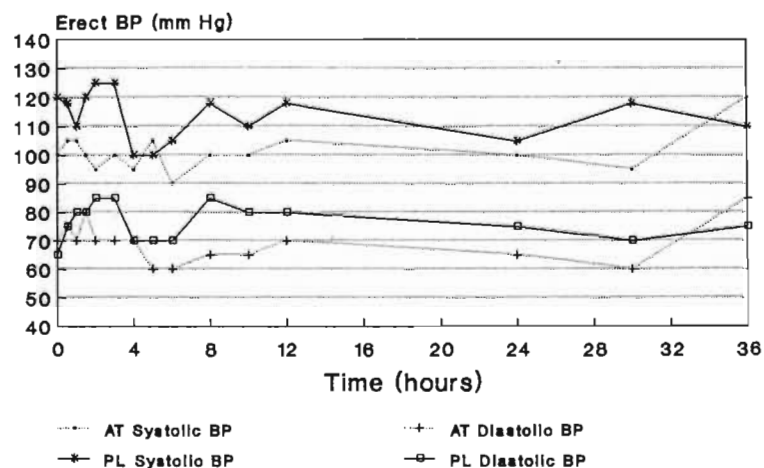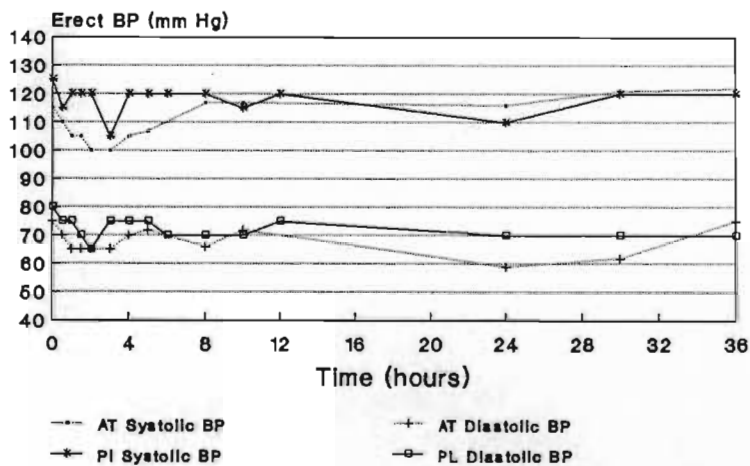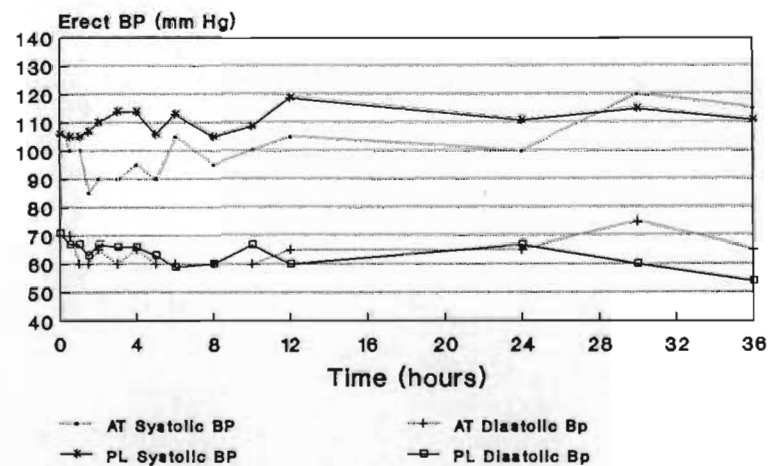
Fig A2.11. Erect blood pressures in white individuals.
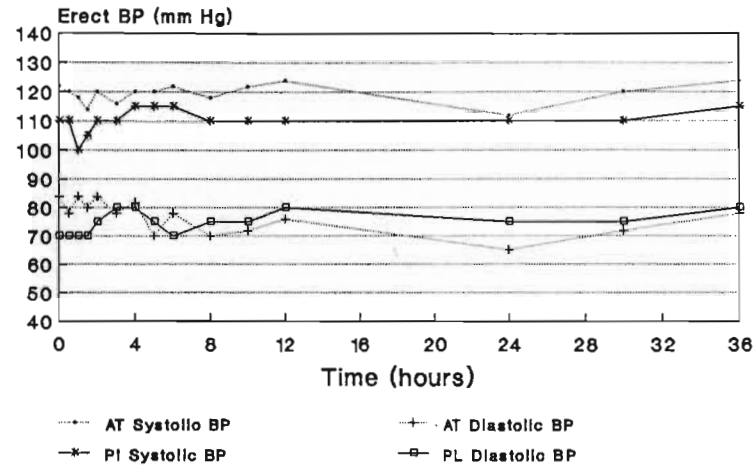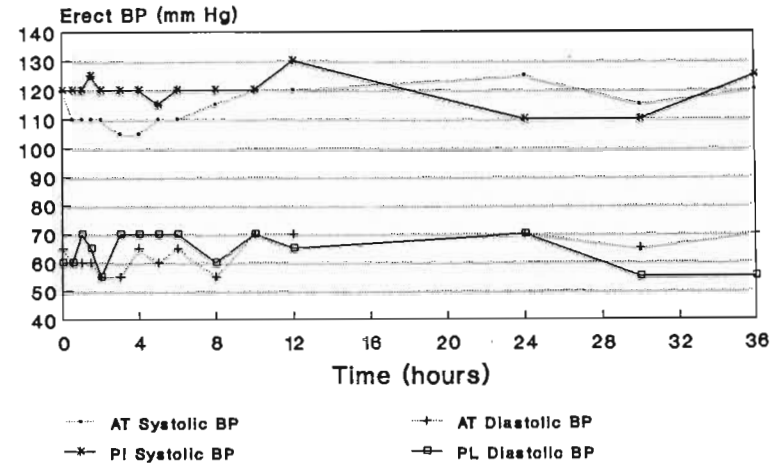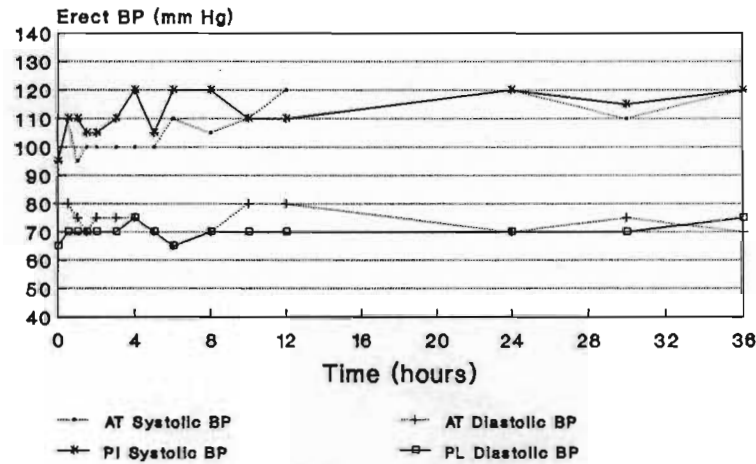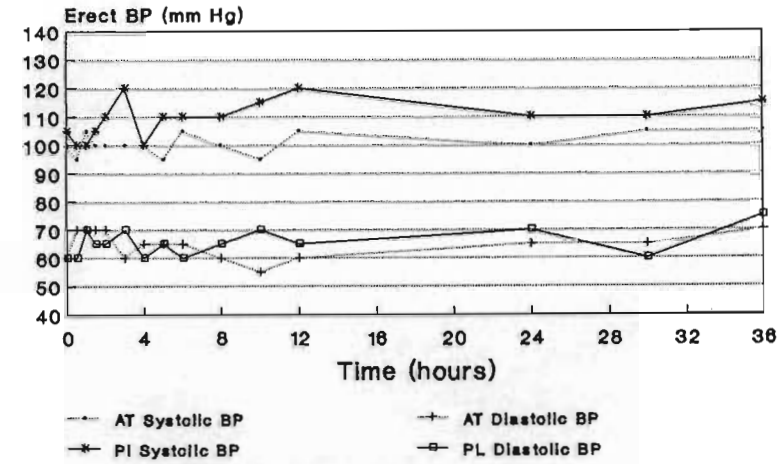
Fig A2.12. Erect blood pressures in white individuals.
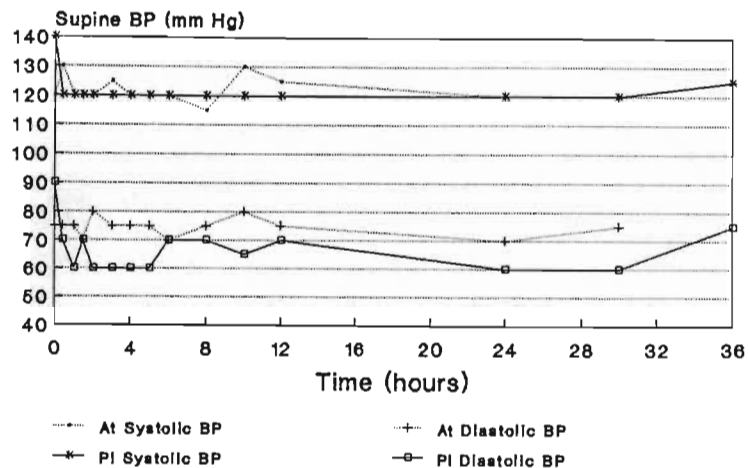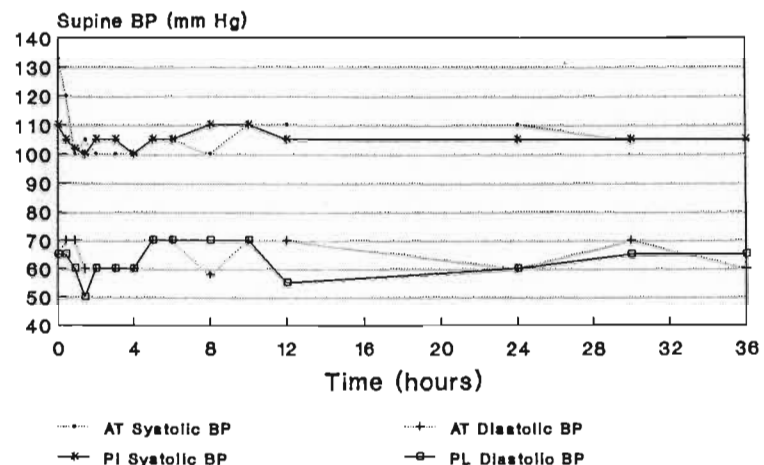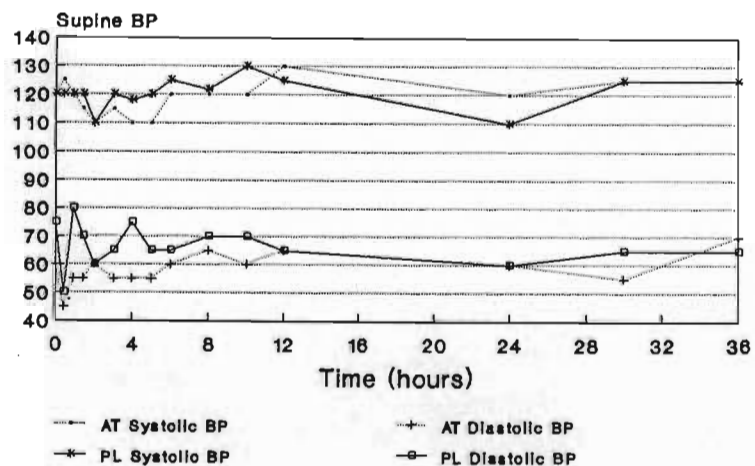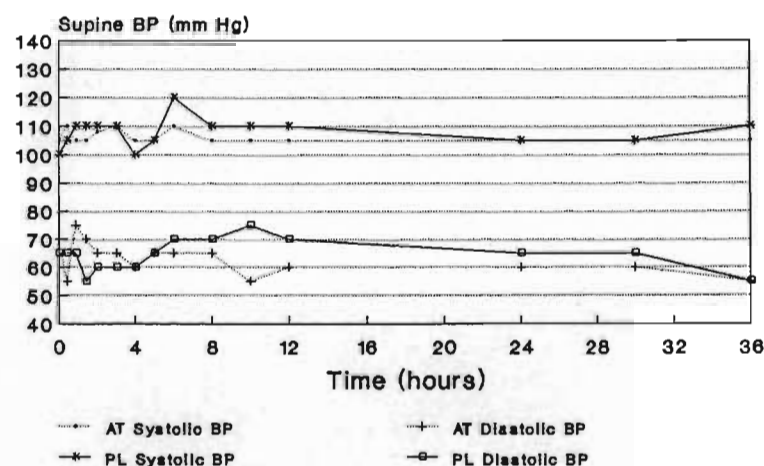
Fig A2.13. Supine blood pressures in black individuals.
