# THE DESCRIPTION AND PREDICTION OF

## ANTIHYPERTENSIVE DRUG RESPONSE

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE FACULTY OF MEDICINE, UNIVERSITY OF GLASGOW

By

© RICHARD DONNELLY, M.B., Ch.B. (Hons)

Department of Materia Medica                    August, 1988

Stobhill General Hospital,

Glasgow, G21 3UW.

ProQuest Number: 10998228

ProQuest 10998228

# PREFACE

The work presented in this thesis was carried out
during my appointment as a Clinical Research Fellow in the
University Department of Materia Medica, Stobhill General
Hospital, Glasgow.

I was primarily responsible for conducting and
analysing the studies described and the preparation of this
thesis was entirely my own work.    I am particularly
grateful to many colleagues in the Department of Materia
Medica for their encouragement and for invaluable assistance
in performing the laboratory assays and the pharmacokinetic
analysis.    Their help is formally acknowledged.

This work was supported by a project grant awarded to
the Department of Materia Medica by the Medical Research
Council.    Several individual studies have been presented at
scientific meetings and accepted for publication in
referenced journals.    A list of these communications and
publications is given at the end.

<div align="right">

Richard Donnelly.

</div>

# C O N T E N T S

4

three study days simultaneously.

LIST OF FIGURES

## CHAPTER 5

## ACKNOWLEDGMENTS

SUMMARY

In recent years there has been a tendency to move away
from a standardised stepped care regimen for treating
patients with hypertension and to adopt instead a more
flexible approach in which antihypertensive treatment is
tailored to the needs of individual patients.  A wider
choice of drugs is now available and some of the newer
agents such as calcium antagonists, ACE inhibitors and
$alpha_1$ adrenoceptor antagonists represent reasonable
alternatives to a diuretic or beta blocker as first-line
treatments.  An individualised approach to treatment is a
laudable goal but factors which determine the response to
antihypertensive therapy - both kinetic and dynamic - are
not clearly understood and at present we are unable to
predict which patients will respond to which drugs.  An
additional problem is that very little is known about dose-
effect relationships for antihypertensive drugs -
information which would constitute a basis for optimising
drug therapy prospectively in individual patients.  It has
been suggested that for a number of antihypertensive drugs
no predictable concentration-effect relationship exists but
this probably reflects the negative findings of those
previous studies which considered the response for groups of
subjects rather than for individuals.

In a series of single blind studies 46 patients with
mild to moderate essential hypertension received treatment
with placebo for 2 weeks followed by nifedipine, or

enalapril, or doxazosin, or ketanserin. Each active treatment was administered as monotherapy for 4-6 weeks and patients attended for a series of 8-hour study days to evaluate the effects of placebo, 1st dose and chronic (1-6 weeks) therapy. At frequent intervals during each study day, and at 24 hours after dosing, blood pressure and heart rate were recorded and venous blood samples collected for measurement of plasma drug concentration. Additional blood samples were obtained for plasma renin activity, aldosterone and catecholamines. Pressor responsiveness to intravenous infusions of the selective $alpha_1$ agonist phenylephrine (PE) and the non-adrenergic vasoconstrictor angiotensin II (AII) was measured on each study day.

The pharmacokinetics and pharmacodynamic effects were evaluated after acute and chronic treatment. Drug concentration-effect analysis was used to characterise the antihypertensive response of each individual patient in terms of kinetic as well as dynamnic parameters and to describe the temporal discrepancy for the plasma concentration-effect relationship ($K_{eq}$).

In each study there was no simple direct relationship between plasma drug concentration and the placebo-corrected fall in blood pressure. However, using the integrated kinetic-dynamic model drug levels were well correlated with reductions in both systolic and diastolic blood pressure in individual patients. The kinetic-dynamic relationships for nifedipine, doxazosin and ketanserin were most appropriately

18

described by the simpler linear model and responses of individual patients were characterised in terms of the fall in blood pressure per unit drug concentration. For example, responsiveness to nifedipine (m), as the mean of the group, was -0.48 following the first dose, -0.45 after 1 week and -0.49 mmHg systolic/ng/ml after 6 weeks. There was an average reduction of 30% in the responsiveness to doxazosin during chronic treatment compared with single dose administration: for example, the mean responsiveness for the group was -2.1 following the first dose and -1.4 mmHg systolic/ng/ml after 6 weeks. There was a similar reduction in responsiveness to ketanserin from -0.47 to -0.25 mmHg systolic/ng/ml after 1 month and additionally there was a significant increase in $K_{eq}$ from 0.49 (1st dose) to 1.86 hours$^{-1}$ (1 month).

The pharmacokinetics and kinetic-dynamic relationships of enalapril were different in several respects compared with the other three drugs. A conventional pharmacokinetic model did not satisfactorily describe all the features of the disposition, particularly the accumulation of enalaprilat during chronic therapy. An alternative approach using a physiologically realistic model which assumes saturable binding of the drug to ACE was most appropriate for characterising both the kinetics and the concentration-effect relationships. In the case of enalapril, but with none of the other drugs, the linear concentration-effect model was inferior to the full Langmuir

($E_{max}$) equation for describing the kinetic-dynamic

relationships. Accordingly individual patient responses to

enalapril were quantified by the parameters $E_{max}$ and $C_e50$.

In terms of blood pressure reduction, the vasodilator

activities of nifedipine, enalapril and doxazosin were

broadly similar but the three drugs produced contrasting

effects on adrenergic and non-adrenergically mediated

vascular pressor responses. The alpha blocker doxazosin

produced significant attenuation of the pressor response to

phenylephrine but had no effect on responses to AII. In

contrast, the two non-adrenergic vasodilators, nifedipine

and enalapril, affected both PE and AII mediated

vasoconstriction. Nifedipine attenuated the responses to

AII and PE but treatment with enalapril was associated with

increased responsiveness to both pressor agents. This may

reflect receptor re-setting in the case of the calcium

antagonist and receptor up-regulation in the case of the ACE

inhibitor.

Pharmacokinetic as well as pharmacodynamic variability

account for interindividual differences in blood pressure

response. To date, kinetic and dynamic variability have

been addressed separately because no clear or consistent

relationship between drug concentration and effect has been

identified. Having demonstrated an integrated method for

describing antihypertensive response, it is now feasible to

investigate factors responsible for the inter and

intrasubject variability in responsiveness. There was no

relationship between patient age and pretreatment plasma renin activity and the responsiveness to the drugs studied. However, important determinants of response during longterm treatment are the height of the starting blood pressure and the response to the first dose.

This work has shown that drug concentration-effect relationships can be identified in individual hypertensive patients. The parameters derived from concentration-effect analysis can be used to investigate antihypertensive mechanisms and additionally provide not only a useful means of evaluating the kinetic and dynamic variability of drugs but also a potential basis for optimising longterm treatment in individual patients.

# CHAPTER 1

## GENERAL INTRODUCTION

## 1.1. <u>DRUG TREATMENT OF ESSENTIAL HYPERTENSION</u>

It has been recognised since the early 1940s that strokes, cardiac failure, coronary heart disease and progressive impairment of renal function occur more frequently and at an earlier age in people with above average blood pressures. Furthermore, the risk of these complications is directly proportional to the level of blood pressure, even when measured in quite casual circumstances (Robertson, 1983). Hamilton and his colleagues in 1964 were among the first to show that antihypertensive drug therapy conferred protection against cardiovascular complications in patients with pretreatment diastolic blood pressures of 110 mmHg and above and this was later confirmed by the larger Veterans Administration studies of 1967 and 1970. Since then there has been a progressive lowering of the presenting blood pressure above which antihypertensive drug therapy can demonstrate a protective effect (Robertson, 1984) but the value of treatment in mild hypertension has been more difficult to establish and required studies of large numbers of patients (Veterans Administration, 1970; Australian Therapeutic Trial, 1980; Hypertension Detection Follow-up Programme, 1982; MRC Trial, 1985).

Antihypertensive therapy is widely prescribed for patients with moderate or severe hypertension but the choice of a drug and its dosage is often empirical and based on a 'trial and error' approach. Furthermore, we know very little about factors which determine the response to

treatment and attempts to predict the most effective drug or an optimum dosage schedule for an individual patient have so far been unsuccessful.  This may be partly related to the apparent lack of a useful dose-response relationship for the commonly used drugs:  for example, beta adrenoceptor antagonists and thiazide diuretics are reported to have relatively flat dose-response curves (Hansson et al, 1974; MacGregor et al, 1983) and the relationship between plasma concentration and drug effect for vasodilators is ill-defined.  In practice, therefore, as the clinical response - blood pressure fall - is readily measurable, little attempt is made to rationalise therapy prospectively:  drug dose is adjusted retrospectively.

Thus, in contrast to developments in other areas of therapeutics, e.g. with anticonvulsant, antiarrhythmic and bronchodilator drugs, little attempt has been made to apply recent developments in clinical pharmacokinetics to improve drug use in hypertension.  A direct consequence of this has been that misleading and conflicting statements have been made about dose schedules and about variations in responsiveness related to factors such as age, ethnic origin and biochemical indices.  For example, it has been suggested that the response of hypertensive patients to calcium antagonists is not only quantitatively but qualitatively different from normotensives (Buhler and Hulthen, 1982), implicating abnormalities of smooth muscle calcium as a primary pathogenic mechanism in hypertension.

These claims have been based on incomplete and sometimes
anecdotal data, with observations being made of responses to
different doses at different times and with no account taken
of interindividual and time-related differences in plasma
drug concentrations.

The 'stepped-care' strategy for antihypertensive
treatment emerged in the early 1970s (Zacest et al, 1972),
providing the doctor with a sequence of therapeutic
manoeuvres which would ensure control of the blood pressure
in most cases of hypertension. The drugs used in the first
two steps have remained consistent over the years, namely
beta adrenoceptor antagonists and thiazide diuretics, but at
best only 50% of patients with mild to moderate hypertension
are adequately controlled with either drug alone (Moser,
1978).   In the last few years a great deal of information
has accrued to permit a re-examination of the traditional
stepped-care approach to hypertension.   Several multicentre
clinical trials, which have taken over a decade to conduct,
have reported their results and highlighted some important
limitations of conventional treatments in mild to moderate
hypertension.   One particular message that has emerged from
several of the major trials, and which forms the underlying
theme of this project, is that an individualised approach to
the hypertensive patient should be adopted rather than the
pursuit of an empirical, pragmatic, therapeutic policy.
The scope for improvement in antihypertensive therapy is
particularly well illustrated by the data on coronary heart

disease mortality and by the somewhat surprising results concerning the adverse effects relative to benefit of conventional beta blocker and diuretic regimens.

## Coronary heart disease

In both the Australian (Australian Therapeutic Trial in Mild Hypertension, 1980) and British MRC (Medical Research Council Trial in Mild to Moderate Hypertension, 1985) trials two thirds of all vascular complications were due to ischaemic heart disease but the MRC trial showed clearly that conventional antihypertensive treatment with a beta blocker or diuretic does not prevent coronary events. Several possible explanations may account for the failure to improve coronary heart disease mortality (Reid, 1988). One popular suggestion, however, is that beta adrenoceptor antagonists and thiazide diuretics may have an unfavourable influence on a coronary risk factor which off-sets their beneficial effect on blood pressure. Changes in plasma lipids have been particularly implicated in this hypothesis and considerable attention has been focused on the adverse metabolic effects of diuretics and beta blockers (Berglund and Andersson, 1981; Bauer et al, 1981; Lant, 1985; Weidmann et al, 1985).

A decrease in high density lipoprotein (HDL) cholesterol or increase in low density lipoprotein (LDL) cholesterol may both augment the risk of coronary heart disease (Kannel et al, 1979; Miller, 1982) and a similar

tendency is suspected for elevated blood levels of triglyceride-rich lipoproteins (Carlson and Roessner, 1979; Weidmann et al, 1985). Some beta adrenoceptor antagonist drugs and almost all diuretics have been shown to adversely affect the ratio of LDL/HDL cholesterol (Weidmann et al, 1985), whereas some of the newer antihypertensive agents appear to have neutral or even beneficial effects on blood lipids. Additional concern has also been expressed about some of the other metabolic effects of diuretics (Holme et al, 1984), in particular hypokalaemia, carbohydrate intolerance and uric acid retention, and their possible impact during longterm therapy on cardiovascular morbidity and mortality (Multiple Risk Factor Intervention Trial, 1982).

Appropriate clinical trials are awaited to assess whether or not some of the newer antihypertensive drugs such as calcium antagonists and ACE inhibitors will fare better than conventional treatments in reducing coronary heart disease mortality. However, as discussed in later sections, there is increasing evidence to suggest that the newer drugs may offer some advantages over beta-adrenoceptor antagonists and diuretics.

## The risk-benefit relationship

The protective effect of lowering the blood pressure in severe hypertension has been clearly demonstrated with relatively small numbers of patients (Harington et al, 1959;

Veterans Administration, 1967) but recent trials have shown that the value of treatment in mild hypertension is much less obvious (Australian Therapeutic Trial in Mild Hypertension, 1980; Hypertension Detection Follow-up Programme, 1982; MRC Trial, 1985). The Australian and British MRC Trials showed that antihypertensive treatment in patients with uncomplicated mild hypertension (defined as a diastolic blood pressure between 90 - 109 mmHg and systolic pressure below 200 mmHg) significantly reduced the incidence of all cardiovascular complications, largely by preventing strokes, but in absolute terms the benefits were small: for example, in the MRC Trial 850 patients had to be treated for a year in order to prevent one cerebrovascular event - which may be non-fatal.

A further disappointing result which has emerged from recent studies in mild to moderate hypertension has been the failure to restore the mortality of treated hypertensive patients to that of the normotensive population (Lindholm et al, 1984; Samuelsson et al, 1985; Bulpitt et al, 1986; MacMahon et al, 1986). Since the prognosis in mild hypertension is dominated by ischaemic heart disease, this may reflect the failure of conventional antihypertensive treatments to improve coronary heart disease mortality (Reid, 1988).

As well as evaluating the benefits of treatment in mild hypertension the British MRC Trial produced interesting results about the incidence of adverse effects associated

with the beta adrenoceptor antagonist propranolol and thiazide diuretic bendrofluazide (MRC Report on Adverse Reactions, 1981). The cumulative percentage of men withdrawn from treatment with bendrofluazide after 5 years was 17%, compared with 12.8% of women, and for propranolol the cumulative percentage of withdrawals amounted to 15.5% of men and 18% of women. The corresponding number of withdrawals from the placebo group after 5 years was approximately 5% for both sexes. These results, particularly for bendrofluazide, were somewhat surprising - as reflected by views expressed in a leading article in the Lancet as recently as 1982 which stated 'in mild hypertension ...... those who employ diuretic treatment first do so mainly because of the rarity of symptoms, side effects and low cost' (Lancet Editorial, 1982).

It has become recognised that in order to maximise the beneficial effects of longterm treatment in mild hypertension adverse effects must be reduced to a minimum and this requires careful consideration of drug dose. Thus the high incidence of side effects in the MRC study probably compromised the apparent benefits of treatment and this may have been due to inappropriate (high) doses of propranolol and bendrofluazide.

The modern aim of antihypertensive treatment was summarised in a recent editorial in the New England Journal of Medicine: 'the goal of therapy should be not only to reduce morbidity and mortality but to do so without adverse

effects on the functional well-being of our patients'
(Chobanian, 1986). To achieve this aim in the future, we
will require greater understanding of the dose-effect
relationships for antihypertensive drugs. So far, this has
been a neglected area of clinical pharmacology but
information about the inter-relationship between drug
concentration and effect will form the basis not only for
optimising drug therapy in individual patients but also for
investigating factors which might account for the
intersubject variability in antihypertensive response.

The information gained from the recent major clinical
trials in mild to moderate hypertension, together with the
introduction of newer classes of antihypertensive agents,
has led to a reappraisal of the management of mild to
moderate hypertension (Prichard and Owens, 1986). To improve
the prognosis, more attention has been focused on the
correctable risk factors for ischaemic heart disease,
particularly cigarette smoking and hypercholesterolaemia,
and it has become recognised that non-pharmacological means
of lowering the blood pressure are useful either as an
adjunct to drug therapy or as the initial method of
controlling the blood pressure (Andrews et al, 1982).
While beta-adrenoceptor antagonists and thiazide diuretics
remain the first line treatments, there are now several
other drugs such as calcium antagonists, alpha-adrenergic
blockers and angiotensin converting enzyme (ACE) inhibitors
which represent reasonable alternatives. The apparent

limitations of "conventional treatments" has therefore
resulted in a more flexible approach in which the choice of
the first-line drug is tailored to suit individual patient
requirements (Hansson, 1985).

### 1.1.1. Calcium antagonists

The calcium antagonists are a heterogeneous group of
drugs which have in common the property of inhibiting the
influx of calcium ions into cardiac and vascular smooth
muscle cells (Braunwald and Epstein, 1982) thus leading to a
reduction in the contractile force (Stone et al, 1980).
The original classification of calcium antagonist drugs
described by Fleckenstein (1983) has recently been
superseded to include four types (Singh, 1986). The Type 1
agents - the phenylalkylamine derivatives such as verapamil
and gallopamil, and the benzothiazepine derivatives such as
diltiazem - besides dilating blood vessels have important
action on cardiac conduction tissue, prolonging
atrioventricular conduction and refractoriness, but have
little effect on atrial or ventricular refractory period.
The Type II drugs - the dihydropyridines (nifedipine,
nicardipine, nitrendipine, etc.) - in vivo have no
electrophysiological effects, while they are potent
peripheral vasodilators. The Type III drugs, the
piperazines, include cinnarizine and flunarizine which are
highly selective for vascular smooth muscle relative to
cardiac muscle. Finally, more complex are the Type IV

31

drugs, such as perhexilene, bepridil and lidofluazine, which, as well as their inhibitory action on calcium channels, block the fast sodium channels to a variable degree.

The diversity of molecular structures of calcium antagonists is consistent with differing modes and sites of action and contrasts with the tight binding of alpha and beta adrenergic blockers to specific receptor sites. Thus, the principal drug types bind to slightly different sites on the cell membrane (Glossman, 1984) and exert effects which also are dependent upon slightly different states of "activity" of the calcium channel (Epstein, 1982).

As a class of drugs the calcium antagonists first became established for the treatment of angina pectoris (Lynch et al, 1980; Scheidt et al, 1982) but over the last few years several studies have documented the longterm antihypertensive efficacy of verapamil (Lewis et al, 1978; Leonetti et al, 1980; Doyle, 1983) and nifedipine (Guazzi et al, 1977; McLeay et al, 1983; Hornung et al, 1983). Diltiazem also lowers the blood pressure in hypertensive patients (Yamakado et al, 1983) as do other newer calcium antagonists that have been assessed, e.g. nitrendipine (Burris et al, 1982), nicardipine (Littler et al, 1986) and tiapamil (Chu and De Gori, 1982).

The lowering of blood pressure is achieved by a reduction in peripheral vascular resistance (Olivari et al, 1979; Opie, 1980) due to selective vasodilation of

32

resistance vessels and little or no effect on capacitance vessels (Robinson et al, 1980). Differences in their sites of action may partly explain the different pharmacodynamic effects of the various calcium antagonist drugs (Fleckenstein, 1984). Compared with nifedipine, verapamil has a similar but relatively less marked effect on vascular smooth muscle (Midtbo et al, 1982) and, unlike nifedipine, it has important depressant effects on cardiac conduction (Rowland et al, 1979). The fall in blood pressure with nifedipine and other dihydropyridines is associated acutely with reflex increases in cardiac output (Lederballe-Pedersen, 1981) and plasma noradrenaline (Muiesan et al, 1982) but with verapamil cardiac output is unchanged (Opie, 1980).

Vasodilator drugs such as hydralazine and minoxidil are often associated with counter-regulatory effects involving reflex stimulation of the sympathetic and renin-angiotensin systems leading to increased cardiac output and fluid retention (Dunstan et al, 1972; Zacest et al, 1972) which may counteract their antihypertensive activity (Koch-Weser, 1974). A possible advantage of the calcium antagonists over vasodilators such as hydralazine is that while there is evidence of reflex activity acutely during chronic treatment baroreflex activity attenuates and heart rate returns to normal (McLeay et al, 1983; Bruun et al, 1985).

Since the prognosis in mild-moderate hypertension is dominated by ischaemic heart disease and conventional

treatment with a beta blocker or diuretic appears to have little effect on coronary mortality, there is considerable interest in the effects of the newer antihypertensive drugs on coronary risk factors. There have not been any secondary prevention studies with calcium antagonists but there is some animal evidence suggesting a cardioprotective effect in experimental ischaemia (Nayler and Ferrar, 1979). In addition, some of the ancillary properties of calcium antagonists may have a beneficial effect on ischaemic heart disease: for example, calcium antagonists have been shown to reduce coronary artery spasm (Antman et al, 1980), inhibit platelet aggregation (Dale et al, 1983) and have a favourable effect on blood lipids (Sasaki and Arakawa, 1987).

Side effects are not uncommon with calcium antagonists and symptoms associated with vasodilation, such as headache and flushing, are more common with nifedipine than verapamil (Krebs, 1983). The overall incidence of adverse effects is approximately 20% and this may be related, at least in part, to the dose and drug plasma concentration (Sorkin et al, 1985), and some series have shown relatively high drop-out rates (14-22%) from nifedipine (Bayley et al, 1982; Eggertsen and Hansson, 1982). Ankle oedema due to increased capillary permeability occurs in 0.6% of patients treated with nifedipine and is resistant to diuretics (Krebs, 1983). Constipation is quite common with verapamil (12-42%) but the infrequent gastrointestinal side effect of

nifedipine is usually diarrhoea (Sorkin et al, 1985).
Significant negative inotropic effects may occur in patients
with compromised cardiac function following verapamil, but
it is rarely seen with nifedipine (Krebs, 1983).  Calcium
antagonists may therefore be used to treat patients in whom
beta-adrenoceptor blocking drugs are contraindicated:  for
example, nifedipine may be given to patients with poor left
ventricular function and, in contrast to beta-blockers,
calcium antagonists do not increase airways resistance or
exacerbate peripheral vascular disease.

Despite having widely different chemical structures,
calcium antagonists exhibit common pharmacokinetic
properties.  They all undergo high hepatic extraction which
is mainly dependent on liver blood flow and therefore their
bioavailabilities are low, for example 40-50% for
nifedipine, despite almost complete absorption following
oral administration (Echizen and Eichelbaum, 1986).  A
sensitive and reliable assay for measuring nifedipine in
plasma has only recently become available (McAllister, 1982;
Waller et al, 1984) and therefore there is still a relative
paucity of information about the pharmacokinetics of
nifedipine, particularly in patients with essential
hypertension (Echizen and Eichelbaum, 1986).  In contrast,
the pharmacokinetics of verapamil have been more clearly
characterised.  Several studies have shown a reduction in
verapamil clearance during chronic compared with acute
administration (Freedman et al, 1981;  Kates et al, 1981;

Shand et al, 1981;  Wagner et al, 1982) and this is likely

to reflect drug-induced alterations in hepatic blood flow

(Meredith et al, 1985a) or enzyme activity (Bach et al,

1986).

A feature common to all the calcium antagonists is

marked intra- and inter-individual variations in drug

clearance and bioavailability (Echizen and Eichelbaum, 1986).

In patients with hepatic impairment (e.g. cirrhosis) the

various pharmacokinetic parameters are grossly altered -

clearance decreases, elimination half-life is substantially

prolonged and bioavailability more than doubles (Somogyi et

al, 1981).   Whereas renal disease has no impact on the

pharmacokinetics of diltiazem and verapamil (Mooy et al,

1985), the elimination half-life of nifedipine increases in

relation to the degree of renal impairment due to an increase

in volume of distribution (Kleinbloesem et al, 1984b).

Systemic clearance, however, remains unchanged.


1.1.2. Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE), also known as

kininase II, is responsible for the enzymatic conversion of

angiotensin I to the potent vasoconstrictor peptide

angiotensin II.   The ACE inhibitor drugs, captopril and

enalapril, have recently become established in the treatment

of hypertension (Brunner et al, 1981;  Hodsman et al, 1982;

Velasco et al, 1985) and cardiac failure (Kjekhus et al,

1983;  CONSENSUS trial, 1987).   The fall in blood pressure

is due to arteriolar vasodilation, producing a reduction in peripheral vascular resistance (Velasco et al, 1985; Tarazi et al, 1980) and is partly related to the activity of the renin-angiotensin system (Gavras et al, 1978). Activation of the renin-angiotensin-aldosterone system by posture, exercise, salt and volume depletion, or treatment with diuretics, therefore enhances the antihypertensive effect of ACE inhibition (Brunner et al, 1980; Atkinson et al, 1980). Although the fall in blood pressure is due primarily to a reduction in angiotensin II formation, additional mechanisms have been implicated: for example, changes in baroreflex activity (Mancia et al, 1982) and reduced vascular responsiveness to noradrenaline (Fruncilo et al, 1983). It has additionally been suggested that these effects may be particularly important in explaining the characteristic absence of a reflex tachycardia when the blood pressure is lowered by ACE inhibitors (Cody et al, 1979; Velasco et al, 1985).

Captopril was first used in what now would be regarded as large doses (up to 450 mg a day) in the treatment of severe or renovascular hypertension, and was associated with a high incidence of side effects (e.g. skin rash) and a worrying incidence of potentially serious adverse effects such as neutropenia and deteriorating renal function. With the advent of lower dose regimens, and better patient selection, the incidence of adverse effects associated with captopril is low and appears to be similar

to that caused by enalapril (Veterans Administration, 1982a; Thind et al, 1983; Edwards and Padfield, 1985). The most serious adverse effects are the dramatic decrease in blood pressure, accompanied by bradycardia, which may follow the initial dose and impaired renal function. First dose hypotension occurs most often in patients with congestive cardiac failure, particularly in those treated with large doses of diuretics (Fagard et al, 1980; Whitworth et al, 1982). ACE inhibitors are contraindicated in the presence of bilateral renal artery stenosis, since they lead to a rapid deterioration in renal function, and this probably reflects the importance of angiotensin II in maintaining efferent arteriolar constriction and thus glomerular filtration pressure (Johnston, 1984).

Captopril has a relatively short duration of action on ACE inhibition and blood pressure but enalapril is longer-acting and administered once or twice daily. Following oral administration, enalapril undergoes hepatic de-esterification to the active diacid metabolite enalaprilat which is excreted unchanged via the kidneys (Tocco et al, 1982). Pharmacokinetic studies of enalapril have shown that a lower dose should be used in the elderly (Hockings et al, 1986; Lees and Reid, 1987), in patients with impaired renal function (Johnston, 1984), and in those with congestive cardiac failure (Schwartz et al, 1985).

ACE inhibitors appear to be well tolerated and effective antihypertensive drugs. They do not interfere

with the sympathetic control of blood vessels, therefore
there is no postural hypotension, and they do not cause
reflex tachycardia. Additional advantages include improved
renal blood flow and there is evidence to suggest that
hypertensive left ventricular hypertrophy, which carries a
poor prognosis (McLenachan et al, 1987), resolves more
quickly on treatment with ACE inhibitors than with other
drugs (Dunn et al, 1984).

### 1.1.3. Alpha$_1$-adrenoceptor antagonists

The most useful antihypertensive alpha-adrenoceptor
inhibitor drugs are selective for post-junctional alpha$_1$-
adrenoceptors (Graham, 1984). Several studies have shown
that the alpha$_1$-antagonist prazosin and other related
quinazoline derivatives, such as doxazosin, are effective
antihypertensive drugs (Stanaszek et al, 1983; Lund-
Johansen et al, 1986). Not surprisingly the haemodynamic
effect is greater under those conditions in which the
maintenance of blood pressure is particularly dependent upon
increased sympathetic activity, for example on standing,
after exercise, in a hot environment, after food, or with
reduced blood volume. The haemodynamic profile of alpha$_1$
adrenoceptor inhibitory drugs is such as to reverse the
pathological haemodynamic changes of hypertensives back
towards that seen in normotensives (Taylor, 1982). The
fall in blood pressure is due to a reduction in peripheral
vascular resistance (Lund-Johansen et al, 1986) and is

associated acutely with reflex sympathetic activation
(Elliott et al, 1982).

The principal adverse effect of alpha-adrenergic
blockers is "first dose" orthostatic hypotension and reflex
tachycardia. This was a significant problem during the
early stages of the use of prazosin (Bendall et al, 1975).
The first dose phenomenon is, in part, dose dependent
(Rosendorff, 1976) and may be alleviated by using a low
starting dose given immediately before going to bed. First
dose hypotension is enhanced by a low sodium diet but a high
sodium diet may abolish the effect (Stokes et al, 1977).

Following oral administration, prazosin undergoes high
hepatic extraction and has both a short half-life and a
relatively short duration of action (Bateman et al, 1979),
requiring two or three doses daily. In contrast, doxazosin
has a prolonged terminal elimination half-life (Elliott et
al, 1987) and the maximum antihypertensive effect is delayed
until 5-6 hours, even after intravenous administration
(Elliott et al, 1982). The more gradual onset of action of
doxazosin may make it less likely to cause the acute
postural hypotensive effects associated with prazosin, and
additionally it may be suitable for once daily
administration.

Provided care is taken to minimise or avoid the first-
dose phenomenon, particularly in susceptible patients,
alpha-adrenoceptor antagonist drugs are generally well
tolerated and effective, with no important contraindications

to treatment. Unlike beta-adrenoceptor antagonists, they
also may be useful in cardiac failure (Stanaszek et al,
1983) and they do not increase airways resistance (Marlin et
al, 1982). In addition, alpha-adrenoceptor blocking drugs
increase peripheral blood flow (Coleman, 1981) and have been
used successfully for the treatment of Raynaud's phenomenon
(Clement, 1978). Although tolerance to the alpha blocking
effect has been reported in cardiac failure, clinical
studies in hypertension have shown that blood pressure
control using a fixed dose of prazosin is sustained during
longterm therapy (Stanaszek et al, 1983).

An important potential advantage of prazosin and
related alpha blockers is their effects on blood lipids.
It now seems clear that elevated low density lipoprotein
(LDL) cholesterol is associated with an increased risk of
ischaemic heart disease while the HDL cholesterol fraction
is relatively 'cardioprotective' (Miller, 1982). In
contrast to beta-adrenoceptor antagonists and thiazide
diuretics, which have adverse effects, alpha-adrenoceptor
blocking drugs produce favourable changes in blood lipids,
though the effects are small. Prazosin is reported to
increase the HDL-LDL cholesterol ratio (Kokubu et al, 1982;
Leren et al, 1982) but longterm clinical studies have not
been entirely consistent (Lithell et al, 1982).


## 1.1.4. Antihypertensive combinations

Antihypertensive drugs given as monotherapy are often

effective in controlling the blood pressure but a large proportion of patients require treatment with more than one drug. Combined therapy using two or more antihypertensive agents offers the potential for pharmacokinetic as well as pharmacodynamic drug interactions. The conventional stepped care regime advocates the use of a beta-blocker or diuretic, or both, in combination with a vasodilator (Zacest et al, 1972). Hydralazine is particularly effective for third-drug treatment (McAreavey et al, 1984) but in recent years preference has switched towards newer drugs which have fewer adverse effects, for example the calcium antagonists, ACE inhibitors and alpha blockers.

The fall in blood pressure with a vasodilator is often associated with increased reflex sympathetic activity to the heart (Koch-Weser, 1974) and if this is attenuated, for example with a beta adrenoceptor antagonist, the antihypertensive effect is increased. Thus, the combination of a dihydropyridine calcium antagonist such as nifedipine, or an alpha blocker such as prazosin, with a beta adrenoceptor antagonist results in an additional fall in blood pressure (Elliott et al, 1981; Bayley et al, 1982; Eggertsen and Hansson, 1982). In contrast, heart rate is unchanged when the blood pressure is lowered by an ACE inhibitor and there is no evidence to suggest that a beta blocker combined with an ACE inhibitor has useful additive antihypertensive efficacy (MacGregor et al, 1982a).

Nifedipine added to a combination of a diuretic plus a

42

beta adrenoceptor blocking drug may be effective in patients with severe or resistant hypertension (Dean and Kendall, 1983) but there have been conflicting reports about whether thiazide diuretics and calcium antagonists form a useful combination in the treatment of mild to moderate hypertension (Cappuccio et al, 1987;  Poulter et al, 1987). In contrast, thiazide diuretics and ACE inhibitors form an established treatment combination (Atkinson et al, 1980).

The combination of a beta blocker with a calcium antagonist drug, typically of the dihydropyridine type, is popular and well established for the treatment of both hypertension and angina.  The therapeutic results of such combinations are thought to reflect a summation of the pharmacodynamic effects of each drug but there is recent evidence to suggest that there may be an additional pharmacokinetic interaction leading to a beneficial alteration in the plasma concentrations of the beta blocker (Elliott et al, 1988a).  The oral bioavailabilities of both atenolol and particularly propranolol are significantly increased when co-administered with nisoldipine (Elliott et al, 1988a) and this is thought to reflect, in part, alterations in hepatic, splanchnic and renal blood flow which are associated acutely with calcium antagonists (Feely, 1984;  Meredith et al, 1985a and 1985b).

Antihypertensive combinations usually incorporate a beta blocker or diuretic, or both, with a vasodilator such as a calcium antagonist or an ACE inhibitor.  However,

since there has been concern about the adverse effects of beta blockers and diuretics, particularly the metabolic effects associated with longterm thiazide diuretic administration (Holme et al, 1984), alternative combination treatments require consideration.

Recent open studies in severe hypertension have shown that the addition of a calcium antagonist to treatment with an ACE inhibitor produces a useful synergistic effect with good patient tolerance (Mimran and Ribstein, 1985; White et al, 1986). These observations have been confirmed in a controlled study which was designed to investigate the haemodynamic and pharmacokinetic effects of adding the dihydropyridine calcium antagonist nicardipine to the treatment of patients with mild to moderate hypertension in whom blood pressure control was unsatisfactory with conventional beta-blocker regimens and in whom only a partial response was obtained with the ACE inhibitor enalapril alone (Donnelly et al, 1987). Treatment with enalapril and nicardipine for two weeks produced significant reductions in blood pressure compared with the enalapril-placebo combination, on average 30/19 mmHg supine at 2 hours after drug administration, and the additional treatments were well tolerated. In particular, the introduction of nicardipine was not associated with any significant side effects and this tends to support previous suggestions that at least some of the adverse symptoms which often accompany the acute administration of a calcium antagonist, for

example headache and fluid retention, may be attenuated in the presence of an ACE inhibitor to block the renin-angiotensin system (Brouwer et al, 1985; Bach et al, 1986). There was no evidence of any pharmacokinetic interaction between nicardipine and enalapril. The addition of nicardipine, after both first dose and repeated doses, had no significant effect on the steady-state kinetics of enalaprilat or, more importantly, the profile of plasma ACE inhibition (Donnelly et al, 1987).

Another new drug combination which has been shown to be effective and well tolerated is the combination of a calcium antagonist with an alpha blocker. In both normotensive and hypertensive subjects the fall in blood pressure with the combination of verapamil and prazosin is significantly greater than the simple additive effect from each drug (Pasanisi et al, 1984; Elliott et al, 1988b). This synergistic effect has been explained on the basis of a pharmacokinetic interaction whereby the addition of verapamil significantly increased the systemic bioavailability of prazosin (Elliott et al, 1988b). This may reflect alterations in hepatic blood flow (Meredith et al, 1985a) or enzyme activity (Bach et al, 1986) due to the calcium antagonist drug. The addition of prazosin did not affect the disposition of verapamil.


## 1.2. VARIABILITY IN THERAPEUTIC RESPONSE

The factors which determine the response to

antihypertensive treatment are not clearly understood and in clinical practice the choice of a drug and its appropriate dose is largely empirical. Studies with calcium antagonists, for example, have consistently shown large interindividual differences not only in blood pressure reduction, but also in plasma drug concentrations (Echizen and Eichelbaum, 1986) and such variability clearly contributes to the large differences between patients in the magnitude of therapeutic response. In most previous studies pharmacokinetic and pharmacodynamic variability has been addressed separately and a clear relationship between plasma concentration and effect has not been established. This may reflect the wide range of inter-subject variability in both kinetic and dynamic parameters when group data are evaluated but there is now evidence that for several groups of antihypertensive drugs the fall in blood pressure can be related to the drug concentration in plasma within an individual.

1.2.1. Pharmacodynamic variability

In the early 1970s biochemical indices, particularly plasma renin activity (PRA), were proposed as important determinants of antihypertensive drug response (Laragh, 1973). Buhler and colleagues (1981) developed the hypothesis that essential hypertension evolved from a state of high cardiac output and renin secretion in the early stages to a state of high peripheral vascular resistance in established hypertension. They further suggested that

46

hypertensive patients could be categorised according to PRA such that patients with high levels of PRA responded better to beta adrenoceptor antagonists (Buhler et al, 1972; Hollifield et al, 1976) whereas those with low levels of PRA respond better to diuretics (Adlin et al, 1972). This simplified approach was not generally accepted and in clinical practice it failed to help the clinician in choosing between a beta blocker and a diuretic as the most appropriate first-line drug (Zanchetti, 1985).

The recent introduction of ACE inhibitors and calcium antagonists has revived the debate about the usefulness of PRA as a predictive marker of the haemodynamic response. There is some evidence that the fall in blood pressure due to ACE inhibition is dependent upon renin status (Gavras et al, 1978) but the effectiveness of ACE inhibitors in hypertension is much greater than would be predicted from measurements of PRA alone: for example, patients with low PRA, and even anephric subjects, have been shown to respond adequately to ACE inhibitors (Man in't Veld et al, 1980). Plasma renin activity has also been related to the antihypertensive effect of calcium antagonists (Buhler et al, 1982) with a strong negative correlation between PRA and the fall in blood pressure with verapamil (Figure 1.1.).

Attempts to identify a relationship between blood pressure response and other biochemical measurements, such as plasma catecholamine levels (Schwietzer et al, 1983), urinary aldosterone excretion (Hansson et al, 1974) and

lymphocyte $Na^+-K^+$ concentrations (Costa et al, 1985;
Zanchetti, 1985; M'Buyamba-Kabangu et al, 1988),
have met with little consistent, confirmed success.

Demographic studies, however, have yielded more useful
observations with respect to the variability in drug
response. It has been shown both in Africa (Seedat and
Reddy, 1971) and the USA (Veterans Administration Co-
operative Study, 1982b) that blacks respond better to
thiazide diuretics than to beta-adrenoceptor antagonists and
that whites respond better than blacks to ACE inhibitors.

Age may also be an important determinant of the
response to treatment. Buhler and his colleagues (1982)
have shown that the fall in blood pressure with verapamil is
greater in the elderly (Figure 1.1.), while others have
reported an opposite relationship between blood pressure
reduction and age for the calcium antagonist nitrendipine
(Ferrara et al, 1985). Both these studies have postulated
that age is an important factor in determining the
haemodynamic response to calcium antagonists but neither
study took account of differences in plasma drug
concentrations, which may also depend upon age (Section
1.2.2.). Since kinetic as well as dynamic variability
accounts for interindividual differences in blood pressure
response, it is possible that the observations of Buhler and
Ferrara may have been due to age-related differences in
pharmacokinetics rather than increased responsiveness per se.
It is therefore inappropriate to consider dynamics in
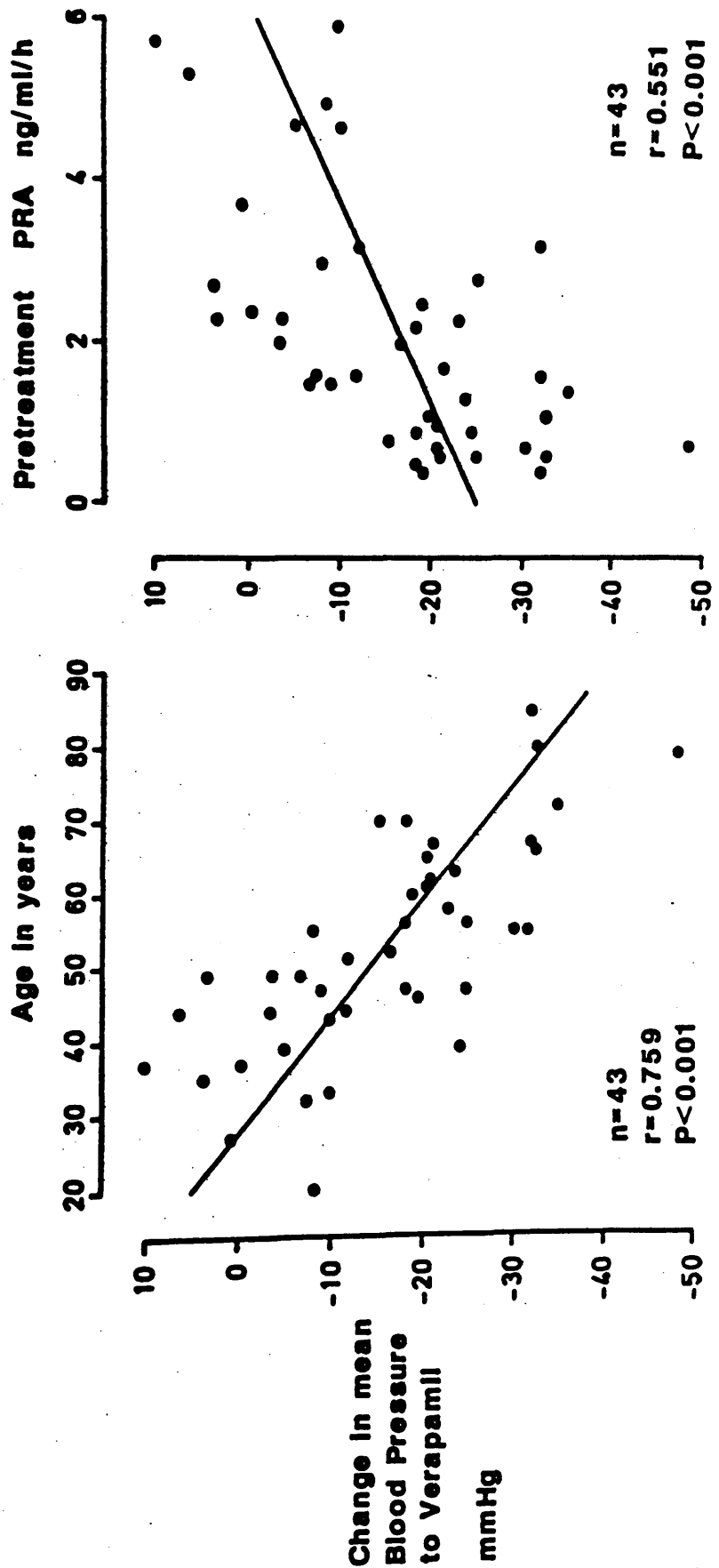
**Figure 1.1.**
The purported relationships between fall in blood pressure with
verapamil and patient age and pretreatment plasma renin activity.
Adapted from Buhler et al, 1982.