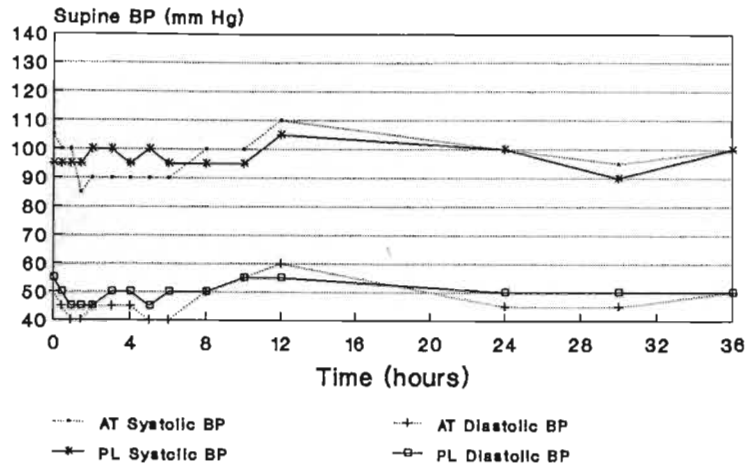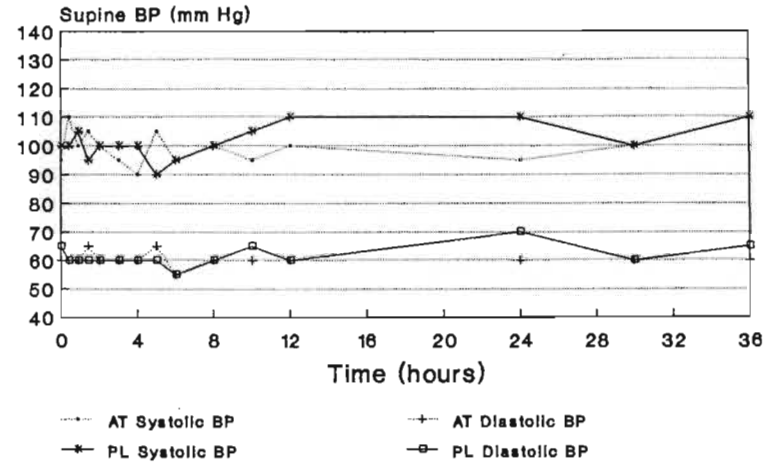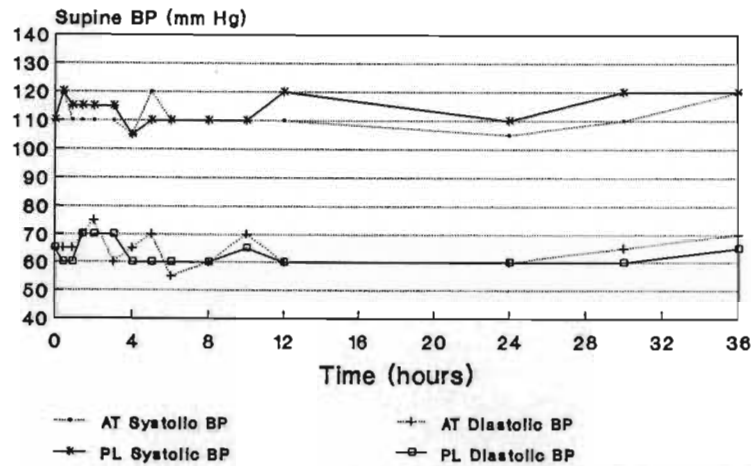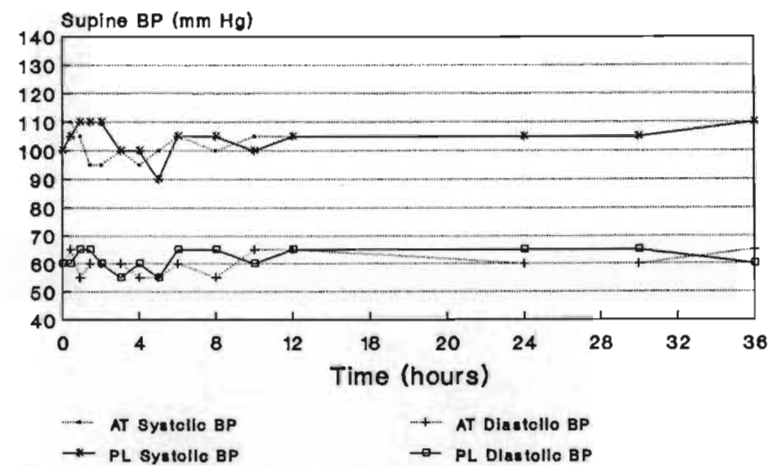
Fig A2.14. Supine blood pressures in black individuals.
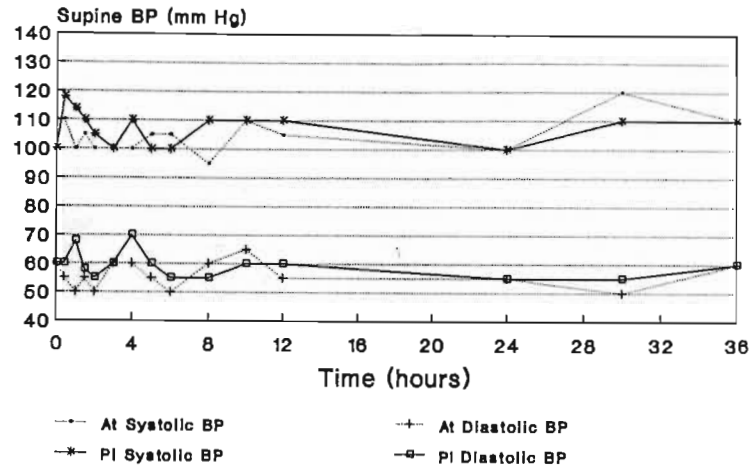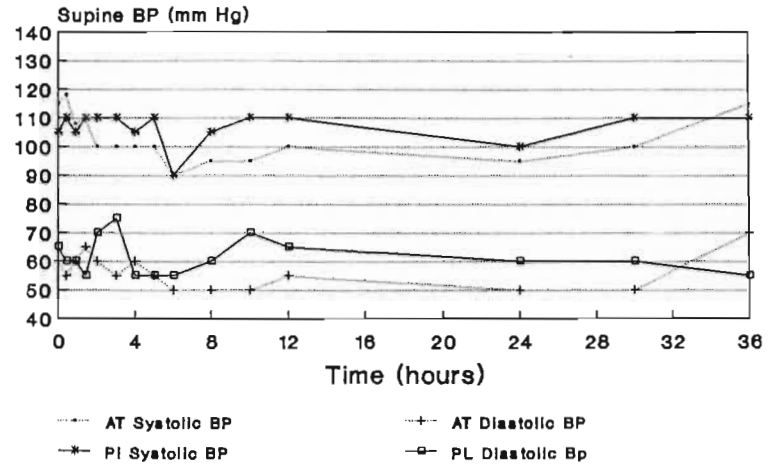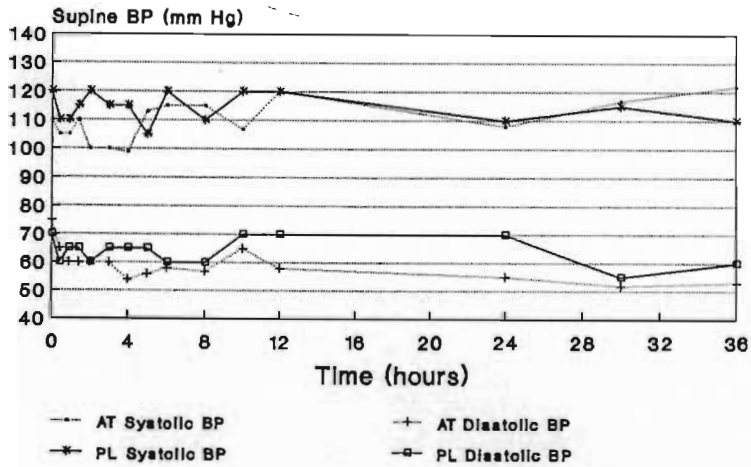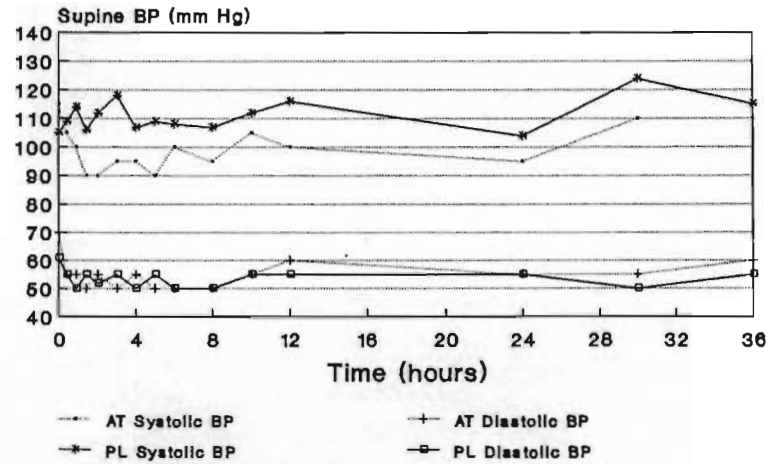
Fig A2.15. Supine blood Pressures in white individuals.
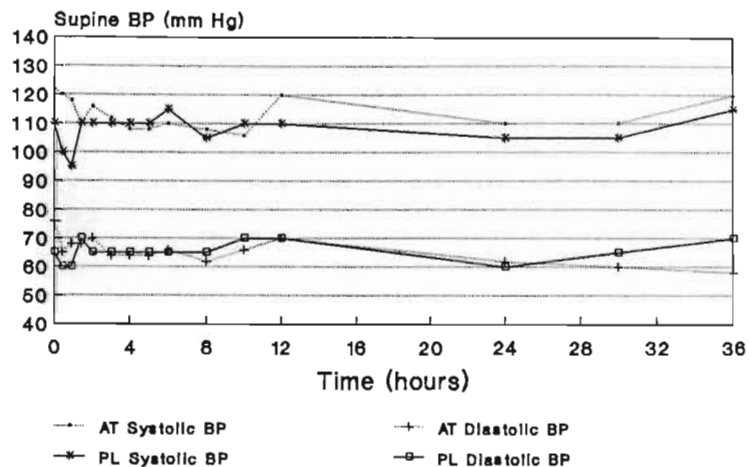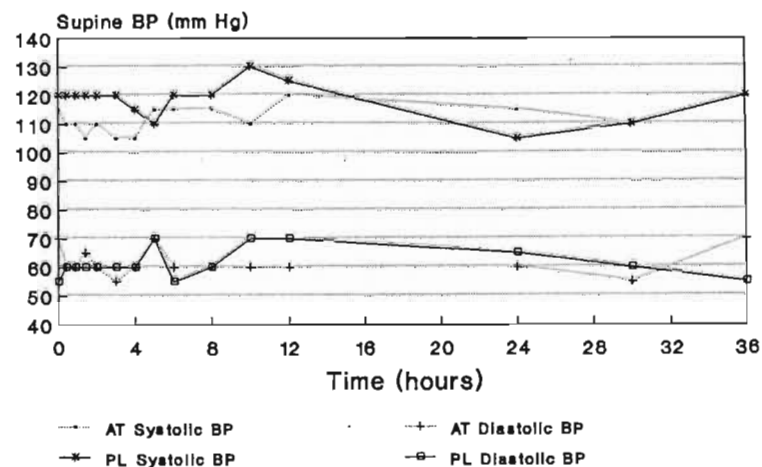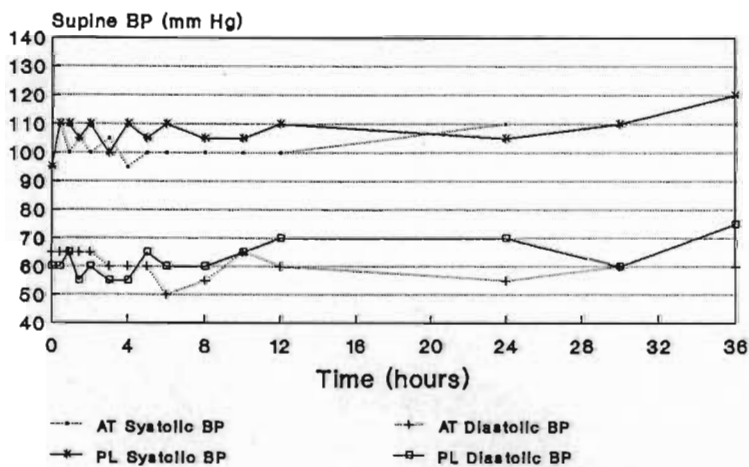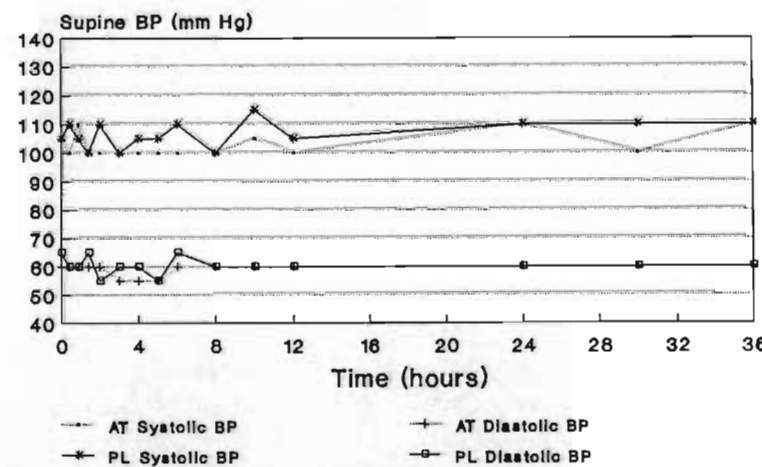
Fig A2.16. Supine blood pressures in white individuals.