49

isolation when assessing the variability or constancy of the antihypertensive response.

One of the conclusions from the MRC Trial (1985) was that the fall in blood pressure with propranolol was less in cigarette smokers than non-smokers, whereas no such difference occurred with bendrofluazide. Similar findings were also reported in the IPPPSH study with another non-selective beta blocker, oxprenolol (IPPPSH Study Group, 1985), but not in the HAPPHY study which used selective $beta_1$ antagonists (Wilhelmsen et al, 1987). While this may reflect a difference in smokers to the haemodynamic effects of beta blockade, it is also possible that a pharmacokinetic basis seems more likely since smoking has been shown to increase the clearance of propranolol (Dawson and Vestal, 1981). This illustrates again the importance of considering kinetic as well as dynamic differences when assessing the variability in antihypertensive drug response.

It has been suggested from recent studies with calcium antagonists that these agents lower blood pressure to a greater extent in hypertensive patients than in normotensive subjects (MacGregor et al, 1982b) and a relationship has been described between the pretreatment or initial blood pressure and the magnitude of the fall with treatment (Erne et al, 1983). However, care is necessary with the statistical methods used in this type of analysis (Gill et al, 1985) and it is probably more appropriate to seek correlations which also take account of interindividual differences in drug

50

concentrations and in the extent of the blood pressure fall
associated with placebo (Sumner et al, 1988a).


## 1.2.2. Pharmacokinetic variability

The pharmacokinetics of some antihypertensive drugs
vary with increasing age and therefore dosage adjustment may
be required in the elderly. Peak plasma levels and the
area under the concentration-time curve for the $alpha_1$-
antagonists prazosin and terazosin are higher in older
subjects (Rubin et al, 1981; McNeil et al, 1987) and there
are similar age-related reductions in the clearance of
nifedipine (Robertson et al, 1988) and enalapril (Hockings
et al, 1986; Lees and Reid, 1987).

The oral pharmacokinetics of drugs which undergo high
hepatic extraction, for example the calcium antagonists, are
mainly dependent on liver blood flow and hepatic enzyme
activity (Echizen and Eichelbaum, 1986). Changes in these
parameters are likely to explain the reduction in verapamil
clearance during chronic administration (Section 1.1.1.) and
the increased bioavailability of verapamil in patients with
liver cirrhosis (Somogyi et al, 1981). In addition, the
acute effect of verapamil on liver and splanchnic blood flow
probably accounts for its pharmacokinetic interaction with
prazosin (Elliott et al, 1988b). The pharmacokinetics of
ACE inhibitors, in contrast to calcium antagonists, are
dependent more on renal than hepatic function (Hockings et
al, 1986).

The intersubject variability in plasma concentrations of an antihypertensive drug may therefore reflect several factors, including differences in hepato-renal function and including the further effects of aging on these organs. Some drugs show a change in kinetics during chronic compared with acute administration, for example verapamil (Freedman et al, 1981) and the serotonin ($5HT_2$) antagonist ketanserin (Persson et al, 1987), and some antihypertensive drugs may modify the disposition of others, as in the case of verapamil and prazosin (Elliott et al, 1988b).

## 1.3. DRUG CONCENTRATION-EFFECT RELATIONSHIPS

Pharmacokinetics describes and characterises the change in plasma drug concentration per unit time but provides only indirect information about the onset, intensity and duration of the effect. For some drugs there is a simple direct correlation between the time course of plasma drug concentration and the response implying a rapid equilibration between drug concentration in the plasma and drug concentration at the receptor site. For many drugs, however, the relationship is not simple and the time course of the effect is displaced to the right of the plasma concentration profile i.e. delayed (Figure 1.2.). This time lag or phase discrepancy may reflect the formation of an active metabolite or the delayed penetration of drug into a deep tissue compartment or simply the time taken for the

drug-receptor interaction to produce an effect.

The relationship between a continuously changing plasma drug concentration and the corresponding response is usually depicted as a plot of effect against the log of drug concentration, when it typically takes the form of a sigmoid curve. Following a single dose of a drug, the magnitude of the response relates to both the concentration and the portion of the concentration-response curve covered. Some antihypertensive drugs, particularly beta-blockers and thiazide diuretics, have long been thought to have flat dose-response curves (Hansson et al, 1974; MacGregor et al, 1983) but this may simply reflect the use of doses which produce concentrations at the top end of the concentration-effect curve.

Attempts to identify a relationship for antihypertensive drugs between plasma concentration and the fall in blood pressure have largely been unsuccessful but many previous studies have sought correlations between drug concentration and effect data for groups of subjects (Lehtonen et al, 1977; Biollaz et al, 1982; Johnston et al, 1983; de Leeuw et al, 1983; Kleinbloesem et al, 1987a). A principal component of this failure is likely to be the wide range of intersubject variability in both kinetic and dynamic parameters when group data are evaluated but there is preliminary information that the concentration-effect relationship is potentially more useful when individual patients are considered (Kelman et al, 1983; Pasanisi and

53
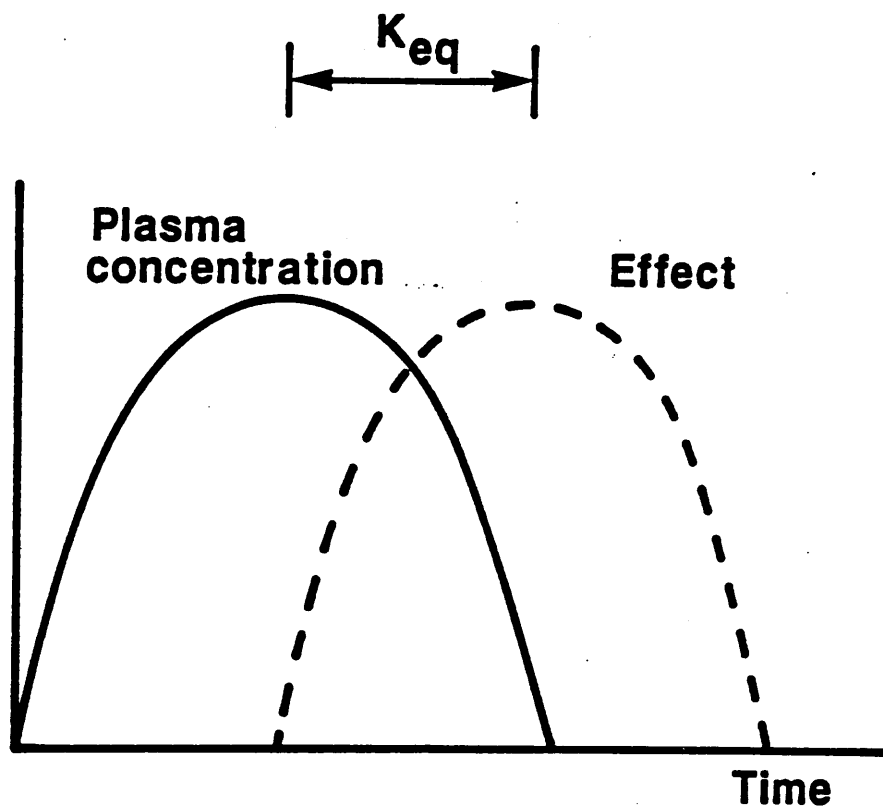
Figure 1.2.
A diagrammatic representation of the temporal discrepancy between
drug plasma concentration and effect which is characteristic of
many types of drug.   From the concentration-effect analysis
(Chapter 2.5.) $K_{eq}$ (hours) characterises the phase discrepancy.

Reid, 1983). An individual approach has been used successfully to define concentration-effect relationships with alpha blockers in normotensive subjects (Meredith et al, 1983; Vincent et al, 1983; Elliott et al, 1984) and it is now feasible to investigate individual hypertensive patients using a wider variety of drugs.

## 1.4. SCOPE OF THE THESIS

In recent years there has been a tendency to move away from a standardised stepped care regimen for treating patients with hypertension and to adopt instead a more flexible approach in which antihypertensive treatment is tailored to the needs of individual patients. "Individualisation" of antihypertensive drug treatment ideally involves an initial selection from 4 or 5 alternative drugs, a rapid assessment that the patient is likely to have a satisfactory response and then the choice of the optimum dosage. Very little is known about factors which determine the outcome of treatment but kinetic as well as dynamic variability account for the large interindividual differences in therapeutic response. Information about the relationship between drug concentration and effect constitutes a basis for determining the therapeutic regimen and dose requirements needed for optimum treatment of individual patients. To date, however, this information has been lacking and a clear relationship between plasma concentration and the fall in blood pressure has not been

55

established in hypertensive patients.

This thesis incorporates a series of studies which evaluated in patients with essential hypertension the pharmacodynamic effects and pharmacokinetics of some of the newer alternative first-line antihypertensive drugs. As well as measuring the fall in blood pressure, counter-regulatory mechanisms were also examined, including changes in baroreflex activity and vascular pressor sensitivity to exogenous vasoconstrictor agonists. An integrated pharmacokinetic and pharmacodynamic model was used to characterise the antihypertensive response for each individual patient in terms of blood pressure reduction per unit drug concentration and to describe the temporal discrepancy for the plasma concentration-effect relationship (Holford and Sheiner, 1981). The derived concentration-effect parameters were used to investigate the underlying antihypertensive mechanisms and reflex responses following acute and chronic drug administration.

Chapters 3-7 demonstrate that drug concentration-effect relationships can be identified in individual hypertensive patients after acute and chronic dosing and illustrate an improved method for incorporating kinetic as well as dynamic information in the description of individual patient responses. Chapter 8 addresses the intersubject variability in "responsiveness" for each drug and identifies factors which may be of clinical importance in predicting the outcome of different antihypertensive treatments.

# CHAPTER 2

## METHODS

## 2.1. GENERAL CLINICAL PROTOCOL

Patients with essential hypertension were recruited from the Hypertension Clinic at Stobhill Hospital and directly from general practices in the area, through the helpful co-operation of local General Practitioners. Forty-six patients with essential hypertension gave informed consent to participate in the principal project, which was approved by the Research and Ethical Committee of the Greater Glasgow Health Board (Northern District), and were entered into one of four studies. Patients were either newly diagnosed and previously untreated essential hypertensives or patients in whom current antihypertensive therapy was ineffective or poorly tolerated. Before entering a study all patients underwent full clinical screening, including physical examination, routine biochemistry, haematology, urinalysis and an electrocardiogram to exclude other significant cardiovascular disease or evidence of significant end-organ damage. Each patient discontinued any previous medication and, after a treatment-free run-in period of at least 6 weeks, was entered into a study if blood pressures on three consecutive occasions were within the range 160/90 - 210/115 mmHg.

The general clinical protocol for each study was similar. In a single blind design a matching placebo tablet was administered for 2 weeks then treatment with nifedipine, or enalapril, or doxazosin, or ketanserin as

monotherapy for 6 weeks.

## Study days

To evaluate the effects of placebo, first dose and
chronic (1-6 weeks) treatment each patient attended for a
series of 8-hour study days in the Clinical Pharmacology
Research Unit (CPRU).  On each occasion, following an
overnight fast, they attended the CPRU at 8 a.m.  Baseline
blood pressure and heart rate measurements were recorded
before the insertion of an indwelling cannula into an
antecubital vein and then placebo or active drug was
administered orally with 100 mls water.  At frequent
intervals during each study day, and at 24 hours after
dosing, blood pressure and heart rate were measured supine
after 10 minutes recumbency and erect after 5 minutes
standing using a Datascope Accutorr semi-automatic
sphygmomanometer.  Venous blood samples were collected at
corresponding times for the measurement of plasma drug
concentrations and additional samples were taken for hormone
measurements and plasma renin and ACE activity.  A standard
light lunch was provided after 4 hours.

## 2.2. VASCULAR PRESSOR RESPONSES

Pressor responses to intravenous infusions of the
selective $alpha_1$-adrenoceptor agonist phenylephrine (PE) and
the "non-adrenergic" vasoconstrictor angiotensin II (AII)
(Hypertensin, Ciba) were measured on each study day using a

similar protocol. The pressor agent in 50 mls of 0.9% NaCl was administered in incremental doses using a Braun Perfusor pump to produce a controlled progressive rise in blood pressure, with a target increase of 20 mmHg in mean arterial pressure. For safety reasons the infusion was terminated if increases in blood pressure above 45 mmHg systolic or 30 mmHg diastolic blood pressure occurred. Each dose was infused for 8 minutes and the mean of the final five sequential blood pressure and heart rate measurements (recorded at 1 minute intervals between minutes 3-8) was calculated for each dose level. Administered doses were within the range 2.5-20 ng/kg/min for angiotensin II and 0.5-9.0 ug/kg/min for phenylephrine.

All data points in each individual patient for the pressor responses to phenylephrine and angiotensin II were fitted to a quadratic function according to the method described by Sumner et al (1982). For each individual pressor dose-response curve the derived $PD_{20}$ value represents the dose of agonist required to raise mean arterial pressure by 20 mmHg. Agonist dose ratios were calculated from the ratio $PD_{20}$active/$PD_{20}$placebo.


## Cardiovascular baroreflex activity

The simultaneous blood pressure and heart rate changes during the infusion of phenylephrine were fitted in individual patients to a linear function and used as an index of cardiovascular baroreflex activity. The derived

60

measurements of baroreflex function are expressed as the change in heart rate per unit increase in systolic blood pressure.


## 2.3. LABORATORY METHODS

Venous blood samples for laboratory assay were withdrawn from the indwelling forearm cannula and collected into chilled lithium heparin and EDTA tubes. Plasma was separated by centrifugation at $4^{o}C$ for 15 minutes at 3000 rpm and stored at $-70^{o}C$ until assay.


### 2.3.1. Plasma aldosterone concentration

Plasma aldosterone concentrations were measured according to the radioimmunoassay technique described by McKenzie and Clements (1974). This method involves the competition between $I^{125}$-labelled aldosterone and the aldosterone contained within the plasma sample, for a fixed number of antibody binding sites. After an incubation period, the amount of labelled aldosterone bound to the antibody is inversely related to the amount of unlabelled aldosterone present in the plasma sample. The quantity of antibody-bound ligand is measured by radioactive counting using a gamma camera.

The normal range for plasma aldosterone in our laboratory is 12-125 pg/ml, and the inter- and intra-assay coefficients of variation were 11% and 7.3% respectively.


61

### 2.3.2. Plasma renin activity

Renin is secreted from the juxtaglomerular apparatus of the renal nephron and is responsible for the enzymatic conversion of angiotensinogen to angiotensin I. Plasma renin activity was measured by incubating plasma with sheep renin substrate (angiotensinogen) and determining the rate of formation of angiotensin I (Derkx et al, 1972). The enzymatic reaction is stopped after a fixed incubation period and angiotensin I levels are measured by radioimmunoassay.

The normal range for plasma renin activity in our laboratory is 0-12 ngA1/ml/hr, and the inter- and intra-assay coefficients of variation were 7.0% and 5.5% respectively.

### 2.3.3. Plasma catecholamine concentrations

Plasma concentrations of adrenaline and noradrenaline were measured using a radioenzymatic assay which is based upon the use of the isolated enzyme catechol-o-methyl transferase (COMT) to transfer a radioactive methyl group from S-adenosyl-L-methionine (SAM) to an endogenous catecholamine acceptor molecule to form a radioactive derivative (da Prada and Zurcher, 1976). Plasma is incubated with $^3$H-SAM and COMT and the resulting products, $^3$H-normetanephrine and $^3$H-metanephrine, are isolated by thin layer chromatography. The radioactivity attributable to each catecholamine is measured by scintillation counting.

The inter- and intra-assay coefficients of variation
were 15% and 13% respectively, and the normal ranges
are 0.3-7.5 nmol/L (supine) for noradrenaline and 0-1.0
nmol/L for adrenaline.


## 2.3.4. Plasma angiotensin converting enzyme activity

Angiotensin converting enzyme (ACE) converts the
decapeptide angiotensin I to the octapeptide angiotensin II
through cleavage of the carboxy-terminal dipeptide histidyl-
L-leucine.  The assay that was used to determine plasma ACE
activity is based on an HPLC technique for measuring the
rate of release of hippuric acid from an artificial
substrate of angiotensin I (Chiknas, 1979).  One unit of
enzyme generates one nanomole of hippuric acid per minute
and the normal range in our laboratory for plasma ACE
activity is 5-32 EU/ml.  The inter- and intra-assay
coefficients of variation were 6% and 2% respectively, with
a limit of detection of 0.1 EU/ml.


## 2.4. PHARMACOKINETIC ANALYSIS

Pharmacokinetics seeks to describe the time-course of
drug concentration in the body and this is usually achieved
with mathematical models which view the body as a series of
compartments.  The rates of transfer of drug from one
compartment to another are governed by first-order processes
defined by equations of the form:

$$\frac{dX_p}{dt} = K_{12}X_c - K_{21}X_p \qquad (1)$$

where X represents the amount of drug in the central and peripheral compartments, and $K_{12}$ and $K_{21}$ are the intercompartmental first-order rate constants.

The parameters which characterise a pharmacokinetic model are determined by fitting plasma concentration-time data to equations which define the model, so that the amount of drug in the central compartment mirrors that actually measured in the plasma. The central compartment therefore corresponds to the plasma but the other compartments probably have little physiological significance.

Solutions to equations of the type shown above (equation 1) lead to the amount of drug in a given compartment, $X_n$, at any time t being described by the summation of a series of exponential terms:

$$X_n = \sum A_n e^{-\alpha_n t} \qquad (2)$$

where $A_n$ is the $n^{th}$ coefficient and $\alpha_n$ is the exponent of the $n^{th}$ exponential term. $A_n$ and $\alpha_n$ are functions related to the first-order intercompartmental rate constants. The values of the parameters $A_n$ and $\alpha_n$ can be estimated by comparing the measured plasma concentrations with those predicted by the model by non-linear least-squares regression analysis. The disposition characteristics of any particular drug will determine the most appropriate

pharmacokinetic model.

In this project plasma drug concentration-time profiles for individual patients on each study day were fitted to a hierarchy of pharmacokinetic models using an "in house" nonlinear least squares fitting program employing the Marquardt algorithm (Bevington, 1969) and in each case the most appropriate model was identified by the general linear test. Measurements were derived for the area under the concentration-time curve (AUC), elimination half life, ($\Delta$) $C_{max}$ and $t_{max}$.

## 2.5. CONCENTRATION-EFFECT ANALYSIS

In recent years considerable attention has been devoted to refining mathematical models for more accurate description of drug disposition in the body and thereby to attempt to optimise dosage regimens. However, the time-course of drug concentration cannot in itself predict the time-course or magnitude of drug effect. Until recently, comparatively little attention has been focused on mathematical modelling of the inter-relationship between the effect of a drug and its concentration in plasma (Whiting and Kelman, 1980). This integrated approach to pharmacodynamics and pharmacokinetics has been variously called 'concentration-effect analysis' or 'pharmacodynamic modelling'.

One of the most striking features of concentration-effect analysis is that the measured effect is not in phase

with the amount of drug in any of the predetermined pharmacokinetic compartments (Whiting and Kelman, 1980). Characteristically, there is a variable time-lag between the effect of a drug and the concentration in plasma and this is thought to reflect an equilibration delay in drug reaching the effector site (Figure 1.2.). To take account of this phase discrepancy, Sheiner et al (1979) developed a unified modelling approach which integrates kinetic and dynamic data to characterise the drug concentration-effect relationship in individual subjects. This method involves extending the simple pharmacokinetic model to incorporate an additional "effect" compartment which is constrained to be small enough so as not to perturb the pharmacokinetic parameters defined by the original model (Figure 2.1.). The amount of drug in the effect compartment, $X_e$, is described by the equation:

$$\frac{dX_e}{dt} = K_{1e}X_1 - K_{eq}X_e \qquad (3)$$

where $X_1$ is the amount of drug in the central compartment and $K_{1e}$ and $K_{eq}$ are first-order rate constants. $K_{eq}$ describes the removal of drug from the effect compartment and characterises the temporal discrepancy for the plasma concentration-effect relationship, i.e. it defines the phase lag shown diagrammatically in Figure 1.2.

The measured effect, in this case blood pressure reduction, is then described as a function of drug concentration, $C_e$, in the effect compartment:

$$E = f(C_e) \tag{4}$$

This function is likely to be sigmoid in configuration and therefore defined accurately by the Hill or Langmuir ($E_{max}$) equations:

$$E = \frac{E_{max} \cdot C_e}{C_{e(50)} + C_e} \qquad \text{Langmuir } (E_{max}) \text{ model} \tag{5}$$

where E is the measured effect and $C_e$ the drug concentration in the effect compartment. However, in clinical studies most data points are usually obtained within a relatively restricted concentration-response range and therefore a linear equation is often more appropriate (Figure 2.2.):

$$E = mC_e + i \qquad \text{Linear model} \tag{6}$$

For the linear model the slope of the relationship, m, represents the "responsiveness" to the drug in terms of effect (in mmHg) per unit drug concentration in the effect compartment, while for the Langmuir model $E_{max}$ is the maximum possible effect and $C_{e(50)}$ is the concentration required to produce 50% of $E_{max}$ (Holford and Sheiner, 1981).

Using this technique, the pharmacodynamic effects of a number of drugs have been correlated with their pharmacokinetic properties: for example, the prolongation

# EXTENDED KINETIC MODEL



**linear model**

$$E = mC_e + i$$

$$m = \text{responsiveness}$$
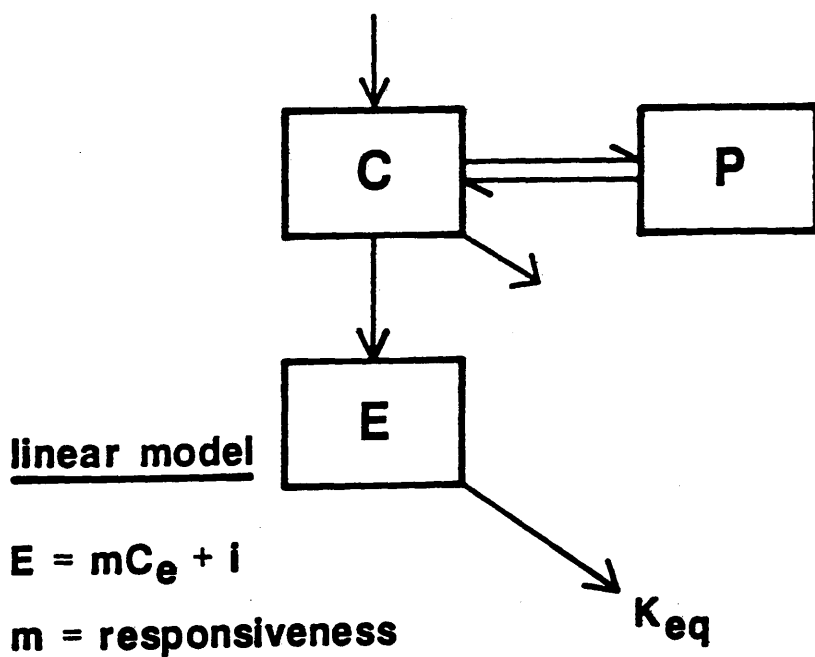
Figure 2.1.
For the concentration-effect analysis the simple pharmacokinetic
model, for example with central (C) and peripheral (P) compartments,
is extended to incorporate an additional "effect" compartment (E).
$K_{eq}$ is the rate constant which determines the removal of drug from E.
In most clinical studies the linear model satisfactorily describes the
relationship between drug effect and drug concentration in $E(C_e)$.

68
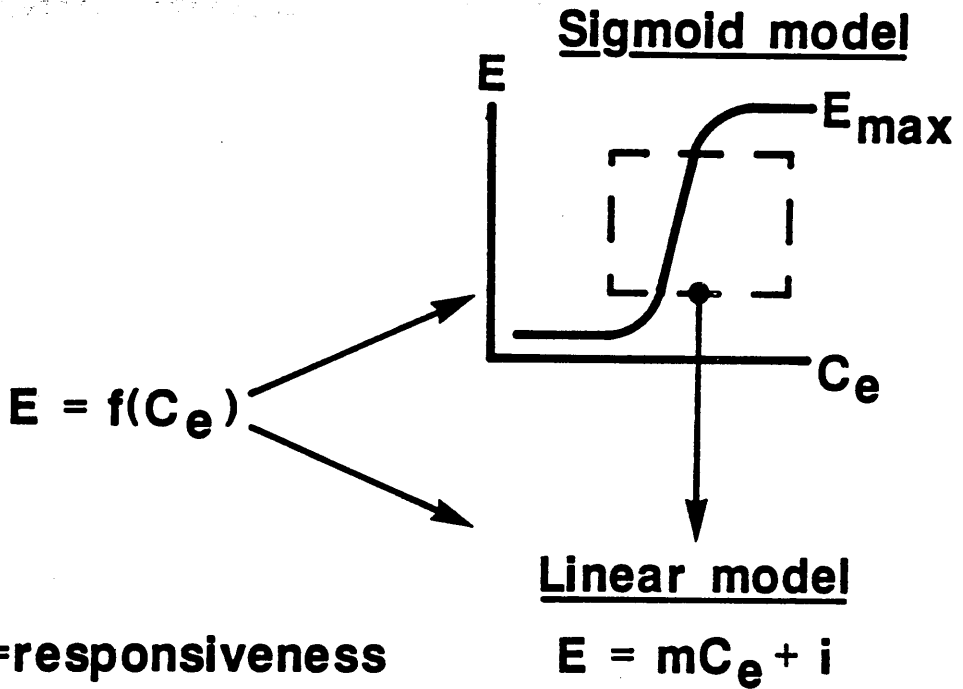
## Figure 2.2.

The effect, in this case blood pressure reduction, is related as a function of drug concentration in the effect compartment ($C_e$). This relationship is sigmoid in configuration and therefore described by the Langmuir equation, but in most clinical studies data points are usually obtained over a restricted portion of the curve and thus a simpler linear model is often more appropriate. The slope of the linear relationship, m, represents the responsiveness in terms of effect (in mmHg) per unit drug concentration.

of the QT interval on the electrocardiogram in response to disopyramide (Whiting et al, 1980) or quinidine (Holford et al, 1981), the change in the force of muscle contraction following d-tubocurarine (Sheiner et al, 1979), and the improvement in respiratory function in response to theophylline (Whiting et al, 1981). In this project the same method has been applied with antihypertensive drugs to define concentration-effect relationships in individual patients and thereby characterise antihypertensive responses in terms of kinetic as well as dynamic parameters.

Having firstly defined the pharmacokinetic model and the appropriate parameters in individual patients the pharmacodynamic data was then fitted to both the $E_{max}$ and linear effect models using an "in-house" non-linear least squares fitting procedure. The most appropriate model was identified on the basis of the general linear test and the concentration-effect parameters, m (or $E_{max}$) and $K_{eq}$, derived for individual patients on each study day. The data sets for nifedipine, doxazosin and ketanserin were satisfactorily described using the linear effect model and the responsiveness (m) was calculated for individual patients in terms of the placebo-subtracted fall in blood pressure per unit change in drug concentration. The Langmuir model was fitted most appropriately to the kinetic-dynamic relationships for enalapril and $E_{max}$ values (in mmHg) were expressed in terms of the placebo-subtracted reduction in both systolic and diastolic blood pressure.

## 2.6. STATISTICAL ANALYSIS

Blood pressure and heart rate measurements were evaluated by repeated measures analysis of variance. The derived pharmacokinetic and concentration-effect parameters, and the measurements of plasma renin activity, aldosterone, catecholamines and ACE activity, were compared between study days by repeated measures analysis of variance.

Linear regression analysis was used to investigate the relationship between the concentration-effect parameter, m (or $E_{max}$), and factors such as patient age, plasma renin activity and starting blood pressure.

For the pressor response analysis the $PD_{20}$ values, which represent the dose of agonist required to raise mean arterial pressure by 20 mmHg, were compared by repeated measures analysis of variance.

Measurements throughout are expressed as mean $\pm$ standard deviation.

# CHAPTER 3

## NIFEDIPINE IN ESSENTIAL HYPERTENSION: RESPONSES AND CONCENTRATION-EFFECT RELATIONSHIPS IN INDIVIDUAL PATIENTS

## 3.1. INTRODUCTION

The calcium antagonist drug nifedipine, which is widely used in the treatment of angina pectoris and essential hypertension, shows large inter-individual differences not only in drug disposition and dose requirements but also in the magnitude of the antihypertensive response (Bayley et al, 1982; Kiowski et al, 1983; Kleinbloesem et al, 1984a and 1984b; Landmark, 1985). Attempts to identify a relationship between plasma drug concentration and the fall in blood pressure have produced conflicting reports and a clear relationship between plasma concentration and blood pressure reduction has not been established (Lederballe-Pedersen et al, 1979 and 1980; Aoki et al, 1982; Taburet et al, 1983). This may reflect the wide range of inter-subject variability in both kinetic and dynamic parameters when group data are evaluated but there is preliminary information that the concentration-effect relationship is potentially more applicable when individual patients are considered (Pasanisi and Reid, 1983).

This study investigates the pharmacodynamics and pharmacokinetics of monotherapy with nifedipine in patients with essential hypertension and, by integrated pharmacokinetic and pharmacodynamic modelling (Holford and Sheiner, 1981), characterises the responses to acute and chronic nifedipine in individual patients.

## 3.2. PATIENTS AND METHODS

### 3.2.1. General

Fourteen patients (7 male, 7 female) with mild to moderate essential hypertension, age range 33-66 years, gave consent to participate in this study. Individual patient details are shown in Table 3.1.

Following a preliminary assessment period of at least 6 weeks (without treatment) the average entry blood pressure was 181/105 ± 20/8 mmHg supine and 183/107 ± 17/5 mmHg erect. Thereafter, in a single blind design, patients received placebo for 2 weeks followed by 6 weeks treatment with nifedipine 20 mg b.i.d using a delayed release formulation tablet (Adalat Retard, BAYER UK Ltd). Each patient attended four 8-hour study days in the Clinical Pharmacology Research Unit (CPRU) to evaluate the effects of placebo, 1st dose nifedipine and then 1 week and 6 weeks of nifedipine therapy.

The protocol for study days is described in detail in Chapter 2.1. At frequent intervals during each study day, and at 24 hours after dosing, supine and erect blood pressure and heart rate were measured and venous blood samples collected for plasma nifedipine concentrations. Additional blood samples were obtained at 1.5 and 6 hours for plasma renin activity, aldosterone and catecholamines.

### 3.2.2. Nifedipine concentrations

Blood and plasma samples were placed into tubes

**TABLE 3.1.**

**NIFEDIPINE STUDY.  INDIVIDUAL PATIENT DETAILS**

| PATIENT | AGE | SEX | WEIGHT (kg) | RELEVANT MEDICAL HISTORY | PREVIOUS ANTI-HYPERTENSIVE THERAPY | CHOLESTEROL | SMOKER | ENTRY BP SUPINE | EREC |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 33 | F | 90 | Newly diagnosed EH | Nil | 5.9 | - | 160/94 | 15 |
| 2 | 49 | F | 62 | EH diagnosed 4 years ago | Diuretic-tiredness Propranolol-headache | 6.1 | + | 159/100 | 16 |
| 3 | 64 | F | 77 | EH diagnosed 2 years ago Mild IHD | Atenolol - dyspnoea | 5.9 | + | 187/110 | 1 |
| 4 | 53 | F | 69 | EH diagnosed 5 years ago | Diuretic-poor BP control Atenolol-tiredness | 5.8 | - | 184/104 | 1 |
| 5 | 58 | M | 72 | EH diagnosed 10 years ago LVH Mild IHD | Atenolol-headache Diuretic-poor BP control Methyldopa-nausea | 5.8 | + | 203/103 | 2 |
| 6 | 59 | M | 88 | EH diagnosed 5 years ago | Atenolol-headache | 5.2 | - | 188/108 | |
| 7 | 55 | M | 96 | EH diagnosed prior to entry asthma | Diuretic-poor BP control | 6.4 | - | 176/103 | |
| 8 | 49 | F | 75 | Newly diagnosed EH | Nil | 8.4 | + | 210/110 | |
| 9 | 66 | F | 63 | Newly diagnosed EH | Nil | 6.7 | - | 183/104 | |
| 10 | 56 | M | 93 | Newly diagnosed EH | Nil | 6.6 | - | 173/105 | |
| 11 | 46 | M | 77 | Newly diagnosed EH | Nil | 5.8 | - | 162/104 | |
| 12 | 41 | M | 80 | EH diagnosed 4 years ago LVH | Atenolol + diuretic poor BP control | 6.3 | - | 165/99 | |
| 13 | 58 | M | 90 | Newly diagnosed EH | Nil | 8.1 | - | 174/105 | |
| 14 | 44 | F | 52 | EH diagnosed 8 | Atenolol-poor BP | 7.4 | + | 194/115 | |
| MEAN ± SD | 52 ± 9 | | | | | | | 181/105 ± 20/8 | |

Key:  EH = essential hypertension;  IHD = ischaemic heart disease;  LVH = left ventricular hypertrophy

75

wrapped with aluminium foil to prevent photodegradation of
nifedipine. Plasma nifedipine concentrations were measured
using the reverse phase HPLC technique described by Waller
et al (1984). The extraction procedure was carried out
under sodium light and the recovery of nifedipine was
between 70-80%. Ultra-violet detection was used, and the
inter and intra-assay coefficients of variation for the drug
assay were 8% and 5% respectively, with a limit of detection
of 3-5 ng/ml.


### 3.2.3. Pharmacokinetics and concentration-effect analysis

Plasma nifedipine concentration-time profiles for
individual patients on each study day were most
appropriately described by a one compartment pharmacokinetic
model with first order input and inverse weighting of the
drug concentrations. Measurements derived from fitting this
model to the data were the apparent elimination half-life,
area under the concentration-time curve (AUC), $C_{max}$ and
$t_{max}$.

For the concentration-effect analysis the standard
pharmacokinetic model was augmented by an "effect"
compartment, as described in Chapter 2.5. The effect of
nifedipine on blood pressure was then related to the drug
concentration in the effect compartment by means of both the
linear and non-linear models (Holford and Sheiner, 1981).
In all cases, both acutely and chronically, the data were
most appropriately described by the linear model on the

basis of the general linear test. The concentration-effect parameters, m and $K_{eq}$, were derived for individual patients on each study day and the responsiveness (m) to nifedipine was calculated in terms of the placebo-subtracted change in both erect systolic and diastolic blood pressure per unit change in drug concentration.

## 3.3. RESULTS

### 3.3.1. Blood pressure

Nifedipine produced significant reductions ($p < 0.01$) in supine and erect blood pressure, as illustrated by the erect systolic and diastolic blood pressures (Figure 3.1.). The maximum antihypertensive effect of this formulation of nifedipine occurred 5-6 hours after drug administration (Figure 3.1.): for example at 5 hours after the first dose, erect blood pressure had fallen from a baseline of 166/104 $\pm$ 12/10 to 135/86 $\pm$ 16/8, compared with 171/105 $\pm$ 16/9 to 162/97 $\pm$ 9/7 mmHg following placebo. The average maximal fall in blood pressure following the first dose (baseline- and placebo-corrected) was 21/11 $\pm$ 11/8 mmHg supine and 27/13 $\pm$ 18/10 mmHg erect.

With continued treatment there was a sustained antihypertensive effect ($p < 0.01$): for example, baseline measurements of supine blood pressure (recorded 12 hours after the last dose) after 1 week and 6 weeks were respectively 23/11 and 33/15 mmHg lower than with placebo. In addition, there were further reductions in blood pressure after drug administration, reaching a nadir at 5 hours of

77

135/80 ± 13/9 supine and 129/84 ± 11/8 mmHg erect after 1
week and 136/81 ± 10/7 supine and 132/82 ± 11/10 mmHg erect
after 6 weeks (Figure 3.1.).


### 3.3.2. Heart rate

The acute reduction in blood pressure, particularly
following the first dose and after 1 week of nifedipine, was
associated with significant increases in heart rate (Figure
3.2.).    Erect heart rate increased from a baseline of 87 ±
13 to 108 ± 14 bpm 5 hours after the first dose, compared
with a corresponding change from 86 ± 14 to 94 ± 12 bpm
following placebo.    After 1 week of nifedipine, reflex
tachycardia was considerably reduced but significant
increases in heart rate were again observed at 4-5 hours
(Figure 3.2.).    Heart rate profiles after 6 weeks were not
significantly different from placebo.


### 3.3.3. Hormone measurements

The first dose of nifedipine was associated with a
significant increase in plasma noradrenaline: for example
at 1.5 hours, 4.2 ± 2.1 compared with 2.5 ± 1.3 nmol/L
following placebo (Table 3.2.).    After 1 week of nifedipine
plasma noradrenaline was again increased at 1.5 hours (3.9 ±
1.7 nmol/L) and there were additional significant increases
in plasma renin activity and aldosterone (Table 3.2.).
Measurements after 6 weeks were not significantly different
from placebo.

## ERECT BLOOD PRESSURE
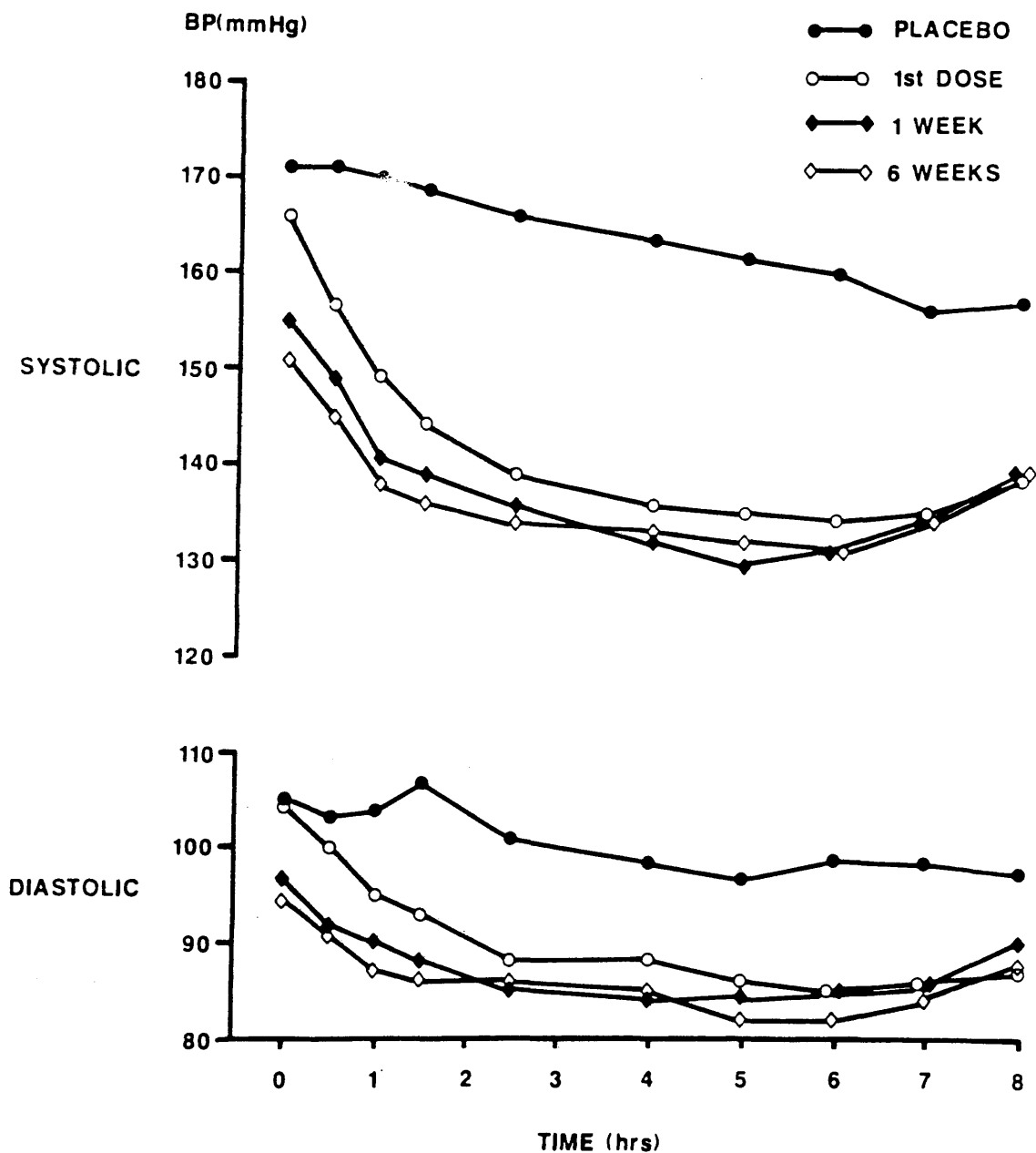


Figure 3.1.
Mean profiles of erect systolic and diastolic blood pressure after placebo ( ● ), 1st dose nifedipine ( ○ ) and after 1 week ( ◆ ) and 6 weeks ( ◇ ) nifedipine treatment.

**ERECT HR**

**GROUP MEANS**
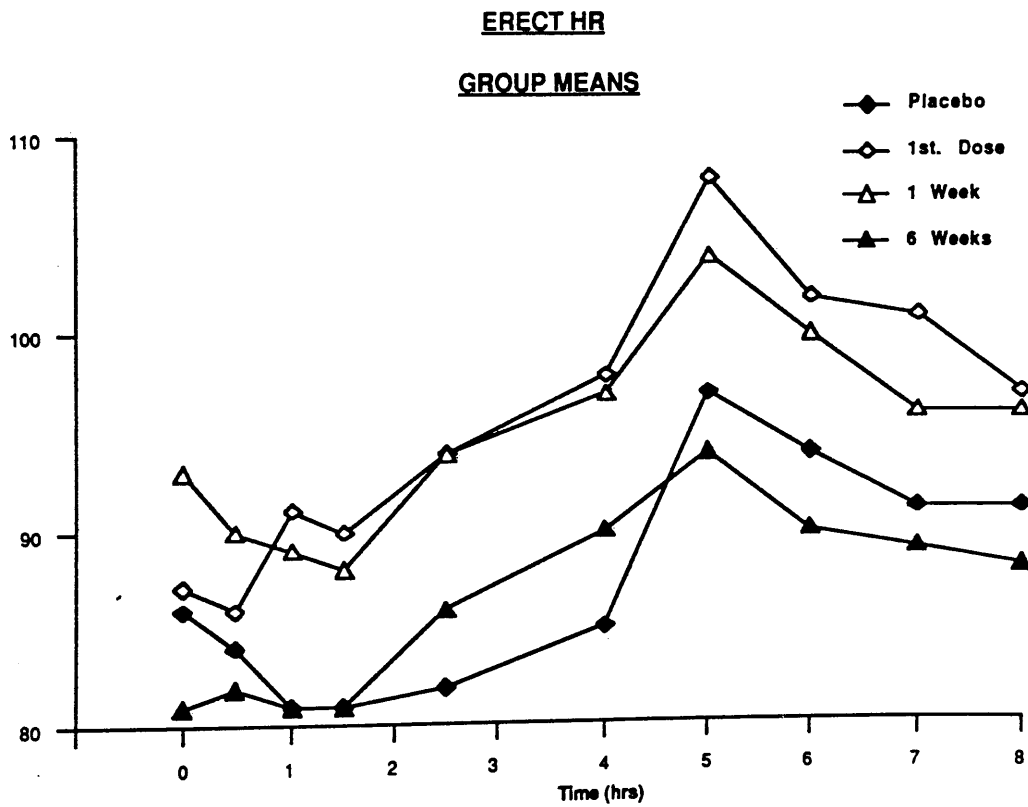
Figure 3.2.
Mean profiles of erect heart rate after placebo ( ◆ ), 1st dose
nifedipine ( ◇ ) and after 1 week ( △ ) and 6 weeks ( ▲ ) nifedipine
treatment.

80

TABLE 3.2.

NIFEDIPINE STUDY. HORMONE MEASUREMENTS AT 1.5 AND 6 HOURS
AFTER DRUG ADMINISTRATION.
MEAN ± SD

| | TIME (HRS) | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---|---|---|---|---|---|
| Plasma renin activity (ngA1/ml/hr) | 1.5 | 1.5 ± 1.4 | 1.8 ± 1.0 | 2.6* ± 1.4 | 3.3 ± 4.9 |
| | 6 | 1.7 ± 1.2 | 1.8 ± 1.1 | 2.5* ± 2.1 | 2.9 ± 3.2 |
| Plasma aldosterone (pg/ml) | 1.5 | 76 ± 33 | 99 ± 60 | 110* ± 58 | 106 ± 79 |
| | 6 | 75 ± 44 | 110 ± 60 | 111* ± 57 | 103 ± 71 |
| Plasma noradrenaline (nM/L) | 1.5 | 2.5 ± 1.3 | 4.2** ± 2.1 | 3.9* ± 1.7 | 3.0 ± 1.6 |
| | 6 | 2.8 ± 1.5 | 4.2** ± 2.4 | 3.3 ± 1.6 | 3.0 ± 0.9 |

* P < 0.03      ** P < 0.006

### 3.3.4. Pharmacokinetics

There were large inter-subject differences in plasma
nifedipine concentrations but the intra-individual mean
pharmacokinetic parameters were not significantly different
across the three study days (Tables 3.3. - 3.5.).
Following the first dose, after 1 week and after 6 weeks, the
mean values for AUC (ng.h.ml$^{-1}$) were respectively 824 $\pm$ 327,
813 $\pm$ 282 and 880 $\pm$ 814; for apparent elimination half-life
(hrs), 6.0 $\pm$ 2.8, 10.0 $\pm$ 3.1 and 7.5 $\pm$ 2.3; for $C_{max}$
(ng.ml$^{-1}$), 74 $\pm$ 25, 53 $\pm$ 15 and 77 $\pm$ 68; for $t_{max}$ (hrs),
2.5 $\pm$ 1.0, 2.0 $\pm$ 0.7 and 2.0 $\pm$ 0.6. There was a significant
correlation between age and the maximum concentration of
nifedipine achieved following the first dose (Figure 3.3.).

### 3.3.5. Concentration-effect relationships

In individual patients, as illustrated  by patient 9
(figure 3.4.), there was no simple direct relationship
between the plasma nifedipine concentration and the fall in
blood pressure. Using the linear concentration-effect model
the data for all individuals were satisfactorily fitted and
the two examples shown in Figures 3.5. and 3.6. illustrate
above and below average goodness of fit for changes in
systolic blood pressure. Figure 3.7. illustrates fits for
diastolic blood pressure in a representative patient. The
derived m and $K_{eq}$ values and the "goodness" of fit (R) for
the data sets of individual patients are shown in Tables
3.6. and 3.7. Responsiveness to nifedipine in terms of

TABLE 3.3.

NIFEDIPINE PHARMACOKINETICS AFTER THE FIRST DOSE

| PATIENT | AUC ($ng.h.ml^{-1}$) | APPARENT ELIMINATION HALF-LIFE (hours) | $C_{max}$ (ng/ml) | $T_{max}$ (hours) |
|---------|------|------|------|------|
| 1 | 495 | 6.4 | 44 | 2.2 |
| 2 | 408 | 1.3 | 77 | 2.2 |
| 3 | 404 | 6.4 | 19 | 1.0 |
| 4 | 661 | 4.6 | 90 | 1.6 |
| 5 | 1237 | 3.7 | 90 | 5.4 |
| 6 | 673 | 7.4 | 53 | 2.0 |
| 7 | 1087 | 6.6 | 101 | 2.1 |
| 8 | 757 | 8.1 | 59 | 2.1 |
| 9 | 986 | 4.4 | 111 | 2.4 |
| 10 | 428 | 1.2 | 89 | 2.1 |
| 11 | 1378 | 11.3 | 70 | 3.1 |
| 12 | 1181 | 7.0 | 89 | 3.0 |
| 13 | 906 | 5.9 | 81 | 2.8 |
| 14 | 933 | 9.4 | 58 | 3.1 |
| MEAN ± SD | 824 ± 327 | 6.0 ± 2.8 | 74 ± 25 | 2.5 ± 1.0 |

TABLE 3.4.

NIFEDIPINE PHARMACOKINETICS AFTER TREATMENT FOR 1 WEEK

| PATIENT | AUC $(ng.h.ml^{-1})$ | APPARENT ELIMINATION HALF-LIFE (hours) | $\triangle C_{max}$ (ng/ml) | $T_{max}$ (hours) |
|---------|---------------------|----------------------------------------|-----------------------------|-------------------|
| 1 | 746 | 11.2 | 42 | 1.7 |
| 2 | 452 | 8.1 | 30 | 3.0 |
| 3 | 524 | 9.0 | 36 | 1.4 |
| 4 | 689 | 7.3 | 57 | 2.1 |
| 5 | 1328 | 13.0 | 69 | 1.9 |
| 6 | 559 | 9.5 | 37 | 1.9 |
| 7 | 885 | 11.5 | 49 | 2.1 |
| 8 | 768 | 6.9 | 74 | 0.8 |
| 9 | 697 | 6.2 | 74 | 0.7 |
| 10 | 713 | 5.7 | 65 | 2.9 |
| 11 | 1150 | 16.0 | 46 | 2.0 |
| 12 | - | - | - | - |
| 13 | 1305 | 13.7 | 56 | 3.1 |
| 14 | 751 | 10.9 | 47 | 1.9 |
| MEAN ± SD | 813 ± 282 | 10.0 ± 3.1 | 53 ± 15 | 2.0 ± 0.7 |

TABLE 3.5.

NIFEDIPINE PHARMACOKINETICS AFTER TREATMENT FOR 6 WEEKS

| PATIENT | AUC $(ng.h.ml^{-1})$ | APPARENT ELIMINATION HALF-LIFE (hours) | $\triangle C_{max}$ $(ng/ml)$ | $T_{max}$ (hours) |
|---------|------|-----|-----|-----|
| 1 | 839 | 5.7 | 96 | 1.9 |
| 2 | 464 | 8.9 | 33 | 1.6 |
| 3 | 410 | 5.4 | 42 | 1.8 |
| 4 | 636 | 7.9 | 54 | 1.3 |
| 5 | 806 | 5.0 | 99 | 2.6 |
| 6 | 497 | 8.4 | 38 | 1.3 |
| 7 | 550 | 6.7 | 46 | 2.2 |
| 8 | 727 | 10.0 | 44 | 2.3 |
| 9 | 814 | 4.0 | 120 | 1.1 |
| 10 | 461 | 5.9 | 52 | 2.3 |
| 11 | 954 | 10.6 | 55 | 2.1 |
| 12 | 406 | 11.3 | 22 | 2.2 |
| 13 | 1162 | 9.3 | 84 | 2.0 |
| 14 | 3597 | 6.4 | 290 | 3.5 |
| MEAN ± SD | 880 ± 814 | 7.5 ± 2.3 | 77 ± 68 | 2.0 ± 0.6 |

# FIRST DOSE

$C_{max}$(ng/ml)



r=0.61
(P<0.03)

age (years)
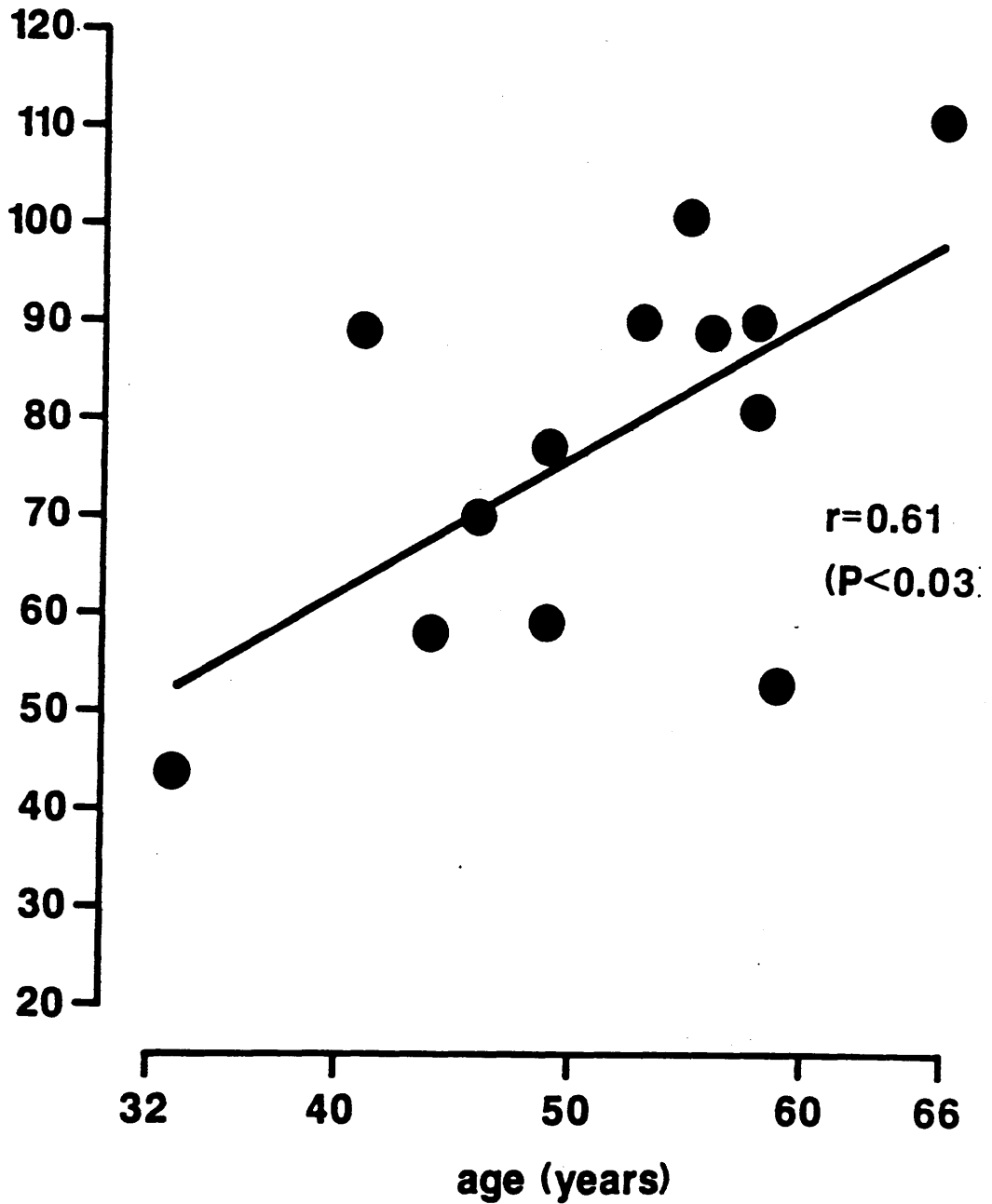
<u>Figure 3.3.</u>
Nifedipine study. Correlation between patient age and the maximum
plasma concentration ($C_{max}$) of nifedipine after the first dose.

systolic blood pressure, as the mean of the group, was -0.48 mmHg/ng/ml following the first dose, -0.45 after 1 week and -0.49 after 6 weeks. The corresponding values for changes in diastolic blood pressure were -0.25 (first dose), -0.24 (1 week) and -0.26 mmHg/ng/ml (6 weeks). There were significant correlations both acutely and chronically between the responsiveness to nifedipine in terms of systolic and diastolic blood pressure (Figure 3.8.). In addition, for individual patients there were significant correlations ($p < 0.001$) between the responsiveness to the first dose of nifedipine and the responsiveness after 1 week ( $r = 0.83$) and after 6 weeks treatment ($r = 0.78$), as illustrated in Figure 3.9., the slope of both these regression lines being not significantly different from unity. There were no significant differences in $K_{eq}$ between the three study days.

There was a significant positive correlation ($p < 0.02$) between the responsiveness to the first dose of nifedipine and the baseline (pretreatment) blood pressure ($r = 0.6$; Figure 3.10a.). There was no significant correlation between responsiveness and the maximal change in heart rate although there was a trend towards an inverse relationship (Figure 3.10b.).

There was no significant relationship between the responsiveness to nifedipine and patient age, pretreatment plasma renin activity (Figure 3.11.) or plasma noradrenaline.

**PATIENT 9**

**First Dose**

ΔErect Systolic BP

Conc. (ng/ml)
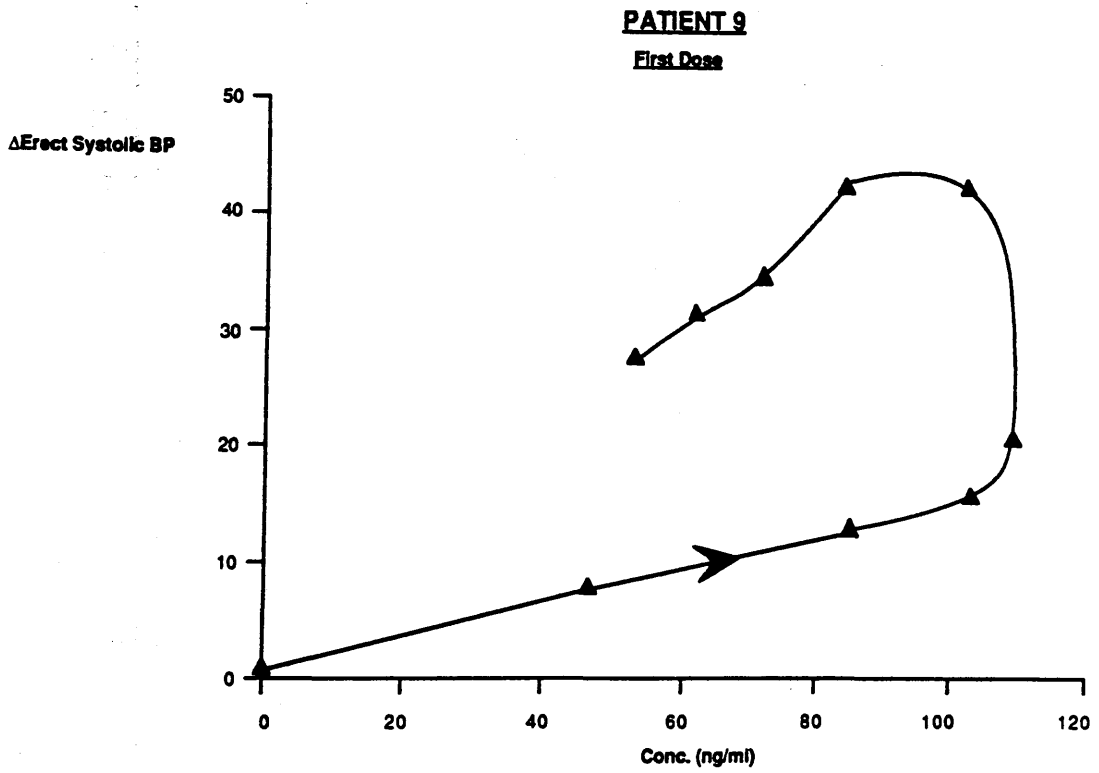
Figure 3.4.
The relationship between plasma nifedipine concentration and the placebo-subtracted fall in erect systolic blood pressure in an individual patient after the 1st dose of nifedipine.
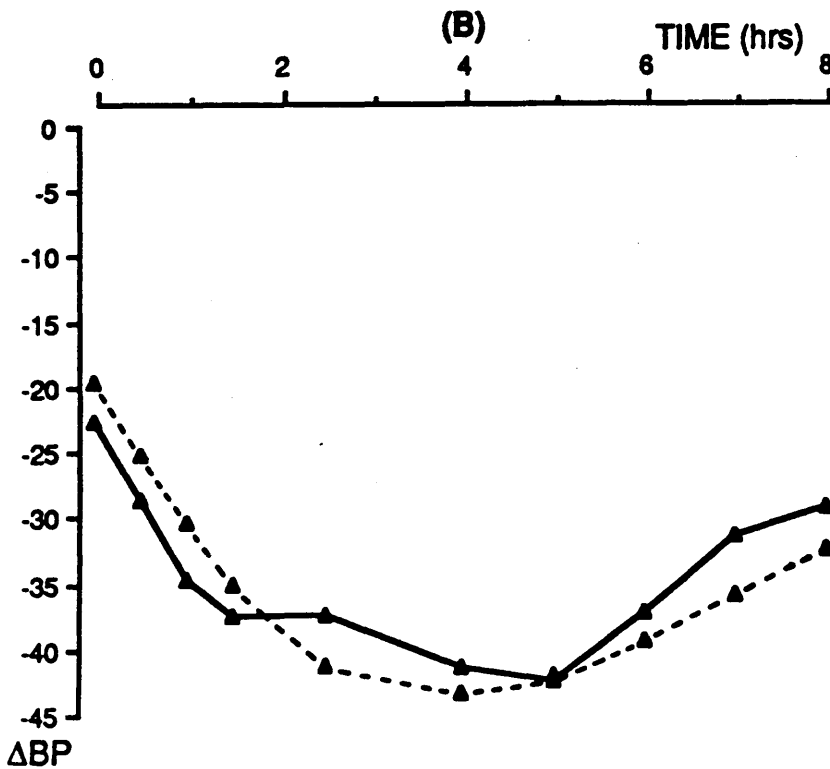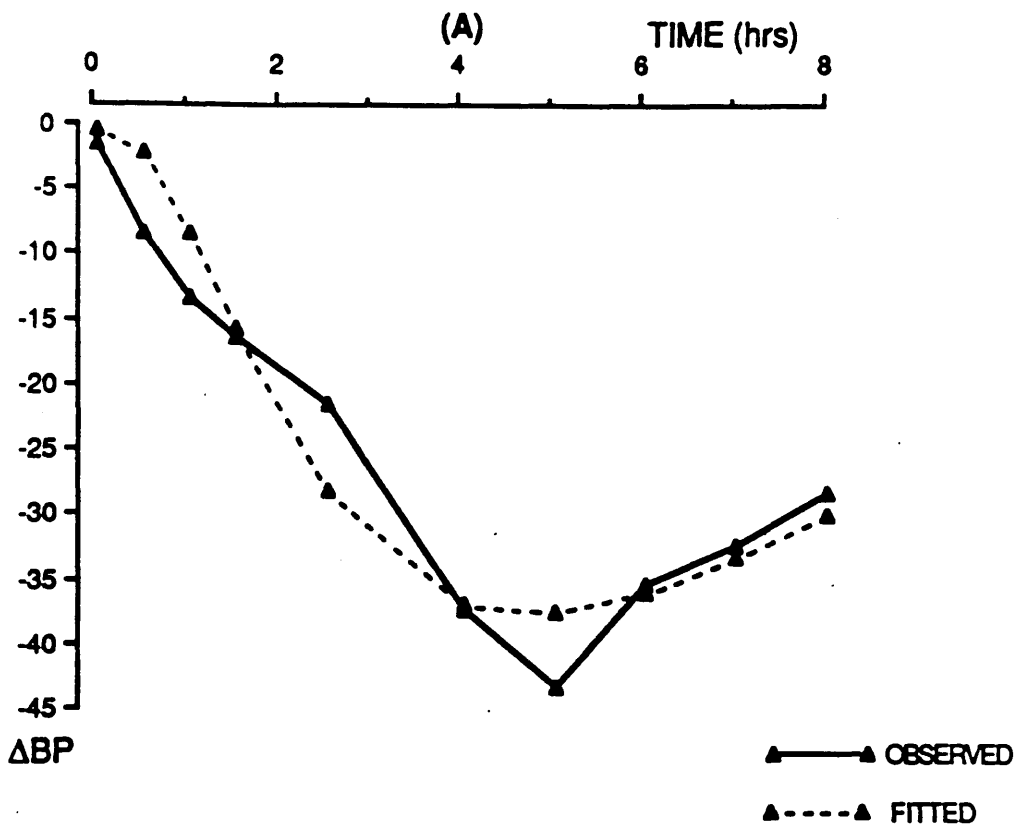
Figure 3.5.
Nifedipine concentration-effect analysis. The observed
( ▲——▲ ) and fitted ( ▲-----▲ ) effect of nifedipine on erect
systolic BP after the 1st dose (A) and after 6 weeks (B) in a
representative patient (patient 9), illustrating above average
goodness of fit.

89
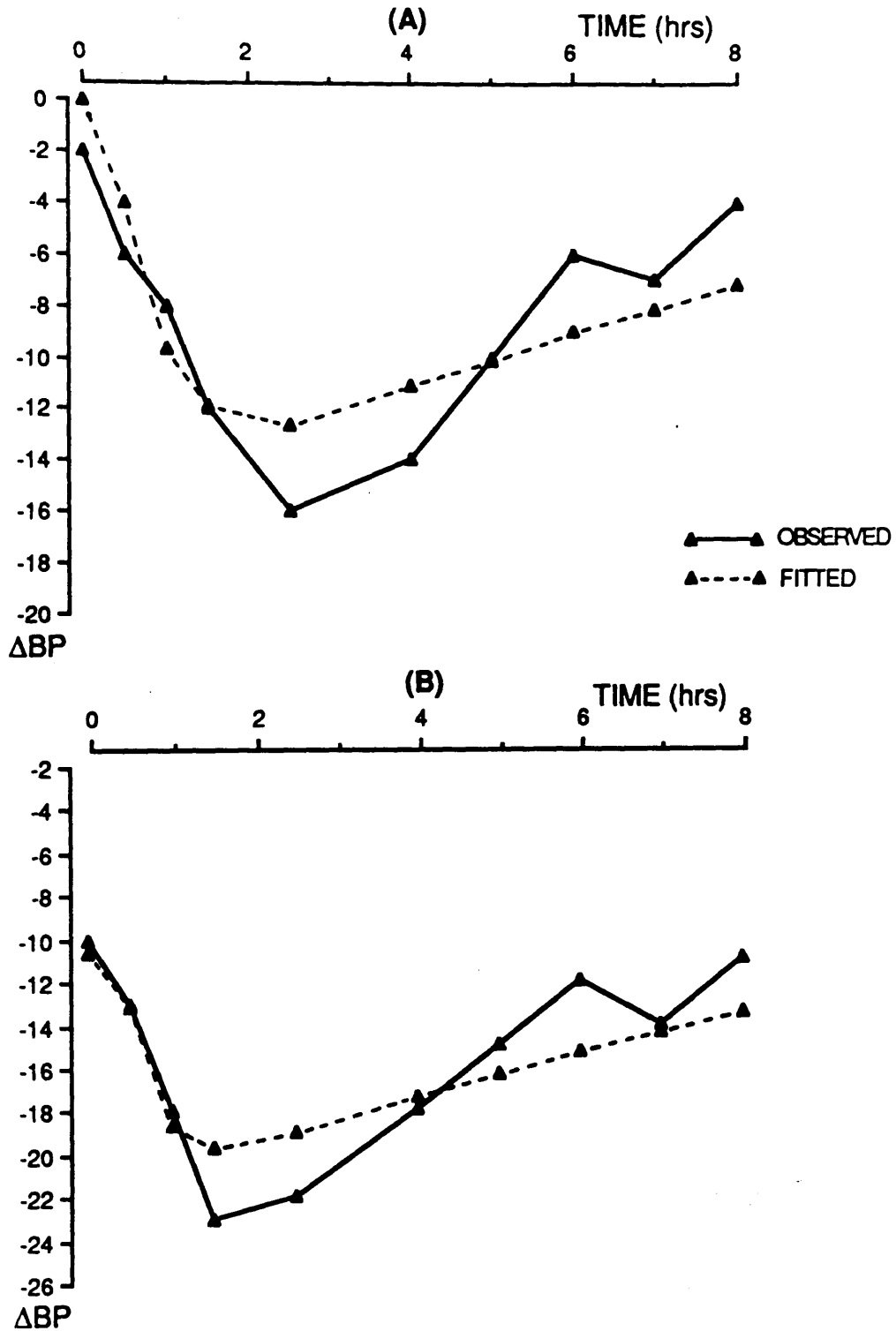
Figure 3.6.
Nifedipine concentration-effect analysis. The observed ( ▲——▲ )
and fitted ( ▲-----▲ ) effect of nifedipine on erect systolic BP
after the 1st dose (A) and after 6 weeks (B) in a representative
patient (patient 3), illustrating below average goodness of fit.

# PATIENT 8



TIME (hrs)

FIRST DOSE

$m = -0.24$ mmHg/ng/ml
$K_{eq} = 4.5$ hours[1]

ΔERECT DIASTOLIC BP

OBSERVED
FITTED

TIME (hrs)

6 WEEKS

$m = -0.27$ mmHg/ml
$K_{eq} = 3.9$ hours[1]

ΔERECT DIASTOLIC BP
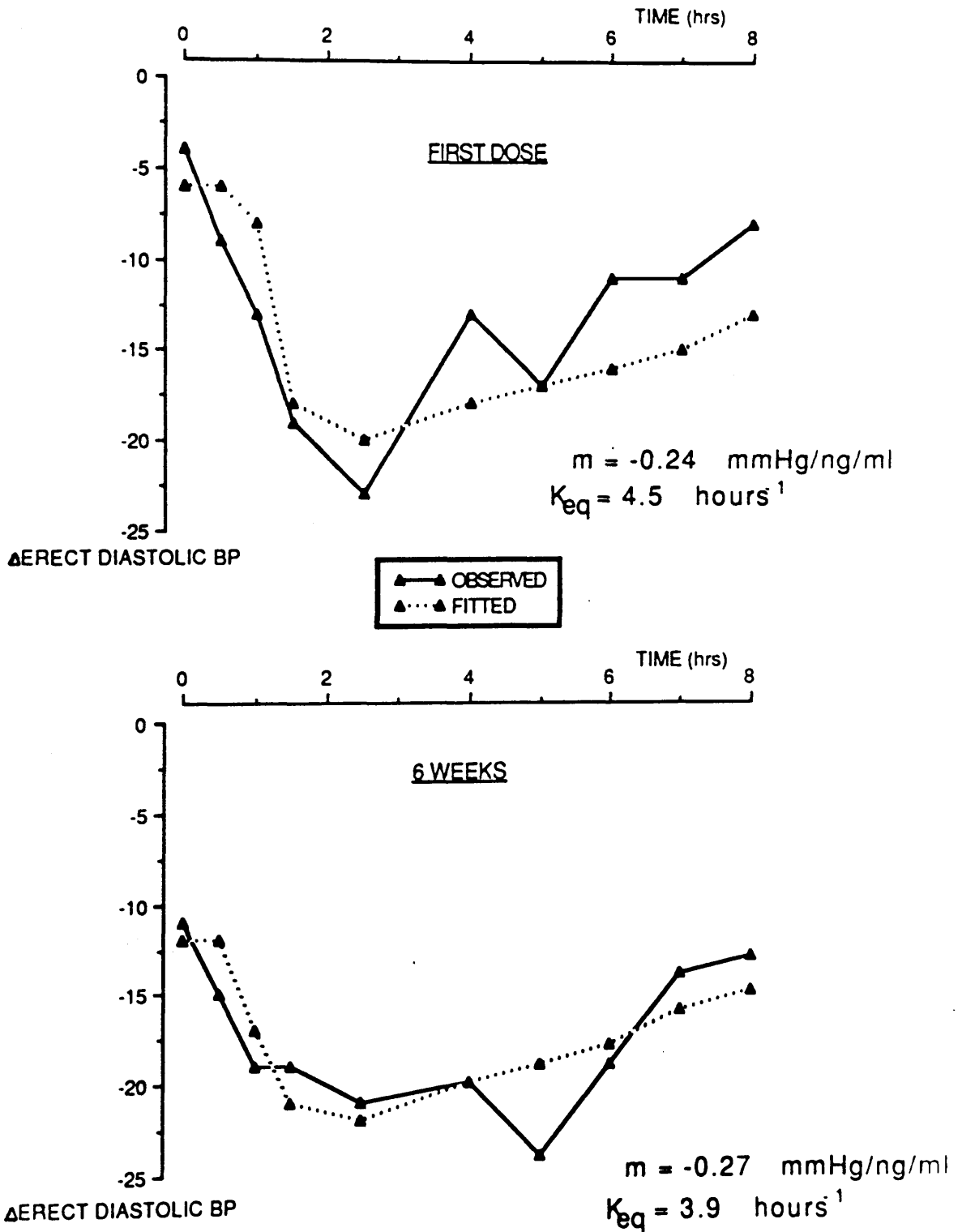
Figure 3.7.
Nifedipine concentration-effect analysis. The observed
( ▲——▲ ) and fitted ( ▲-----▲ ) effect of nifedipine on erect
diastolic blood pressure after the 1st dose and after 6 weeks in
a representative patient (patient 8).

91

TABLE 3.6.

NIFEDIPINE CONCENTRATION-EFFECT PARAMETERS, m (mmHg/ng/ml) and $K_{eq}$ ($h^{-1}$)
AND THE GOODNESS OF FIT R (AS A FRACTION OF UNITY)
FOR CHANGES IN ERECT SYSTOLIC BLOOD PRESSURE

| PATIENT | 1st DOSE | | | 1 WEEK | | | 6 WEEKS | | |
| | m | $K_{eq}$ | R | m | $K_{eq}$ | R | m | $K_{eq}$ | R |
|---|---|---|---|---|---|---|---|---|---|
| 1 | -0.29 | 49.6 | 0.84 | -0.24 | 12.5 | 0.88 | -0.24 | 0.2 | 0.67 |
| 2 | -0.79 | 2.1 | 0.92 | -0.95 | 0.9 | 0.81 | -0.87 | 1.0 | 0.88 |
| 3 | -0.63 | 1.9 | 0.92 | -0.55 | 0.8 | 0.74 | -0.61 | 0.9 | 0.90 |
| 4 | -0.84 | 0.8 | 0.88 | -0.58 | 3.7 | 0.95 | -0.56 | 0.1 | 0.83 |
| 5 | -0.34 | 12.2 | 0.92 | -0.34 | 12.5 | 0.89 | -0.37 | 0.2 | 0.76 |
| 6 | -0.39 | 2.0 | 0.91 | -0.46 | 46.9 | 0.85 | -0.51 | 2.4 | 0.92 |
| 7 | -0.18 | 1.1 | 0.86 | -0.25 | 7.6 | 0.76 | -0.27 | 0.6 | 0.84 |
| 8 | -0.43 | 1.8 | 0.90 | -0.42 | 1.3 | 0.71 | -0.46 | 4.7 | 0.78 |
| 9 | -0.43 | 0.5 | 0.96 | -0.50 | 0.6 | 0.83 | -0.48 | 0.3 | 0.85 |
| 10 | -0.55 | 0.6 | 0.97 | -0.39 | 3.8 | 0.90 | -0.46 | 0.1 | 0.87 |
| 11 | -0.52 | 0.3 | 0.93 | -0.37 | 0.9 | 0.84 | -0.36 | 0.5 | 0.71 |
| 12 | -0.57 | 0.9 | 0.93 | - | - | - | -0.48 | 0.1 | 0.56 |
| 13 | -0.18 | 9.3 | 0.62 | -0.25 | 0.8 | 0.77 | -0.39 | 1.1 | 0.70 |
| 14 | -0.67 | 29.1 | 0.94 | -0.54 | 1.5 | 0.91 | -0.78 | 1.1 | 0.69 |
| Mean ± SD | -0.48± 0.20 | 8.0± 14.3 | 0.89± 0.10 | -0.45± 0.19 | 7.2± 12.7 | 0.83± 0.07 | -0.49± 0.17 | 0.9± 1.2 | 0.78± 0.10 |

TABLE 3.7.

NIFEDIPINE CONCENTRATION-EFFECT PARAMETERS m (mmHg/ng/ml) AND $K_{eq}$ ($h^{-1}$)
AND THE GOODNESS OF FIT R (AS A FRACTION OF UNITY)
FOR CHANGES IN ERECT DIASTOLIC BLOOD PRESSURE

| PATIENT | 1st DOSE | | | 1 WEEK | | | 6 WEEKS | | |
| | m | $K_{eq}$ | R | m | $K_{eq}$ | R | m | $K_{eq}$ | R |
|---|---|---|---|---|---|---|---|---|---|
| 1 | -0.24 | 4.4 | 0.94 | -0.19 | 17.7 | 0.63 | -0.18 | 26.1 | 0.72 |
| 2 | -0.51 | 7.0 | 0.96 | -0.45 | 3.1 | 0.89 | -0.40 | 3.8 | 0.89 |
| 3 | -0.47 | 28.2 | 0.78 | -0.34 | 1.1 | 0.72 | -0.40 | 1.3 | 0.88 |
| 4 | -0.25 | 5.3 | 0.79 | -0.19 | 27.1 | 0.85 | -0.22 | 6.3 | 0.95 |
| 5 | -0.10 | 8.3 | 0.88 | -0.14 | 49.9 | 0.62 | -0.17 | 4.8 | 0.95 |
| 6 | -0.25 | 3.9 | 0.95 | -0.19 | 2.9 | 0.87 | -0.28 | 1.9 | 0.85 |
| 7 | -0.15 | 1.7 | 0.97 | -0.22 | 1.1 | 0.81 | -0.25 | 1.1 | 0.95 |
| 8 | -0.24 | 4.5 | 0.76 | -0.21 | 1.5 | 0.90 | -0.27 | 3.9 | 0.78 |
| 9 | -0.08 | 2.3 | 0.88 | -0.28 | 2.6 | 0.86 | -0.18 | 1.3 | 0.96 |
| 10 | -0.25 | 0.6 | 0.88 | -0.23 | 2.7 | 0.79 | -0.16 | 17.4 | 0.78 |
| 11 | -0.35 | 0.4 | 0.87 | -0.15 | 1.3 | 0.78 | -0.28 | 0.6 | 0.87 |
| 12 | -0.20 | 1.1 | 0.81 | - | - | - | -0.34 | 3.1 | 0.83 |
| 13 | -0.18 | 2.6 | 0.94 | -0.24 | 1.6 | 0.83 | -0.20 | 1.9 | 0.83 |
| 14 | -0.23 | 12.9 | 0.86 | -0.35 | 22.2 | 0.92 | -0.33 | 5.8 | 0.82 |
| Mean ± SD | -0.25± 0.12 | 5.9± 7.2 | 0.88± 0.07 | -0.24± 0.09 | 10.4± 14.9 | 0.80± 0.1 | -0.26± 0.08 | 5.7± 7.2 | 0.86± 0.07 |

**RESPONSIVENESS IN TERMS OF SYSTOLIC VERSUS DIASTOLIC B.P.**

6 weeks

r = 0.68

P < 0.008
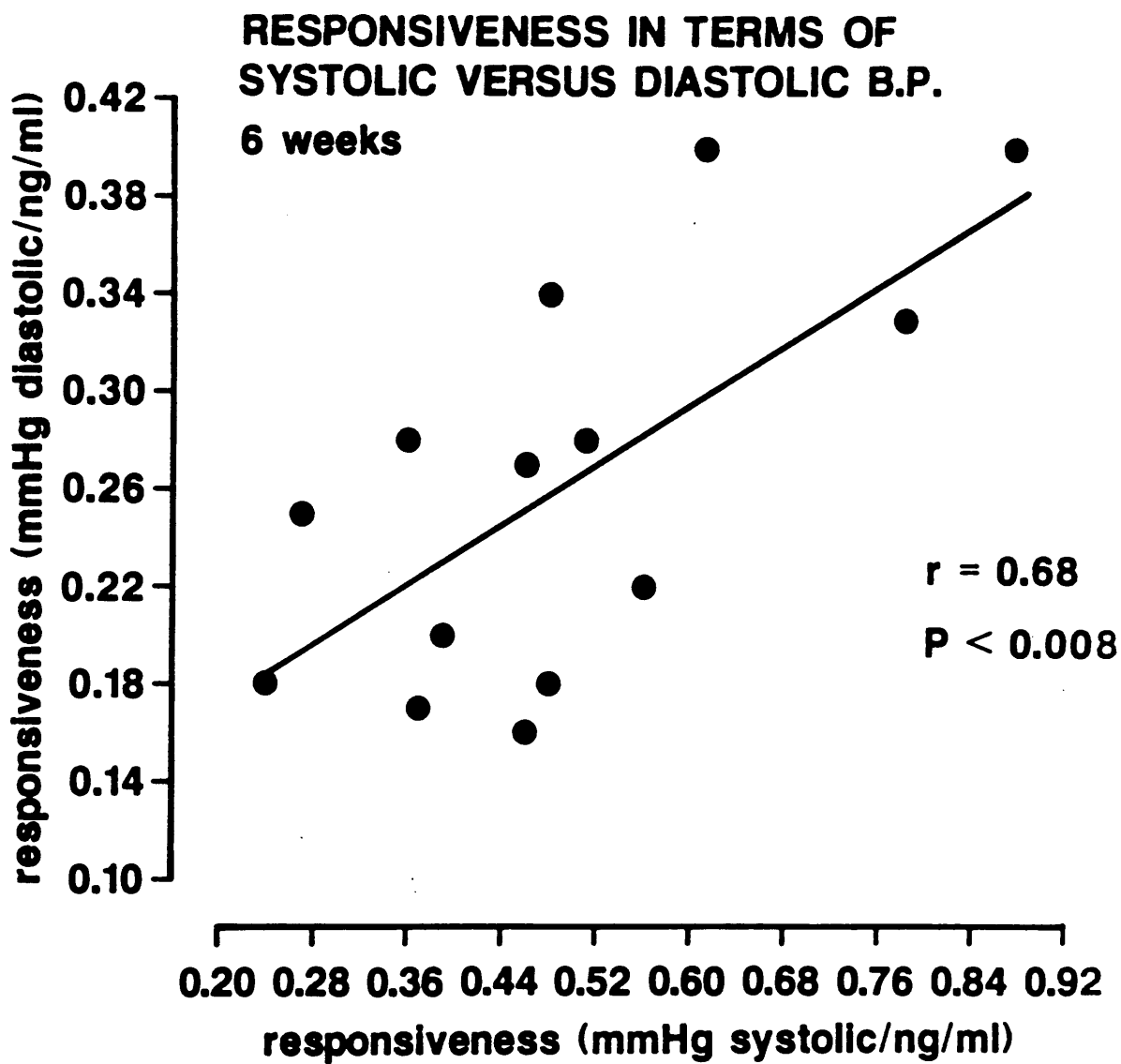
Figure 3.8.
Nifedipine study. Correlation between the responsiveness to nifedipine (m) after 6 weeks in terms of systolic and diastolic blood pressure.