MN
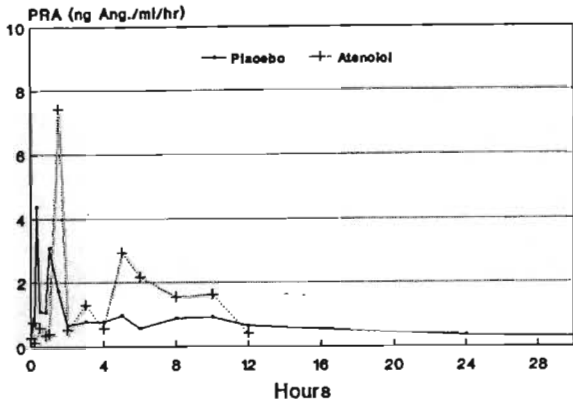
Fig A2.17. PRA in black individuals.

CM

VL

ZN

AP

A52

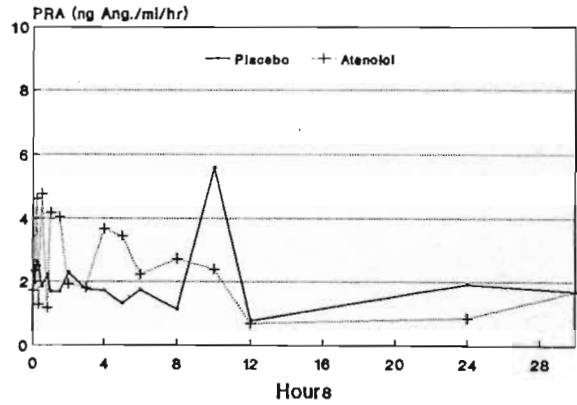# NV

HA

BB

ACA

NF
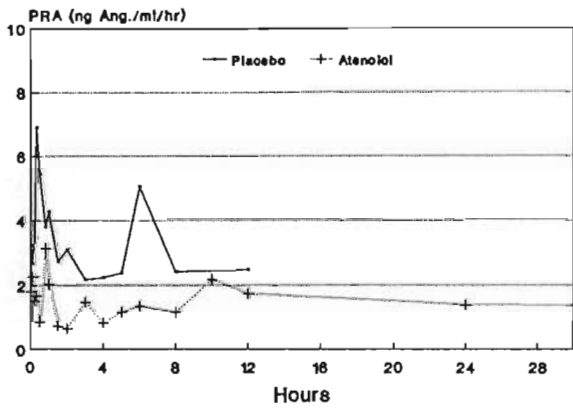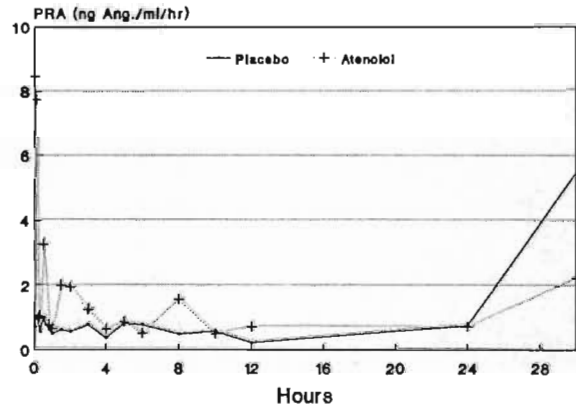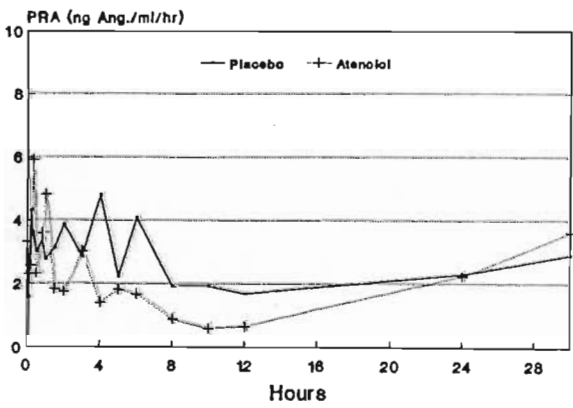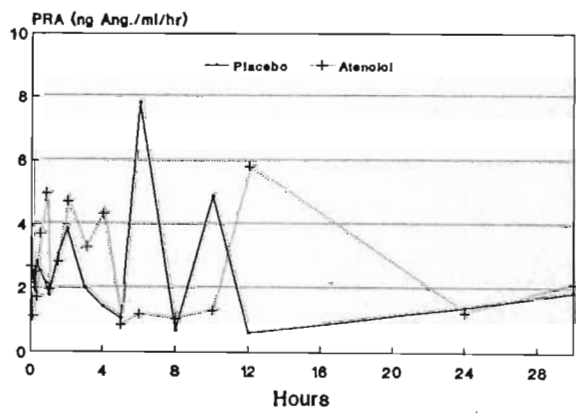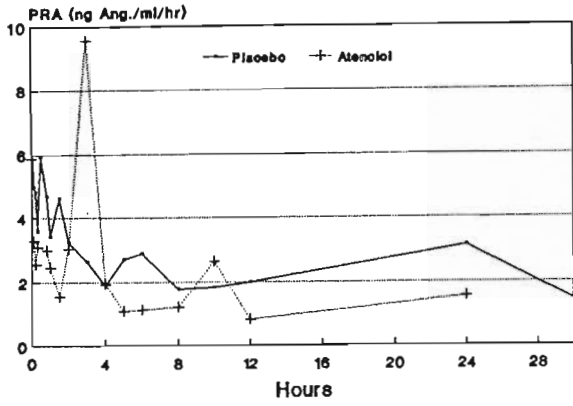
Fig A2.18. PRA in white individuals.
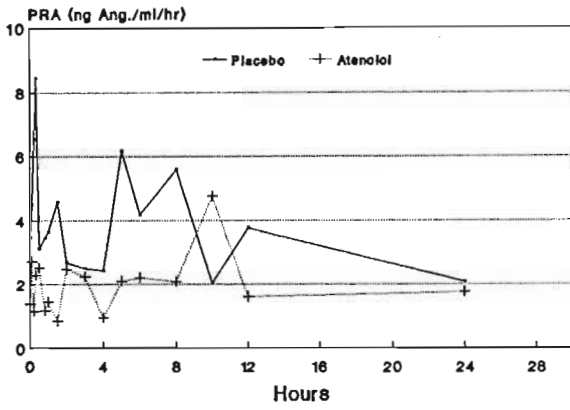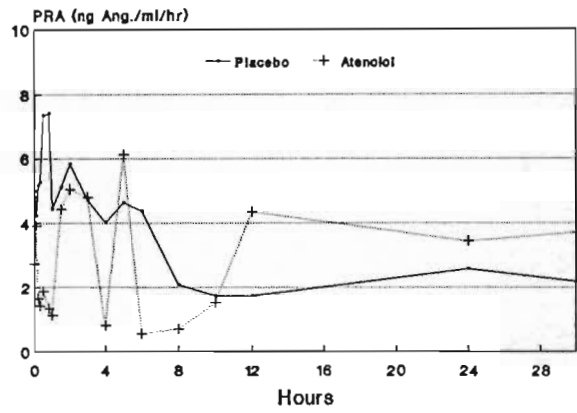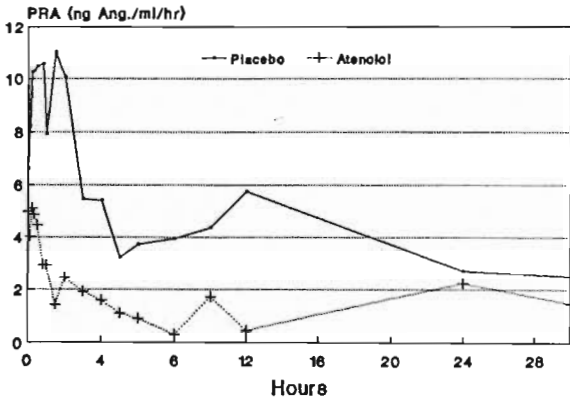
APPENDIX 3
Appendix to Chapter 5

Table A3.1. Atenolol plasma concentration (ng/ml) versus time (hours after start of infusion) data for black volunteers.

MN		CM		VL		AP		ZN		DS		NM	
Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml
0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0
0.17	1337	0.20	1209	0.20	1429	0.21	1126	0.18	1519	0.19	1575	0.19	N/A
0.26	1055	0.25	1078	0.25	1179	0.27	946	0.22	1487	0.23	1416	0.24	1091
0.32	783	0.32	878	0.34	867	0.37	737	0.32	1001	0.33	996	0.34	645
0.37	698	0.41	725	0.41	683	0.43	604	0.39	849	0.40	961	0.42	637
0.50	618	0.70	446	0.63	N/A	0.74	472	0.64	661	0.65	675	0.64	435
0.89	418	0.89	482	0.90	436	0.89	390	0.99	424	0.88	591	0.91	335
1.11	369	1.16	363	1.16	370	1.14	355	1.24	448	1.20	486	1.14	303
1.64	314	1.70	298	1.67	300	1.74	285	1.64	398	1.85	443	1.74	275
2.11	302	2.14	270	2.17	260	2.24	225	2.24	338	2.23	363	2.14	231
3.11	193	3.02	227	3.17	214	3.34	199	3.14	258	3.15	294	3.14	215
4.21	154	4.04	196	4.14	N/A	4.14	166	4.09	N/A	4.15	212	4.28	174
5.29	146	5.14	176	5.14	N/A	5.14	155	5.14	156	5.10	209	5.03	140
6.07	113	6.12	157	6.17	114	6.24	N/A	6.14	136	6.25	162	6.09	130
8.16	81	8.06	124	8.17	105	7.94	128	8.14	96	8.20	97	8.16	96
10.2	N/A	10.2	103	10.2	50	10.0	64	10.0	64	10.2	N/A	10.2	80
12.0	47	12.1	88	12.0	41	11.7	68	12.1	64	11.9	92	12.1	64
23.4	20	23.6	17	24.0	N/A	24.0	N/A	25.0	N/A	25.7	N/A	25.4	24
29.0	14	28.6	12	30.0	<10	30.0	20	31.0	22	29.1	<10	30.6	20
36.0	<10	36.0	<10	36.0	<10	36.0	16	36.0	10	36.0	<10	36.0	N/A

N/A No sample.
<10 less than 10 ng/ml, below assay sensitivity.

Table A3.2. Atenolol plasma concentration (ng/ml) versus time (hours after start of infusion) data for white volunteers.

| NV		BB		ACA		NF		JFI		JFO		ACL	
Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/ml	Time hrs	Conc ng/m	Time hrs	Conc ng/ml
0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0
0.18	1335	0.16	1139	0.16	1071	0.20	976	0.18	956	0.18	980	0.22	1100
0.23	1037	0.20	1100	0.23	996	0.26	784	0.23	N/A	0.25	831	0.27	1080
0.30	802	0.32	858	0.31	935	0.29	625	0.31	704	0.37	810	0.39	678
0.39	686	0.42	718	0.38	840	0.39	571	0.39	662	0.40	751	0.46	644
0.64	443	0.62	599	0.62	524	0.62	446	0.66	440	0.62	N/A	0.74	398
0.88	408	0.89	522	0.91	495	0.81	330	0.90	318	0.89	N/A	1.07	N/A
1.10	357	1.12	465	1.13	399	1.14	272	1.23	294	1.14	405	1.34	363
1.68	293	1.62	401	1.73	345	1.64	263	1.63	261	1.69	338	1.84	N/A
2.12	235	2.12	371	2.13	283	2.36	234	2.13	185	2.14	249	2.24	264
3.11	170	3.12	247	3.23	245	3.14	191	3.23	169	3.14	222	3.14	210
4.46	161	4.22	241	4.23	243	4.24	153	4.23	172	4.14	207	4.14	167
5.15	142	5.12	207	5.33	209	5.24	118	5.33	130	5.24	137	5.04	152
6.11	143	6.12	164	6.23	166	6.14	90	6.13	120	6.14	131	6.04	121
8.08	97	8.22	124	8.13	136	8.14	77	8.13	81	8.14	123	8.14	N/A
10.4	75	10.2	92	10.1	64	10.1	60	10.2	67	10.0	54	10.2	48
12.4	N/A	12.1	68	12.0	62	12.2	40	11.8	52	11.9	N/A	11.8	37
24.1	14	23.7	10	24.1	46	24.4	<10	25.2	14	25.2	12	25.1	<10
30.0	N/A	30.0	<10	29.8	N/A	30.3	<10	30.4	11	30.0	<10	30.0	<10
36.0	12	36.2	<10	36.0	<10	36.0	<10	36.0	<10	36.0	<10	36.0	<10

N/A No sample.
<10 less than 10 ng/ml, below assay sensitivity.