**- responsiveness (6 weeks) mmHg/ng/ml**

**NIFEDIPINE**

r=0.78
(P<0.001)

**- responsiveness (1st dose) mmHg/ng/ml**
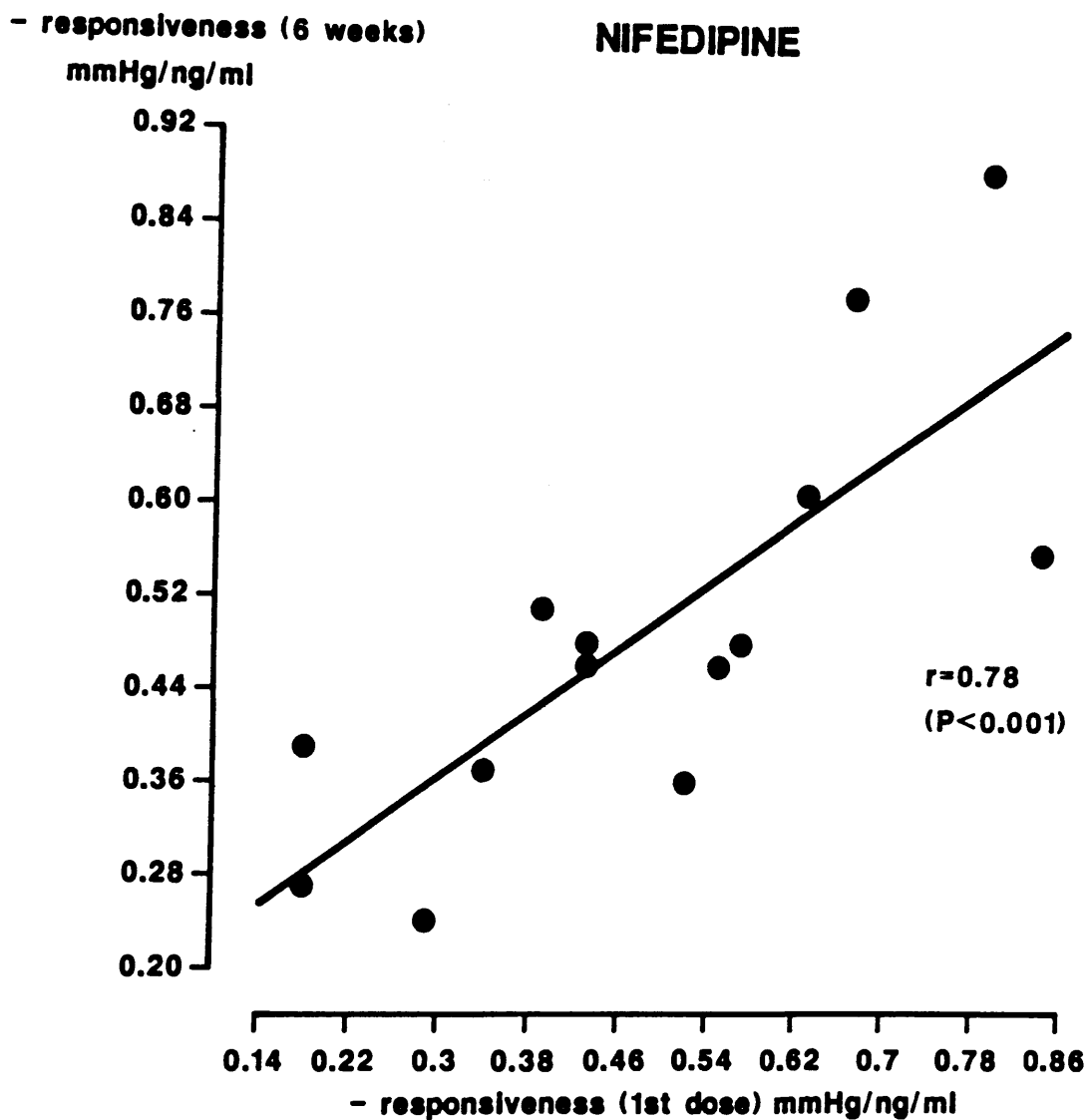
Figure 3.9.
Nifedipine study. Correlation between the responsiveness to the
1st dose of nifedipine (in terms of systolic BP) and the
responsiveness after 6 weeks.

**FIRST DOSE NIFEDIPINE**

(A)

(B)

r=0.60
(P<0.02)

r=-0.50
(P<0.07)
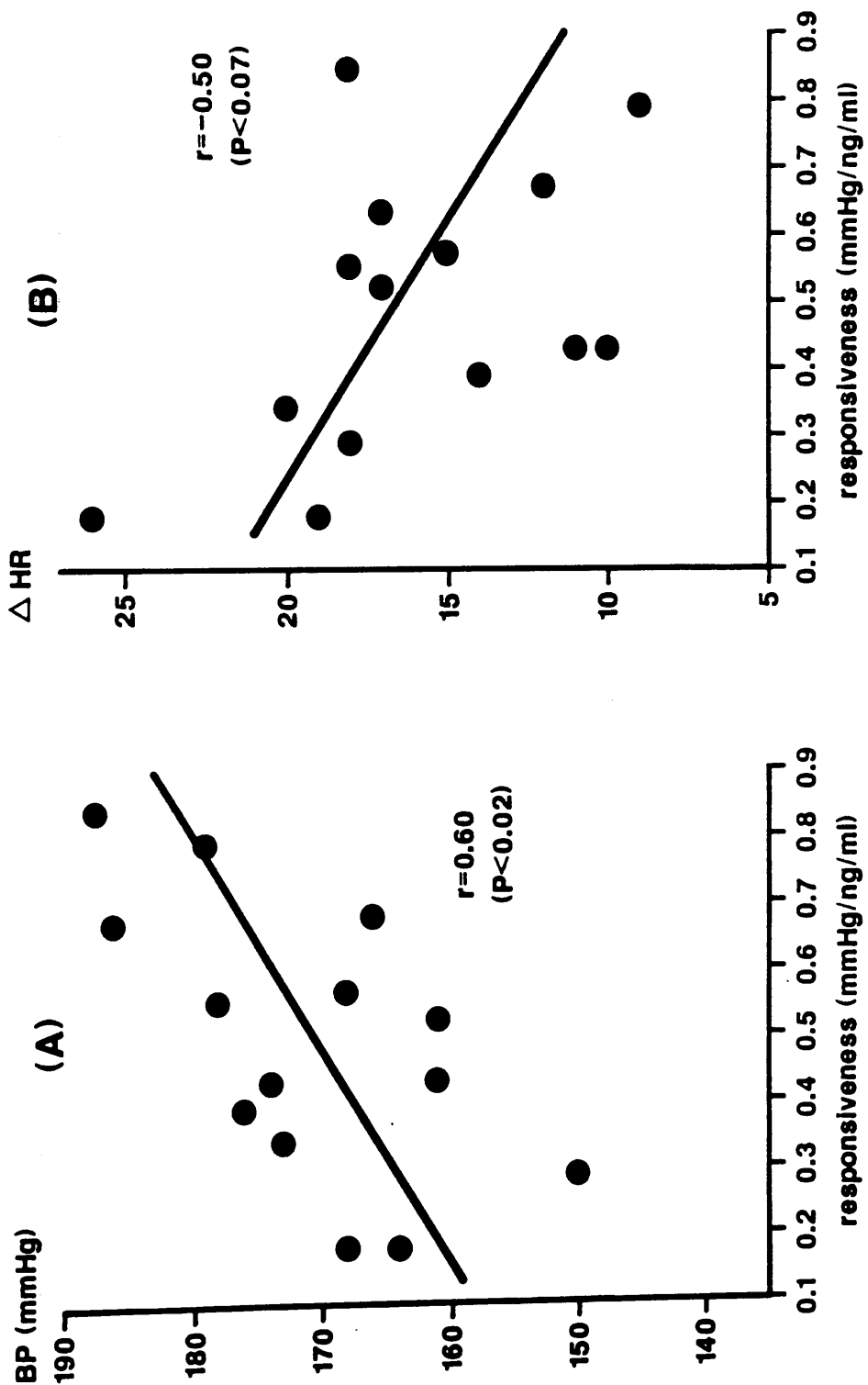
**Figure 3.10.**
First dose nifedipine. A: correlation between the responsiveness to
nifedipine and the height of the pretreatment systolic blood pressure.
B: a trend towards an inverse relationship between responsiveness and
the maximal (placebo and baseline-corrected) increase in erect heart
rate (N.S.).

96
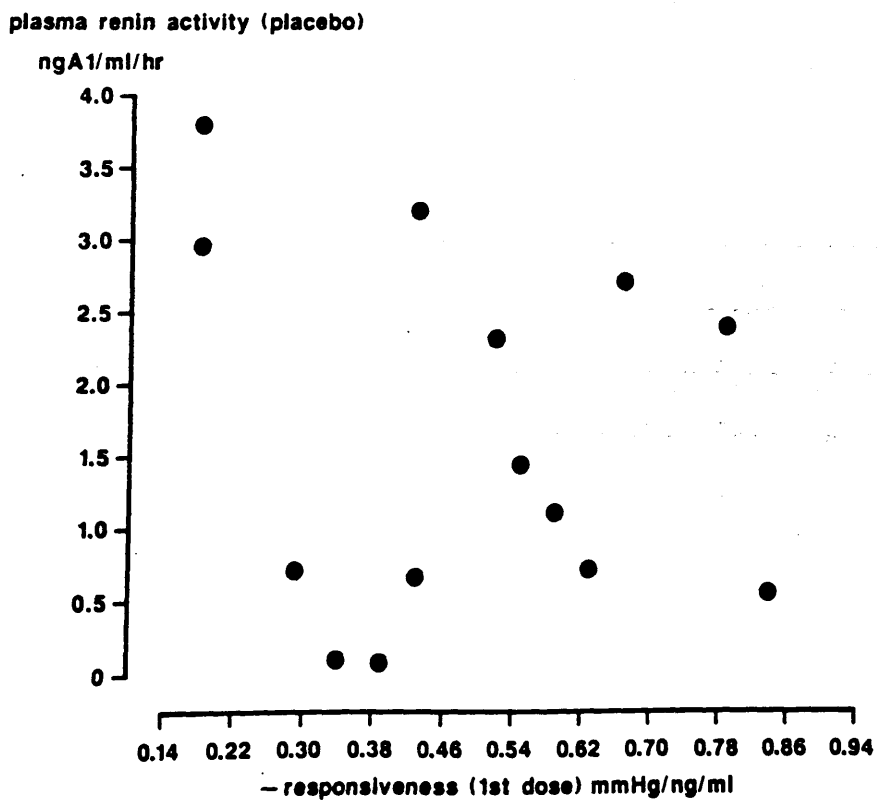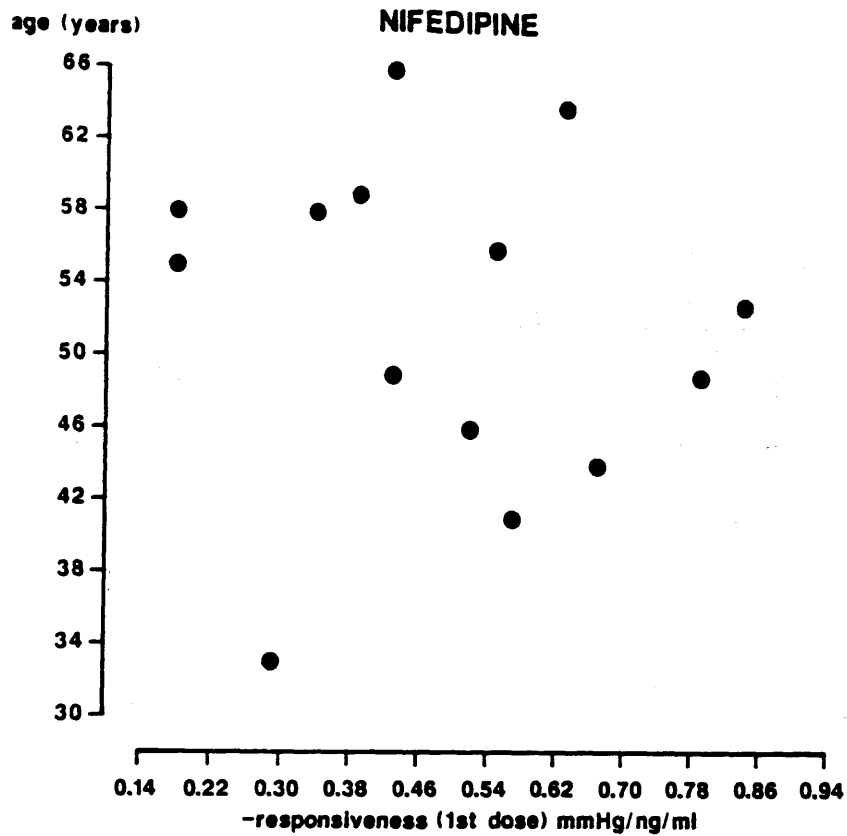
**Figure 3.11.**
Relationships between the responsiveness to nifedipine (1st dose)
and patient age and pretreatment plasma renin activity.

## 3.4.  DISCUSSION

Reliable assays for measuring nifedipine in plasma have only recently become available and there is still a relative paucity of information about the pharmacokinetics of nifedipine and, more importantly, about the kinetic-dynamic relationships in essential hypertension (Kleinbloesem et al, 1987a).   An interesting feature of the pharmacokinetics of other calcium antagonists, particularly verapamil, which potentially might complicate the concentration-effect relationship, is the observed reduction in drug clearance during chronic compared with single dose administration (Shand et al, 1981).   A similar finding has been observed with the dihydropyridine nicardipine (Donnelly et al, 1987) and also with nifedipine itself when the kinetics of intravenous administration have been determined following chronic treatment with oral nifedipine (Kleinbloesem et al, 1987b).   These changes in clearance have been ascribed to drug-related alterations in hepatic blood flow (Feely, 1984; Meredith et al, 1985b) or enzyme activity (Bach et al, 1986). Such a change in pharmacokinetics was not observed in this study but the use of a delayed release formulation of nifedipine obviously did not permit full characterisation of the disposition, particularly the terminal elimination phase of nifedipine.

It has been reported in healthy, elderly subjects that there is an age-related decline in the clearance of

nifedipine (Robertson et al, 1988; Scott et al, 1988).
Across the relatively narrow range of middle-aged
hypertensive subjects in this study there was no obvious
relationship between age and nifedipine disposition but
there was a significant correlation between age and first
dose $C_{max}$, which is consistent with an age-related effect on
absorption or first pass hepatic extraction. Similarly, it
has been suggested that there is bimodal distribution within
a population for the rate of metabolism of nifedipine
(Kleinbloesem et al, 1984b) but there was no evidence of
bimodality in this relatively small study.

It has been suggested that there is no predictable
concentration-effect relationship for nifedipine but this
probably reflects the negative findings of those previous
studies which considered the response for groups of
patients rather than for individuals (Lederballe-Pedersen et
al, 1979 and 1980; Aoki et al, 1982; Taburet et al, 1983).
This study has shown that nifedipine concentrations are
correlated with the reductions in both systolic and
diastolic blood pressure in individual hypertensive patients
and has extended the preliminary findings of Pasanisi and
Reid (1983) by defining individual concentration-response
relationships which are applicable during chronic treatment.
Additionally, there were significant correlations between
the parameters derived from the first dose and those after 1
week and 6 weeks treatment, which suggests that the first
dose response may be used to forecast the steady state

effect for an individual patient.  Clearly this has
potential application in therapeutics as a means of quickly
identifying poor or non-responders and for determining
individual dose requirements for optimum longterm blood
pressure control.  During the first week of nifedipine
treatment there was evidence that the fall in blood pressure
was associated with reflex sympathetic activation but this
did not perturb the correlation with the response obtained
at 6 weeks, when baroreflex mechanisms had apparently
"reset".  Despite these changes in sympathetic activity,
the responsiveness to nifedipine after six weeks, in
contrast to that reported for nisoldipine (Waller and
Ramsay, 1987), showed no significant reduction and this
study has highlighted the importance of considering kinetic
as well as dynamic parameters when assessing the constancy
of the antihypertensive response.

Changes in heart rate with nifedipine have been
correlated with acute reductions in blood pressure in young
healthy normotensives (Kleinbloesem et al, 1984a).  In this
study of hypertensive patients there was an opposite trend
whereby the responsiveness to nifedipine following the first
dose tended to be greatest in those showing the smallest
increase in heart rate.  A possible explanation is that the
increase in heart rate is a component of the reflex
mechanism attempting to counteract the acute
antihypertensive or vasodilator response to nifedipine, as
seen in healthy normotensives, but if the compensatory

increase in heart rate and resultant cardiac output is
inadequate then the reduction in blood pressure will tend to
be more pronounced. Since reflex mechanisms are blunted in
the elderly (Vestal et al, 1979), this may partly explain
why calcium antagonists have been reported to be more
effective in the older age group (Erne et al, 1983).

The relationship between pretreatment or initial blood
pressure and the magnitude of the fall with treatment has
been described previously (MacGregor et al, 1982b; Erne et
al, 1983). Care is necessary with the statistical methods
used in this type of analysis (Gill et al, 1985) and it is
probably more appropriate to seek correlations which also
take account of inter-individual differences in drug
concentrations and in the extent of the blood pressure fall
associated with placebo (Sumner et al, 1988a). In this
study, illustrated by the placebo-corrected reduction in
erect systolic blood pressure, there was a significant
relationship between the baseline (pre-treatment) blood
pressure and responsiveness (m) to the first dose of
nifedipine. It has also been suggested that plasma renin
activity influences the antihypertensive effect of
nifedipine (Erne et al, 1983) but in this study there was no
significant relationship between the pretreatment plasma
renin activity and the responsiveness to nifedipine.

In conclusion, this study has evaluated the
pharmacokinetics of nifedipine in essential hypertension and
characterised the antihypertensive response to nifedipine in

101

individual patients.    The derived concentration-effect

parameters provide not only a useful means of evaluating

factors which influence the kinetic and dynamic variability

of nifedipine but also a potential basis for optimising

longterm treatment in individual patients.

# CHAPTER 4

## ENALAPRIL IN ESSENTIAL HYPERTENSION:
## RESPONSES AND CONCENTRATION-EFFECT RELATIONSHIPS
## IN INDIVIDUAL PATIENTS

## 4.1. INTRODUCTION

The angiotensin converting enzyme (ACE) inhibitor drugs, captopril and enalapril, have become established in the treatment of both hypertension (Brunner et al, 1980; Hodsman et al, 1982) and cardiac failure (Kjekhus et al, 1983; CONSENSUS 1987). In contrast to captopril which itself is active, enalapril is a prodrug and following oral administration undergoes de-esterification (principally in the liver) to the active diacid metabolite enalaprilat (Tocco et al, 1982). In general, there is a relationship between the dose and plasma concentration of an ACE inhibitor and its effects on blood pressure and the renin-angiotensin system but previous studies, which have examined data for groups of subjects, have reported variable relationships between drug levels, blood pressure reduction and ACE inhibition (Biollaz et al, 1982; Johnston et al, 1983; de Leeuw et al, 1983; Johnston et al, 1984; Schwartz et al, 1985). While this is likely to reflect the intersubject variability in both kinetic and dynamic parameters, there is preliminary evidence that concentration-effect relationships for ACE inhibitors are potentially more useful when individual subjects are considered (Kelman et al, 1983) and this approach has been used successfully in single-dose studies in healthy volunteers (Witte et al, 1984; Francis et al, 1987).

This study in patients with essential hypertension evaluates the pharmacodynamic effects, including

inhibition of plasma ACE activity, and the pharmacokinetics of enalapril after acute and chronic administration, and using an integrated kinetic-dynamic model (Holford and Sheiner, 1981) characterises the antihypertensive responses and concentration-effect relationships in individual patients.

## 4.2. PATIENTS AND METHODS

### 4.2.1. General

Thirteen patients (6 male and 7 female) with mild to moderate essential hypertension, age range 41-66 years, participated in this study. Individual patient details are shown in Table 4.1. Each patient discontinued all medication and at the end of a drug-free run-in period of at least 6 weeks the mean entry blood pressures were 181/101 $\pm$ 15/8 (supine) and 175/101 $\pm$ 13/6 mmHg (erect). In a single-blind design placebo was then administered for 2 weeks, followed by enalapril 20 mg once daily for 6 weeks, and each patient attended 8-hour study days in the Clinical Pharmacology Research Unit (CPRU) to evaluate the effects of placebo, 1st dose enalapril and after 1 week and 6 weeks treatment.

The clinical protocol is described in detail in Chapter 2.1. At frequent intervals during each study day, and at 24 hours after dosing, supine and erect blood pressure and heart rate were recorded and venous blood samples collected for measurement of plasma enalaprilat concentration and ACE

activity. Additional blood samples were obtained in 7
patients at 12 and 32 hours after dosing. Blood was also
collected at 0, 1.5 and 6 hours on each study day for plasma
renin activity, aldosterone and catecholamines.


4.2.2. Enalaprilat concentrations

Plasma concentrations of enalaprilat were measured
using a specific radioimmunoassay technique (Hichens et al,
1981). Plasma is incubated with antibody and a radioactive
label (an iodinated precursor of MK-521). The antibody
bound fraction is precipitated by a second antibody,
separated by centrifugation and counted using a gamma
counter. The amount of enalaprilat in the sample is
inversely proportional to the amount of antibody bound
label. The inter and intra-assay coefficients of variation
for the enalaprilat assay were 8.5% and 7% respectively, and
the limit of detection was 0.4 ng/ml.


4.2.3. Pharmacokinetics and concentration-effect analysis

The pharmacokinetics of enalapril were evaluted by a
number of different approaches because previous studies
have described some unusual characteristics of ACE
inhibitor kinetics. The most appropriate method, as
assessed by the general linear test was to fit the plasma
enalaprilat concentration-time profiles for individual
patients on the three study days simultaneously to a
unified one compartment pharmacokinetic model with

## TABLE 4.1.

## ENALAPRIL STUDY. INDIVIDUAL PATIENT DETAILS

| PATIENT | AGE | SEX | WEIGHT (kg) | RELEVANT MEDICAL HISTORY | PREVIOUS ANTI-HYPERTENSIVE THERAPY | CHOLESTEROL | SMOKER | ENTRY BP SUPINE | ENTRY BP ERECT |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 41 | M | 118 | Newly diagnosed EH | Nil | 7.5 | - | 220/115 | 209/111 |
| 2 | 57 | M | 80 | Newly diagnosed EH | Atenolol - poor BP control | 6.1 | - | 195/112 | 184/107 |
| 3 | 61 | F | 74 | EH diagnosed 10 years ago LVH | Atenolol - headache Methyldopa - poor BP control Prazosin - dizziness | 6.6 | - | 179/107 | 181/106 |
| 4 | 58 | F | 75 | Newly diagnosed EH | Nil | 7.1 | - | 184/100 | 176/98 |
| 5 | 66 | F | 73 | Newly diagnosed EH | Nil | 5.7 | + | 178/88 | 181/91 |
| 6 | 44 | F | 57 | Newly diagnosed EH | Nil | 6.0 | + | 176/101 | 168/97 |
| 7 | 45 | M | 95 | Newly diagnosed EH | Nil | 6.8 | - | 183/93 | 169/101 |
| 8 | 55 | F | 97 | Newly diagnosed EH | Diuretic - poor BP control | 7.0 | + | 171/96 | 168/99 |
| 9 | 65 | F | 60 | EH diagnosed 6 months prior to entry | Atenolol + diuretic Tiredness | 6.5 | + | 188/103 | 181/104 |
| 10 | 59 | M | 82 | EH diagnosed 5 years ago | Atenolol + diuretic Poor BP control | 6.5 | - | 165/102 | 158/106 |
| 11 | 53 | F | 70 | EH diagnosed 3 years ago | Nifedipine - headache | 6.0 | - | 173/103 | 161/98 |
| 12 | 56 | M | 75 | EH diagnosed 6 months ago TIA 2 years ago | Oxprenolol - headache | 6.0 | + | 178/95 | 176/97 |
| 13 | 58 | M | 70 | EH diagnosed 8 years ago | Atenolol - tiredness Hydralazine | 6.8 | - | 171/100 | 168/99 |
| MEAN ± SD | 55 ± 7.7 | | | | | | | 181/101 ± 15/8 | 175/101 ± 13/6 |

Key: EH = essential hypertension; LVH = left ventricular hypertrophy on ECG; TIA = transient ischaemic attack.

saturable protein binding.

For the concentration-effect analysis the standard pharmacokinetic model was augmented by an "effect" compartment, as described in Chapter 2.5. The effects of enalapril on both systolic and diastolic blood pressure were then related to the concentration of enaprilat in the effect compartment by means of both the linear and non-linear models (Holford and Sheiner, 1981). In each case, after acute and chronic dosing, the data were most appropriately described by the Langmuir-$E_{max}$ model (Chapter 2.5.).

The pharmacodynamic data were fitted independently for each study day and simultaneously for all three study days and the concentration-effect parameters, $E_{max}$, $C_e(50)$ and $K_{eq}$, were derived for individual patients. $E_{max}$ was calculated in terms of the placebo-subtracted fall in both erect systolic and diastolic blood pressure and $C_e(50)$ represents the concentration required to produce 50% of $E_{max}$ (chapter 2.5.).

## 4.2.4. Statistical analysis

The statistical methods are described in general in Chapter 2.6. Measurements of plasma ACE activity at individual times after dosing were compared between study days by repeated measures analysis of variance.

## 4.3. RESULTS

### 4.3.1. Patient tolerance

Enalapril was generally well tolerated and there were no significant adverse effects reported. In particular, there were no symptomatic 'hypotensive' responses to the first dose and there were no significant changes in serum urea and creatinine during the study.

### 4.3.2. Blood pressure

Enalapril was associated with significant reductions in both supine and erect blood pressure following the first dose: for example, erect blood pressure was reduced from a baseline of $171/101 \pm 17/10$ to $122/80 \pm 20/13$ mmHg at 6 hours, compared with a change from $178/106 \pm 21/10$ to $155/94 \pm 11/7$ 6 hours after placebo (Figure 4.1.). The maximum antihypertensive effect of enalapril occurred at 5-6 hours after drug administration (Figure 4.1.) and there was no significant orthostatic component: baseline-corrected reductions in supine and erect blood pressure 6 hours after the first dose were 46/27 and 49/21 mmHg respectively.

The antihypertensive effect of enalapril was sustained during chronic treatment and there were significant reductions in predose blood pressures: for example, measurements of supine blood pressure recorded 24 hours after the last dose were $153/93 \pm 23/12$ after 1 week and $157/94 \pm 18/12$ mmHg after 6 weeks, compared with $187/105 \pm 17/10$ mmHg following placebo. In addition, there were

further significant reductions in blood pressure following drug administration, reaching a nadir at 6 hours of 123/76 ± 18/9 supine and 118/76 ± 26/10 erect after 1 week and 122/73 ± 18/10 supine and 122/77 ± 19/13 mmHg erect after 6 weeks (Figure 4.1.).

### 4.3.3. Heart rate

The fall in blood pressure with enalapril, particularly after the first dose, was not associated with any significant change in heart rate (Figure 4.2.). Average supine and erect heart rates over the 8 hours were respectively 71 and 84 bpm after the first dose; 71 and 85 bpm after 1 week; and 68 and 83 bpm after 6 weeks; compared with 73 and 84 bpm after placebo.

### 4.3.4. Angiotensin converting enzyme activity

The first dose of enalapril was associated with a prompt reduction in plasma ACE activity (Figure 4.3.), significant at 1 hour and reaching a nadir at 3-4 hours after drug administration: for example, ACE activity was reduced from a baseline of 39.3 ± 11.9 to 4.1 ± 1.5 EU/ml at 4 hours, compared with a corresponding change from 36.8 ± 12.6 to 34.9 ± 12.2 EU/ml after placebo (Table 4.2.). Significant inhibition of ACE activity was sustained for up to 24 hours after the first dose: 22.0 ± 8.2 compared with 35.9 ± 12.1 EU/ml 24 hours after placebo. During chronic treatment with enalapril predose measurements of plasma ACE activity

# ENALAPRIL
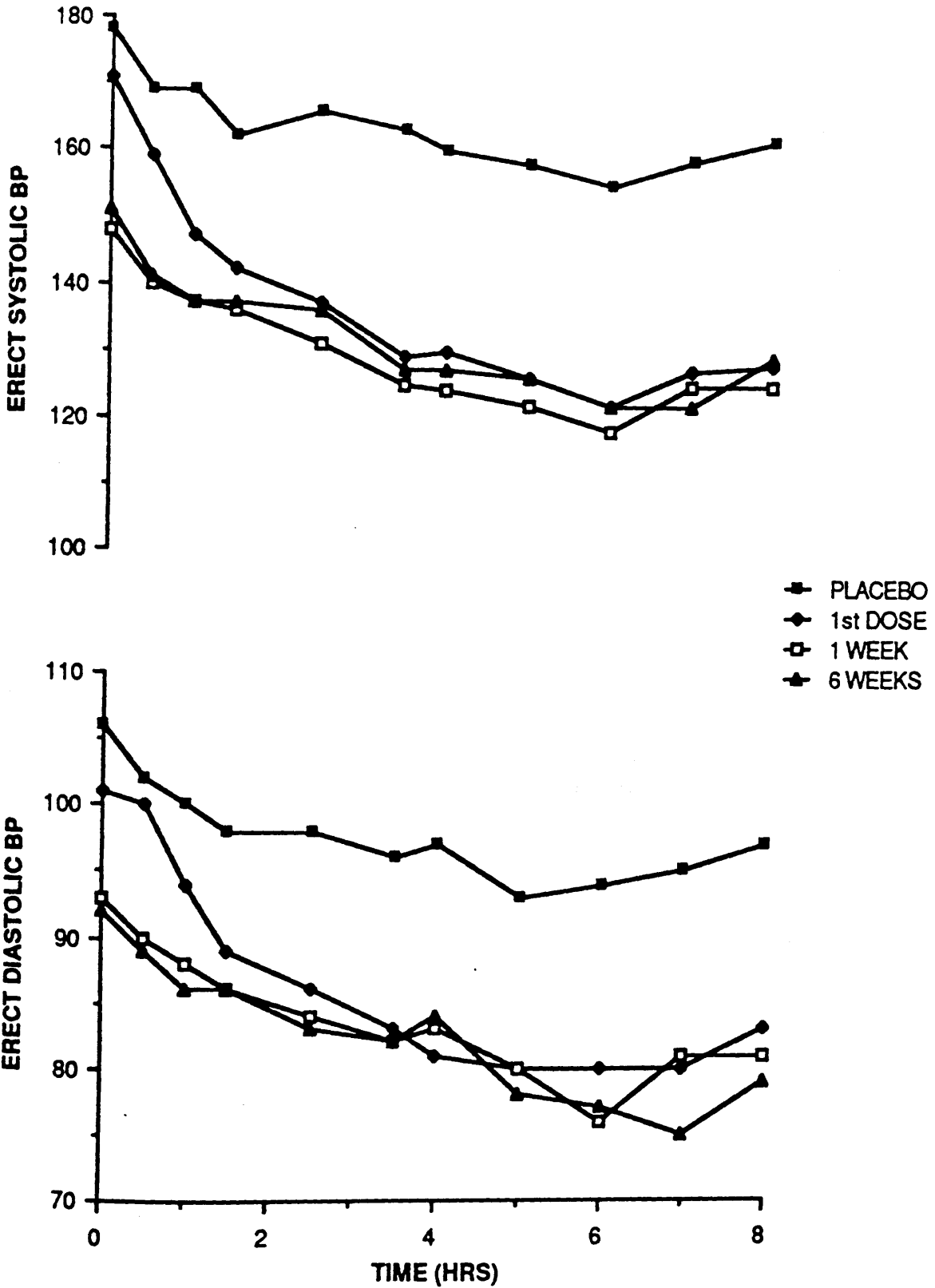


Figure 4.1.
Mean profiles of erect systolic and diastolic blood pressure after placebo ( ■ ), 1st dose enalapril ( ♦ ) and after 1 week     ( ☐ ) and 6 weeks ( ▲ ) enalapril treatment.

**ENALAPRIL**

Legend:
- ■ PLACEBO
- ◆ 1st DOSE
- □ 1 WEEK
- ▲ 6 WEEKS
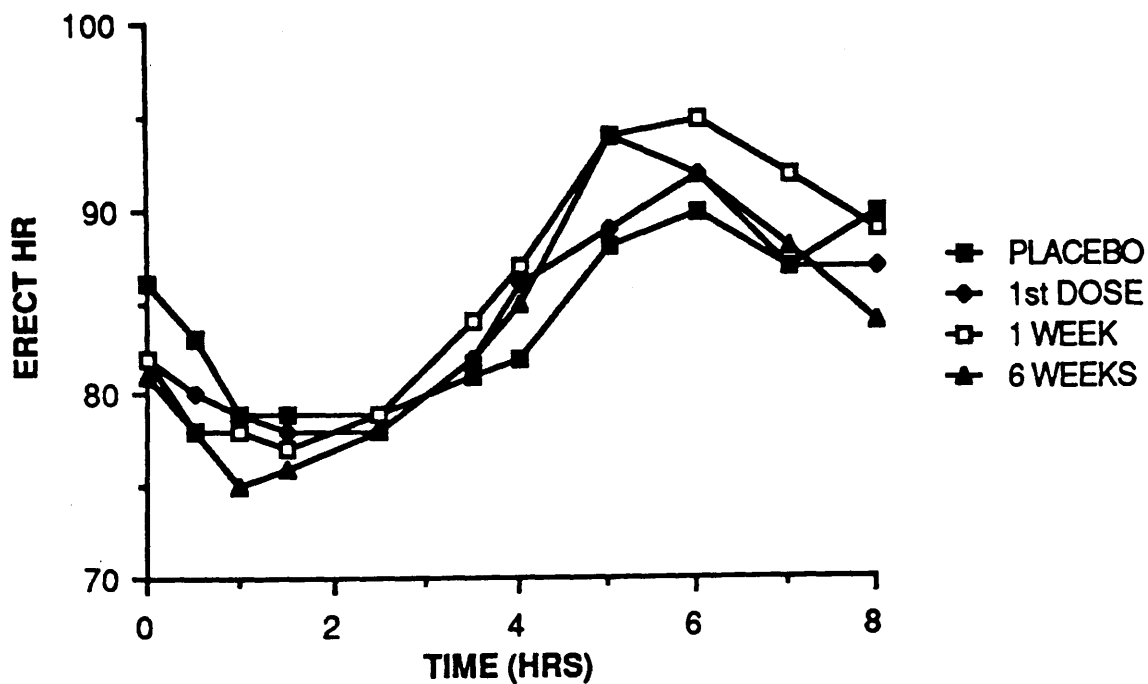
Figure 4.2.
Mean profiles of erect heart rate after placebo ( ■ ), 1st dose
enalapril ( ◆ ) and after 1 week ( □ ) and 6 weeks ( ▲ ) enalapril
treatment.

(recorded 24 hours after the last dose) were not significantly reduced: 33.7 ± 18.9 after 1 week and 32.2 ± 11.1 after 6 weeks, compared with 36.8 ± 12.6 EU/ml following placebo (Table 4.2. and Figure 4.3.). In addition, although there was significant inhibition of plasma ACE activity during the 8 hour study day, measurements at 24 hours had returned towards placebo values: 31.7 ± 18.5 (1 week) and 32.3 ± 16.9 EU/ml (6 weeks), compared with 35.9 ± 12.1 EU/ml at 24 hours after placebo (Figure 4.3.).

### 4.3.5. Hormone measurements

Enalapril produced significant increases in plasma renin activity (PRA), particularly during chronic treatment and at 6 hours after drug administration (Table 4.3.): for example, measurements of PRA at 6 hours increased progressively from 5.1 (placebo) to 12.4 (first dose), 50.3 (1 week) and 58.0 ngA1/ml/hr after 6 weeks. In addition, there were modest but significant reductions in plasma aldosterone concentration after 1 week: for example at 6 hours, 58 pg/ml compared with 102 pg/ml after placebo (Table 4.3.). Measurements of plasma aldosterone after 6 weeks were not significantly different compared with placebo. Enalapril had no significant effect on plasma noradrenaline (Table 4.3.).

## ANGIOTENSIN CONVERTING ENZYME ACTIVITY
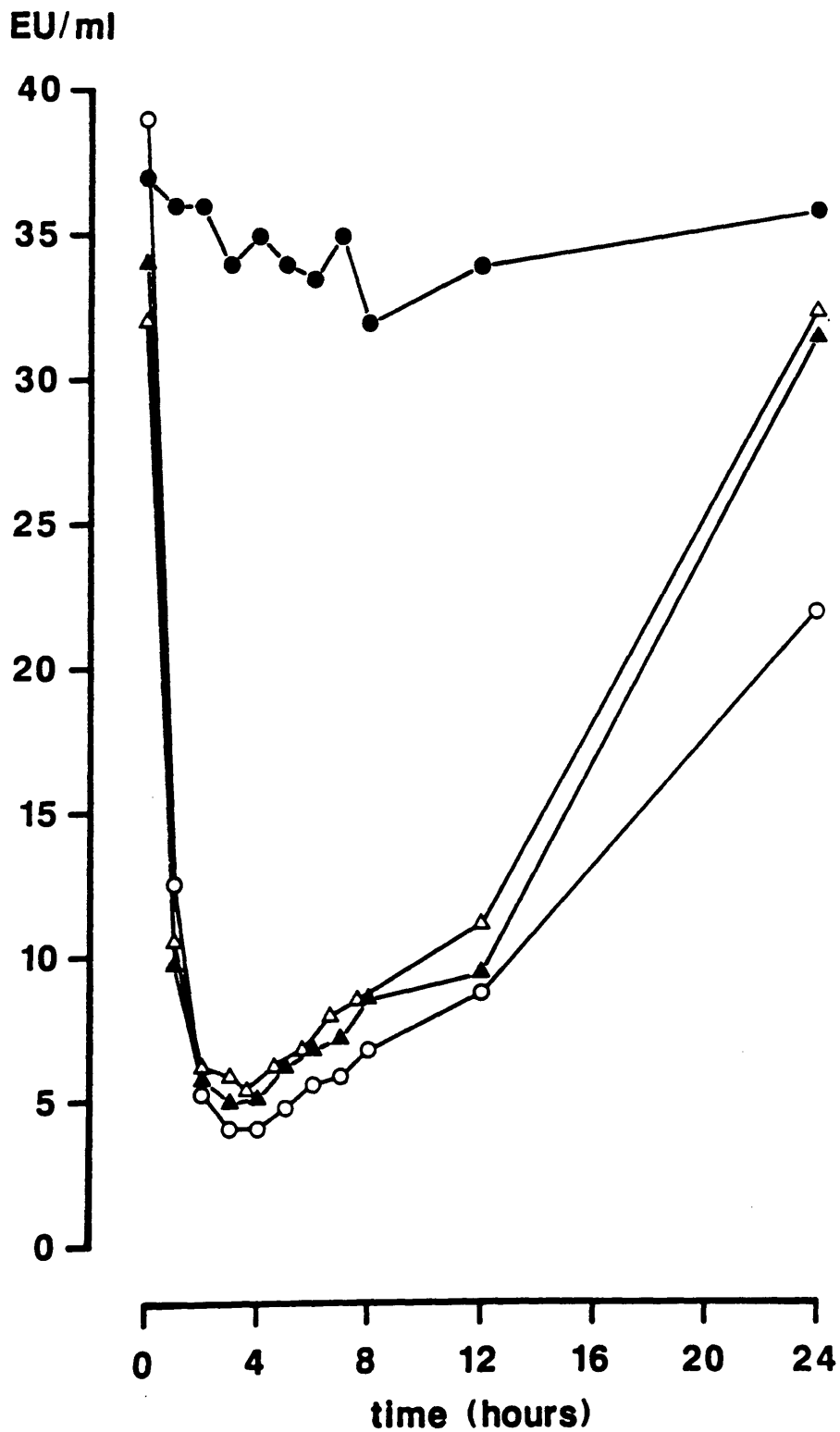


Figure 4.3.
Enalapril study. Mean profiles of plasma ACE activity after placebo ( ● ), 1st dose enalapril ( ○ ) and after 1 week ( ▲ ) and 6 weeks ( △ ) enalapril treatment.

TABLE 4.3.

ENALAPRIL STUDY. MEASUREMENTS OF PLASMA RENIN ACTIVITY, ALDOSTERONE AND NORADRENALINE AT 0, 1.5 AND 6 HOURS AFTER DRUG ADMINISTRATION. MEAN ± SD

| TIME (HRS) | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---|---|---|---|---|
| Plasma renin activity (ngA1/ml/hr) | | | | |
| 0 | 4.0 ± 3.8 | 7.4 ± 5.3 | 23.0 ± 22.2** | 20.3 ± 19.5** |
| 1.5 | 3.6 ± 3.5 | 6.9 ± 6.9 | 18.3 ± 14.4* | 18.0 ± 17.5* |
| 6 | 5.1 ± 7.3 | 12.4 ± 12.1* | 50.3 ± 40.1** | 58.0 ± 77.2** |
| Plasma aldosterone (pg/ml) | | | | |
| 0 | 116 ± 64 | 97 ± 32 | 92 ± 45 | 131 ± 98 |
| 1.5 | 82 ± 54 | 69 ± 45 | 67 ± 41* | 85 ± 34 |
| 6 | 102 ± 74 | 53 ± 31* | 58 ± 46* | 71 ± 24 |
| Plasma noradrenaline (nmol/L) | | | | |
| 0 | 3.8 ± 1.8 | 3.8 ± 1.7 | 3.5 ± 1.9 | 3.7 ± 1.5 |
| 1.5 | 3.2 ± 1.5 | 3.0 ± 1.3 | 2.7 ± 1.2 | 2.3 ± 0.9 |
| 6 | 3.8 ± 2.2 | 2.9 ± 1.2 | 3.0 ± 0.9 | 2.7 ± 1.1 |

\*   $p < 0.01$
\*\*   $p < 0.001$

## 4.3.6. Pharmacokinetics

The pharmacokinetics of enalapril were evaluated by a number of different approaches.  The initial approach adopted was to fit a hierarchy of conventional kinetic compartmental models, governed by first order processes, to the enalaprilat concentration data from each study day independently.  In all subjects on both acute and steady state study days a two compartment open model was most appropriately fitted to the data and the parameters obtained from this approach are shown in Table 4.4.  It is apparent from Table 4.4. that the kinetics evaluated in this manner suggest significant differences in enalaprilat disposition between acute and steady state dosing.  Although there are no significant differences in the apparent elimination half-life of enalaprilat in translation from acute to chronic therapy, the AUC values at steady state are significantly smaller than those after the first dose:  for example, 864 $\pm$ 378 ng.h.ml$^{-1}$ after 6 weeks compared with 1279 $\pm$ 452 following the first dose (Table 4.4.).  Additionally, if one predicts a steady state trough drug concentration from the first dose kinetics the values predicted are in all patients greater than the measured values.

These findings are entirely consistent with those of Till et al (1984) who suggested that a conventional pharmacokinetic approach was inappropriate for ACE inhibitors and that such analysis should be based on urinary drug excretion data.  Francis et al (1987) adopted a

modelling approach which successfully attributed the kinetic

characteristics of the ACE inhibitor cilazapril to binding

of drug to ACE.  Accordingly a similar approach was adopted

in this study, with a pharmacokinetic model which assumes

saturable protein binding.  Using this method it was

demonstrated, by a number of criteria of goodness of fit,

that a unified approach fitting this model simultaneously to

acute and steady state data was superior both to the

original 'conventional' approach and to independent fitting

to each study day.  The derived pharmacokinetic parameters

for free and bound enalaprilat are shown in Table 4.5.

The mean values for free and bound drug respectively were

$1388 \pm 451$ and $147 \pm 95$ ng.h.ml$^{-1}$ for AUC and $2.7 \pm 0.5$ and

$16.8 \pm 9.4$ hours for elimination half-life (Table 4.5.).

There was no significant relationship between patient

age and any of the pharmacokinetic parameters for

enalaprilat.


4.3.7. Concentration-effect relationships

There was no simple direct relationship between plasma

enalaprilat concentration and the fall in blood pressure, as

illustrated for an individual patient (Figure 4.4.).

However, using concentration-effect analysis, drug levels

were well correlated with reductions in both systolic and

diastolic blood pressure in individual patients, and in each

case the kinetic-dynamic relationships after acute and

chronic dosing were described most appropriately by the

118

TABLE 4.4.

THE PHARMACOKINETIC PARAMETERS FOR ENALAPRILAT DERIVED FROM A CONVENTIONAL TWO-COMPARTMENT MODEL BY FITTING THE INDIVIDUAL DATA SETS FOR EACH STUDY DAY INDEPENDENTLY

| PATIENT | AUC ($ng.h.ml^{-1}$) | | | ELIMINATION HALF-LIFE (hrs) | | |
|---|---|---|---|---|---|---|
| | 1ST DOSE | 1 WEEK | 6 WEEKS | 1ST DOSE | 1 WEEK | 6 WEEKS |
| 1 | 815 | 442 | 637 | 3.6 | 2.7 | 3.3 |
| 2 | 1182 | 753 | 942 | 3.5 | 1.6 | 3.9 |
| 3 | 1003 | 684 | 499 | 4.6 | 4.3 | 4.1 |
| 4 | 1288 | 1051 | 1201 | 4.3 | 3.6 | 3.5 |
| 5 | 2273 | 787 | 1447 | 5.0 | 2.9 | 4.3 |
| 6 | 1293 | 1267 | 1499 | 4.6 | 3.9 | 5.0 |
| 7 | 544 | - | 425 | 3.9 | - | 3.6 |
| 8 | 1390 | 1043 | 1011 | 5.0 | 5.8 | 5.3 |
| 9 | 1089 | 634 | 486 | 9.9 | 3.6 | 3.5 |
| 10 | 1307 | 1197 | 814 | 5.3 | 3.9 | 4.1 |
| 11 | 1484 | 779 | 331 | 3.6 | 4.3 | 3.9 |
| 12 | 1951 | 1161 | 1011 | 5.0 | 3.6 | 3.2 |
| 13 | 1002 | 1079 | 929 | 3.6 | 3.5 | 5.1 |
| MEAN ± SD | 1279 ± 452 | 906 ± 260 | 864 ± 378 | 4.8 ± 1.7 | 3.6 ± 1.0 | 4.1 ± 0.7 |

TABLE 4.5.

THE PHARMACOKINETIC PARAMETERS FOR FREE AND BOUND ENALAPRILAT DERIVED FROM
A ONE COMPARTMENT MODEL WITH SATURABLE PROTEIN BINDING. THE MOST
APPROPRIATE FIT WAS OBTAINED USING A UNIFIED APPROACH FITTING THE DATA SETS
FOR ALL THREE STUDY DAYS SIMULTANEOUSLY

| PATIENT | AUC (ng.h.ml$^{-1}$) | | ELIMINATION HALF-LIFE (hrs) | |
| | FREE | BOUND | FREE | BOUND* |
| --- | --- | --- | --- | --- |
| 1 | 1001 | 84 | 2.3 | - |
| 2 | 1328 | 60 | 2.6 | - |
| 3 | 1025 | 101 | 2.8 | 15.4 |
| 4 | 2506 | 103 | 3.3 | - |
| 5 | 1543 | 161 | 2.6 | - |
| 6 | 1359 | 396 | 2.2 | - |
| 7 | 722 | 106 | 3.3 | 28.9 |
| 8 | 1595 | 238 | 3.7 | 21.7 |
| 9 | 1667 | 166 | 2.3 | 8.3 |
| 10 | 1014 | 115 | 2.4 | 7.3 |
| 11 | 1401 | 230 | 2.6 | 8.0 |
| 12 | 1736 | 60 | 2.9 | 27.7 |
| 13 | 1152 | 86 | 2.5 | - |
| MEAN ± SD | 1388 ± 451 | 147 ± 95 | 2.7 ± 0.5 | 16.8 ± 9.4 |

* This parameter was characterised only in the 7 patients from
  whom additional blood samples were collected at 12 and 32
  hours after dosing.

Langmuir-$E_{max}$ model.

The pharmacodynamic data, i.e. the reductions in systolic and diastolic blood pressure, were fitted independently for each study day and simultaneously for all three study days. The concentration-effect parameters derived from these different approaches for changes in systolic blood pressure are shown in Tables 4.6. and 4.7. and the correlation coefficients are shown in Table 4.8. On the basis of the goodness of fit, i.e. the R values shown in Table 4.8., the unified simultaneous approach was the most appropriate in all patients and fits for representative subjects are illustrated in Figures 4.5. and 4.6. The concentration-effect parameters for changes in diastolic blood pressure derived from simultaneous fits are shown in Table 4.9.

Responsiveness to enalapril ($E_{max}$), as the mean of the group, in terms of systolic and diastolic blood pressure was -46.1 ± 16.5 and -19.7 ± 3.8 mmHg respectively (Tables 4.7. and 4.9.). There was no significant relationship between $E_{max}$ and patient age or pretreatment plasma renin activity (Figure 4.7.). However, there was a significant correlation between $E_{max}$ and the height of the starting blood pressure, as illustrated for erect systolic blood pressure (Figure 4.8.).

The parameters derived from fitting the data sets for each study day independently (Table 4.6.) were examined to compare first dose with steady state responses. There was

# PATIENT 3-FIRST DOSE ENALAPRIL

**Placebo-corrected fall in erect systolic BP**



**Plasma enalaprilat conc. (ng/ml)**
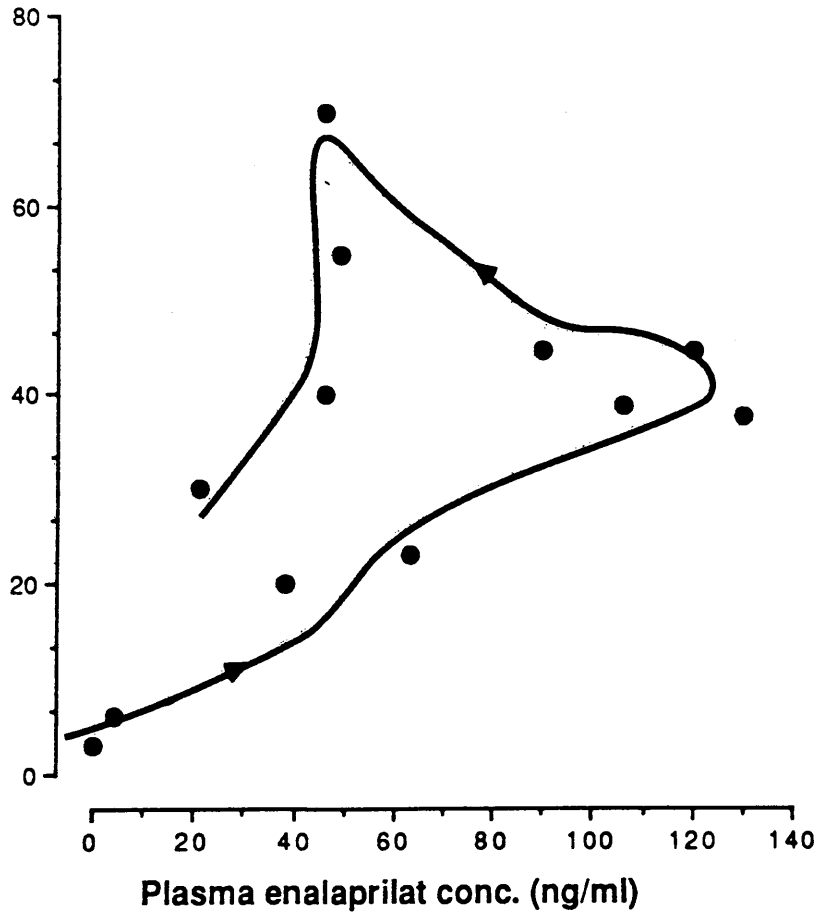
Figure 4.4.
The relationship between plasma enalaprilat concentration and the placebo-subtracted fall in erect systolic blood pressure in an individual patient (patient 3) after the 1st dose of enalapril.

**TABLE 4.6.**

THE ENALAPRILAT CONCENTRATION-EFFECT PARAMETERS $E_{max}$, $C_e50$ AND $K_{eq}$ FOR CHANGES

IN ERECT SYSTOLIC BP DERIVED FROM FITTING THE DATA SETS FOR EACH STUDY DAY

INDEPENDENTLY

| PATIENT | $E_{max}$(mmHg) | | | $C_e50$ (ng/ml) | | | $K_{eq}$(hours$^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1ST DOSE | 1 WEEK | 6 WEEKS | 1ST DOSE | 1 WEEK | 6 WEEKS | 1ST DOSE | 1 WEEK | 6 WEEKS |
| 1 | -58 | -56 | -52 | 68.7 | 60.6 | 59.3 | 0.3 | 0.3 | 0.3 |
| 2 | -71 | -53 | -56 | 73.8 | 85.6 | 85.3 | 0.4 | 0.3 | 0.3 |
| 3 | -78 | -57 | -81 | 89.4 | 20.3 | 14.9 | 0.6 | 1.1 | 0.7 |
| 4 | -30 | -32 | -39 | 86.2 | 62.5 | 95.4 | 2.0 | 2.0 | 2.1 |
| 5 | -63 | -76 | -72 | 79.4 | 84.5 | 88.5 | 0.4 | 0.9 | 0.7 |
| 6 | -51 | -58 | -55 | 103.2 | 113.2 | 109.4 | 1.8 | 2.3 | 2.4 |
| 7 | -81 | - | -76 | 78.3 | - | 78.9 | 0.7 | - | 0.9 |
| 8 | -21 | -42 | -37 | 96.0 | 71.9 | 69.0 | 1.1 | 1.7 | 2.3 |
| 9 | -29 | -26 | -25 | 72.0 | 67.2 | 72.9 | 1.9 | 0.7 | 1.8 |
| 10 | -22 | -31 | -37 | 50.8 | 56.7 | 63.8 | 0.3 | 0.8 | 1.5 |
| 11 | -24 | -26 | -23 | 72.1 | 72.2 | 54.9 | 1.0 | 0.8 | 1.8 |
| 12 | -60 | -48 | -64 | 89.4 | 47.1 | 93.5 | 0.3 | 0.4 | 0.2 |
| 13 | -41 | -28 | -28 | 42.7 | 21.4 | 20.9 | 0.3 | 0.3 | 0.3 |
| MEAN ± SD | -48 ± 22 | -44 ± 20 | -50 ± 20 | 77.1 ± 16.9 | 63.6 ± 26.2 | 69.8 ± 27.8 | 0.9 ± 0.7 | 1.0 ± 0.7 | 1.2 ± 0.8 |

TABLE 4.7.

THE ENALAPRILAT CONCENTRATION-EFFECT PARAMETERS $E_{max}$, $C_e 50$ AND $K_{eq}$
FOR CHANGES IN ERECT SYSTOLIC BP DERIVED FROM THE UNIFIED APPROACH
FITTING THE DATA SETS FOR ALL THREE STUDY DAYS SIMULTANEOUSLY

| PATIENT | $E_{max}$ (mmHg) | $C_e 50$ (ng/ml) | $K_{eq}$ (hours$^{-1}$) |
|---|---|---|---|
| 1 | -56 | 64.9 | 0.3 |
| 2 | -49 | 99.6 | 0.3 |
| 3 | -58 | 43.0 | 0.6 |
| 4 | -31 | 72.1 | 1.9 |
| 5 | -69 | 56.1 | 0.3 |
| 6 | -53 | 100.5 | 2.2 |
| 7 | -73 | 68.2 | 0.7 |
| 8 | -35 | 64.4 | 0.6 |
| 9 | -26 | 66.4 | 2.1 |
| 10 | -33 | 47.8 | 0.3 |
| 11 | -24 | 64.7 | 0.8 |
| 12 | -59 | 82.1 | 0.3 |
| 13 | -34 | 29.4 | 0.3 |
| MEAN ± SD | -46.1 ± 16.5 | 66.1 ± 20.2 | 0.8 ± 0.7 |

124

TABLE 4.8.

THE GOODNESS OF FIT (R) FOR THE PHARMACODYNAMIC MODELLING OF
ERECT SYSTOLIC BP USING AN INDEPENDENT APPROACH WITH EACH
STUDY DAY SEPARATELY AND A UNIFIED APPROACH WITH THE THREE
STUDY DAYS FITTED SIMULTANEOUSLY

CORRELATION COEFFICIENTS (R)

| PATIENT | 1ST DOSE | 1 WEEK | 6 WEEKS | UNIFIED FIT |
|---------|----------|--------|---------|-------------|
| 1 | 0.96 | 0.82 | 0.74 | 0.93 |
| 2 | 0.96 | 0.74 | 0.89 | 0.90 |
| 3 | 0.98 | 0.98 | 0.95 | 0.96 |
| 4 | 0.88 | 0.91 | 0.87 | 0.87 |
| 5 | 0.97 | 0.91 | 0.91 | 0.87 |
| 6 | 0.98 | 0.96 | 0.80 | 0.89 |
| 7 | 0.98 | - | 0.96 | 0.97 |
| 8 | 0.93 | 0.91 | 0.84 | 0.85 |
| 9 | 0.92 | 0.94 | 0.67 | 0.90 |
| 10 | 0.86 | 0.87 | 0.86 | 0.84 |
| 11 | 0.93 | 0.94 | 0.84 | 0.92 |
| 12 | 0.93 | 0.95 | 0.94 | 0.92 |
| 13 | 0.98 | 0.82 | 0.71 | 0.86 |
| MEAN ± SD | 0.94 ± 0.04 | 0.89 ± 0.07 | 0.84 ± 0.09 | 0.91 ± 0.04 |

# PATIENT 3 - UNIFIED FITS
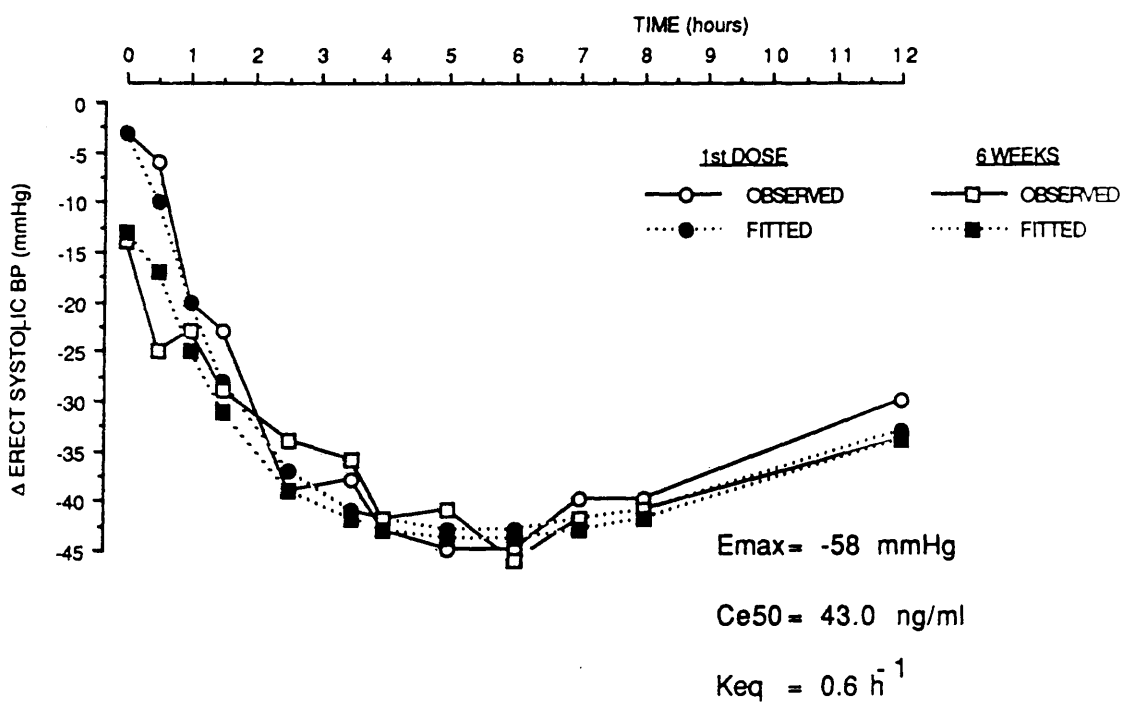


**Figure 4.5.**
Enalaprilat concentration-effect analysis. The observed (————)
and fitted (—————) effects of enalaprilat on erect systolic BP in a
representative patient (patient 3) after the 1st dose and after 6
weeks fitted simultaneously to a unified model;  illustrating above
average goodness of fit. (The data at 1 week is omitted for clarity,
though represented in the derived parameters).

## PATIENT 13 - UNIFIED FITS

TIME (hours)

1st DOSE
OBSERVED
FITTED

6 WEEKS
OBSERVED
FITTED

Emax = -34 mmHg

Ce50 = 29.4 ng/ml

Keq = 0.3 $h^{-1}$
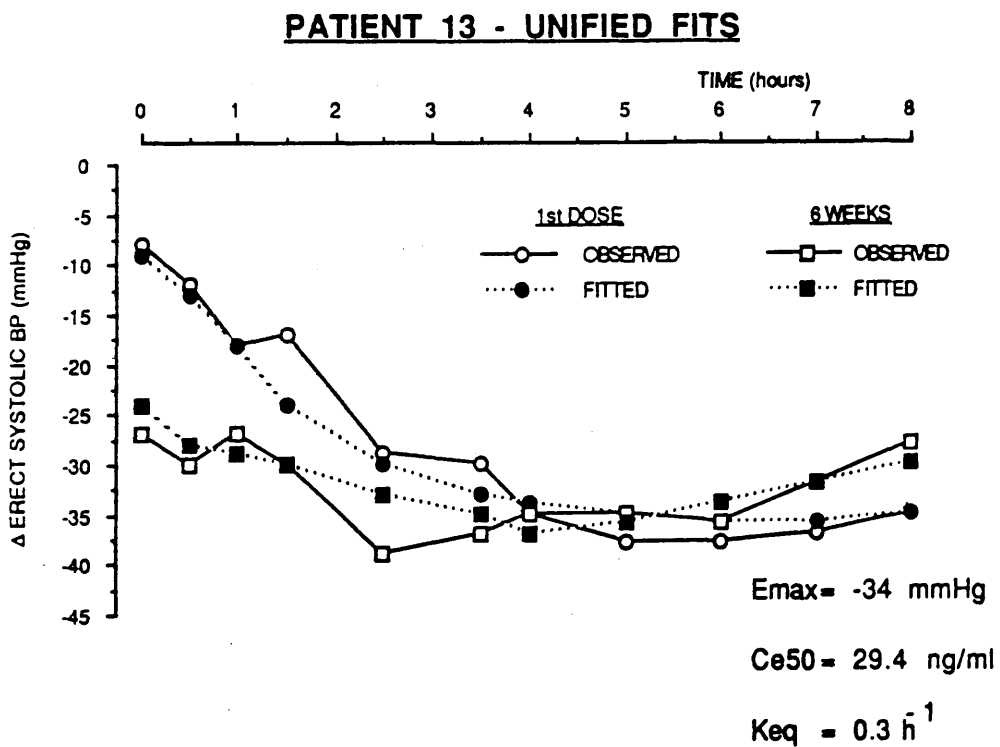
Figure 4.6.
Enalaprilat concentration-effect analysis. The observed (————)
and fitted (------) effects of enalaprilat on erect systolic BP in a
representative patient (patient 13) after the 1st dose and after 6
weeks fitted simultaneously to a unified model; illustrating below
average goodness of fit. (The data at 1 week is omitted for clarity,
though represented in the derived parameters).

TABLE 4.9.

THE ENALAPRILAT CONCENTRATION-EFFECT PARAMETERS $E_{max}$, $C_e50$ AND $K_{eq}$
AND GOODNESS OF FIT (R), FOR CHANGES IN ERECT DIASTOLIC BP DERIVED
FROM THE UNIFIED APPROACH FITTING THE DATA SETS FOR ALL THREE STUDY
DAYS SIMULTANEOUSLY

| PATIENT | $E_{max}$ (mmHg) | $C_e50$ (ng/ml) | $K_{eq}$ (hours$^{-1}$) | R |
|---------|------------------|-----------------|-------------------------|------|
| 1 | -22 | 48.0 | 0.32 | 0.83 |
| 2 | -21 | 41.2 | 0.37 | 0.96 |
| 3 | -12 | 41.3 | 0.98 | 0.82 |
| 4 | -19 | 89.1 | 1.13 | 0.88 |
| 5 | -18 | 58.4 | 0.28 | 0.81 |
| 6 | -22 | 102.0 | 2.13 | 0.87 |
| 7 | -28 | 48.3 | 1.71 | 0.90 |
| 8 | -20 | 72.2 | 0.87 | 0.91 |
| 9 | -18 | 59.0 | 0.33 | 0.83 |
| 10 | -21 | 55.6 | 2.13 | 0.85 |
| 11 | -16 | 78.3 | 1.91 | 0.91 |
| 12 | -22 | 84.4 | 1.32 | 0.83 |
| 13 | -17 | 22.7 | 0.33 | 0.93 |
| MEAN ± SD | -19.7 ± 3.8 | 61.6 ± 22.5 | 1.1 ± 0.7 | 0.87 ± 0.05 |
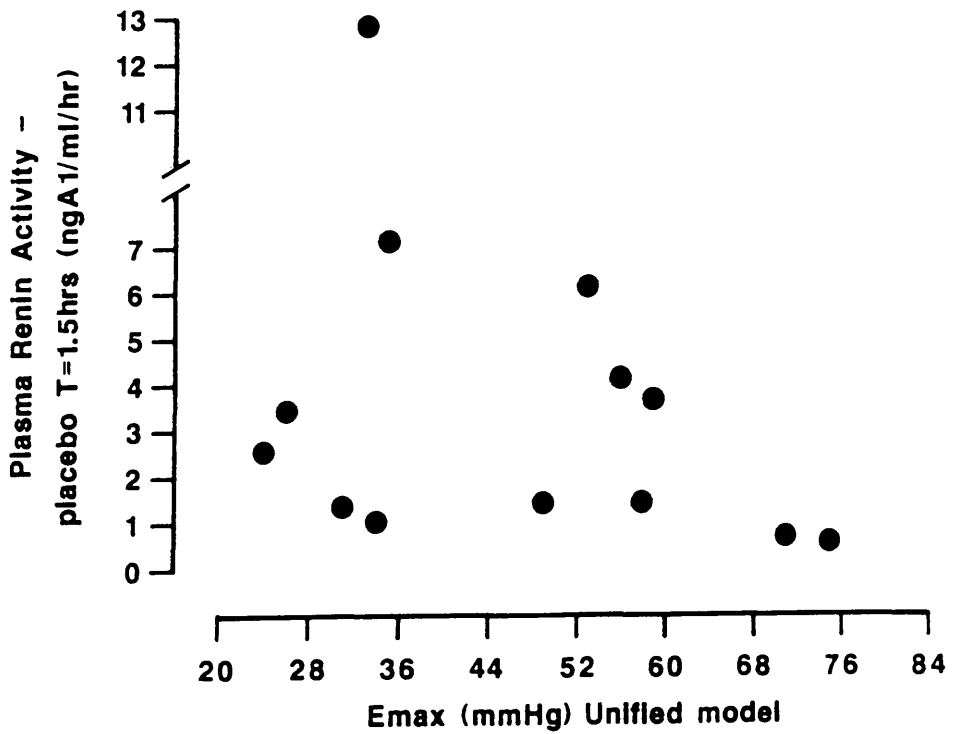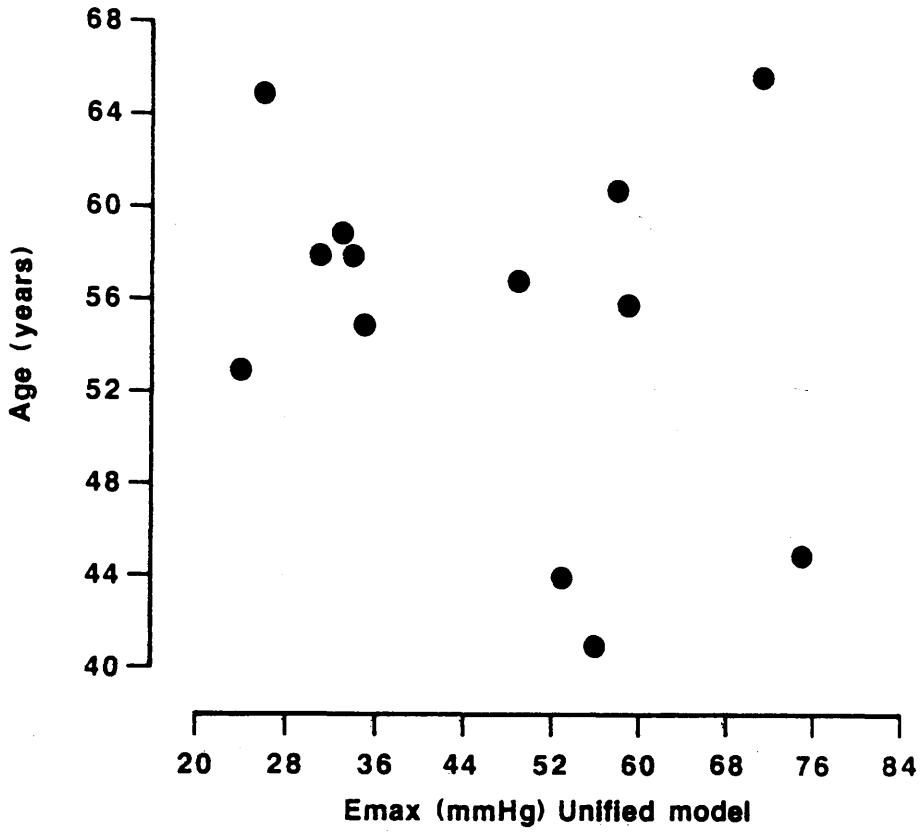
Figure 4.7.
Relationships between the responsiveness to enalaprilat ($E_{max}$) after the 1st dose and patient age and pretreatment plasma renin activity.

R = 0.69
P < 0.009
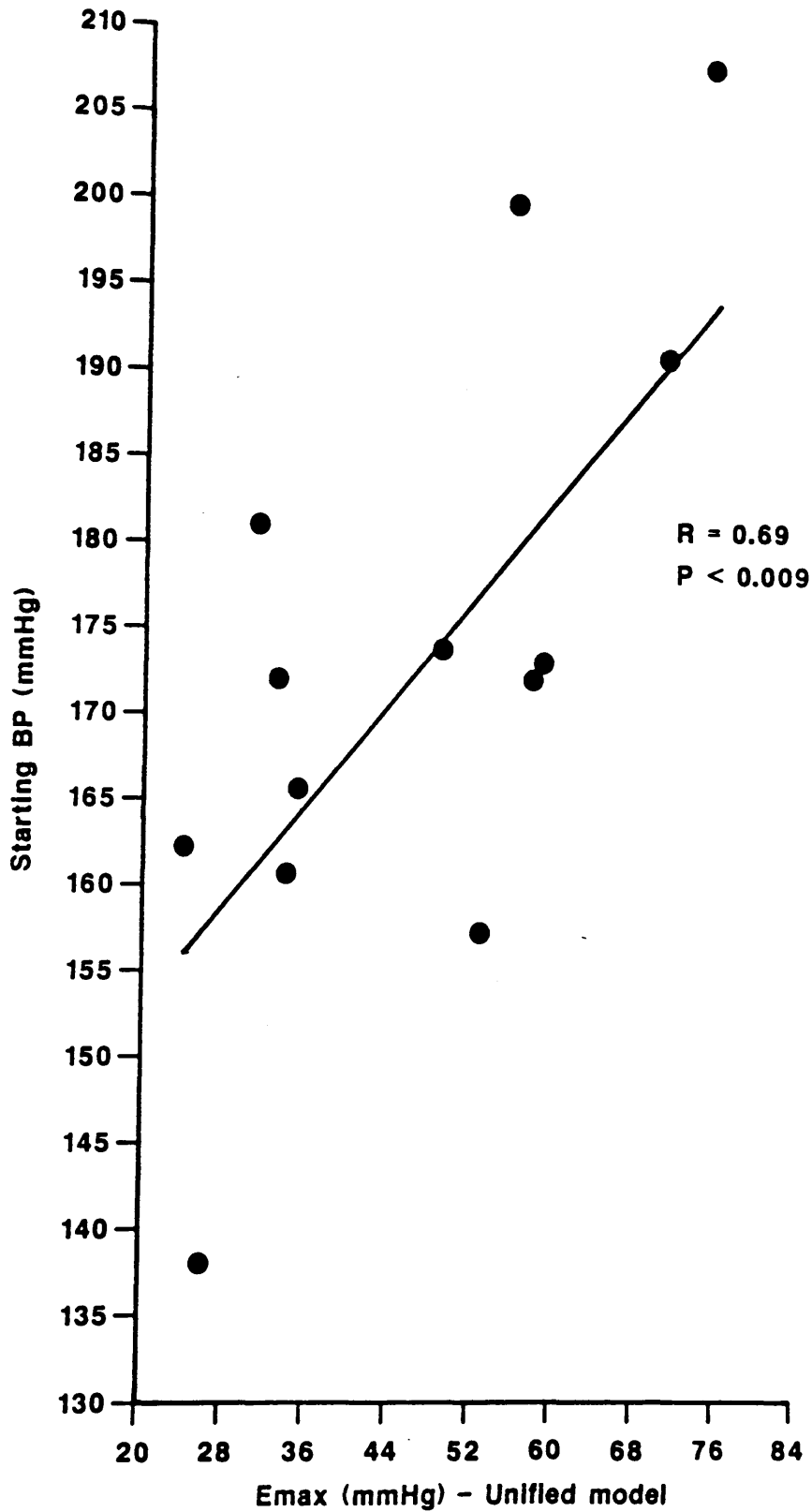
Figure 4.8.
Correlation between the responsiveness to enalaprilat ($E_{max}$) after
the 1st dose and the height of the pretreatment systolic blood pressure.

**Independent fits : correlation between Emax 1st dose and Emax after 6 weeks**

R = 0.89
P < 0.0001

(x-axis) Emax 1st dose (mmHg)
(y-axis) Emax 6 weeks (mmHg)
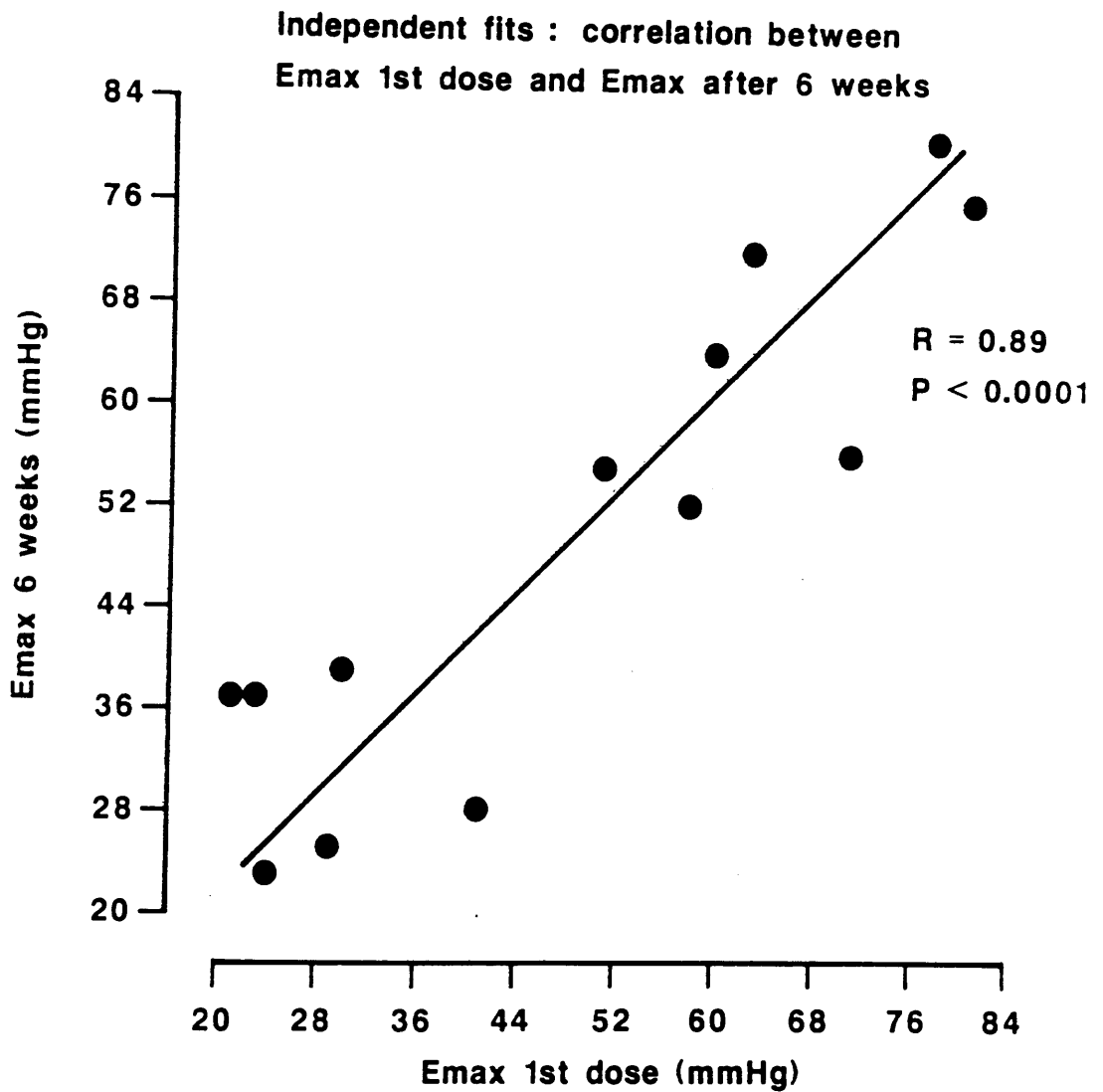
Figure 4.9.
From the concentration-effect parameters derived from fitting the enalaprilat data for each study day independently, there was a significant correlation between the responsiveness to the 1st dose ($E_{max}$) and the responsiveness after 6 weeks.

a highly significant correlation between the responsiveness ($E_{max}$) to the first dose of enalapril and the responsiveness obtained after 6 weeks (Figure 4.9.).

## 4.4. DISCUSSION

In this group of salt replete patients enalapril was generally well tolerated and in particular no patient showed excessive reductions in blood pressure after the first dose. The antihypertensive effect of enalapril was sustained for 24-hour blood pressure control with a dosage regimen of 20 mg once daily. After treatment for 6 weeks, predose blood pressures recorded 24 hours after the last dose were significantly reduced, on average 157/94 supine and 151/92 mmHg erect, and in 9 patients the blood pressure was less than 150/90 mmHg. There was no significant orthostatic component to the antihypertensive effect: for example, baseline-corrected reductions in supine and erect blood pressure at 6 hours after the first dose were 46/27 and 49/21 mmHg respectively. Additionally, in contrast to the reflex sympathetic activation which is often seen with other vasodilators, the fall in blood pressure with enalapril, particularly after the first dose, was not associated with any significant change in heart rate or plasma noradrenaline. The absence of a reflex tachycardia during converting enzyme inhibition has been reported previously with enalapril (Millar et al, 1982a; Velasco et al, 1985) and with a number of other ACE inhibitors (Cody et al, 1979;

132

Richer et al, 1987) but the underlying mechanism has not been clearly established. There is evidence that it may reflect changes in both the set-point and sensitivity of baroreflex mechanisms (Ibsen et al, 1983; Giudicelli et al, 1985) but these have not been consistent observations (Mancia et al, 1982; Warren et al, 1983) and Millar et al (1982a) have shown that enalapril has no effect on autonomic reflexes. Other studies have led to an alternative explanation that ACE inhibitors produce enhancement of parasympathetic vagal tone (Millar et al, 1982b; Ajayi et al, 1985).

The increase in plasma renin activity (PRA) after enalapril is thought to be due to the removal of angiotensin inhibition on renal renin release (Davies et al, 1984). In this study, it was noted that the increase in PRA during chronic treatment with enalapril was higher than that seen after the first dose. One possible explanation is that with chronic administration there is a further rise in PRA in response to decreased plasma renin substrate concentration, which occurs during longterm treatment with an ACE inhibitor due to withdrawal of angiotensin II-mediated stimulation of hepatic angiotensinogen synthesis (Rasmussen et al, 1981). The largest increase in PRA occurred at 6 hours after drug administration, which coincided with the peak hypotensive effect of enalapril, and in previous studies similar relationships have been described between maximal blood pressure reductions and changes in endocrine parameters

(Johnston et al, 1983).

During chronic treatment with an ACE inhibitor there is a sustained reduction in plasma ACE activity and increased plasma renin. In contrast, however, plasma angiotensin II and plasma aldosterone levels tend to return towards pretreatment values (Johnston et al, 1979; Staessen et al, 1981; Biollaz et al, 1982) and in this study there was a significant reduction in plasma aldosterone concentration after 1 week but not after 6 weeks treatment. The transient fall in plasma aldosterone is consistent with the natriuretic effect associated acutely with ACE inhibitors (Millar et al, 1982a; de Leeuw et al, 1983) and also with the known effects of ACE inhibitors on renal blood flow (de Leeuw et al, 1983; Dunn et al, 1984).