Table A3.3. Intermediate model independent pharmacokinetic parameters for blacks and whites.

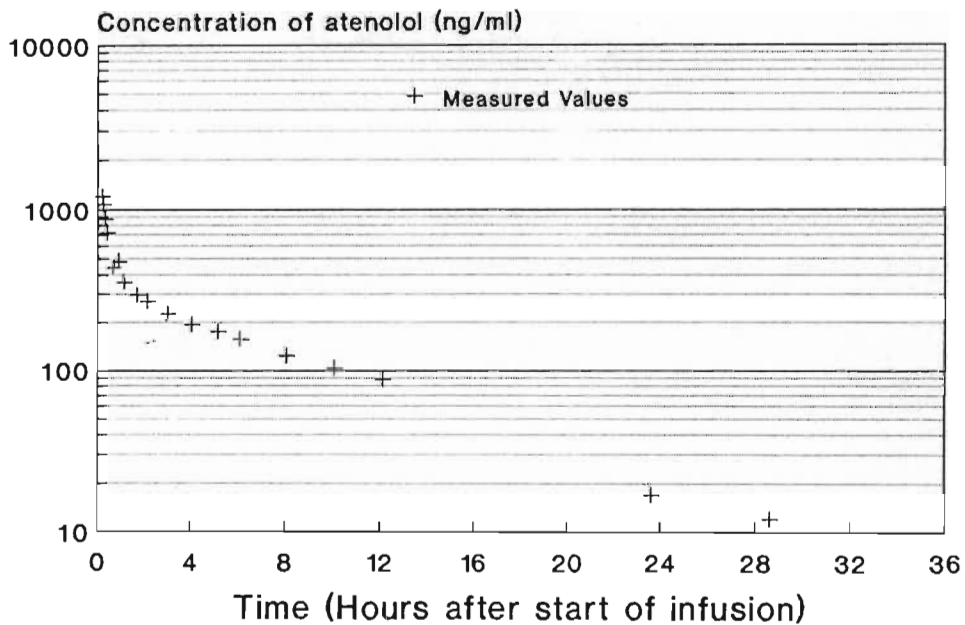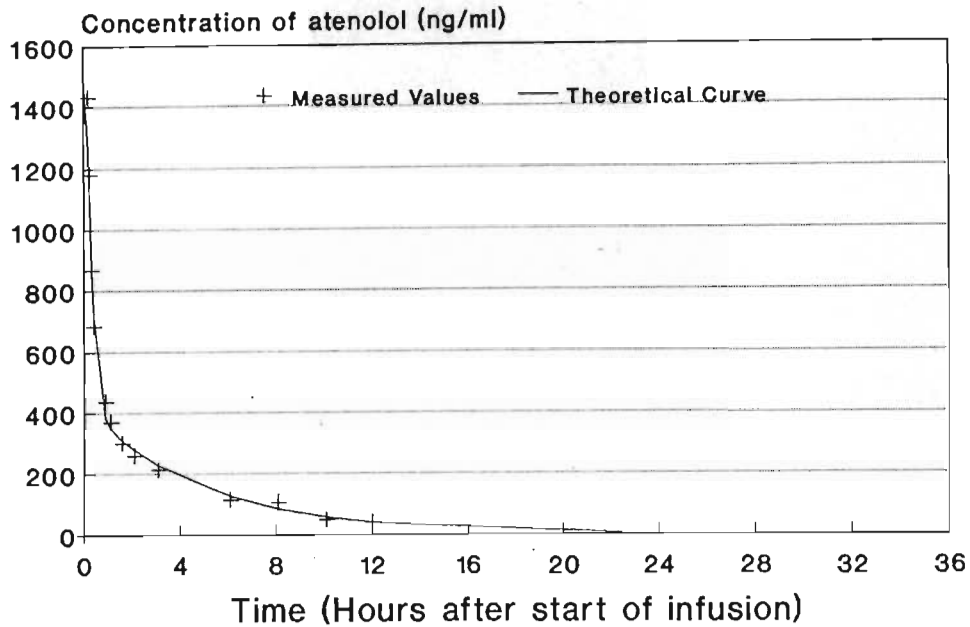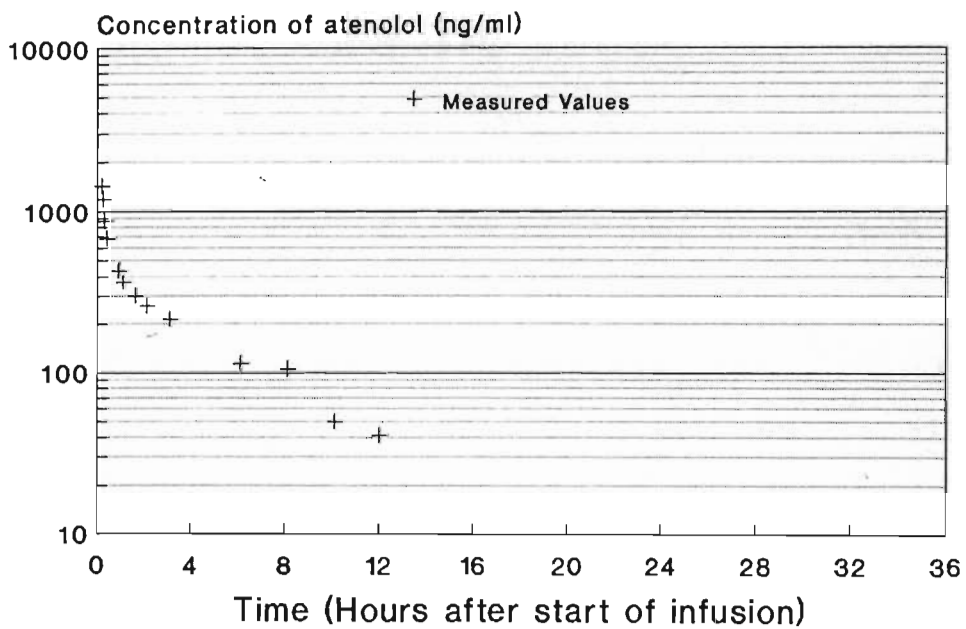|	Cn (ug/L)	tn (hr)	$\lambda_z(r^2)$ (hr^{-1})	AUC_{0-tn} (ug/L.hr)	$AUC_{0-\infty}$ (ug/L.hr)	$AUMC_{0-tn}$	$AUMC_{0-\infty}$	MRT_{INF}	MRT_{IV}
Blacks									
MN	14	29.0	0.097(.968)	2640	2784	15572	21246	7.63	7.56
CM	12	28.6	0.119(.994)	3169	3270	20396	24127	7.38	7.31
VL	41	12.0	0.196(.910)	2231	2440	7410	10987	4.50	4.43
AP	16	36.0	0.073(.949)	3108	3327	24949	35841	10.77	10.70
ZN	10	36.0	0.078(.955)	3054	3182	25049	31308	9.84	9.74
DS	92	11.9	0.121(.842)	2947	3707	10334	25666	6.92	6.85
NM	20	30.6	0.080(.973)	2794	3044	20613	31388	10.31	10.24
Whites									
NV	12	36.0	0.090(.934)	2808	2941	19075	25356	8.62	8.55
BB	10	23.7	0.162(.999)	3168	3230	16637	18481	5.72	5.65
ACA	46	24.1	0.084(.729)	3264	3812	21022	40739	10.68	10.61
NF	40	12.2	0.155(.971)	1824	2082	6634	11447	5.50	5.43
JFI	11	30.4	0.103(.977)	2400	2507	15261	19545	7.80	7.73
JFO	12	25.2	0.129(.956)	2718	2811	13468	16533	5.88	5.81
ACL	37	11.8	0.206(.996)	2085	2265	6817	9808	4.33	4.26

Fig A3.1a. MN: Plasma concentration-time plot.
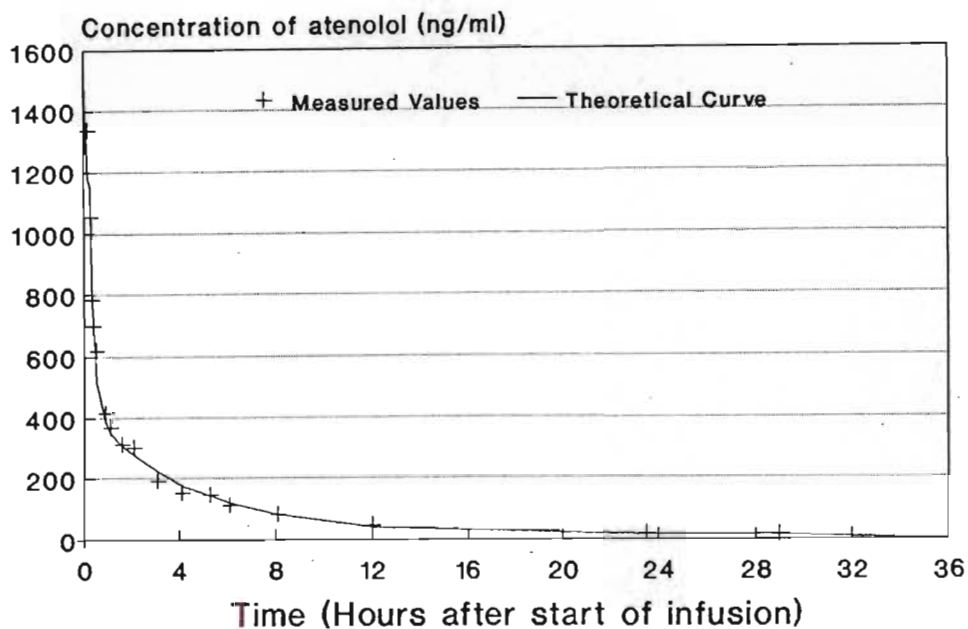
3 Compartment Model

Fig A3.1b. MN: Log Plasma concentration-time plot.
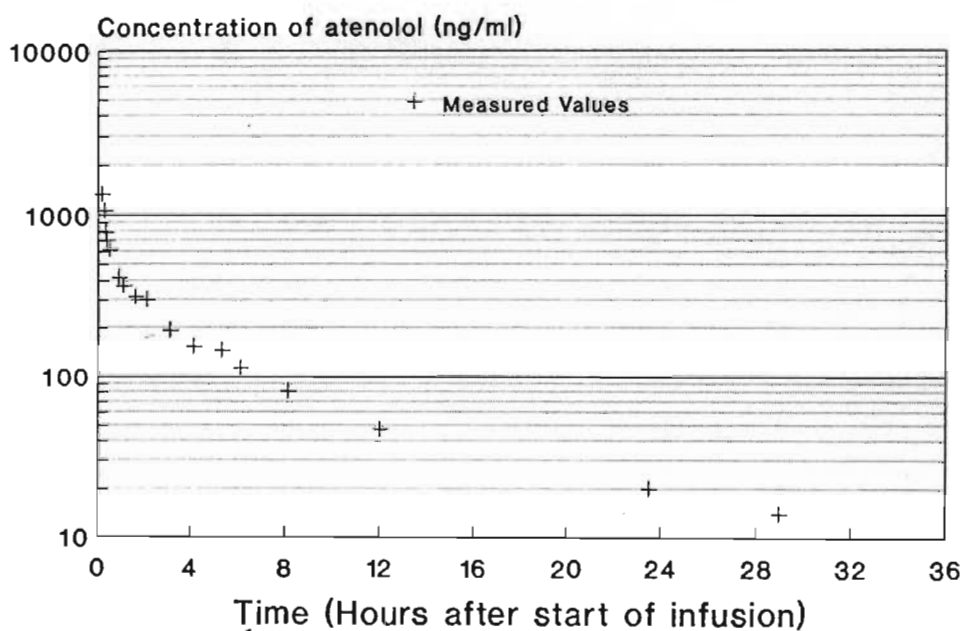
Fig A3.2a. CM: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)
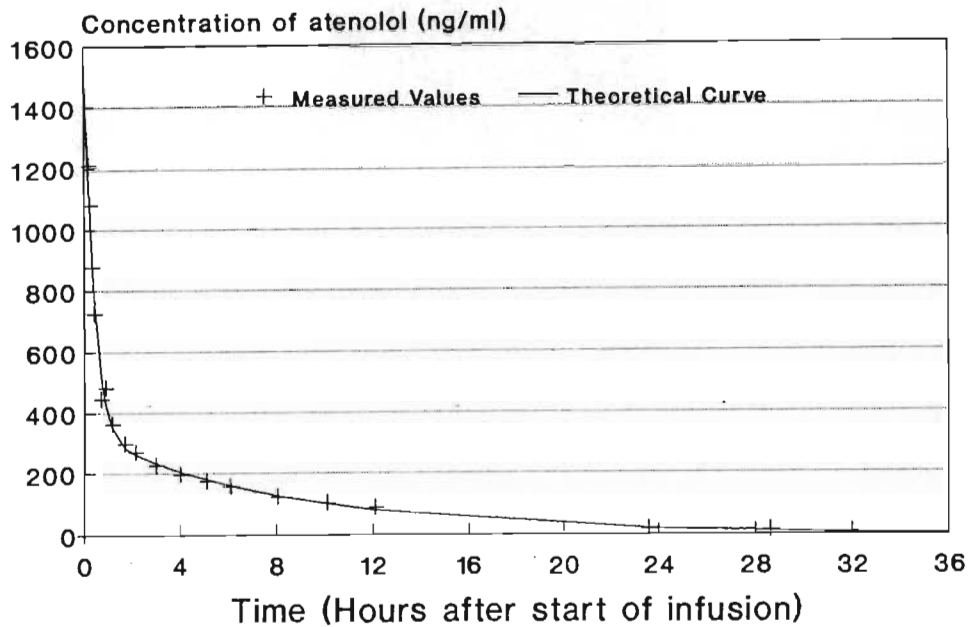
2 Compartment Model