In contrast to the antihypertensive effect during chronic treatment with enalapril which was sustained for 24 hours, the inhibitory effect on plasma ACE activity was significantly attenuated during the latter part of a dosage interval, with measurements of ACE activity at 24 hours returning towards placebo values. This confirms previous observations that the fall in blood pressure after administration of an ACE inhibitor can be temporally dissociated from plasma ACE inhibition (Velletri and Bean, 1981; Unger et al, 1985). These findings, together with the evidence that ACE inhibitors are effective in low or normal renin states (Gavras et al, 1981), suggests that the antihypertensive response to ACE inhibition cannot be

explained solely by the suppression of the circulating renin-angiotensin system. An alternative explanation for the hypotensive effect of ACE inhibitors is inhibition of localised tissue ACE (Velletri and Bean, 1981; Cohen and Kurz, 1982; Unger et al, 1985) and a number of studies have demonstrated local angiotensin II formation in peripheral vascular tissue (Mizuno et al, 1988), brain, kidney, adrenal and lung (Sakaguchi et al, 1988). It has been shown that the degree and time course of ACE inhibition in different tissues varies markedly in response to treatment with an ACE inhibitor and often bears little relationship to the profile of circulating ACE inhibition (Sakaguchi et al, 1988). In particular, the duration of inhibition of tissue ACE is much longer than that for plasma ACE (Sakaguchi et al, 1988), suggesting that in this study sustained tissue, but not plasma, ACE inhibition accounts for the 24 hour antihypertensive effect.

During the latter part of the dosage interval for enalapril there was a tendency after chronic treatment for plasma ACE activity to recover more quickly compared with the first dose: for example, at 12 and 24 hours respectively plasma ACE activity was 11.1 and 32.3 EU/ml after 6 weeks compared with 8.7 and 22.0 EU/ml after the first dose. This is consistent with induction of ACE, which has been described both in animals and man after chronic administration of an ACE inhibitor (La Rochelle et al, 1979; Fyhrquist et al, 1983). The term 'activity'

refers to circulating uninhibited enzyme only, whereas converting enzyme 'concentration' refers to the total concentration of circulating ACE, i.e. the sum of inhibited and uninhibited enzyme. Although ACE 'activity' is suppressed during longterm treatment with an ACE inhibitor, there is evidence of a gradual increase in converting enzyme 'concentration' over a period of several weeks consistent with enhanced ACE biosynthesis (Boomsma et al, 1981).

Thus, measurements of plasma ACE activity are of limited value in studying the antihypertensive mechanism of ACE inhibitors. In contrast, measurements of ACE concentration and ACE activity in different tissues are much more relevant.

The pharmacokinetics of enalaprilat were consistent with the 24 hour blood pressure control and there was no significant change in drug disposition during chronic compared with acute administration. Because of the biotransformation of enalapril to enalaprilat, the $t_{max}$ for enalaprilat was approximately 4-5 hours, which is consistent with previous observations (Ulm et al, 1982; Kubo and Cody, 1985). In this study patients were fasted, but it has been shown that food has no effect on the absorption of enalapril or the kinetics of enalaprilat (Ferguson et al, 1983).

A number of different pharmacokinetic models were fitted to the concentration data. Consistent with the observations of Till et al (1984), a conventional pharmacokinetic model did not satisfactorily describe all

136

the features of the disposition, particularly the accumulation of enalaprilat during chronic therapy. The short elimination half-life derived from the two compartment model implied that there was a rapid elimination process and suggested that almost no drug accumulation should occur on repeated administration, but from the observed trough concentration data this was clearly not the case. Accordingly an alternative approach was evaluated using a physiologically realistic model that is based on the saturable binding of the drug to converting enzyme (Francis et al, 1987). This model was the most appropriate for describing the enalaprilat kinetics as well as the kinetic-dynamic relationships and essentially the model is identical to that for any drug whose clearance is governed by Michaelis-Menten kinetics, or for which saturable protein binding makes a significant contribution. The theoretical basis for such models and the practical implications have been investigated extensively (McNamara et al, 1979; Keller et al, 1984) but what is unusual about enalaprilat and other ACE inhibitors is that the binding protein is an enzyme which is intimately associated with the therapeutic response.

The short half-life for unbound drug corresponds to free, or excess, drug clearance, but the long half-life for bound drug, on average 16.8 hours, reflects the high affinity of enalaprilat for the enzyme and confirms that once daily administration should be adequate to maintain a

24-hour pharmacological response.

There is evidence that age has an important effect on the pharmacokinetics of enalapril, with reduced clearance and clearance/bioavailability of enalaprilat in the elderly (Hockings et al, 1986; Lees and Reid, 1987), but in this relatively small study, across a fairly narrow age range, there was no clear relationship between age and the disposition of enalaprilat.

Several studies have reported that ACE inhibitors have shallow or flat dose-response curves (Davies et al, 1984; Nelson et al, 1985) and that an increase in dose of an ACE inhibitor, although producing higher drug plasma concentrations (Kubo and Cody, 1985), extends the duration of action but has no effect on the magnitude of the blood pressure response (Gomez et al, 1985). For example, 10 and 20 mg doses of enalapril were indistinguishable in terms of peak reductions in blood pressure but the hypotensive effect of the 20 mg dose persisted longer (Webster et al, 1987). In addition, drug concentration-effect relationships for ACE inhibitors have been ill-defined. Although maximal blood pressure reductions have been correlated with peak plasma concentrations of enalaprilat (Schwartz et al, 1985), no direct concentration-effect relationship has been identified in individual hypertensive patients. Previous studies with enalapril have sought correlations between drug concentration and effect data for groups of subjects and the relationships obtained, although generally linear, have been

widely variable (Biollaz et al, 1982; de Leeuw et al, 1983; Johnston et al, 1983 and 1984). From single dose studies in healthy volunteers it has been suggested that concentration-effect relationships can be defined more consistently and are potentially more useful when data for individuals, rather than for groups of subjects, is considered (Kelman et al, 1983; Francis et al, 1987), and this study in hypertensive patients has extended these observations by defining individual concentration-response relationships which are applicable during chronic treatment.

There was no simple direct plasma concentration-effect relationship, but using concentration-effect analysis enalaprilat levels were well correlated with reductions in both systolic and diastolic blood pressure in individual patients. In most clinical studies of this type data points are usually obtained over a relatively restricted concentration-response range and therefore the concentration-effect relationship is often best described by the simpler linear model (Chapter 2.5.). In this study with enalapril, and in a similar study with another ACE inhibitor (Francis et al, 1987), the kinetic-dynamic relationships were defined most appropriately by the full Langmuir ($E_{max}$) equation, suggesting that at least some of the data points were situated close to the top end of a sigmoid-shaped concentration-effect curve. This may partly explain why ACE inhibitors have been reported to have flat dose-response curves, since previous studies may have used

doses which produce drug levels at the top end of the $E_{max}$ curve.

It has been shown both with captopril (Laragh et al, 1980) and with enalapril (Brunner et al, 1983) that it takes several weeks to achieve maximal blood pressure 'response' and additionally it has been suggested that the first dose response to an ACE inhibitor bears no relationship to the response obtained during longterm treatment (Bidiville et al, 1988).  In this study, which incorporated kinetics as well as dynamics in the description of response, there was no significant change in the responsiveness to enalapril after 6 weeks compared with single dose administration.  In addition, for individual patients there were significant correlations between the responsiveness ($E_{max}$) to the first dose and the responsiveness after 6 weeks.

It has been shown that the hypotensive response to ACE inhibition is partly related to the activity of the renin-angiotensin system (Gavras et al, 1978).  Thus, conditions which lead to an increase in renin release, for example a low salt diet or treatment with a diuretic, enhance the antihypertensive effect of an ACE inhibitor (Atkinson et al, 1980).  Although extremes of sodium intake undoubtedly influence the haemodynamic effects of ACE inhibitors, there has been some dispute about the importance of plasma renin activity in routine clinical practice as a predictive marker of blood pressure response (Cody et al, 1983).  There is good evidence that ACE inhibitors may be effective in

patients with low plasma renin activity (Gavras et al, 1981), and even in anephric subjects (Man in't Veld et al, 1980), and this study has shown that in a typical group of salt replete patients the responsiveness to enalapril cannot be usefully predicted by age or measurements of pretreatment plasma renin activity. In contrast, there was a significant correlation between the responsiveness to enalapril and the height of the starting blood pressure.

In summary, this study has shown that enalaprilat concentrations are correlated with reductions in both systolic and diastolic blood pressure in individual hypertensive patients. The kinetic-dynamic relationships for enalapril were described most appropriately by the Langmuir ($E_{max}$) model rather than the simpler linear model. The pretreatment blood pressure and the response to the first dose were important determinants of response during longterm treatment.

# CHAPTER 5

## CONCENTRATION-EFFECT RELATIONSHIPS AND ALPHA$_1$ ADRENOCEPTOR ANTAGONIST EFFECTS OF DOXAZOSIN IN ESSENTIAL HYPERTENSION

## 5.1. INTRODUCTION

The alpha$_1$ adrenoceptor antagonist doxazosin, which is a quinazoline derivative related to prazosin, has been shown to lower blood pressure in patients with essential hypertension (Frick et al, 1986; Baez et al, 1986; Cox et al, 1986). In comparison to prazosin, doxazosin has a prolonged terminal elimination half-life (Elliott et al, 1987) and, even after intravenous administration, a more gradual onset of antihypertensive effect (Elliott et al, 1982) and so it may be suitable for once daily dosing (Cubeddu et al, 1987; Elliott et al, 1987). The blood pressure fall after the first dose of prazosin has been shown to be directly correlated with drug concentrations in blood (Bateman et al, 1979; Seideman et al, 1981; La Rochelle et al, 1982) but for doxazosin no comparable simple direct relationship exists between plasma concentration and the fall in blood pressure (Elliott et al, 1982; Cubeddu et al, 1987). In normotensive volunteers using an integrated kinetic-dynamic modelling technique, the acute hypotensive effect of doxazosin has been shown to correlate with the concentration of drug in the "effect" compartment (Vincent et al, 1983). However, a concentration-effect relationship which is applicable during chronic treatment in hypertensive patients has not been established.

This study in patients with essential hypertension evaluates the pharmacodynamics, including alpha$_1$

adrenoceptor antagonist activity, and the pharmacokinetics of doxazosin after acute and chronic administration and, using an integrated kinetic-dynamic model (Holford and Sheiner, 1981), characterises the concentration-effect relationships and antihypertensive responses in individual patients.

## 5.2. PATIENTS AND METHODS

### 5.2.1. General

Ten patients (4 male, 6 female) with mild to moderate essential hypertension, age range 47-70 years, participated in this study. Individual patient details are shown in Table 5.1. Patients discontinued all medication for at least 6 weeks prior to the study and at the end of this drug-free run-in period the average entry blood pressure was 180/103 ± 11/4 supine and 174/102 ± 8/5 mmHg erect. In a single blind design patients then received placebo for 2 weeks followed by doxazosin 2 mg once daily for 6 weeks. Each patient attended four 8-hour study days in the CPRU to evaluate the effects of placebo, 1st dose doxazosin and 1 week and 6 weeks treatment.

The clinical protocol is described in detail in Chapter 2.1. At frequent intervals during each study day, and at 24 hours after dosing, supine and erect blood pressure and heart rate were measured and venous blood samples collected for plasma doxazosin concentrations. Additional blood samples were obtained at 1.5 and 6 hours for plasma renin

TABLE 5.1.

PATIENT DETAILS FOR DOXAZOSIN STUDY

| PATIENT | AGE | SEX | WEIGHT (kg) | RELEVANT MEDICAL HISTORY | PREVIOUS ANTI-HYPERTENSIVE THERAPY | CHOLESTEROL | SMOKER | ENTRY BP SUPINE | ENTRY BP ERECT |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 53 | M | 63 | Newly diagnosed EH | Nil | 5.9 | - | 170/105 | 168/92 |
| 2 | 47 | M | 120 | Newly diagnosed EH Bronchitis | Nil | 6.4 | - | 177/104 | 175/107 |
| 3 | 65 | F | 65 | EH diagnosed 3 months ago Mild IHD | Methyldopa - Poor BP control | 7.2 | - | 185/108 | 174/106 |
| 4 | 56 | F | 70 | Newly diagnosed EH | Nil | 7.0 | + | 183/103 | 169/101 |
| 5 | 67 | F | 65 | Newly diagnosed EH | Nil | 6.9 | - | 207/111 | 195/110 |
| 6 | 70 | F | 50 | Newly diagnosed EH | Nil | 8.1 | - | 175/103 | 171/102 |
| 7 | 55 | M | 68 | EH diagnosed 4 years ago Bronchitis IHD | Atenolol - wheeze Nifedipine - headache | 7.3 | - | 170/98 | 173/100 |
| 8 | 59 | F | 92 | EH diagnosed 3 months prior to entry | Atenolol - ineffective Nifedipine - oedema | 7.4 | + | 171/96 | 168/99 |
| 9 | 59 | F | 71 | EH diagnosed 3 years ago | Atenolol - tiredness | 7.1 | + | 176/105 | 170/103 |
| 10 | 58 | M | 60 | Newly diagnosed EH | Nil | 5.8 | - | 183/102 | 178/105 |
| MEAN ± SD | 58.9 ± 6.9 | | 72.4 ± 19.8 | | | | | 180/103 ± 11/4 | 174/102 ± 8/5 |

Key: EH = essential hypertension; IHD = ischaemic heart disease.

activity, aldosterone and catecholamines. Fasting plasma triglyceride and total cholesterol levels were measured at the start of each study day.

## Additional (short) study day

On the third day of doxazosin treatment patients were instructed to take their dose at 8 a.m. and attend the Clinical Pharmacology Research Unit 5 hours later. They rested supine for one hour and at 6 hours after dosing a venous cannula was inserted, blood pressure and heart rate recorded and a blood sample collected for doxazosin concentration. A pressor infusion of phenylephrine (PE) was then administered as described below.

## Pressor responsiveness

During each full study day, between 1.5 - 3 hours (early) and at 6 hours (late), and at 6 hours after drug administration on the short study day, pressor responsiveness to the selective alpha$_1$ agonist phenylephrine (PE) was measured according to the method described in Chapter 2.2. In addition, using a similar method, pressor responsiveness to angiotensin II was measured during the early period of each full study day.

Early and late pressor infusions were designed to roughly coincide with peak plasma doxazosin concentrations at 2-3 hours and the maximum antihypertensive effect of doxazosin at 5-6 hours after drug administration.

146

## 5.2.2. Doxazosin concentrations

Plasma concentrations of doxazosin were measured using the reverse phase HPLC method described by Rubin et al, 1980. An alkaline extraction procedure was used with back-extraction into sulphuric acid. The internal standard was prazosin and levels were measured by fluorescence detection. The inter and intra-assay coefficients of variation for the doxazosin assay were 7.5% and 5.8% respectively over the concentration range 4-45 ng/ml


## 5.2.3. Pharmacokinetic and concentration-effect analysis

Plasma doxazosin concentration-time profiles for individual patients on each study day were most appropriately fitted to a single compartment model with first order input and inverse weighting of the concentration data.

For the concentration-effect analysis the standard pharmacokinetic model was augmented by an "effect" compartment, as described in Chapter 2.5., and the effect on blood pressure was then related to the drug concentration in the effect compartment by means of both the linear and non-linear models (Holford and Sheiner, 1981). In each case, after both acute and chronic dosing, the data were most appropriately described by the linear model.

The concentration-effect parameters, m and $K_{eq}$, were derived for individual patients on each study day. The responsiveness to doxazosin was calculated in terms of the

(placebo-subtracted) fall in both erect systolic and
diastolic blood pressure per unit drug concentration.


## 5.3. RESULTS

### 5.3.1. Patient tolerance

Doxazosin was generally well tolerated but symptomatic
postural hypotension occurred in 4 patients 5-6 hours after
the first dose.  During chronic treatment no adverse
effects were reported.


### 5.3.2. Blood pressure

There were significant reductions in supine and erect
blood pressure following the first dose of doxazosin (Figure
5.1.):  for example, from a baseline of $170/102 \pm 13/5$
supine and $165/102 \pm 15/8$ mmHg erect to $127/77 \pm 14/11$
supine and $114/69 \pm 18/12$ mmHg erect at 6 hours, compared
with $175/105 \pm 16/7$ supine and $173/107 \pm 13/6$ erect to
$147/88 \pm 7/8$ supine and $151/93 \pm 11/6$ mmHg erect at 6 hours
after placebo.  The maximum antihypertensive effect of
doxazosin occurred 5-6 hours after drug administration
(Figure 5.1.).  Continued treatment with doxazosin
significantly reduced predose blood pressures:  measurements
of supine blood pressure (recorded 24 hours after the last
dose) were $155/94 \pm 13/6$ after 1 week and $157/95 \pm 17/8$
after 6 weeks, compared with $175/105 \pm 16/7$ mmHg following
placebo.  In addition, blood pressure control was
particularly good during the 8 hours of each study day, with

average blood pressures of 137/82 supine and 133/82 erect
after 1 week, and 140/85 supine and 135/84 mmHg erect after
6 weeks.


## 5.3.3. Heart rate

The fall in blood pressure following the first dose of
doxazosin was associated with a significant increase in
heart rate, particularly in the erect position 4-5 hours
after drug administration (Figure 5.2.). Erect heart rate
increased from a baseline of 79 $\pm$ 10 to 92 $\pm$ 10 bpm 4 hours
after the first dose, compared with a corresponding change
from 79 $\pm$ 13 to 77 $\pm$ 11 bpm following placebo. After 1
week of treatment with doxazosin the heart rate increase was
attenuated, although still significant, from a baseline of
81 $\pm$ 9 to 87 $\pm$ 11 bpm erect at 4 hours, but after 6 weeks of
doxazosin the heart rate profiles were not significantly
different from placebo (Figure 5.2.). Average supine and
erect heart rates during the 8-hours were respectively 73
and 85 bpm after 1 week and 70 and 82 bpm after 6 weeks,
compared to 70 and 79 bpm following placebo.


## 5.3.4. Hormone measurements and plasma lipids

There were significant increases in plasma
noradrenaline following the first dose of doxazosin (Table
5.2.): for example at 6 hours, 5.1 $\pm$ 2.6 compared with 2.8 $\pm$
0.9 nmol/L after placebo. The increase in plasma
noradrenaline was partially attenuated after 1 week of

**DOXAZOSIN**
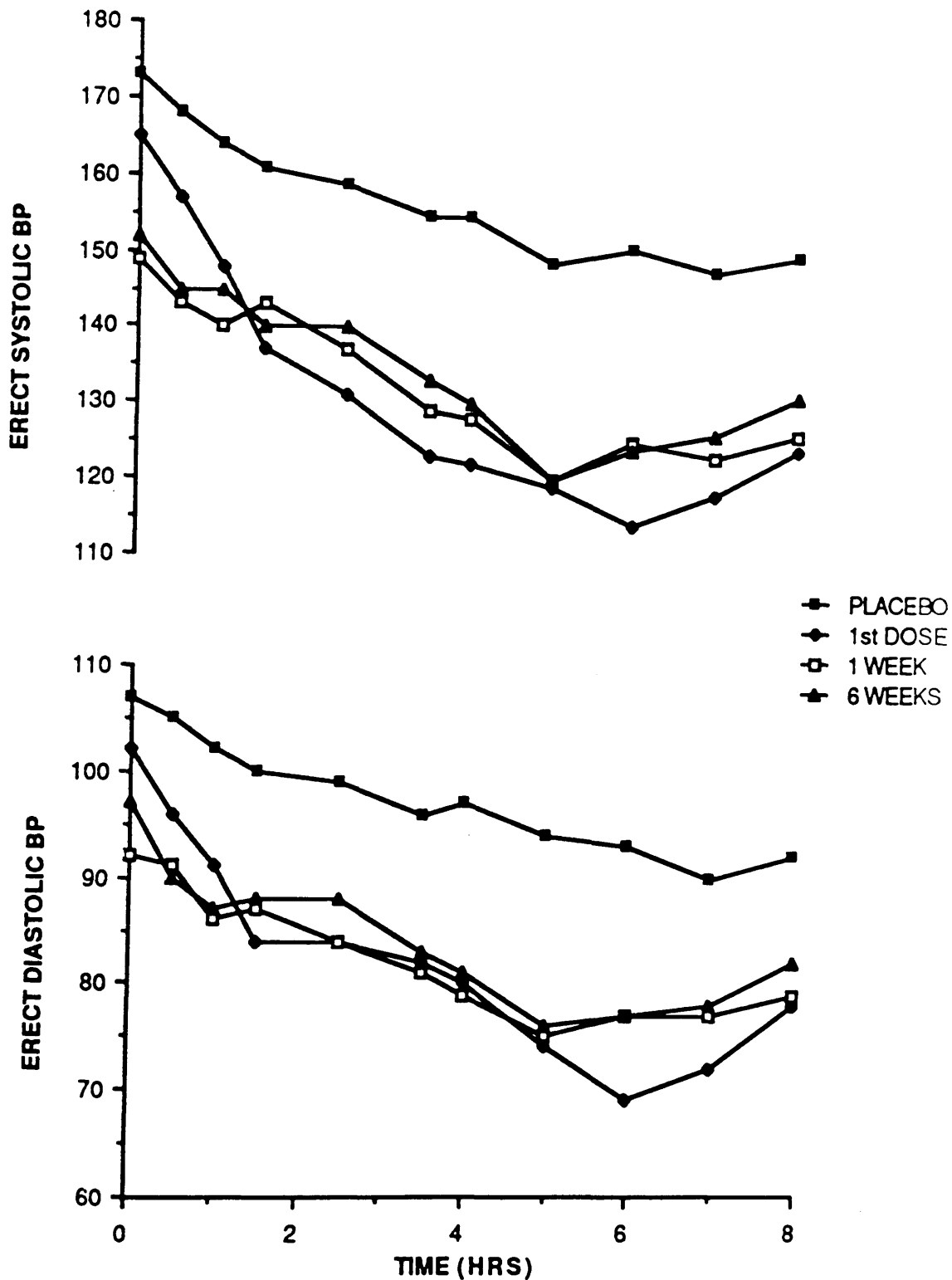
Figure 5.1.
Mean profiles of erect systolic and diastolic blood pressure after
placebo ( ■ ), 1st dose doxazosin ( ◆ ) and after 1 week
( □ ) and 6 weeks ( ▲ ) doxazosin treatment.

150
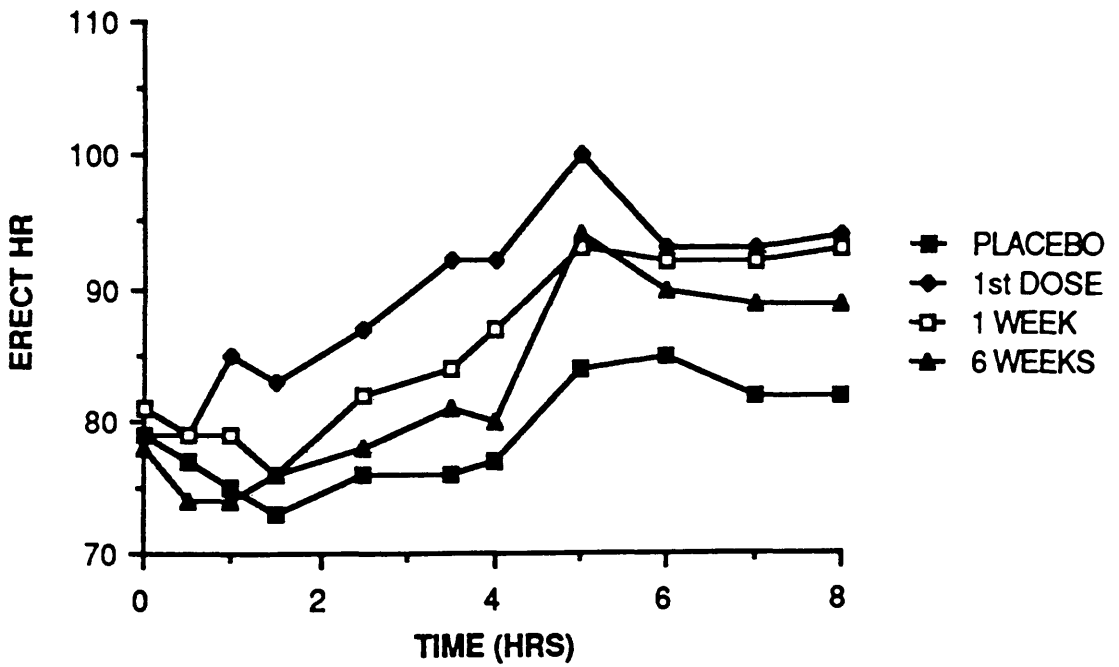
**DOXAZOSIN**



Figure 5.2.
Mean profiles of erect heart rate after placebo ( ■ ), 1st dose
doxazosin ( ◆ ) and after 1 week ( □ ), and 6 weeks ( ▲ )
doxazosin treatment.

treatment with doxazosin but significantly higher
measurements were again observed at 6 hours: 4.4 ± 2.0
nmol/L.    Measurements of plasma noradrenaline at 6 weeks
were not significantly different from placebo (Table 5.2.).
Doxazosin had no significant effect on plasma renin activity
or aldosterone (Table 5.2.).

Doxazosin had no significant effect on fasting plasma
triglyceride and total cholesterol levels.    Mean values for
plasma triglyceride (mmol/L) and total cholesterol (mmol/L)
were respectively 1.9 ± 0.7 and 7.0 ± 0.4 in the placebo
phase; 2.2 ± 0.9 and 6.6 ± 0.4 after the 1st dose;  2.0 ±
0.8 and 6.5 ± 0.6 after 1 week;  and 1.8 ± 0.9 and 6.6 ± 1.0
after 6 weeks.


## 5.3.5. Pressor responses

Doxazosin produced significant parallel rightward
shifts of the phenylephrine pressor dose-response curves, as
would be expected of this competitive $alpha_1$ adrenoceptor
antagonist.    Pressor dose-response curves for early and
late PE infusions in a representative patient are shown in
Figure 5.3.    There was a significant increase in the $PD_{20}$
values following doxazosin, shown for early and late
infusions in Tables 5.3. and 5.4. : for example, for
infusions in the early period the mean $PD_{20}$ increased from
1.9 (placebo) to 5.7 (1st dose), 8.7 (1 week) and 6.2
ug/kg/min after 6 weeks (Table 5.3.).

On each study day there was no significant difference

TABLE 5.2.

DOXAZOSIN STUDY. HORMONE MEASUREMENTS AT 1.5 AND 6 HOURS
AFTER DRUG ADMINISTRATION
MEAN ± SD

| | TIME (HRS) | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---|---|---|---|---|---|
| Plasma noradrenaline (nmol/L) | 1.5 | 3.1 ± 2.7 | 3.7 ± 2.8 | 4.0 ± 1.6 | 3.0 ± 1.9 |
| | 6 | 2.8 ± 0.9 | 5.1 ±** 2.6 | 4.4 ±* 2.0 | 3.3 ± 1.6 |
| Plasma adrenaline (nmol/L) | 1.5 | 0.3 ± 0.2 | 0.5 ± 0.3 | 0.3 ± 0.2 | 0.3 ± 0.2 |
| | 6 | 0.4 ± 0.3 | 0.4 ± 0.5 | 0.5 ± 0.5 | 0.3 ± 0.3 |
| Plasma aldosterone (pg/ml) | 1.5 | 95 ± 56 | 94 ± 50 | 79 ± 38 | 71 ± 52 |
| | 6 | 117 ± 73 | 117 ± 28 | 101 ± 33 | 87 ± 40 |
| Plasma renin activity (ngA1/ml/hr) | 1.5 | 1.6 ± 1.0 | 2.3 ± 1.5 | 2.1 ± 1.5 | 2.4 ± 1.4 |
| | 6 | 2.2 ± 1.6 | 2.8 ± 1.5 | 2.8 ± 3.0 | 2.2 ± 1.9 |

** $p < 0.02$      * $p < 0.05$

in pressor responsiveness to PE between the early and late
infusions but there was a trend towards higher dose ratios
(i.e. greater $alpha_1$ antagonist activity) at 6 hours after
dosing.  The maximum $alpha_1$ antagonist effect of doxazosin
occurred during the first week of treatment (on both the
short study day and at one week) and there was a significant
attenuation of the alpha blockade by 6 weeks:  for
example, for infusions in the late period the mean $PD_{20}$ was
significantly reduced (p < 0.02) from 7.2 (1 week) to 5.6
ug/kg/min (6 weeks).

The relationship between the simultaneous blood
pressure and heart rate changes during the infusion of PE
was used as an approximate index of cardiovascular
baroreflex activity (Chapter 2.2.).  Doxazosin had no
significant effect on this relationship (Table 5.5.).

Doxazosin had no significant effect on pressor
responsiveness to angiotensin II (Table 5.6.).


## 5.3.6. Pharmacokinetics

The derived pharmacokinetic parameters AUC, $t_{1/2}$, $C_{max}$
and $t_{max}$ obtained by fitting a one compartment model with
first order input to the data are shown in Tables 5.7. and
5.8.  Analysis of variance revealed a significant increase
in terminal elimination half-life in translation from acute
to steady state therapy, with mean values of 12.5 ±
3.3 and 12.3 ± 2.5 hours at 1 and 6 weeks respectively
compared to 8.8 ± 2.3 hours on first dosing (Table 5.7).

**DOXAZOSIN**
**PE Infusion (T = 1.5–3hrs)**

**PE Infusion (T = 5–6hrs)**
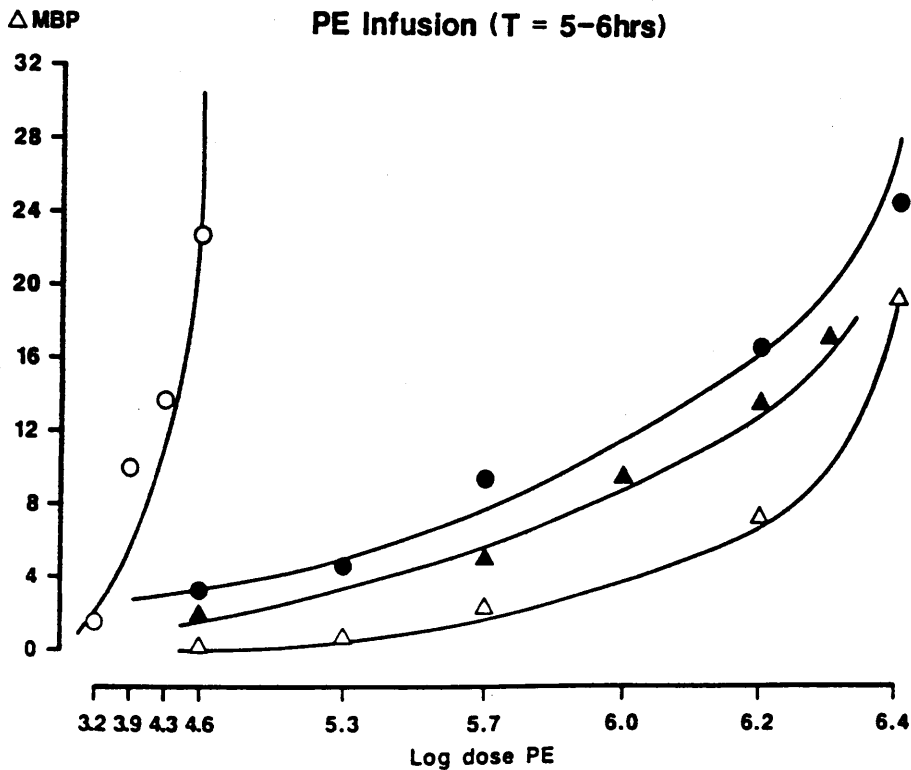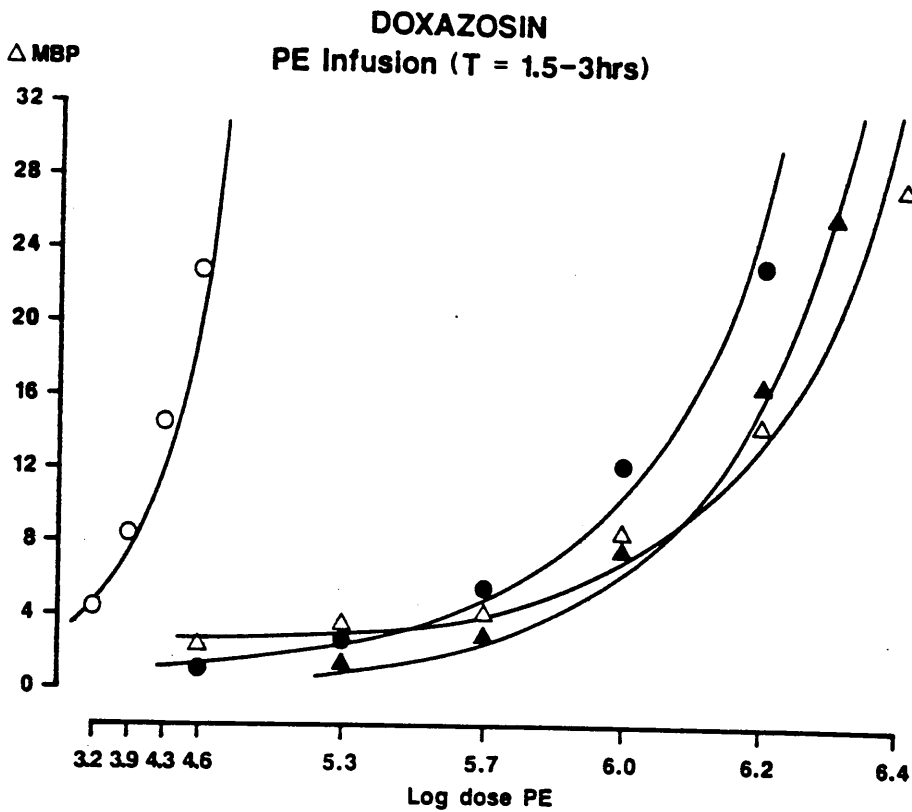
Figure 5.3.
Pressor dose–response curves for phenylephrine in a representative
patient during early (Top) and late (Bottom) infusions after placebo ( O
), 1st dose doxazosin ( ● ) and after 1 week ( △ ) and 6 weeks ( ▲ )
doxazosin treatment.

155

TABLE 5.3

THE EFFECT OF DOXAZOSIN ON PRESSOR RESPONSIVENESS TO
PHENYLEPHRINE (EARLY INFUSION)

$PD_{20}$ (ug/kg/min)

| PATIENT | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---------|---------|----------|--------|---------|
| 1 | 2.0 | 8.0 | 11.2 | 10.1 |
| 2 | 1.8 | 3.3 | 3.1 | 4.6 |
| 3 | 3.7 | 6.5 | 12.3 | 7.0 |
| 4 | 2.0 | 6.6 | 13.4 | 11.8 |
| 5 | 2.2 | 2.7 | 3.8 | 3.3 |
| 6 | 2.0 | 2.5 | 13.3 | 9.7 |
| 7 | 1.6 | 9.9 | 12.6 | 7.0 |
| 8 | 1.3 | 5.0 | 7.4 | 3.1 |
| 9 | 1.7 | 10.3 | 6.8 | 4.1 |
| 10 | 0.9 | 2.7 | 3.0 | 1.5 |
| MEAN ± SD | 1.9± 0.7 | 5.7*± 3.0 | 8.7**± 4.3 | 6.2*x± 3.4 |

Comparison with placebo:  * p < 0.0005
                                 ** p < 0.0001

Comparison with 1 week:   x p < 0.01

TABLE 5.4.

THE EFFECT OF DOXAZOSIN ON PRESSOR RESPONSIVENESS TO
PHENYLEPHRINE (LATE INFUSION)

$PD_{20}$ (ug/kg/min)

| PATIENT | PLACEBO | 1ST DOSE | SHORT DAY (3rd DOSE) | 1 WEEK | 6 WEEKS |
|---------|---------|----------|----------------------|--------|---------|
| 1 | - | - | - | - | - |
| 2 | 1.2 | 5.6 | 5.4 | 5.4 | 5.8 |
| 3 | 2.9 | 4.9 | 9.6 | 4.7 | 7.0 |
| 4 | 0.9 | 5.8 | 13.9 | 12.7 | 10.7 |
| 5 | 0.8 | 2.2 | 2.4 | 3.3 | 3.5 |
| 6 | 1.0 | 3.3 | 11.4 | 3.7 | 5.0 |
| 7 | 2.2 | 5.7 | 14.1 | 12.8 | 8.7 |
| 8 | 1.5 | 3.3 | 9.6 | 5.5 | 5.5 |
| 9 | 0.8 | 2.4 | 5.1 | 10.7 | 3.1 |
| 10 | 1.0 | 1.9 | 3.3 | 5.9 | 1.6 |
| MEAN ± SD | 1.4± 0.7 | 3.9*± 1.6 | 8.3**± 4.4 | 7.2**± 3.8 | 5.6*x± 2.8 |

Comparison with placebo:   * $p < 0.0001$
                          ** $p < 0.00001$

Comparison with 1 week and short study day:   x $p < 0.02$

TABLE 5.5.

THE EFFECT OF DOXAZOSIN ON THE CHANGE IN HR PER UNIT INCREASE
IN SYSTOLIC BP DURING PHENYLEPHRINE INFUSION (EARLY PERIOD)

bpm/mmHg

| PATIENT | PLACEBO | 1st DOSE | 1 WEEK | 6 WEEKS |
|---------|---------|----------|--------|---------|
| 1 | -0.25 | -0.40 | -0.41 | -0.46 |
| 2 | -0.35 | -0.21 | -0.62 | -0.48 |
| 3 | -0.60 | -0.42 | -0.25 | -0.30 |
| 4 | -0.56 | -0.48 | -0.58 | -0.45 |
| 5 | -0.16 | -0.25 | -0.30 | -0.13 |
| 6 | -0.40 | -0.51 | -0.85 | -0.42 |
| 7 | -0.27 | -0.49 | -1.12 | -0.85 |
| 8 | -0.42 | -0.68 | -0.78 | -0.41 |
| 9 | -0.33 | -0.54 | -0.70 | -0.29 |
| 10 | -0.33 | -0.22 | -0.24 | -0.14 |
| MEAN ± SD | -0.37± 0.13 | -0.42± 0.15 | -0.58± 0.29 | -0.39± 0.20 |

158

TABLE 5.6.

THE EFFECT OF DOXAZOSIN ON PRESSOR RESPONSIVENESS
TO ANGIOTENSIN II

$PD_{20}$ (ng/kg/min)

| PATIENT | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---------|---------|----------|--------|---------|
| 1 | 6.1 | 6.9 | 5.5 | 14.1 |
| 2 | 6.2 | 3.6 | 3.7 | 6.7 |
| 3 | 3.2 | 3.6 | 6.6 | 3.5 |
| 4 | 4.6 | 7.1 | 3.9 | 4.1 |
| 5 | 3.0 | 4.1 | 3.3 | 4.0 |
| 6 | 5.3 | 2.6 | 3.3 | 4.3 |
| 7 | 8.1 | 4.2 | 4.3 | 10.3 |
| 8 | 7.4 | 7.4 | 4.1 | 6.1 |
| 9 | 4.0 | 3.8 | 4.3 | 2.6 |
| 10 | 1.0 | 3.3 | 4.2 | 2.9 |
| MEAN ± SD | 4.9± 2.2 | 4.7± 1.8 | 4.3± 1.0 | 5.9± 3.7 |

The apparent increase in half-life with chronic therapy is paralleled by a significant increase in AUC (and thereby a reduction in oral clearance) from $287.2 \pm 104.8$ ng.h.ml$^{-1}$ with acute dosing to $372.6 \pm 136.3$ and $369.4 \pm 133.2$ ng.h.ml$^{-1}$ at 1 and 6 weeks respectively (Table 5.7.). No significant changes in maximum concentration ($C_{max}$) or time to attain $C_{max}$ ($t_{max}$) were observed (Table 5.8.)

There was no relationship between patient age and the pharmacokinetics of doxazosin.


## 5.3.7. Concentration-effect relationships

In individual patients, there was no simple direct relationship between the plasma doxazosin concentration and the fall in blood pressure but in each case following both acute and steady state treatment the kinetic-dynamic relationships were best described by the linear model. Using this model, doxazosin concentrations were well correlated with changes in both systolic and diastolic blood pressure in individual patients and the examples shown in Figures 5.4. and 5.5. illustrate above and below average goodness of fit for changes in systolic blood pressure. Figure 5.6. illustrates the fits for diastolic blood pressure in a representative patient after acute and chronic dosing. The derived m and $K_{eq}$ values for effects on systolic and diastolic blood pressure in individual patients are shown in Tables 5.9. and 5.10.

There was a significant reduction ($p < 0.03$) in the

TABLE 5.7.

DOXAZOSIN PHARMACOKINETICS. DERIVED PARAMETERS. AUC AND
ELIMINATION HALF-LIFE

| Patient | AUC $(ng.n.ml^{-1})$ | | | $t1/2$ (h) | | |
|---|---|---|---|---|---|---|
| | 1st dose | 1 week | 6 weeks | 1st dose | 1 week | 6 weeks |
| 1 | 191.9 | 258.3 | 292.3 | 7.7 | 11.3 | 11.6 |
| 2 | 136.9 | 126.5 | 147.6 | 6.6 | 7.1 | 9.0 |
| 3 | 248.6 | 327.6 | 308.0 | 8.8 | 10.9 | 10.0 |
| 4 | 439.8 | 400.0 | 613.2 | 9.5 | 12.7 | 15.0 |
| 5 | 309.6 | 432.2 | 402.0 | 12.0 | 15.5 | 14.9 |
| 6 | 295.8 | 487.5 | 373.1 | 6.5 | 13.1 | 9.2 |
| 7 | 320.1 | 427.9 | 468.5 | 8.9 | 11.5 | 12.6 |
| 8 | 310.1 | 371.6 | 324.6 | 11.4 | 13.9 | 15.0 |
| 9 | 449.4 | 620.0 | 501.2 | 11.2 | 19.2 | 14.7 |
| 10 | 169.6 | 274.0 | 263.9 | 5.4 | 10.2 | 11.1 |
| MEAN ± SD | 287.2 ± 104.8 | 372.6*± 136.3 | 369.4**± 133.2 | 8.8 ± 2.3 | 12.5**± 3.3 | 12.3**± 2.5 |

Comparison with 1st dose:   \* $p < 0.0015$
\*\* $p < 0.003$

161

TABLE 5.8.