Fig A3.2b. CM: Log Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

Fig A3.3a. VL: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

+ Measured Values   — Theoretical Curve

Time (Hours after start of infusion)

2 Compartment Model

Fig A3.3b. VL: Log Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

+ Measured Values
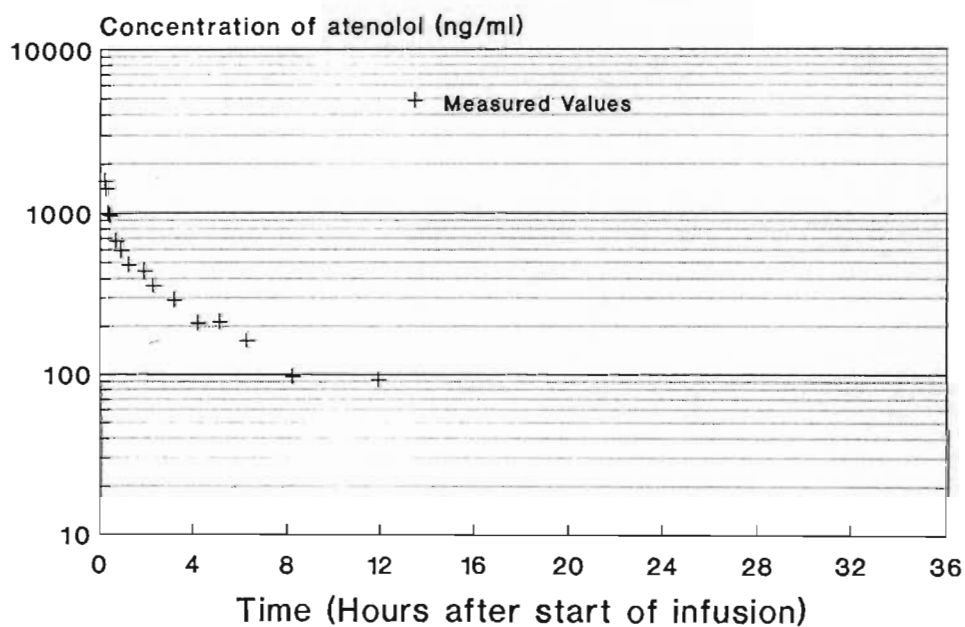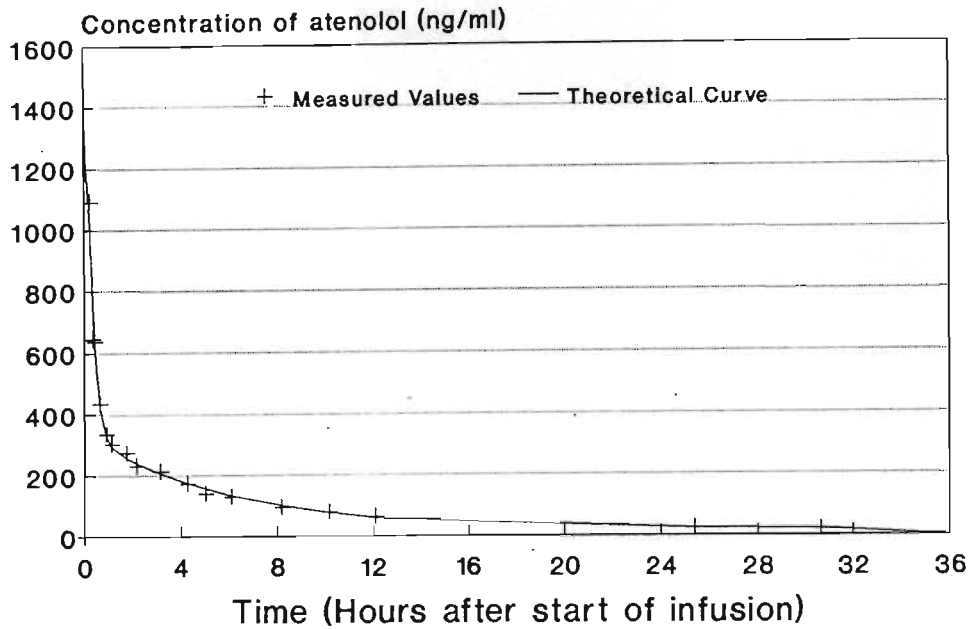
Time (Hours after start of infusion)

Fig A3.4a. AP: Plasma concentration-time plot.
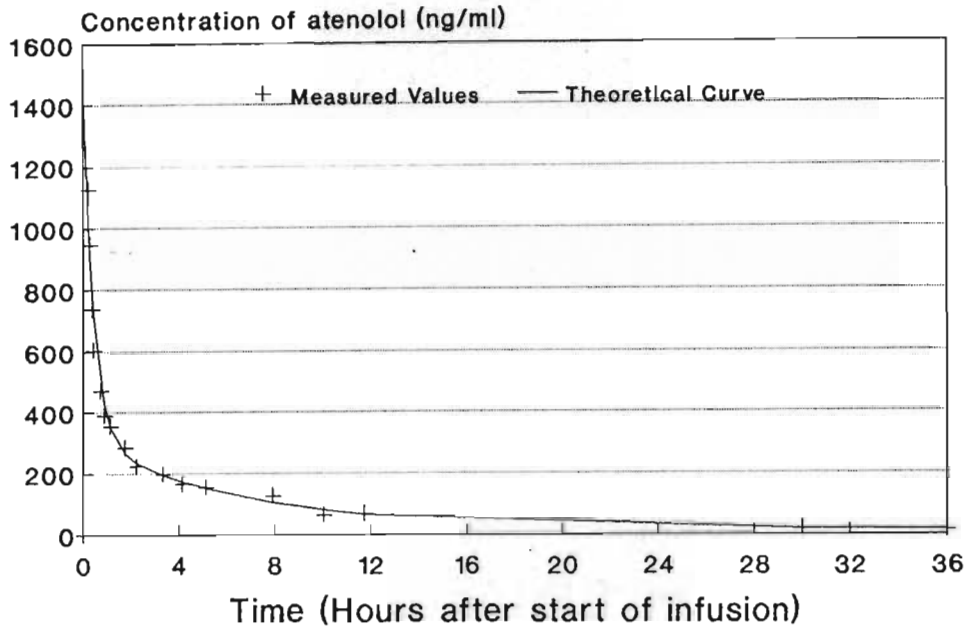
3 compartment

Fig A3.4b. AP: Log Plasma concentration-time plot.
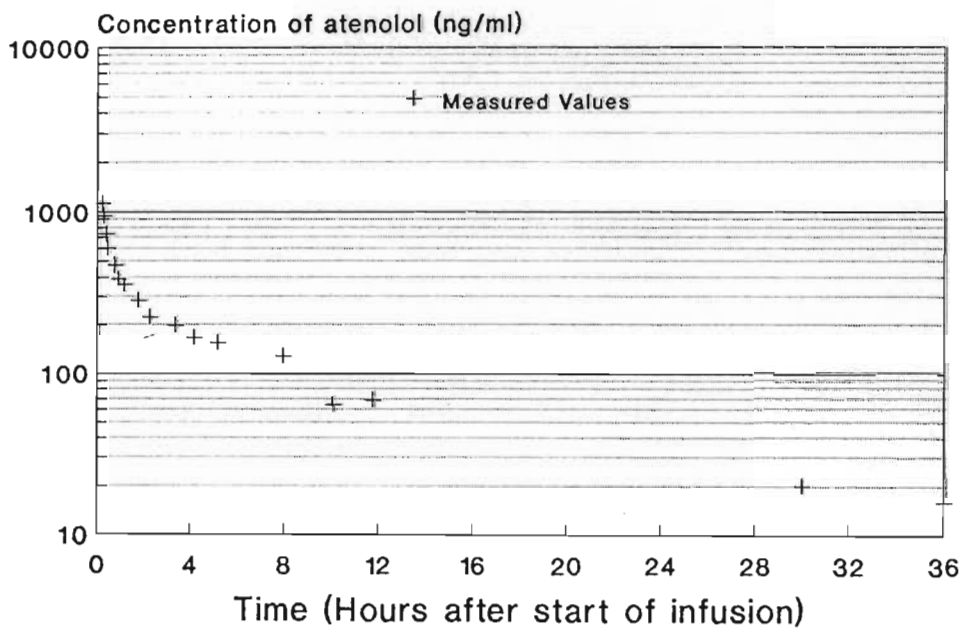
Fig A3.5a. ZN: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)
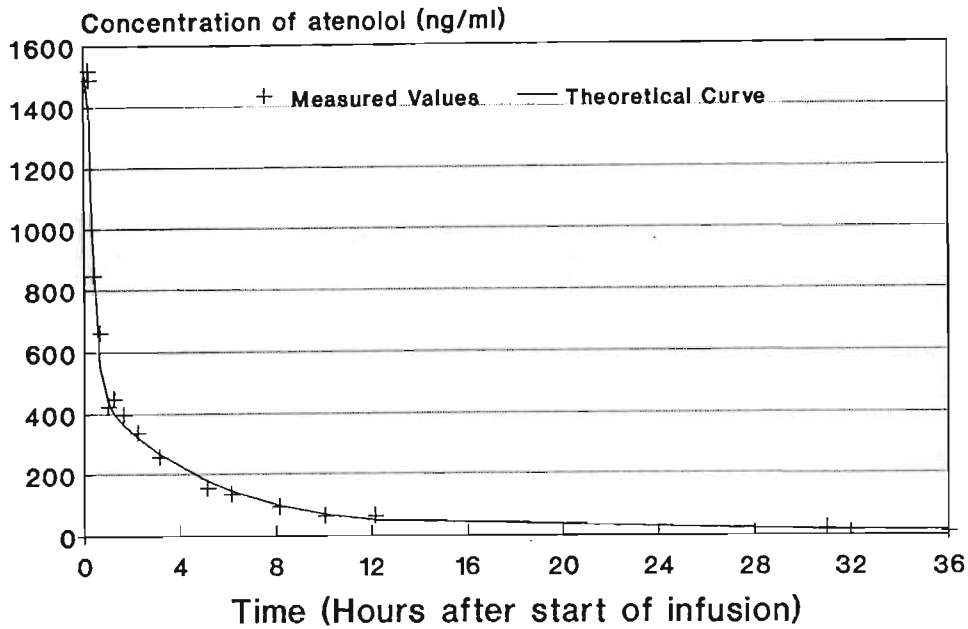
3 Compartment Model

Fig A3.5b. ZN: Log Plasma concentration-time plot.