DOXAZOSIN PHARMACOKINETICS.    DERIVED PARAMETERS. $C_{max}$ and $t_{max}$

| Patient | $(\Delta)C_{max}$ (ng/ml) | | | $t_{max}$ (hrs) | | |
| | 1st dose | 1 week | 6 weeks | 1st dose | 1 week | 6 weeks |
|---|---|---|---|---|---|---|
| 1 | 14.7 | 14.3 | 15.9 | 2.1 | 2.0 | 1.9 |
| 2 | 7.5 | 6.6 | 8.4 | 7.5 | 7.0 | 4.4 |
| 3 | 15.9 | 19.6 | 21.2 | 3.1 | 2.9 | 0.8 |
| 4 | 27.8 | 21.0 | 26.5 | 3.0 | 2.5 | 2.6 |
| 5 | 16.1 | 17.9 | 16.0 | 2.1 | 2.3 | 3.9 |
| 6 | 29.0 | 22.8 | 27.3 | 1.1 | 3.6 | 0.7 |
| 7 | 21.6 | 23.8 | 25.5 | 2.5 | 1.8 | 0.4 |
| 8 | 16.1 | 17.8 | 14.5 | 3.1 | 1.2 | 1.6 |
| 9 | 21.7 | 21.0 | 21.1 | 4.7 | 2.6 | 3.2 |
| 10 | 15.9 | 14.2 | 13.0 | 2.9 | 6.2 | 4.1 |
| MEAN SD | 18.6 ± 6.5 | 17.9 ± 5.1 | 18.9 ± 6.4 | 3.2 ± 1.8 | 3.2 ± 1.9 | 2.4 ± 1.5 |

responsiveness to doxazosin during chronic compared with acute administration: for example, the mean responsiveness in terms of the change in systolic blood pressure was -2.1 mmHg/ng/ml following the first dose, -1.5 after 1 week and -1.4 after 6 weeks (Table 5.9). Although, on average, there was a 30% fall in the responsiveness during chronic treatment, for individual patients there was a significant correlation between the responsiveness to the first dose of doxazosin and the responsiveness after 1 week (r = 0.65) and 6 weeks (r = 0.63) treatment (Figure 5.7.). In addition, after both acute and chronic dosing there were significant correlations (p < 0.002) between the responsiveness (m) calculated in terms of change in systolic blood pressure and the responsiveness for effects on diastolic blood pressure (Figure 5.8.). There was no significant change in $K_{eq}$ between the three study days.

There was a trend towards a relationship between the responsiveness to doxazosin after the first dose and the degree of peripheral $alpha_1$ adrenoceptor antagonism (Figure 5.9) but this did not achieve statistical significance (p < 0.055). There was a significant correlation (p < 0.03) between the responsiveness to the first dose of doxazosin and the height of the baseline (pretreatment) blood pressure as illustrated for erect systolic blood pressure in Figure 5.10. In addition there was a significant negative correlation (p < 0.017) between the responsiveness to doxazosin acutely and the placebo-corrected maximal change

163

# PATIENT 6
# DOXAZOSIN
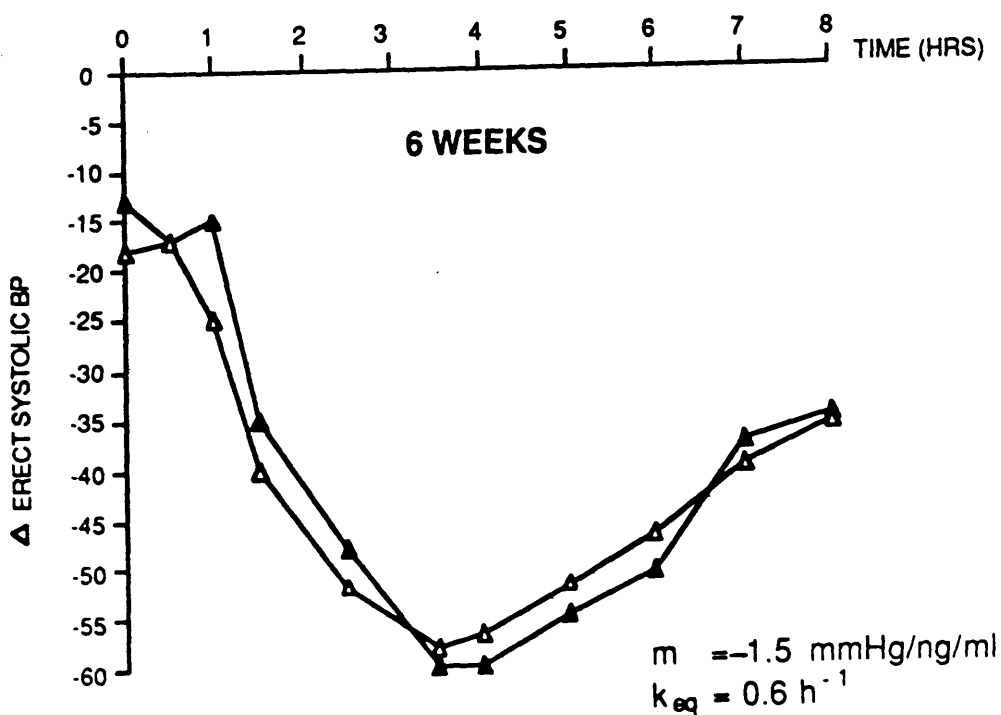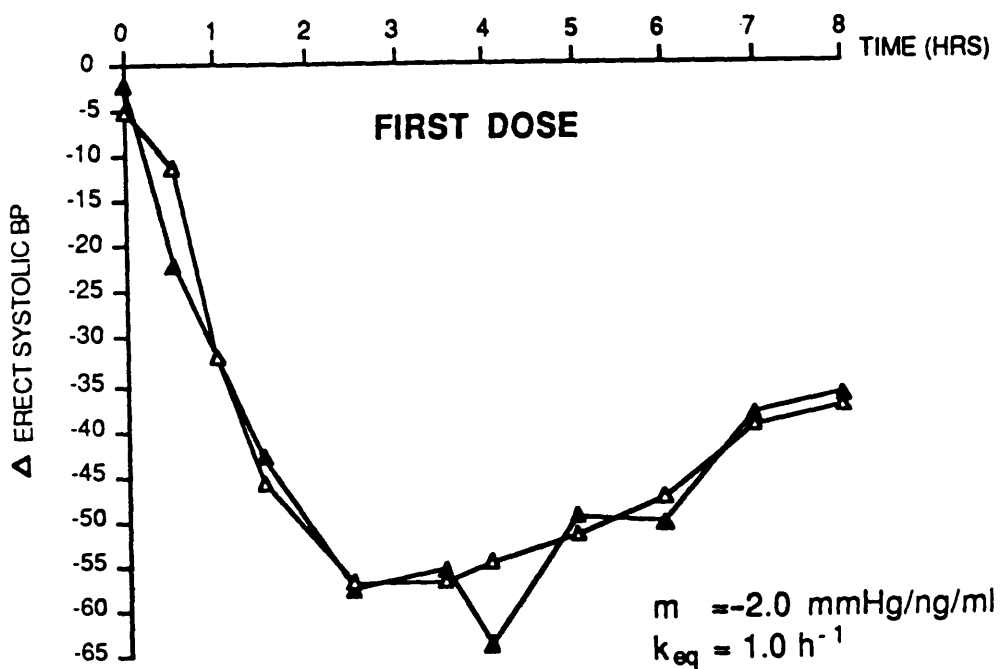


Figure 5.4.
Doxazosin concentration-effect analysis. The observed
( ▲——▲ ) and fitted ( △———△ ) effect of doxazosin on erect
systolic blood pressure after the 1st dose and after 6 weeks in a
representative patient (patient 6), illustrating above average
goodness of fit.

# PATIENT 3
# DOXAZOSIN



**FIRST DOSE**

$m = -2.3$ mmHg/ng/ml
$k_{eq} = 1.6$ h$^{-1}$

**6 WEEKS**

$m = -1.9$ mmHg/ng/ml
$k_{eq} = 0.7$ h$^{-1}$
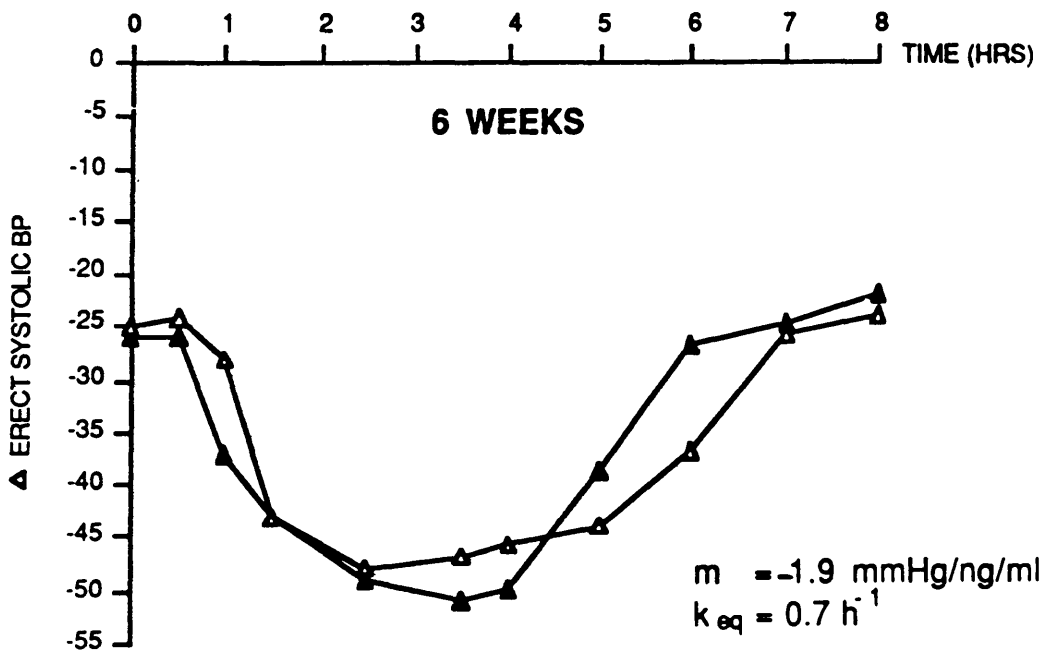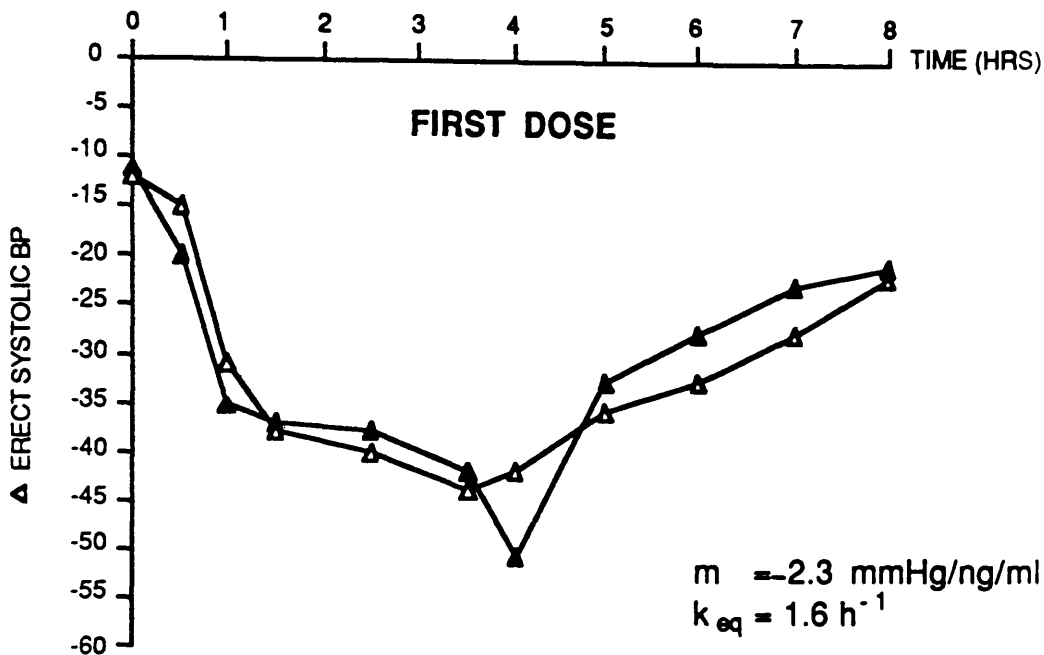
Figure 5.5.
Doxazosin concentration-effect analysis. The observed
( ▲——▲ ) and fitted ( △——△ ) effect of doxazosin on erect
systolic blood pressure after the 1st dose and after 6 weeks in a
representative patient (patient 3), illustrating below average
goodness of fit.

165

# DOXAZOSIN
# PATIENT 3
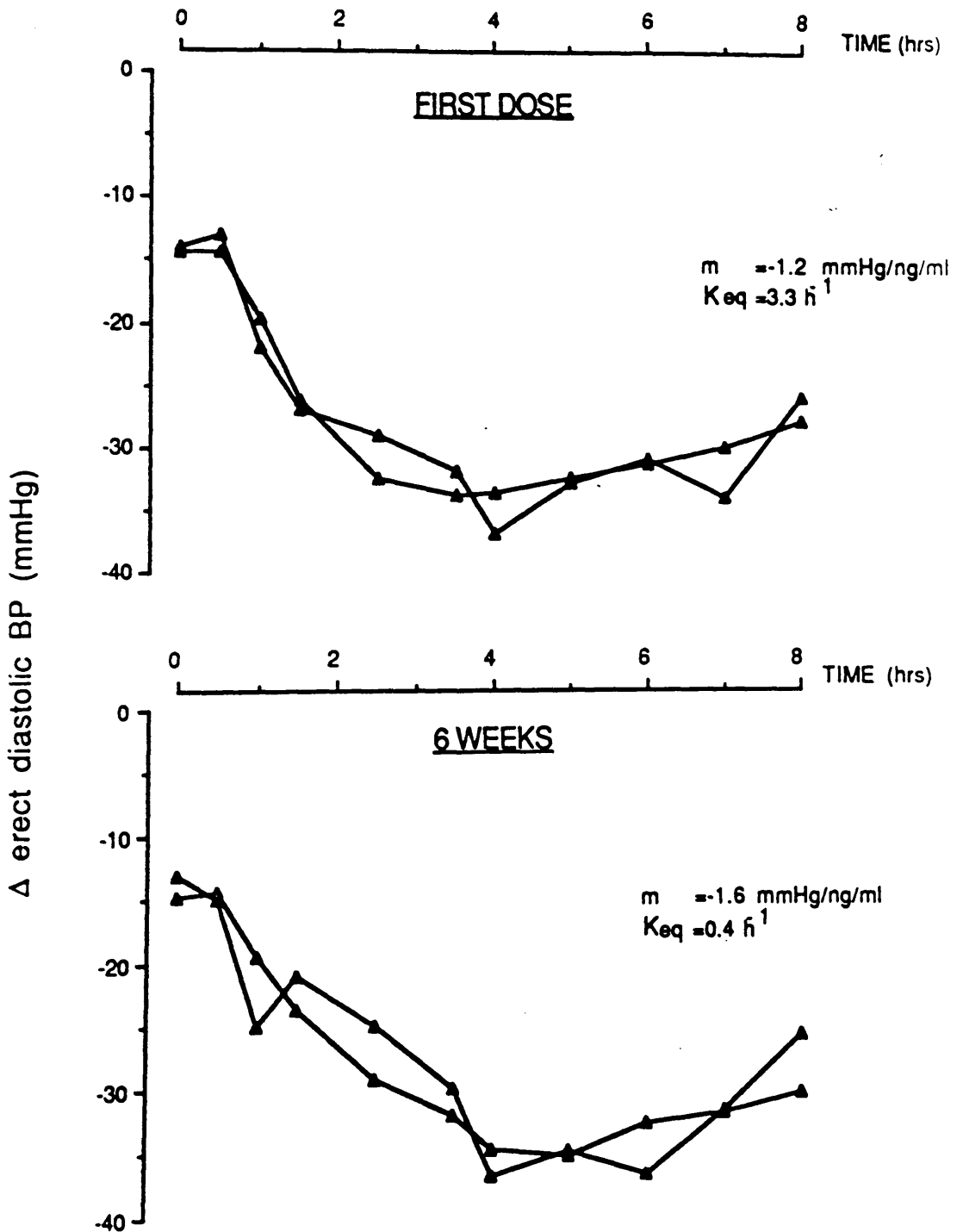


Figure 5.6.
Doxazosin concentration-effect analysis. The observed
( ▲——▲ ) and fitted ( △——△ ) effect of doxazosin on erect
diastolic blood pressure after the 1st dose and after 6 weeks in
a representative patient (patient 3).

166

TABLE 5.9.

DOXAZOSIN CONCENTRATION-EFFECT RELATIONSHIPS.  THE DERIVED
PARAMETERS, m (mmHg/ng/ml) AND $K_{eq}(h^{-1})$, AND THE GOODNESS OF FIT
(R) AS A FRACTION OF UNITY FOR CHANGES IN ERECT SYSTOLIC BP.

| PATIENT | 1ST DOSE | | | 1 WEEK | | | 6 WEEKS | | |
| | m | $K_{eq}$ | R | m | $K_{eq}$ | R | m | $K_{eq}$ | R |
|---|---|---|---|---|---|---|---|---|---|
| 1 | -3.2 | 0.4 | 0.93 | -1.1 | 0.6 | 0.80 | -1.0 | 0.8 | 0.75 |
| 2 | -3.2 | 8.5 | 0.96 | -4.3 | 0.3 | 0.87 | -3.1 | 0.2 | 0.90 |
| 3 | -2.3 | 1.6 | 0.95 | -1.8 | 0.4 | 0.94 | -1.9 | 0.7 | 0.81 |
| 4 | -1.1 | 4.2 | 0.95 | -0.6 | 2.3 | 0.87 | -0.6 | 2.3 | 0.92 |
| 5 | -3.2 | 3.9 | 0.90 | -1.7 | 2.4 | 0.79 | -1.7 | 6.0 | 0.82 |
| 6 | -2.0 | 1.0 | 0.96 | -2.0 | 1.1 | 0.84 | -1.5 | 0.6 | 0.84 |
| 7 | -1.3 | 1.1 | 0.96 | -0.7 | 0.5 | 0.90 | -0.7 | 0.5 | 0.92 |
| 8 | -1.3 | 4.5 | 0.93 | -0.7 | 0.8 | 0.88 | -0.6 | 1.8 | 0.81 |
| 9 | -2.1 | 2.1 | 0.98 | -1.2 | 0.7 | 0.96 | -0.9 | 1.0 | 0.91 |
| 10 | -1.4 | 2.4 | 0.96 | -1.1 | 4.7 | 0.86 | -1.6 | 2.2 | 0.94 |
| MEAN SD | -2.1 ± 0.8 | 3.0 ± 2.4 | 0.95 ± 0.02 | -1.5*± 1.1 | 1.4 1.4 | 0.87 0.05 | -1.4*± 0.8 | 1.6 1.7 | 0.86 ± 0.06 |

Comparison with m (1st dose):  * p < 0.03.

167

TABLE 5.10.

DOXAZOSIN CONCENTRATION-EFFECT RELATIONSHIPS.  THE DERIVED PARAMETERS, m (mmHg/ng/ml) AND $K_{eq}(h^{-1})$, AND THE GOODNESS OF FIT (R) AS A FRACTION OF UNITY FOR CHANGES IN ERECT DIASTOLIC BP.

| PATIENT | 1ST DOSE | | | 1 WEEK | | | 6 WEEKS | | |
| | m | $K_{eq}$ | R | m | $K_{eq}$ | R | m | $K_{eq}$ | R |
|---|---|---|---|---|---|---|---|---|---|
| 1 | -2.2 | 0.3 | 0.89 | -0.6 | 0.8 | 0.97 | -0.7 | 1.0 | 0.91 |
| 2 | -2.2 | 3.1 | 0.98 | -1.0 | 0.7 | 0.74 | -1.9 | 0.2 | 0.92 |
| 3 | -1.2 | 3.3 | 0.95 | -1.1 | 0.4 | 0.95 | -1.6 | 0.4 | 0.91 |
| 4 | -0.9 | 0.6 | 0.96 | -0.5 | 1.2 | 0.94 | -0.4 | 3.8 | 0.81 |
| 5 | -1.6 | 8.3 | 0.96 | -0.6 | 19.7 | 0.92 | -0.8 | 4.1 | 0.88 |
| 6 | -1.2 | 1.3 | 0.93 | -0.6 | 0.7 | 0.89 | -0.7 | 1.0 | 0.98 |
| 7 | -0.9 | 0.6 | 0.90 | -0.7 | 1.8 | 0.94 | -0.6 | 1.0 | 0.92 |
| 8 | -1.1 | 1.8 | 0.98 | -0.8 | 0.9 | 0.83 | -0.8 | 1.0 | 0.97 |
| 9 | -1.9 | 1.0 | 0.90 | -0.6 | 0.6 | 0.85 | -0.5 | 1.2 | 0.77 |
| 10 | -1.1 | 2.6 | 0.90 | -0.7 | 7.3 | 0.91 | -1.2 | 1.0 | 0.96 |
| MEAN SD | -1.4 ± 0.5 | 2.3 ± 2.4 | 0.93 ± 0.03 | -0.7*± 0.2 | 3.4 6.1 | 0.89 0.07 | -0.9*± 0.5 | 1.5 1.3 | 0.90 ± 0.07 |

Comparison with m (1st dose):  * $p < 0.02$.

## CORRELATION BETWEEN THE RESPONSIVENESS TO THE FIRST DOSE OF DOXAZOSIN AND THE RESPONSIVENESS AFTER 6 WEEKS



Figure 5.7.
Correlation between the responsiveness (m) to the 1st dose of doxazosin and the responsiveness after 6 weeks.

## CORRELATION BETWEEN THE RESPONSIVENESS
## IN TERMS OF SYSTOLIC AND DIASTOLIC B.P.
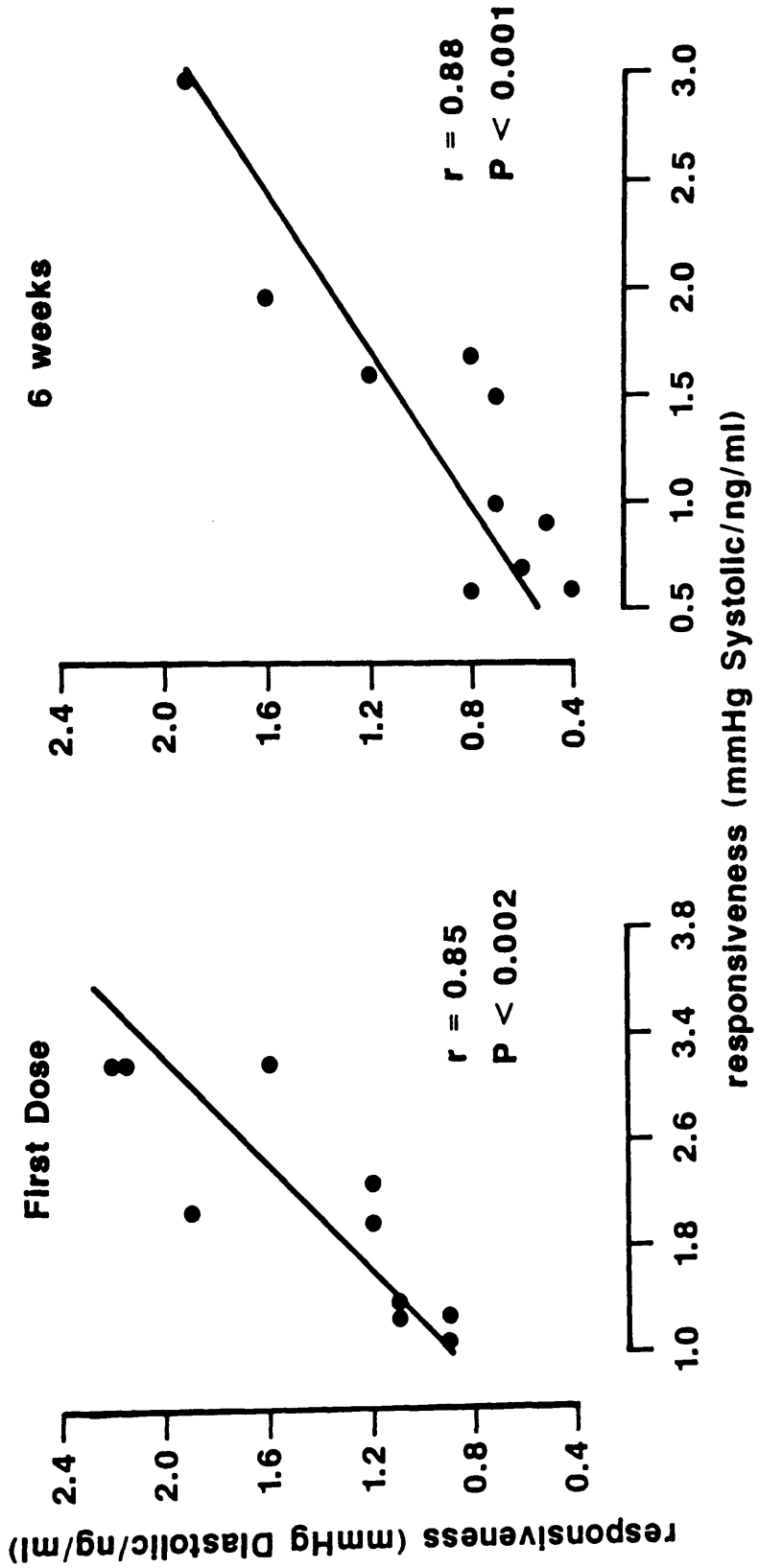
**Figure 5.8.**
Correlations between the responsiveness to doxazosin in terms of
systolic versus diastolic blood pressure after the 1st dose and
after 6 weeks.

# RESPONSIVENESS VERSUS PE DOSE RATIO
## FIRST DOSE DOXAZOSIN

**PE Dose Ratio**
**(late period)**



r = 0.66

P < 0.055 (NS)

**Responsiveness (mmHg/ng/ml)**
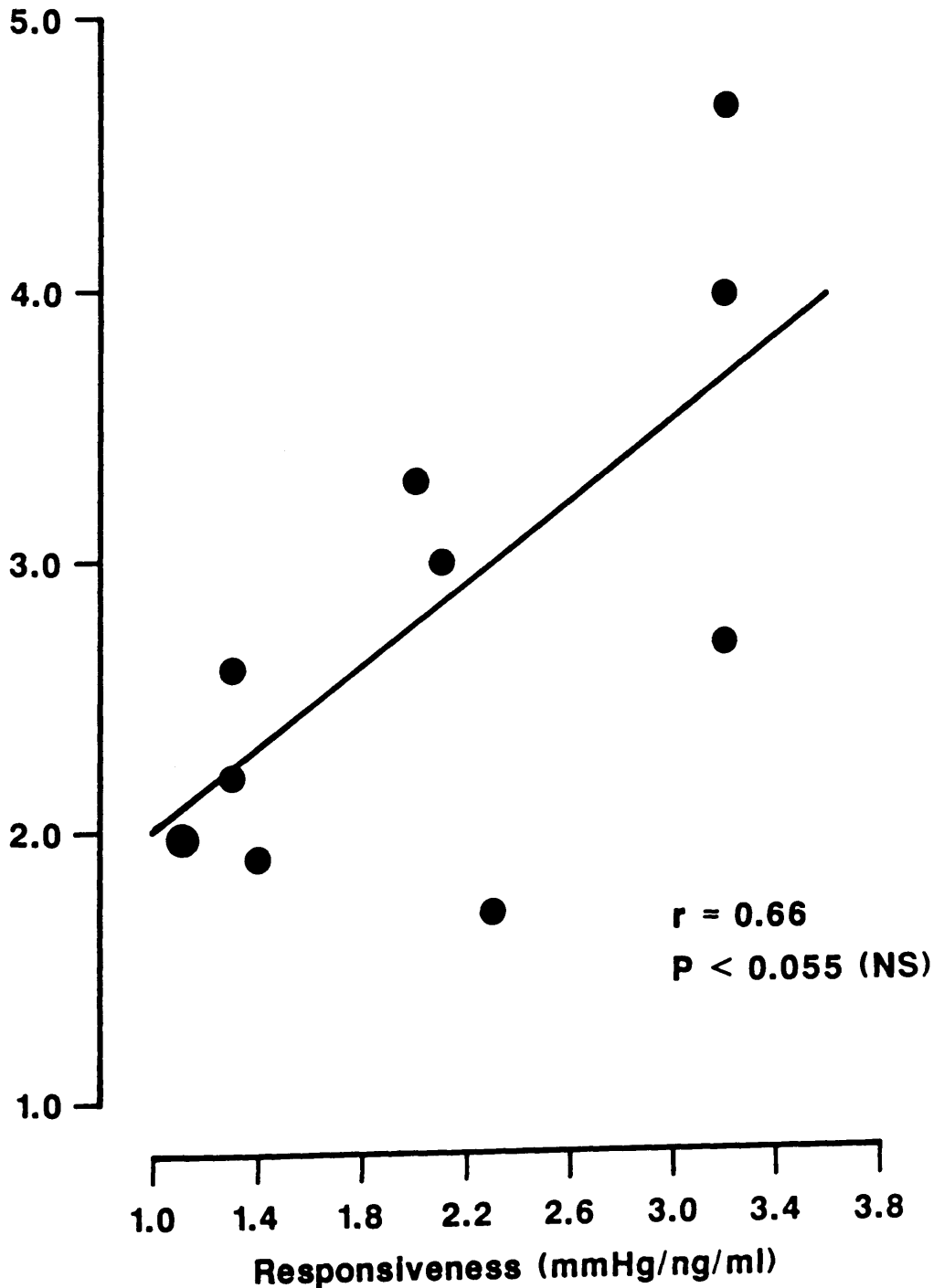
Figure 5.9.
Relationship between the responsiveness to the 1st dose of
doxazosin and the degree of peripheral alpha blockade (i.e. the
phenylephrine dose ratio). Not significant.

# RESPONSIVENESS VERSUS STARTING BLOOD PRESSURE
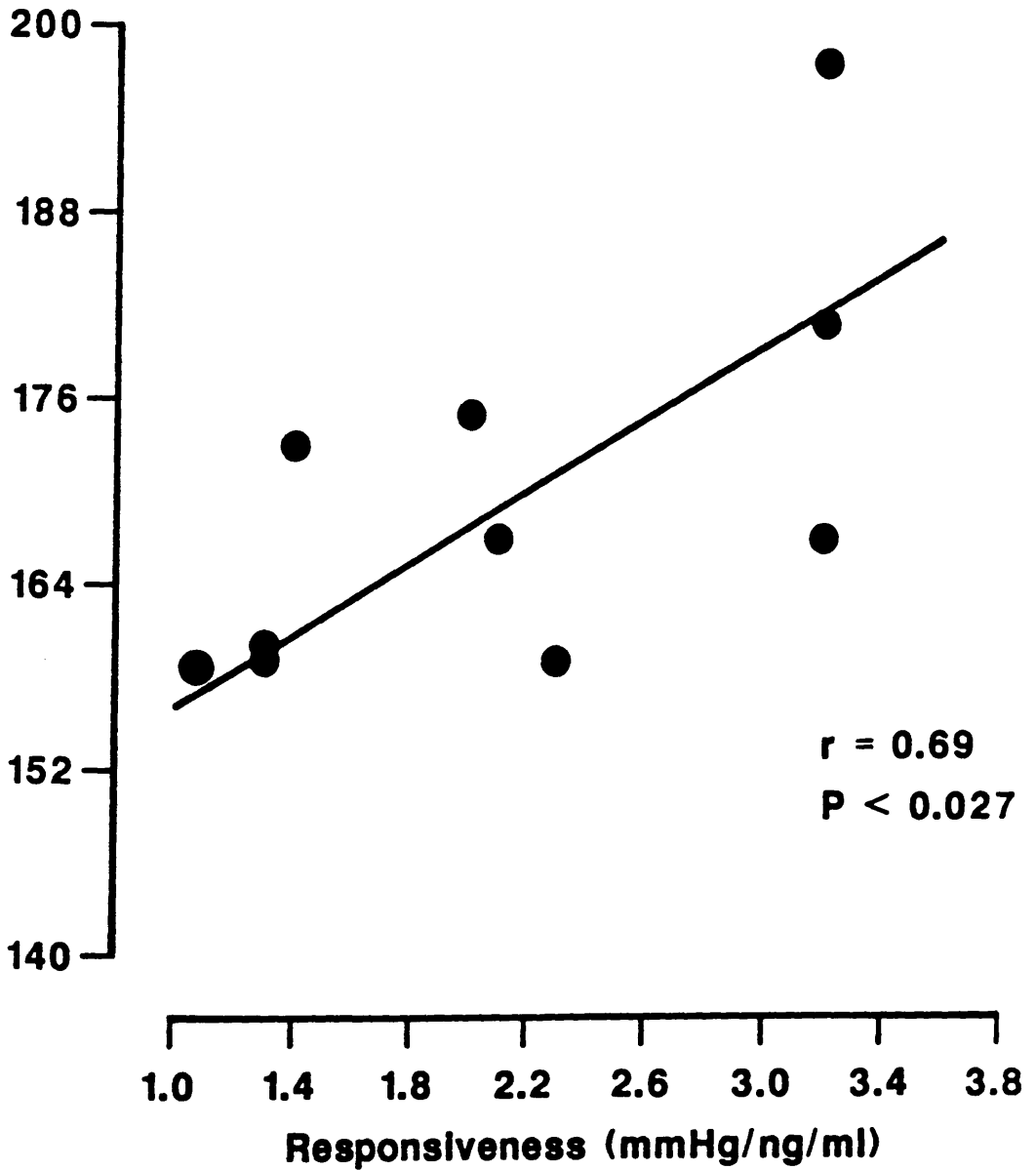


Figure 5.10.
Correlation between the responsiveness to the 1st dose of doxazosin and the pretreatment (baseline) systolic blood pressure.

## RESPONSIVENESS VERSUS THE MAXIMAL (PLACEBO SUBTRACTED) CHANGE IN HR

△Erect HR (bpm)

r = 0.73
P < 0.017

Responsiveness (mmHg/ng/ml)
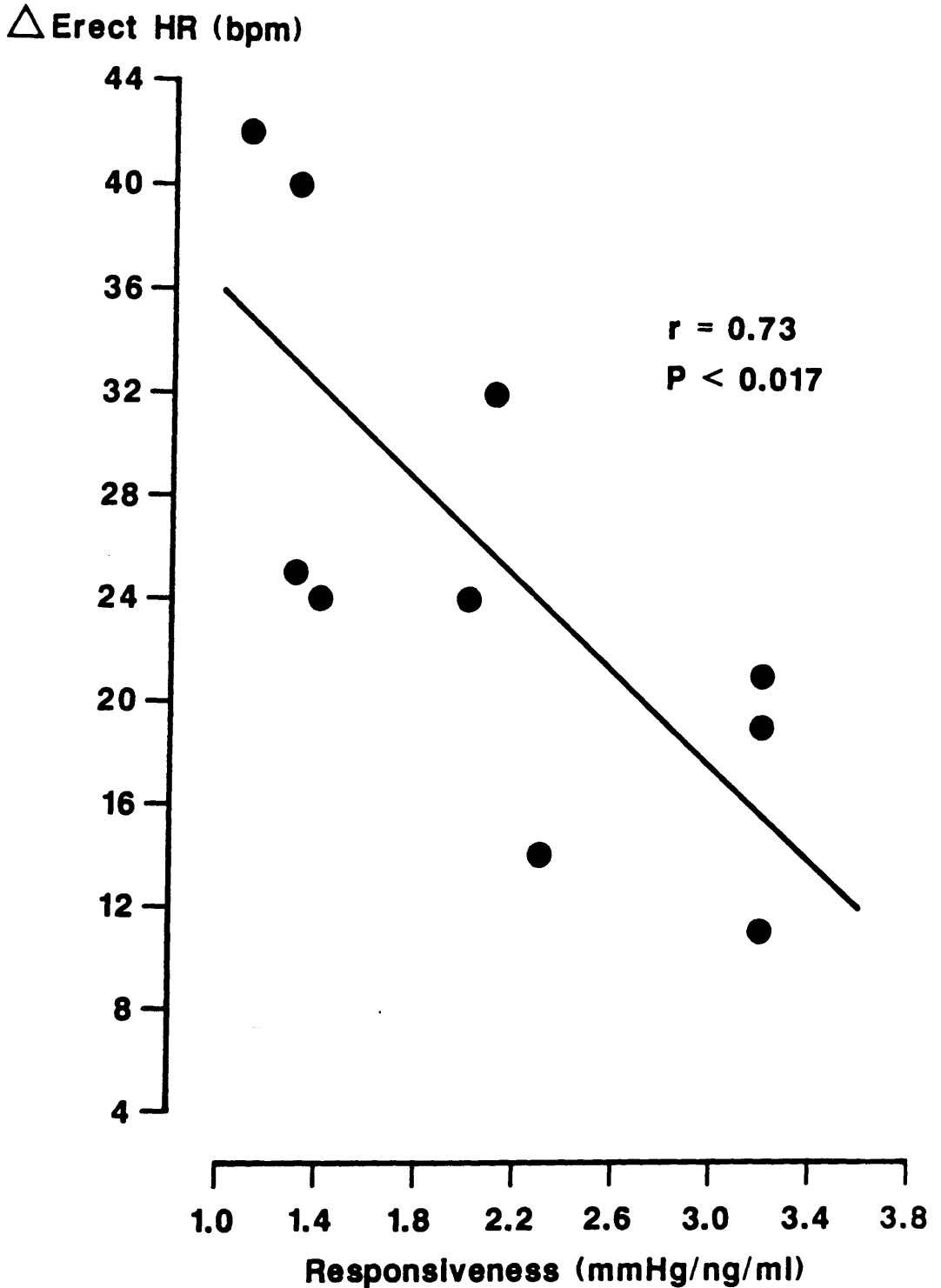
Figure 5.11.
Negative correlation between the responsiveness to the 1st dose
of doxazosin and the maximal (placebo and baseline-subtracted)
change in erect heart rate.

# DOXAZOSIN
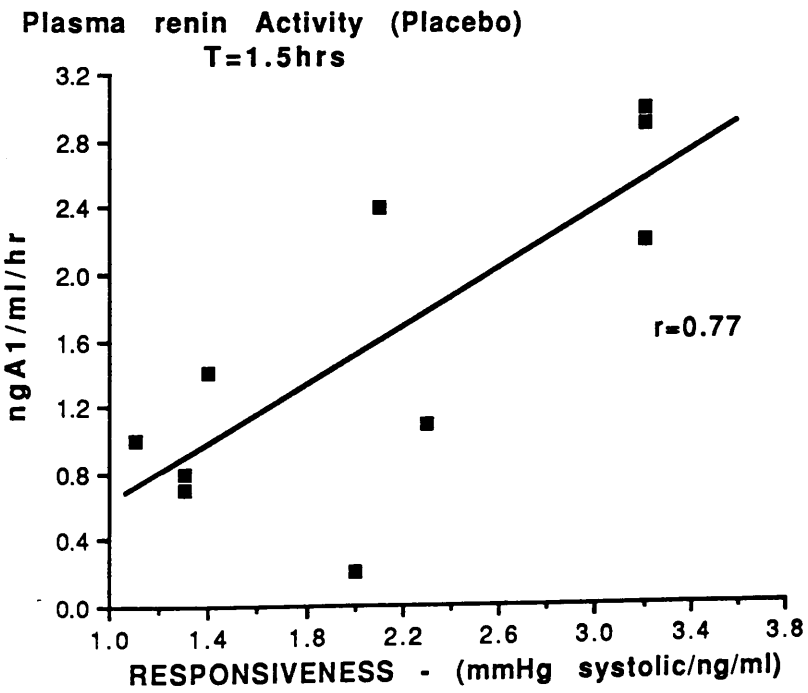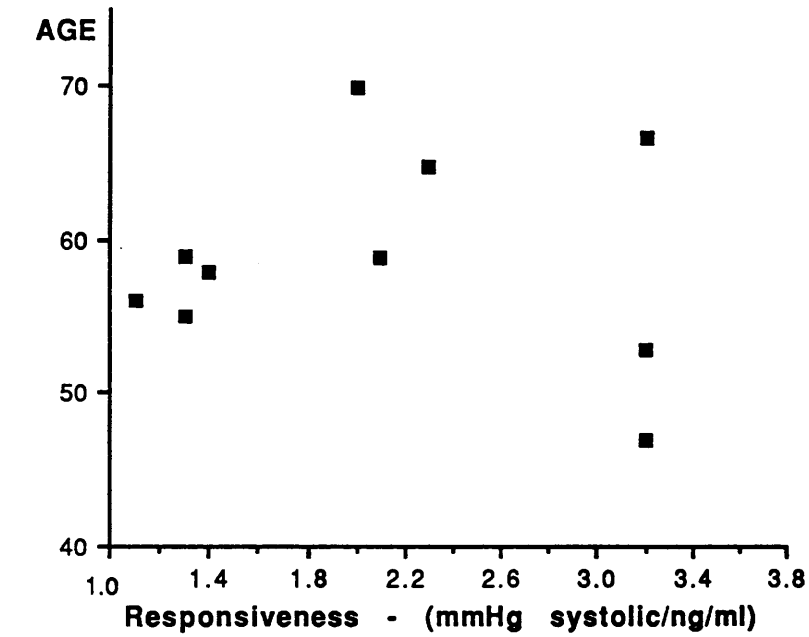




Figure 5.12.
Relationship between age and responsiveness to doxazosin, and the positive correlation between responsiveness and pretreatment plasma renin activity.

in heart rate (Figure 5.11.). There was no relationship between the responsiveness to doxazosin and patient age (Figure 5.12.), but there was a significant positive correlation between responsiveness and the pretreatment plasma renin activity (i.e. on placebo) - Figure 5.12.