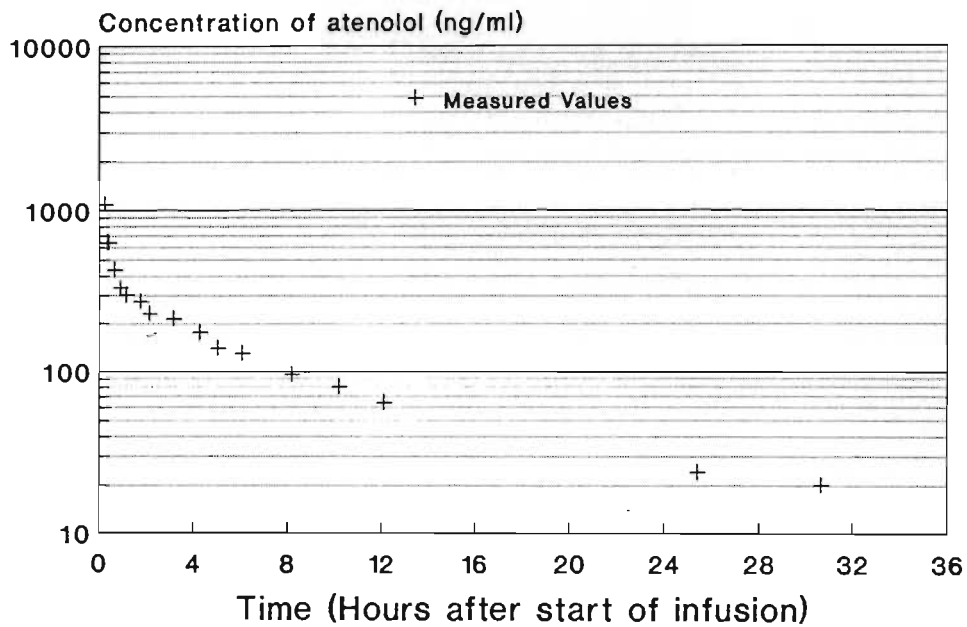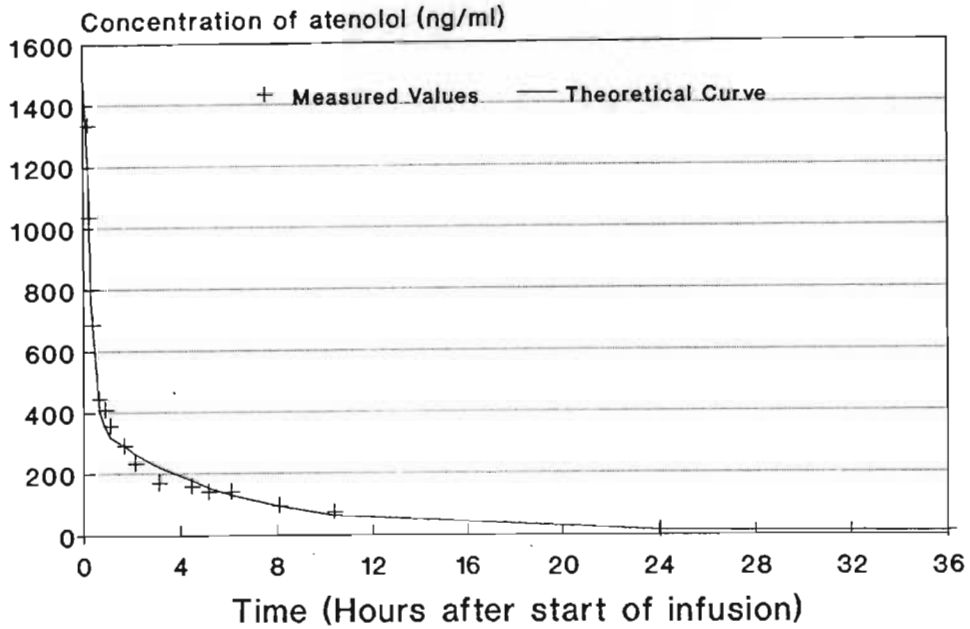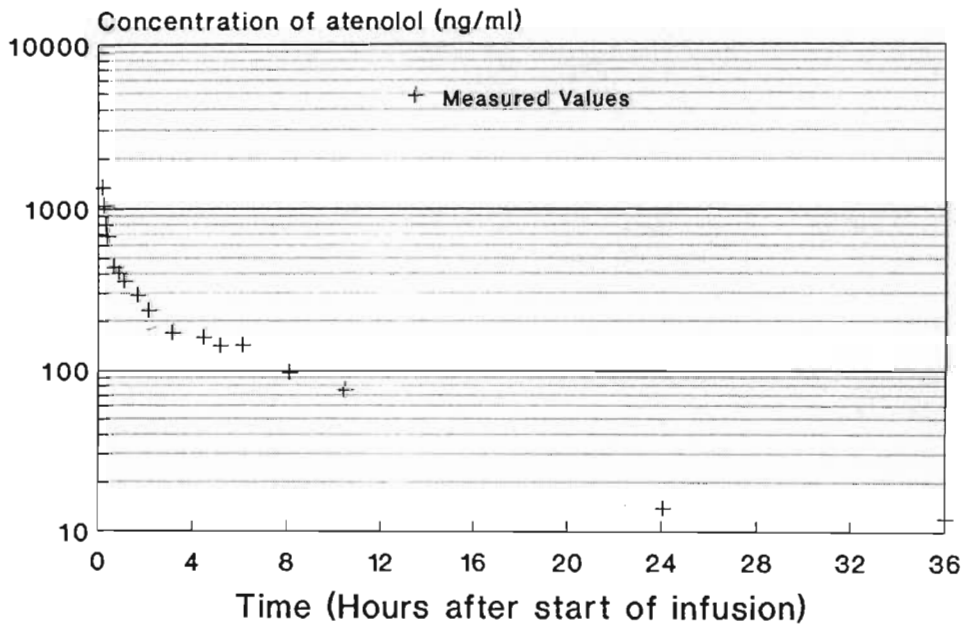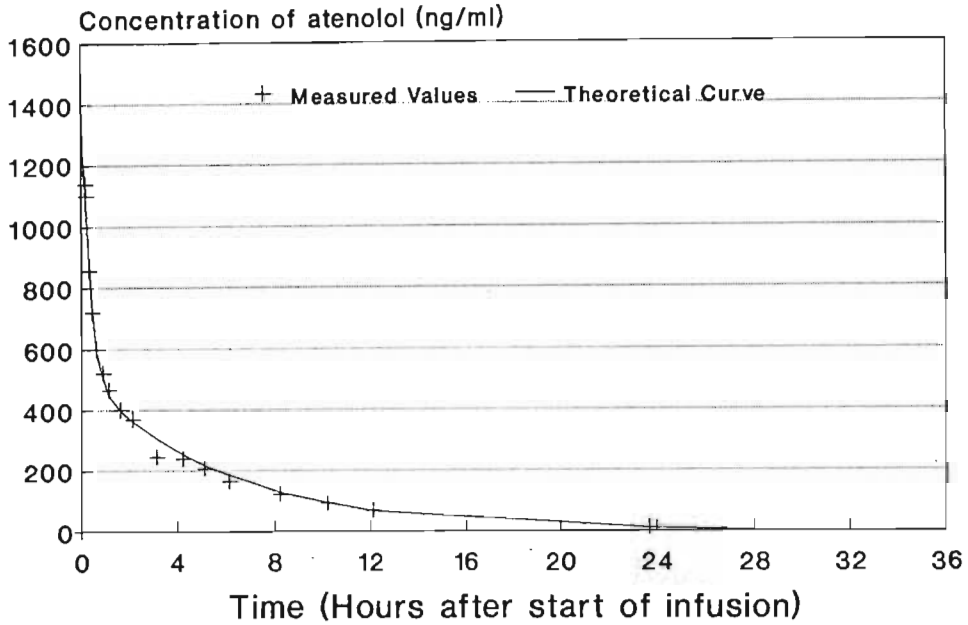Concentration of atenolol (ng/ml)
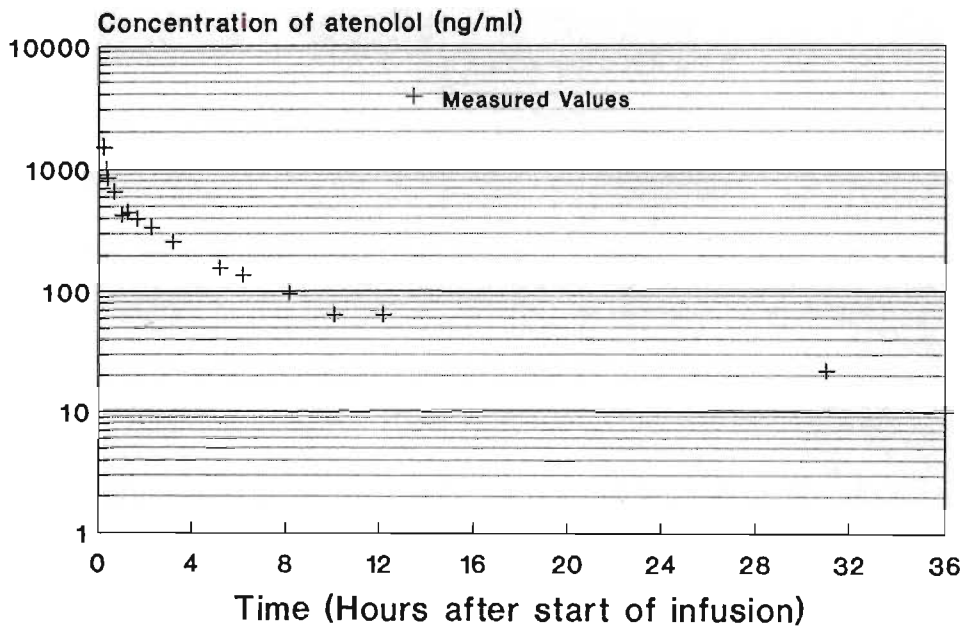
Fig A3.6a. DS: Plasma concentration-time plot.
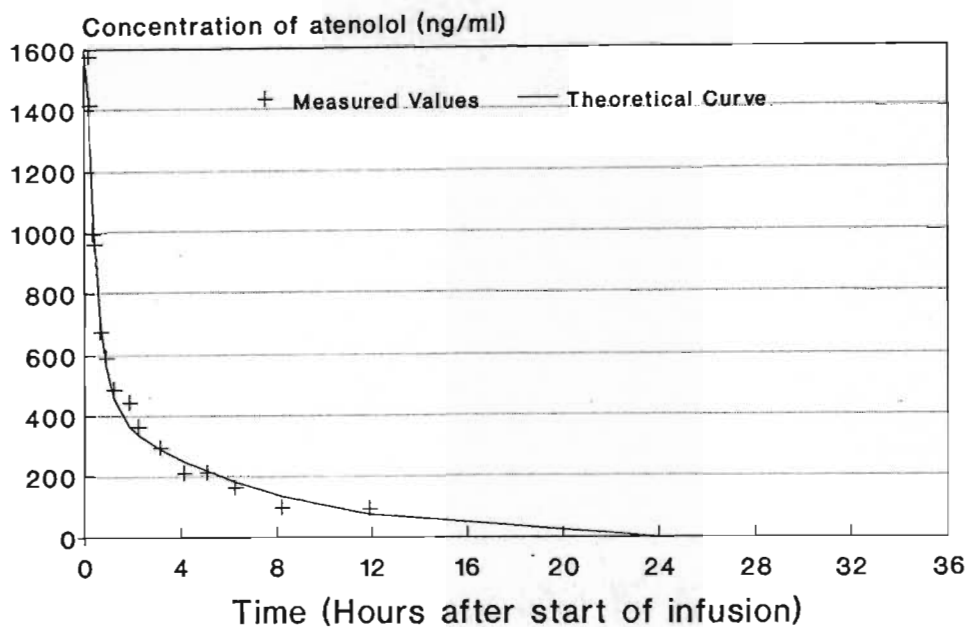
2 Compartment Model

Fig A3.6b. DS: Log Plasma concentration-time plot.

Fig A3.7a. NM: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

3 Compartment

Fig A3.7b. NM: Log Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

Fig A3.8a. NV: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

3 Compartment Model

Fig A3.8b. NV: Log Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

Time (Hours after start of infusion)

Fig A3.9a. BB: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

+ Measured Values _____Theoretical Curve

Time (Hours after start of infusion)

2 Compartment Model

Fig A3.9a. BB: Log Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

+ Measured Values

Time (Hours after start of infusion)

Fig A3.10a. ACA: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

+ Measured Values —— Theoretical Curve

Time (Hours after start of infusion)

3 Compartment Model

Fig A3.10b. ACA: Log Plasma concentration time plot.

Concentration of atenolol (ng/ml)

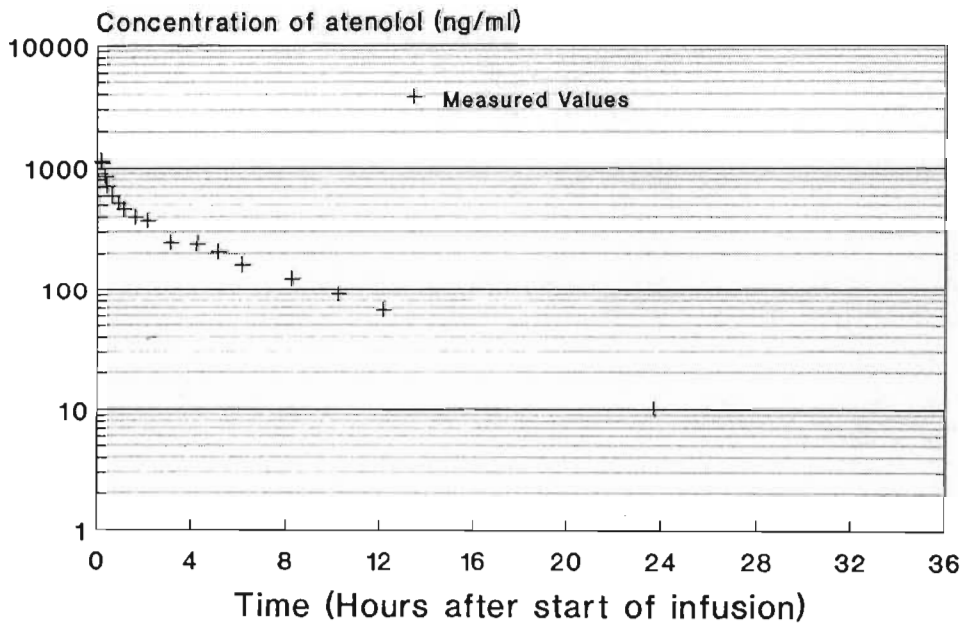+ Measured Values
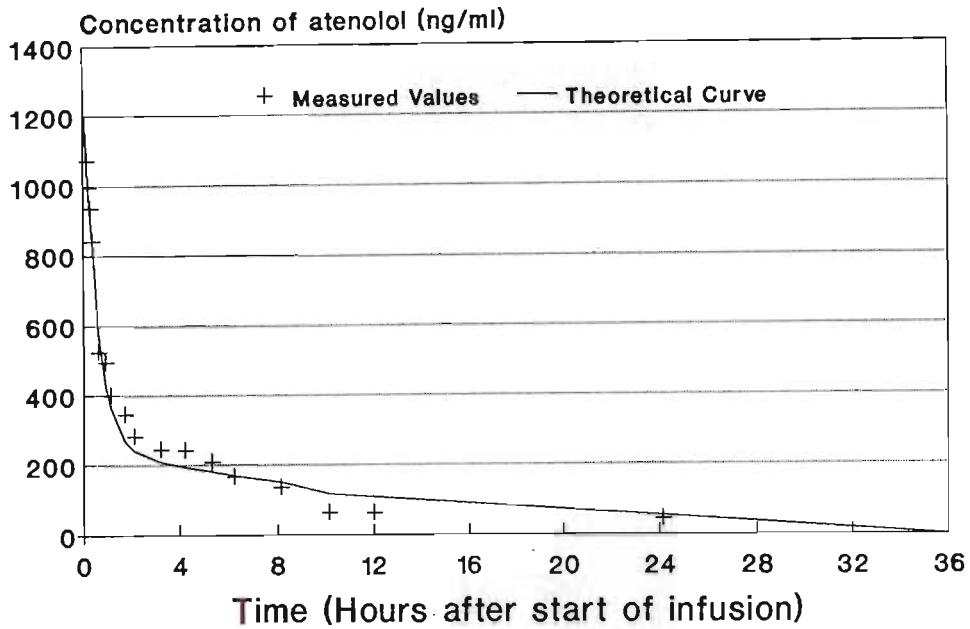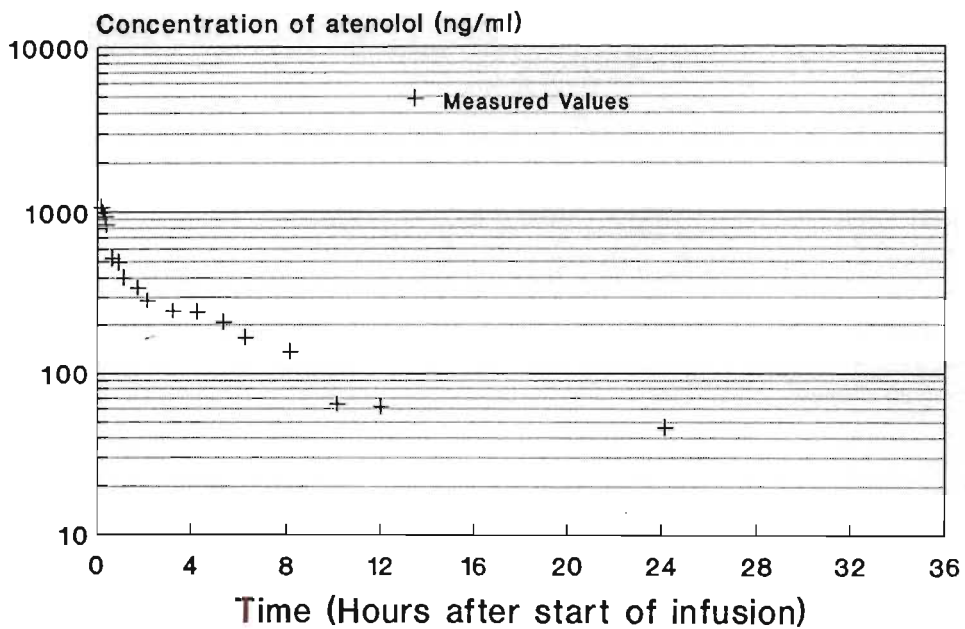
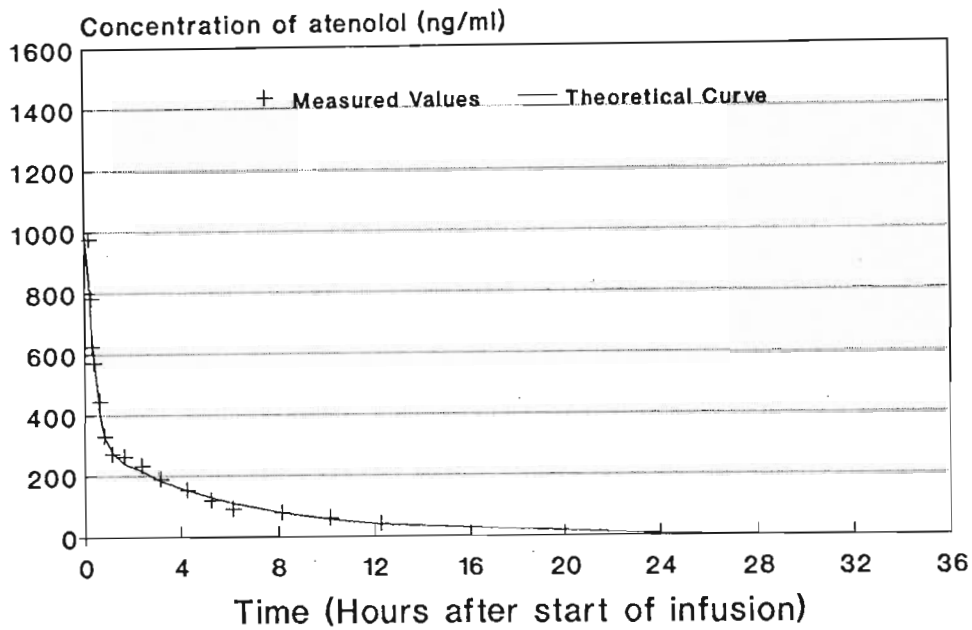Time (Hours after start of infusion)

Fig A3.11a. NF: Plasma concentration-time plot.

2 Compartment Model

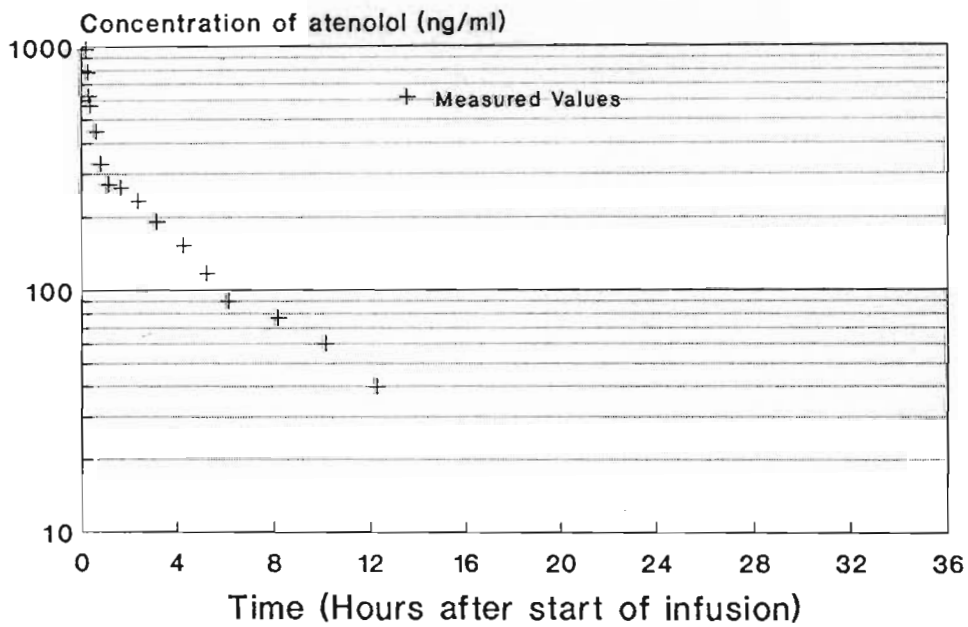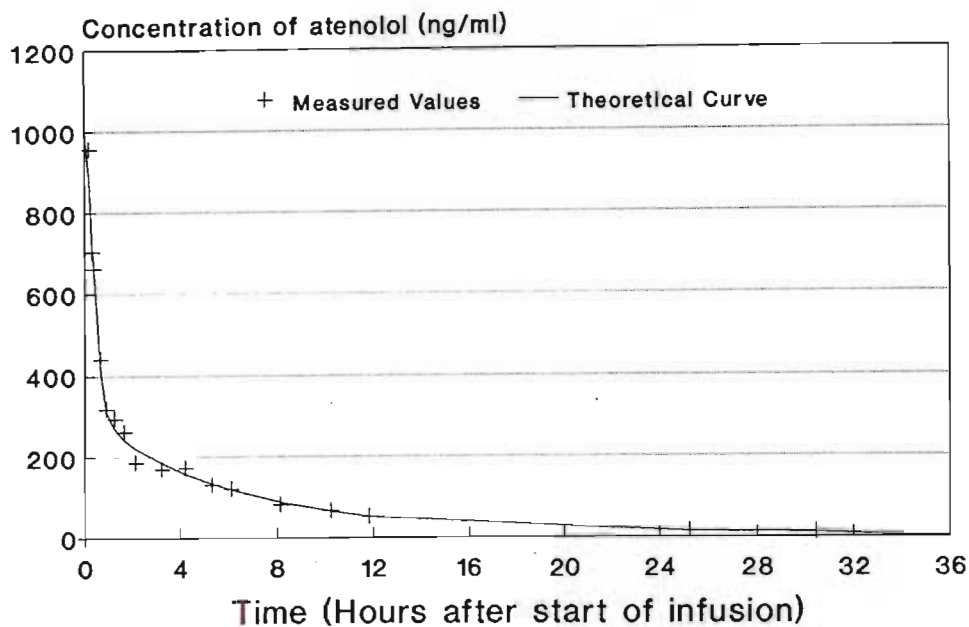# Fig A3.11b. NF: Log Plasma concentration time plot.

Fig A3.12a. JFI: Plasma concentration-time plot.

3 Compartment Model

Fig A3.12b. JFI: Log Plasma concentration-time plot.
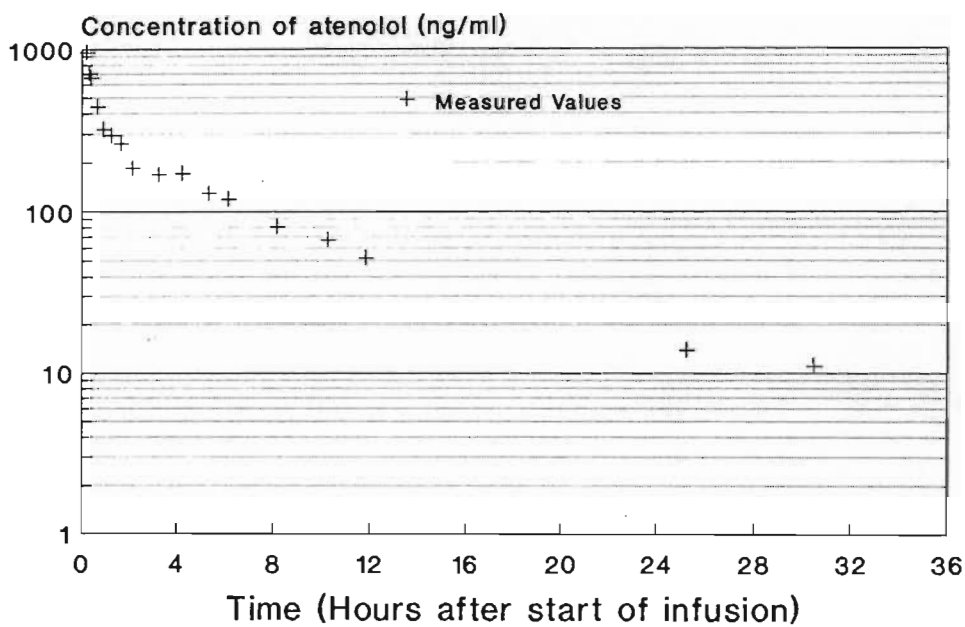
Fig A3.13a. JFO: Plasma concentration-time plot.
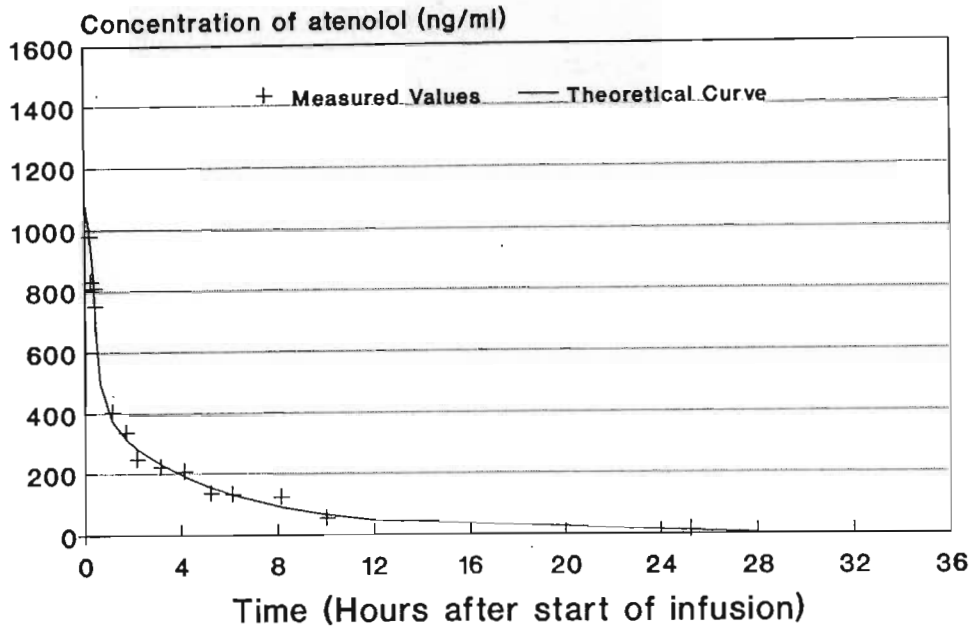
3 Compartment Model

Fig A3.13b. JFO: Log Plasma concentration time plot.
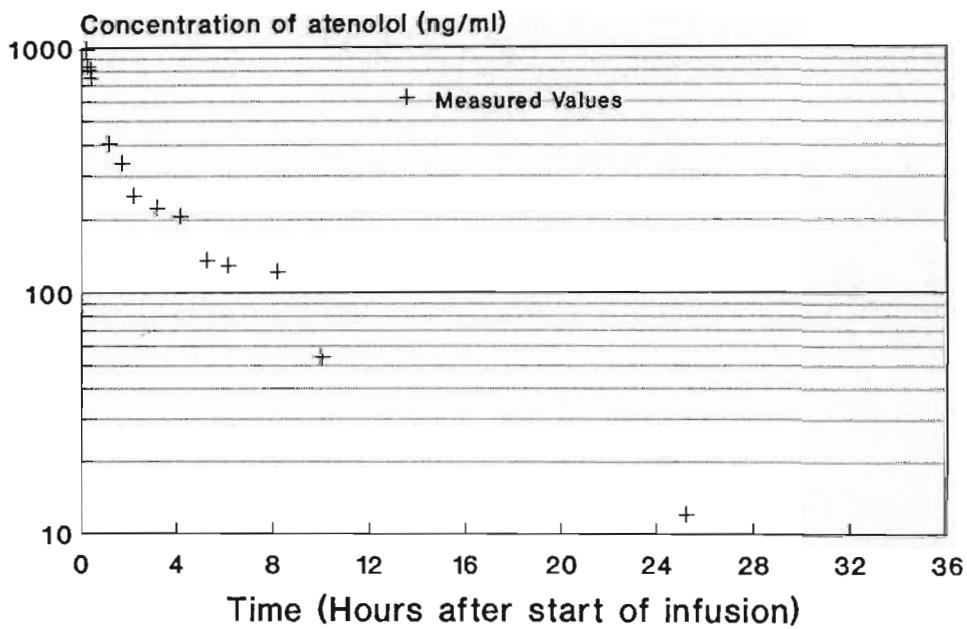
Fig A3.14a. ACL: Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

+ Measured Values   —— Theoretical Curve

Time (Hours after start of infusion)
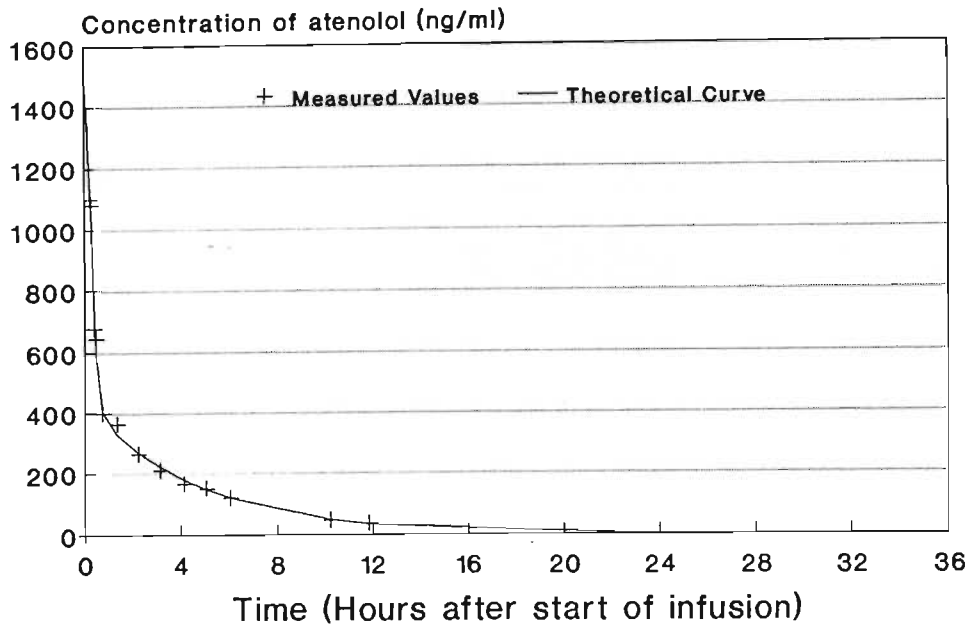
2 Compartment Model

Fig A3.14b. ACL: Log Plasma concentration-time plot.

Concentration of atenolol (ng/ml)

+ Measured Values

Time (Hours after start of infusion)
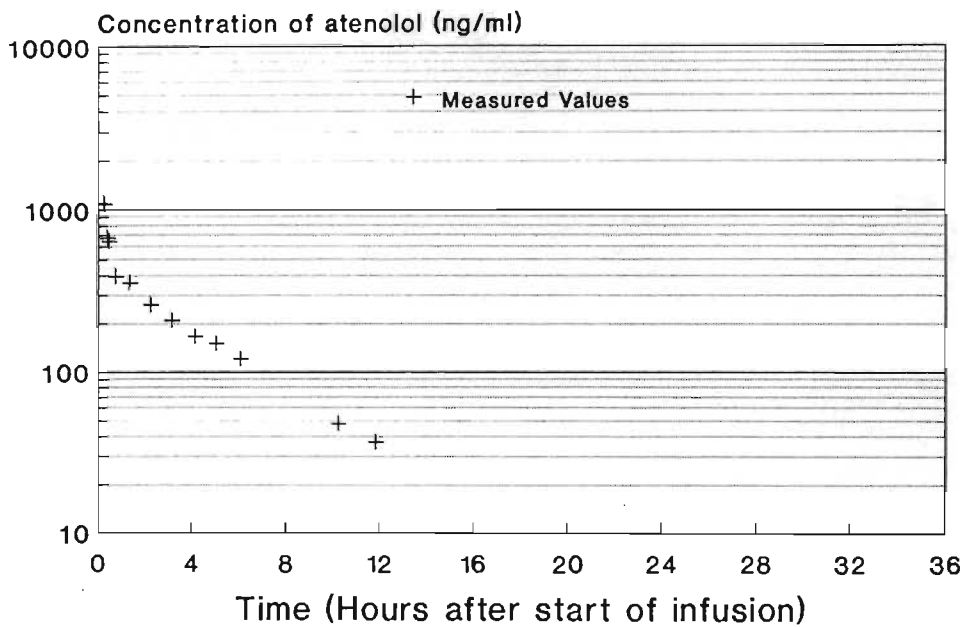
APPENDIX 4
Appendix to Chapter 6

Table **A4.1**. ELS estimation of parameter (S) and standard error of the estimate (SEE) for the linear effect model for each individual together with MOF and random deviation in the effect measurement (expressed as a coefficient of variation (CV %).

SUBJECT	PARAMETER S (SEE)	MOF	σ_ϵ (CV %)
MN (B)	0.122 (0.02)	195.4	63
CM (B)	0.349 (0.10)	254.5	138
VL (B)	Terminated with rounding errors		
AP (B)	0.150 (0.03)	225.2	109
ZN (B)	0.112 (0.01)	222.7	56
DS (B)	0.128 (0.03)	269.2	52
NM (B)	0.184 (0.03)	226.8	69
NV (W)	0.232 (0.04)	230.6	88
BB (W)	0.843 (0.30)	295.0	197
ACA (W)	0.126 (0.02)	221.3	68
NF (W)	1.25 (0.50)	293.6	195
JFI (W)	0.096 (0.01)	184.2	64
JFO (W)	0.267 (0.30)	311.2	109
ACL (W)	0.593 (0.40)	269.4	169

Table A4.2. Individuals ELS parameter estimates (S and I) for the log-linear model with (SEE), together with the MOF, random error in measurement (CV %), correlation between parameters.

SUBJECT	PARAMETER		MOF	σ_ϵ (CV %)	CORRELATION
	S (SEE)	I (SEE)			
MN (B)	Terminated with rounding errors dominating.				
CM (B)	14.0 (0.83)	-1.60 (1.17)	181.2	20	-0.628
VL (B)	10.8 (0.41)	3.09 (0.16)	156.2	15	0.718
AP (B)	10.9 (2.1)	-0.95 (3.5)	185.9	35	-0.907
ZN (B)	Terminated with rounding errors dominating				
DS (B)	Terminated with rounding errors dominating				
NM (B)	18.0 (1.23)	-10.4 (1.50)	178.0	20	-0.982
NV (W)	Terminated with rounding errors.				
BB (W)	11.2 (0.50)	6.26 (0.53)	170.5	15	-0.158
ACA (W)	Terminated with rounding errors.				
NF (W)	12.3 (0.87)	7.39 (0.49)	187.9	24	0.406
JFI (W)	Terminated with rounding errors.				
JFO (W)	Terminated with rounding errors.				
ACL (W)	9.19 (0.97)	-4.36 (0.36)	155.1	44	-0.951

Table A4.3. ELS parameter estimates with standard error or the estimate (SEE) for the E_{max} pharmacodynamic model (E_{max} and IC_{50}) together with the MOF, CV% for deviation of measured from predicted effects and correlation.

SUBJECTS	PARAMETERS		MOF	σ_ϵ (CV%)	CORRELATION
	E_{max} (SEE) (bpm)	IC_{50} (SEE) (ng/ml)			
MN (B)	37.4 (3.6)	124.0 (38.2)	176.4	33	0.711
CM (B)	34.7 (2.0)	18.9 (5.1)	185.6	23	0.422
VL (B)	24.8 (3.4)	2.2 (4.5)	198.9	15	0.460
AP (B)	28.4 (3.1)	27.4 (5.7)	186.3	36	0.819
ZN (B)	50.3 (7.8)	234 (92.1)	208.6	39	0.897
DS (B)	30.8 (3.6)	47.4 (17.8)	228.1	54	0.061
NM (B)	36.2 (2.7)	61.6 (8.9)	179.2	19	0.786
NV (W)	35.5 (2.5)	45.6 (13.1)	193.2	30	0.530
BB (W)	34.3 (2.5)	5.4 (3.0)	178.8	19	0.773
ACA (W)	35.5 (2.2)	86.0 (23.6)	201.9	39	0.151
NF (W)	36.7 (3.5)	4.7 (2.8)	194.5	29	0.708
JFI (W)	42.7 (8.3)	252 (121)	177.7	52	0.912
JFO (W)	36.9 (1.8)	30.8 (3.0)	252.2	26	0.493
ACL (W)	17.6 (3.0)	2.3 (2.5)	163.7	55	0.481

Table A4.4. ELS parameter estimates (E_{max}, IC_{50}, n) together with standard errors of the estimates (SEE) for Sigmoid E_{max} model with MOF, CV(%) for the random deviation of the measured from predicted effect and correlation.

SUBJECTS	PARAMETERS (SEE)			MOF	σ_ϵ (CV %)	CORRELATION		
	E_{max} (bpm)	IC_{50} (ng/ml)	Slope n			E_{max} & IC_{50}	E_{max} & n	IC_{50} & n
MN(B)	52.1 (11.8)	300* (150)	0.722 (0.15)	175.8	32	0.979	−0.837	−0.839
CM(B)	70.0* (37.3)	319 (679)	0.495 (0.17)	177.1	17	0.997	−0.954	−0.962
VL(B)	67.6 (13.3)	1000*(422)	0.340 (0.40)	189.5	42	0.880	0.495	0.251
AP(B)	36.8 (7.7)	59.9 (48.2)	0.566 (0.18)	185.8	35	0.927	−0.731	−0.786
ZN(B)	34.9 (2.5)	95.4 (9.3)	1.86 (0.15)	195.8	30	0.461	−0.614	−0.627
DS(B)	70.0* (19.9)	902 (887)	0.552 (0.08)	224.8	50	0.933	−0.664	−0.686
NM(B)	34.4 (4.1)	53.6 (18.5)	1.10 (0.22)	179.0	19	0.932	−0.834	−0.954
NV(W)	41.2 (8.3)	71.7 (3.6)	0.807 (0.23)	193.0	9	0.937	−0.932	−0.896
BB(W)	45.4 (16.9)	30.1 (65.3)	0.500 (0.22)	172.1	16	0.997	−0.986	−0.990
ACA(W)	49.7 (28.3)	225 (392)	0.598 (0.37)	201.1	38	0.995	−0.992	−0.987
NF	70.0* (17.1)	157 (17.1)	0.444 (0.04)	182.9	21	0.972	−0.891	−0.952
JFI	61.1 (3.2)	488 (112)	5.00* (111)	137.3	50	1.000	−1.000	−1.000
JFO	38.3 (3.2)	34.8 (6.5)	0.918 (0.11)	251.2	75	0.662	−0.866	−0.851
ACL	46.3 (8.4)	1000* (252)	0.392 (0.01)	157.0	51	0.782	−0.920	−0.728

* Parameter on boundary, probably uninterpretable.