DISCUSSION

It has been well established that doxazosin lowers blood pressure (Baez et al, 1986; Frick et al, 1986; Shionoiri et al, 1987) and this study has confirmed that the antihypertensive effect during longterm treatment is sustained for 24-hours with a dosage regimen of 2 mg once daily. After 6 weeks treatment predose blood pressures (recorded 24 hours after the last dose) were significantly reduced: 157/95 (supine) compared with 175/105 mmHg following placebo and blood pressure control was particularly good during the 8 hours of the study day, on average 140/85 supine and 135/84 erect.

For the purposes of this study the dose of doxazosin was fixed at 2 mg. This is larger than the starting dose of 0.5 mg recommended for routine clinical use and, although doxazosin was generally well tolerated throughout the study, the gradual onset of antihypertensive effect did not avert symptoms of first-dose orthostatic hypotension in 4 patients at 5-6 hours after drug administration. Adverse effects after the first dose of an alpha$_1$ antagonist are partly dose dependent (Rosendorff, 1976) and in routine clinical

practice the lower starting dose of 0.5 mg doxazosin appears to be better tolerated (Cox et al, 1986).

The pharmacokinetic profile of doxazosin is compatible with a single daily dosage regimen (Elliott et al, 1987) and in this study the relatively long half-life of 12 hours is consistent with the 24 hour blood pressure control. There was a significant increase in the elimination half life and AUC of doxazosin during chronic compared with acute administration. Similar reductions in drug clearance during chronic doxazosin treatment have been described by others (Shionoiri et al, 1987) and also were reported in a study that sampled drug levels for up to 72 hours after dosing (Cubeddu et al, 1987). The explanation for this apparent reduction in clearance is uncertain. In part it may reflect the schedule of sampling times and achieved plasma concentrations after the first dose but additionally it may reflect saturation of hepatic metabolic enzyme activity since doxazosin is extensively metabolised in the liver (Kaye et al, 1986). There is some evidence with prazosin which undergoes metabolism by the same demethylation pathway that age and the presumptive decline in hepatic function leads to a significant change in drug disposition (Rubin et al, 1981). This has not been a consistent finding (McNeil et al, 1987) and in this relatively small study there was no relationship between age and the pharmacokinetics of doxazosin.

The pharmacodynamic profile of doxazosin, in contrast

to that of prazosin (Seideman et al, 1981), is clearly out of phase with plasma drug levels and therefore no simple direct relationship exists between plasma concentration and the fall in blood pressure (Elliott et al, 1982; Cubeddu et al, 1987). With prazosin, consistent concentration-effect relationships have been identified after acute intravenous dosing (Bateman et al, 1979; Seideman et al, 1981; La Rochelle et al, 1982) but studies of oral dosing, particularly where group data have been analysed, have been less successful (MacCarthy et al, 1980; Grahnen et al, 1981). With doxazosin, Vincent et al (1983) defined concentration-effect relationships in individual subjects for both blood pressure reduction and alpha antagonism and this study has extended these observations to chronic oral treatment in hypertensive patients. In addition, by integrating kinetic and dynamic information the responsiveness of individual patients was characterised in terms of the fall in both systolic and diastolic blood pressure per unit drug concentration.

There was a significant reduction (of approximately 30%) in the responsiveness (m) to doxazosin during chronic compared with acute administration and this was accompanied by an attenuation in the $alpha_1$ adrenoceptor antagonist activity after 6 weeks. Tolerance to the alpha-blocking effect of prazosin has been well documented in cardiac failure (Desch et al, 1979) and there is evidence that adaptive changes in alpha adrenoceptor-mediated responses

occur within a few days (von Bahr et al, 1982) but the nature of the underlying changes in alpha$_1$ adrenoceptor function have not been clearly established (Lefkowitz, 1978; Hamilton and Reid, 1981; von Bahr et al, 1982). It has been suggested that "tolerance" reflects desensitisation of alpha$_1$ receptors and that this may be enhanced by acute rises in catecholamine levels (von Bahr et al, 1982). In this study kinetic differences did not invalidate pressor response comparisons and alpha blockade was maximal during the first week, particularly on the short study day and after 7 days when reflex sympathetic responses were abating. The attenuation in alpha$_1$ antagonist activity after 6 weeks may reflect up-regulation of alpha$_1$ adrenoceptor function during longterm doxazosin treatment as a result of increased receptor density (Lefkowitz, 1978) or changes in post-receptor mechanisms (Hamilton and Reid, 1981).

Despite the reduction during chronic treatment in antihypertensive responsiveness to doxazosin and the changes in the extent of alpha blockade, there were significant correlations between the responsiveness to the first dose and that after 1 week and 6 weeks treatment. This has potential clinical application in that the response to the first dose, for an individual patient, may be used to forecast the response during longterm treatment and thereby allow prompt identification of poor or non-responders.

Very little is known about factors which determine the response to treatment with an alpha blocker (Stokes et al,

1980; MacCarthy et al, 1980) but kinetic as well as dynamic parameters are important. The fall in blood pressure is related to antagonism of alpha$_1$ adrenoceptors in the peripheral vasculature but, acutely, reflex increases in heart rate tend to counteract the fall in blood pressure and if the heart rate response is attenuated, for example with a beta-adrenoceptor antagonist, the acute hypotensive effect of prazosin is enhanced (Elliott et al, 1981). In this study there was a significant negative correlation between the responsiveness to the first dose of doxazosin and the maximal reflex increase in heart rate. Although it has been reported that alpha$_1$ antagonists produce greater haemodynamic effects in the elderly (Stokes, 1984) this is not a confirmed observation and it takes no account of possible age-related differences in pharmacokinetics (Rubin et al, 1981; McNeil et al, 1987). In this study, albeit across a relatively narrow age range, there was no relationship between age and the fall in blood pressure per unit drug concentration. There is some evidence that the antihypertensive effect of prazosin is inversely related to plasma renin activity (Bolli et al, 1981), but in this study there was an opposite relationship whereby responsiveness to doxazosin was directly proportional to the pretreatment PRA. The explanation for this is not entirely clear but activation of the renin-angiotensin-aldosterone system may indirectly reflect enhanced sympathetic nervous activity and increased alpha adrenoceptor mediated vasoconstriction, and

such haemodynamic changes in hypertension are reported to be particularly responsive to treatment with alpha adrenergic inhibitory drugs (Taylor, 1982).

Starting blood pressure may be a more important determinant of the magnitude of the response to treatment with an alpha blocker (Sumner et al, 1988a) and in this study there was a significant correlation between the responsiveness to doxazosin acutely and the pretreatment systolic pressure.

In conclusion, the pharmacokinetic and pharmacodynamic profiles of doxazosin are consistent with 24 hour blood pressure control using a single daily dosage regimen. Concentration-effect relationships have been identified in individual patients for both systolic and diastolic blood pressure after acute and chronic treatment. The responsiveness to doxazosin is related to its $alpha_1$ adrenoceptor antagonist activity and both these parameters are significantly attenuated during continued treatment. However, the attenuation in responsiveness probably occurs early and is not progressive during chronic therapy. Thus, the predictability of the longterm response to doxazosin (albeit 70% magnitude) from the response to the first dose appears to be independent of treatment duration.
The responsiveness to the first dose is dependent upon the pretreatment blood pressure and the degree of reflex sympathetic activation, particularly the heart rate increase, while plasma renin activity may be an additional

contributory factor. The inter-relationship between these
variables and the responsiveness to doxazosin is considered
in further detail in Chapter 8.

CHAPTER 6

VASCULAR PRESSOR RESPONSES IN TREATED AND UNTREATED

ESSENTIAL HYPERTENSION

## 6.1. INTRODUCTION

In essential hypertension structural (Folkow, 1978) and functional (Robinson et al, 1982; Buhler and Bolli, 1985) changes in vascular smooth muscle are associated with an increase in total peripheral resistance (Lund-Johansen, 1986) and enhanced vascular reactivity (Folkow, 1982; Buhler and Bolli, 1985). There is evidence to suggest that the increased vascular reactivity reflects an increased responsiveness to both adrenergic (Amann et al, 1981; Buhler et al, 1981) and non-adrenergic (Robinson et al, 1980) calcium-dependent vasoconstrictor mechanisms. Accordingly, it has been suggested that, independent of vasodilatation per se, reduction of peripheral vascular reactivity is an important mechanism for antihypertensive drugs (Imai et al, 1982a; Elliott et al, 1985; Pasanisi et al, 1985).

Reduction of peripheral vascular resistance underlies the antihypertensive activity of calcium antagonists (Robinson et al, 1980), angiotensin converting enzyme (ACE) inhibitors (Velasco et al, 1985) and $alpha_1$-adrenoceptor antagonists (Lund-Johansen et al, 1986) but differences in their effects on adrenergic and non-adrenergic vascular responses and on neuro-humoral mechanisms, including cardiovascular baroreflex responses, have not been clearly established.

This study in patients with essential hypertension examines the effects of the calcium antagonist nifedipine, the ACE inhibitor enalapril and the $alpha_1$ antagonist

doxazosin on vascular pressor responses to the "adrenergic"
agonist phenylephrine and the "non-adrenergic"
vasoconstrictor angiotensin II.


6.2.   METHODS

6.2.1. General

Thirty-seven patients with essential hypertension
(17M, 20F), age range 33-70 years, participated in one of
the three studies described in Chapters 3-5.  Each patient
discontinued any previous medication prior to entering the
study and at the end of a 6 week drug-free run-in period the
mean supine blood pressure was 181/104 $\pm$ 14/6 mmHg.  In a
series of single blind studies matching placebo tablets were
then administered for 2 weeks, followed by nifedipine retard
20 mg bid (n=14; 52 $\pm$ 9 years), or enalapril 20 mg od (n=13;
55 $\pm$ 8 years), or doxazosin 2 mg od (n=10; 59 $\pm$ 7 years).
Each active treatment was administered as monotherapy for 6
weeks and patients attended for a sequence of 4 study days
to evaluate the effects of placebo, first dose of active
drug and after 1 and 6 weeks drug treatment.  At frequent
intervals during each study day blood pressure and heart
rate were measured and venous blood samples collected for
plasma drug concentrations (Chapter 2.1.).  Additional
blood samples were taken at 1.5 hours after drug
administration for plasma renin activity, aldosterone,
catecholamines and ACE activity.

## 6.2.2. Peripheral vascular pressor responsiveness.

On each study day, between 1.5-3 hours after drug administration, pressor responses to intravenous infusions of the selective alpha$_1$-adrenoceptor agonist phenylephrine (PE) and the non-adrenergic vasoconstrictor angiotensin II (AII) were measured using the protocol described in Chapter 2.2.

All data points in each individual patient for the pressor responses to phenylephrine and angiotensin II were fitted to a quadratic function according to the method of Sumner et al (1982). The simultaneous blood pressure and heart rate changes during the infusion of PE were fitted in individual patients to a linear function and used as an index of cardiovascular baroreflex activity, expressed as the change in heart rate per unit increase in systolic blood pressure.


## 6.2.3. Statistical analysis

From each individual pressor dose-response curve the PD$_{20}$ value was derived: this represents the dose of agonist required to raise mean arterial pressure by 20 mmHg. The logarithmic transformations of the PD$_{20}$ values were compared within studies over the period of treatment using repeated measures analysis of variance. As a quantitative index of the extent of the pressor antagonist effect of each treatment dose ratios were calculated from the ratio PD$_{20}$ active drug/PD$_{20}$ placebo and comparison between studies was

again by analysis of variance. The relationship between age and changes in pressor sensitivity was investigated by linear regression analysis. The derived measurements of baroreflex function expressed as the change in heart rate per unit increase in systolic blood pressure, were compared between studies by repeated measures analysis of variance.


## 6.3. RESULTS

### 6.3.1. Blood Pressure

Nifedipine, enalapril and doxazosin produced significant reductions in blood pressure and at the doses used appeared overall to have comparable antihypertensive activity. Similar blood pressure-time profiles were obtained in the three studies with the maximum antihypertensive effects occurring 5-6 hours after drug administration (Figure 6.1.). In particular, blood pressures on equivalent study days, immediately before the start of the pressor infusions, were not significantly different: for example, supine blood pressure at 1.5 hours after the first dose of nifedipine was 153/93 ± 16/8; after enalapril, 151/90 ± 24/10 and after doxazosin 148/90 ± 19/3 mmHg. Similarly, blood pressures at 1.5 hours on the corresponding placebo days were not significantly different: 175/104 ± 17/6, 171/99 ± 18/9 and 166/99 ± 13/9 mmHg respectively.

During chronic treatment'there were comparable reductions in baseline (pre-dose) blood pressures in each

study:  for example, predose supine blood pressures after 6
weeks were 152/93 ± 15/7 (nifedipine), 157/94 ± 18/12
(enalapril) and 157/95 ± 17/8 mmHg (doxazosin).


## 6.3.2. Heart rate

There was no significant change in heart rate following
the first dose of enalapril but the first doses of both
nifedipine and doxazosin produced significant increases in
supine and erect heart rate.  For nifedipine, erect heart
rate increased from a baseline of 87 ± 13 to a maximum of
108 ± 14 bpm 5 hours after the first dose, compared with a
change from 86 ± 14 to 94 ± 12 bpm following placebo
(Figure 3.2.).  The corresponding maximal changes in
heart rate for doxazosin were 79 ± 10 to 100 ± 11 bpm at 5
hours, compared with 79 ± 13 to 84 ± 12 bpm after placebo
(Figure 5.2.).  During longterm treatment none of the
active drugs produced heart rate profiles which were
significantly different from placebo.


## 6.3.3. Pressor responsiveness

Nifedipine significantly attenuated the pressor
responses to both AII and PE (Tables 6.1. and 6.2.) with
non-parallel rightward shifts of the respective dose-
response curves, as illustrated for a representative
patient in Figure 6.2.  The mean $PD_{20}$ for responses to
AII (ng/kg/min) increased progressively from 8.2 (placebo)
to 9.9 (1st dose), 13.9 (1 week) and 17.4 (6 weeks).  The
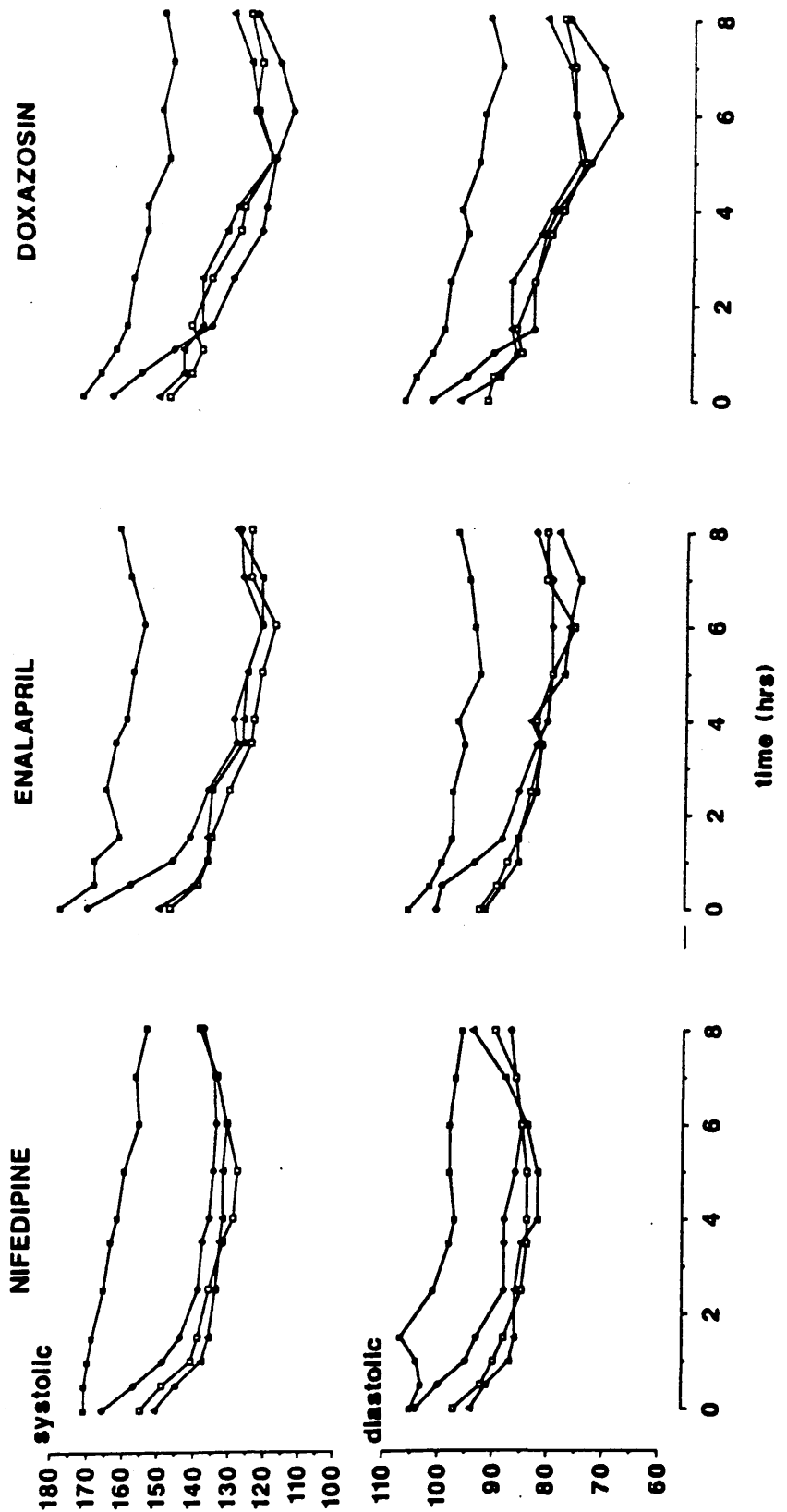
**Figure 6.1.**
Mean profiles of systolic and diastolic blood pressure for each
study after placebo ( ■ ), 1st dose active drug ( ◆ ) and after
1 week ( □ ) and 6 weeks ( ▲ ) drug treatment.

increase in $PD_{20}$ after 6 weeks nifedipine was significantly greater than that following the first dose (Table 6.1.). The attenuating effect of nifedipine on pressor responsiveness to PE was of similar magnitude but was unaffected by treatment duration (Table 6.2.): 1.9 (placebo), 2.8 (1st dose), 3.2 (1 week) and 2.9 ug/kg/min (6 weeks).

In contrast, there were non-parallel shifts of the dose-response curves to the left following enalapril, indicative of enhanced responsiveness to both AII and PE (Figure 6.3.). There were significant reductions in $PD_{20}$ values for AII and PE pressor responses (Tables 6.3. and 6.4.): for example, from 9.7 (placebo) to 6.7 ng/kg/min (6 weeks) for AII (Table 6.3.) and from 2.1 (placebo) to 1.5 ug/kg/min (6 weeks) for PE (Table 6.4.)..

The selective alpha antagonist doxazosin had no effect on pressor responses to AII (Table 5.6.) but was associated with significant parallel rightward shifts of the pressor dose-response curves to PE (Figure 5.3.). The mean $PD_{20}$ increased from 1.9 (placebo) to 5.7 (1st dose), 8.7 (1 week) and 6.2 ug/kg/min after 6 weeks (Table 5.3.). There was a significant reduction in alpha blockade after 6 weeks doxazosin compared with that after 1 week.

For both AII and PE there was no relationship between age and pressor responsiveness ($PD_{20}$) before active treatment i.e. on placebo. Similarly, there was no relationship between age and the pressor responses during

TABLE 6.1.

EFFECT OF NIFEDIPINE ON PRESSOR RESPONSIVENESS TO ANGIOTENSIN II

$PD_{20}$ VALUES (ng/kg/min)

| PATIENT | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---------|---------|----------|--------|---------|
| 1 | 5.3 | 11.4 | 28.0 | 43.8 |
| 2 | 7.0 | 7.0 | 16.6 | 11.1 |
| 3 | 5.8 | 13.6 | 10.8 | 5.0 |
| 4 | 6.1 | 6.8 | 13.7 | 11.6 |
| 5 | 4.7 | 4.4 | 3.3 | 6.7 |
| 6 | 4.7 | 3.6 | 7.3 | 6.7 |
| 7 | 30.2 | 24.1 | 13.5 | 20.9 |
| 8 | 16.6 | 12.8 | 16.7 | 17.5 |
| 9 | 3.5 | 6.1 | 7.5 | 5.7 |
| 10 | 3.9 | 6.3 | 7.1 | 12.9 |
| 11 | 6.5 | 18.0 | 26.0 | 28.6 |
| 12 | 6.9 | 3.5 | - | 3.6 |
| 13 | 9.8 | 11.0 | 17.9 | 33.1 |
| 14 | 4.1 | 10.1 | 12.7 | 36.6 |
| Mean ± SD | 8.2 ± 7.1 | 9.9[*] ± 5.9 | 13.9[*] ± 7.2 | 17.4[**][x] ± 13.2 |

* p < 0.05   ** p < 0.01   x comparison with 1st dose p < 0.02.

190

TABLE 6.2.

EFFECT OF NIFEDIPINE ON PRESSOR RESPONSIVENESS TO PHENYLEPHRINE

$PD_{20}$ VALUES (ug/kg/min)

| PATIENT | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---------|---------|----------|--------|---------|
| 1 | 1.3 | 1.0 | 2.9 | 2.5 |
| 2 | 0.8 | 1.2 | 2.8 | 2.0 |
| 3 | 0.7 | 1.0 | 1.8 | 1.4 |
| 4 | 0.7 | 1.0 | 2.0 | 2.4 |
| 5 | 2.1 | 1.9 | 2.0 | 1.2 |
| 6 | 1.6 | 1.8 | 2.6 | 3.3 |
| 7 | 1.7 | 2.8 | 2.6 | 2.6 |
| 8 | 3.8 | 5.0 | 5.1 | 3.9 |
| 9 | 1.4 | 4.5 | 2.6 | 3.0 |
| 10 | 0.9 | 2.3 | 2.6 | 1.7 |
| 11 | 4.9 | 6.9 | 7.0 | 5.3 |
| 12 | 1.9 | 1.0 | - | 4.1 |
| 13 | 1.9 | 4.2 | 4.6 | 2.4 |
| 14 | 2.5 | 3.9 | 2.7 | 4.8 |
| Mean ± SD | 1.9 ± 1.2 | 2.8* ± 1.9 | 3.2* ± 1.5 | 2.9* ± 1.2 |

\* $p < 0.05$     ** $p < 0.01$
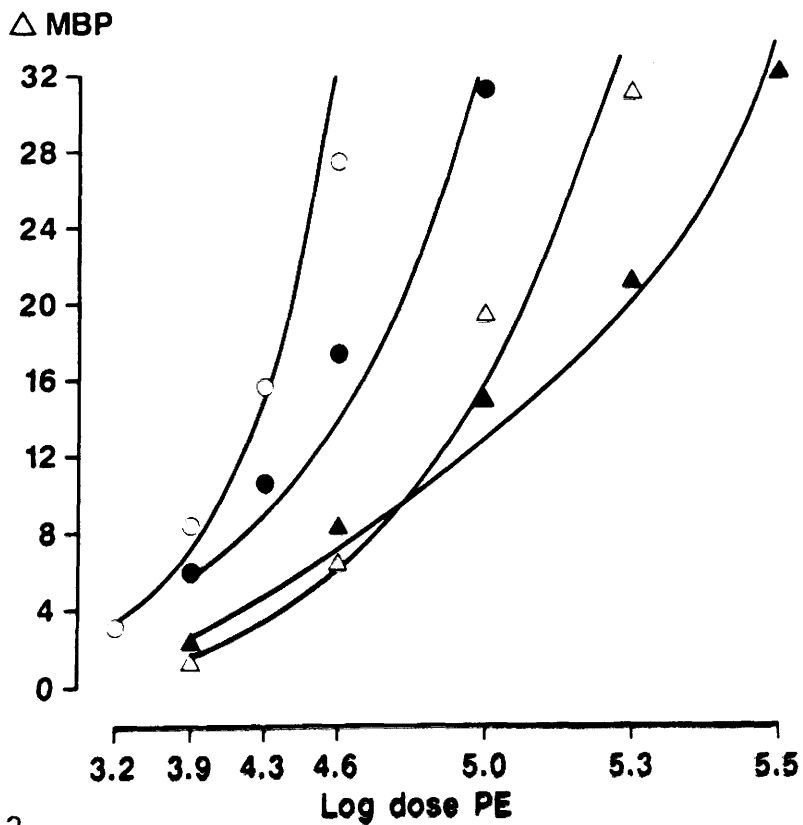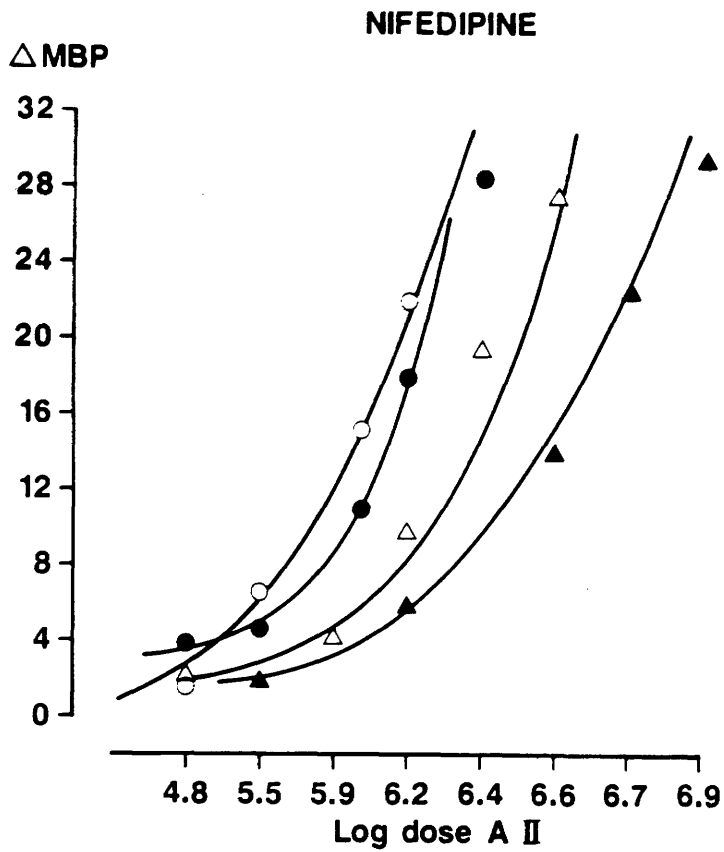
**NIFEDIPINE**

**Figure 6.2.**
Pressor dose-response curves for angiotensin II (Top) and
phenylephrine (Bottom) in a representative patient following
placebo ( O ), 1st dose nifedipine ( ● ) and after 1 week
( △ ) and 6 weeks ( ▲ ) nifedipine treatment.

TABLE 6.3.

EFFECT OF ENALAPRIL ON PRESSOR RESPONSIVENESS TO ANGIOTENSIN II

$PD_{20}$ VALUES (ng/kg/min)

| PATIENT | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---------|---------|----------|--------|---------|
| 1 | 13.3 | 4.5 | 10.8 | 6.9 |
| 2 | 22.8 | 13.2 | 9.5 | 15.3 |
| 3 | 4.8 | 8.9 | 3.7 | 6.3 |
| 4 | 3.1 | 3.8 | 1.9 | 6.0 |
| 5 | 4.3 | 2.5 | 2.8 | 3.3 |
| 6 | 11.7 | 7.5 | 3.6 | 7.2 |
| 7 | 8.9 | 7.4 | - | 4.9 |
| 8 | 5.0 | 4.4 | 4.3 | 6.3 |
| 9 | 2.9 | 3.1 | 2.3 | 2.5 |
| 10 | 18.8 | 13.1 | 11.1 | 14.4 |
| 11 | 4.1 | 3.2 | 3.4 | 2.3 |
| 12 | 18.5 | 11.1 | 6.2 | 6.8 |
| 13 | 8.1 | 8.2 | 7.1 | 4.7 |
| Mean ± SD | 9.7 ± 6.8 | $7.0^{*}$ ± 3.8 | $5.5^{*}$ ± 3.2 | $6.7^{*}$ ± 4.0 |

* $p < 0.05$   ** $p < 0.01$.

TABLE 6.4.

EFFECT OF ENALAPRIL ON PRESSOR RESPONSIVENESS TO PHENYLEPHRINE

$PD_{20}$ VALUES (ug/kg/min)

| PATIENT | PLACEBO | 1ST DOSE | 1 WEEK | 6 WEEKS |
|---------|---------|----------|--------|---------|
| 1 | 2.1 | 1.8 | 1.7 | 1.8 |
| 2 | 2.9 | 1.3 | 2.2 | 1.8 |
| 3 | 2.0 | 1.5 | 1.7 | 1.3 |
| 4 | 1.6 | 0.6 | 0.9 | 1.2 |
| 5 | 2.8 | 1.1 | 1.6 | 2.2 |
| 6 | 4.5 | 3.3 | 4.2 | 2.0 |
| 7 | 0.9 | 0.9 | - | 0.8 |
| 8 | 1.2 | 1.6 | 1.8 | 2.8 |
| 9 | 1.3 | 1.0 | 1.3 | 1.0 |
| 10 | 2.3 | 2.6 | 3.9 | 1.5 |
| 11 | 0.9 | 0.5 | 0.5 | 0.5 |
| 12 | 1.8 | 1.9 | 1.3 | 1.2 |
| 13 | 3.3 | 1.4 | 1.6 | 1.5 |
| Mean ± SD | 2.1 ± 1.0 | $1.5^{*}$ ± 0.8 | $1.8^{*}$ ± 1.1 | $1.5^{*}$ ± 0.6 |

\* $p < 0.05$    \*\* $p < 0.01$

**ENALAPRIL**
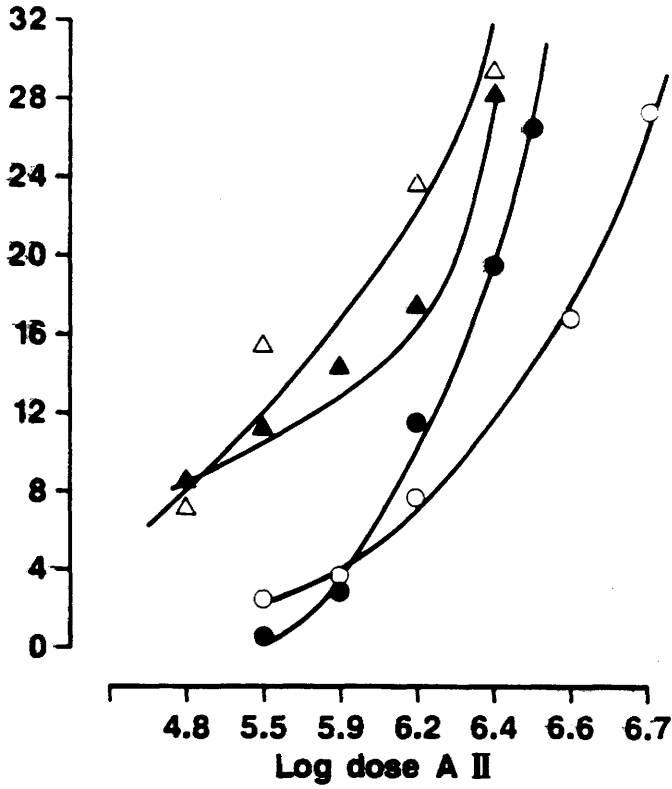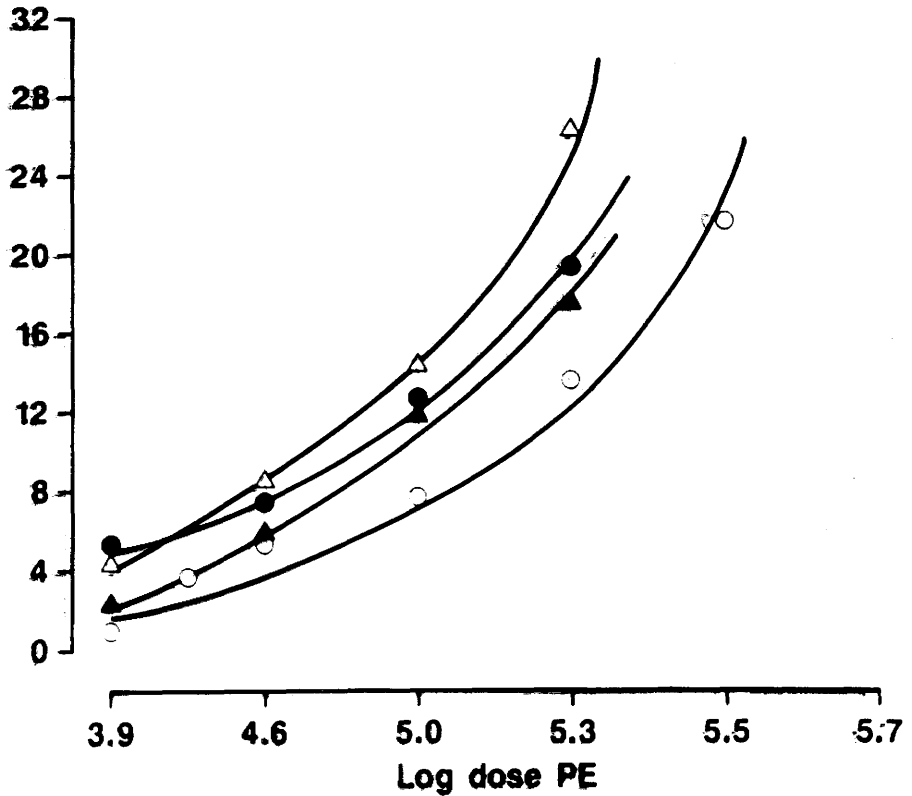
Figure 6.3.
Pressor dose-response curves for angiotensin II (Top) and
phenylephrine (Bottom) in a representative patient following
placebo ( ○ ), 1st dose enalapril ( ● ) and after 1 week
( △ ) and 6 weeks ( ▲ ) enalapril treatment.

195

**ATTENUATION IN PRESSOR SENSITIVITY RELATED TO AGE**
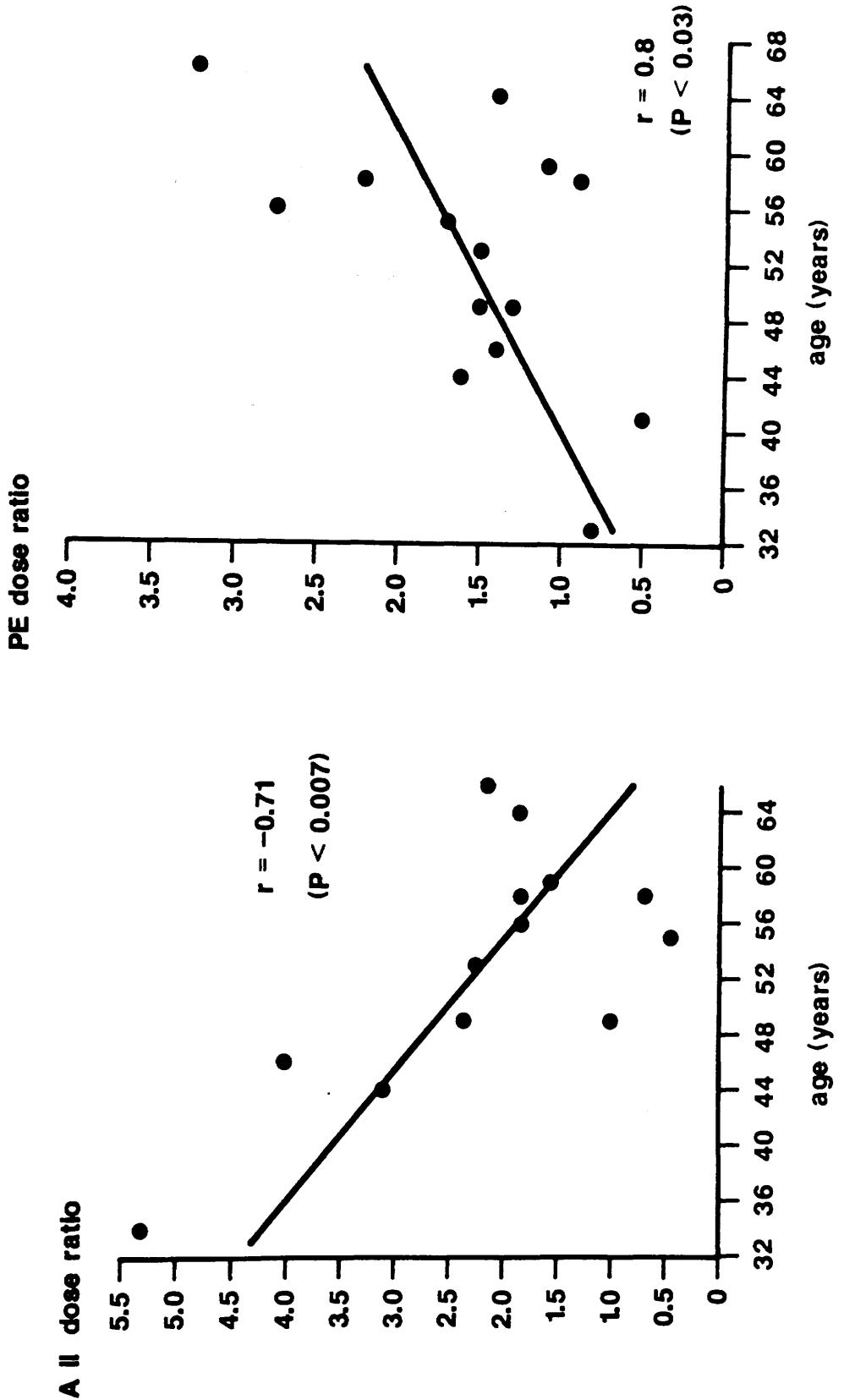
Figure 6.4.
The attenuation in pressor sensitivity by nifedipine related to age. Correlations between patient age and angiotensin II and phenylephrine dose ratios after the 1st dose of nifedipine.

treatment with enalapril and doxazosin but there was a
significant differential age effect on the responses to
both AII and PE during treatment with nifedipine.  There
was a significantly greater attenuation of the pressor
responsiveness to AII in younger patients (Figure 6.4.) but
a significantly greater attenuation of PE responsiveness in
older patients (Figure 6.4.).


Cardiovascular baroreflex activity

In contrast to enalapril and doxazosin which had no
effect (Table 6.5.), nifedipine significantly reduced the
change in heart rate per unit increase in blood pressure
from -0.62 (placebo) to -0.38 (1st dose), -0.35 (1 week) and
-0.31 bpm/mmHg (6 weeks), as illustrated for the group in
Figure 6.5.


6.3.4. Plasma renin activity, aldosterone, catecholamines
       and ACE activity

The first doses of both nifedipine and doxazosin were
associated with significant increases in plasma
noradrenaline (Tables 3.2. and 5.2.).  Enalapril produced
greater than 80% inhibition of plasma ACE activity 1.5 hours
after drug administration (Figure 4.3.) and additionally
there were significant increases in plasma renin activity
(Table 4.3.) from 3.6 (placebo) to 6.9 (1st dose), 18.3 (1
week) and 18.0 ng AI/ml/hr (6 weeks).


197

TABLE 6.5.

THE CHANGE IN HEART RATE PER UNIT INCREASE IN SYSTOLIC BLOOD PRESSURE
DURING PHENYLEPHRINE INFUSION

MEAN $\pm$ S.D. (bpm/mmHg)

|  | PLACEBO | 1st DOSE | 1 WEEK | 6 WEEKS |
|---|---|---|---|---|
| Nifedipine | $-0.62 \pm 0.33$ | $-0.38 \pm 0.36$** | $-0.35 \pm 0.12$** | $0.31 \pm 0.41$** |
| Enalapril | $-0.49 \pm 0.38$ | $-0.40 \pm 0.25$ | $-0.48 \pm 0.29$ | $0.50 \pm 0.37$ |
| Doxazosin | $-0.37 \pm 0.13$ | $-0.42 \pm 0.15$ | $-0.58 \pm 0.29$ | $0.39 \pm 0.20$ |

** $p < 0.01$

# NIFEDIPINE    PE INFUSION
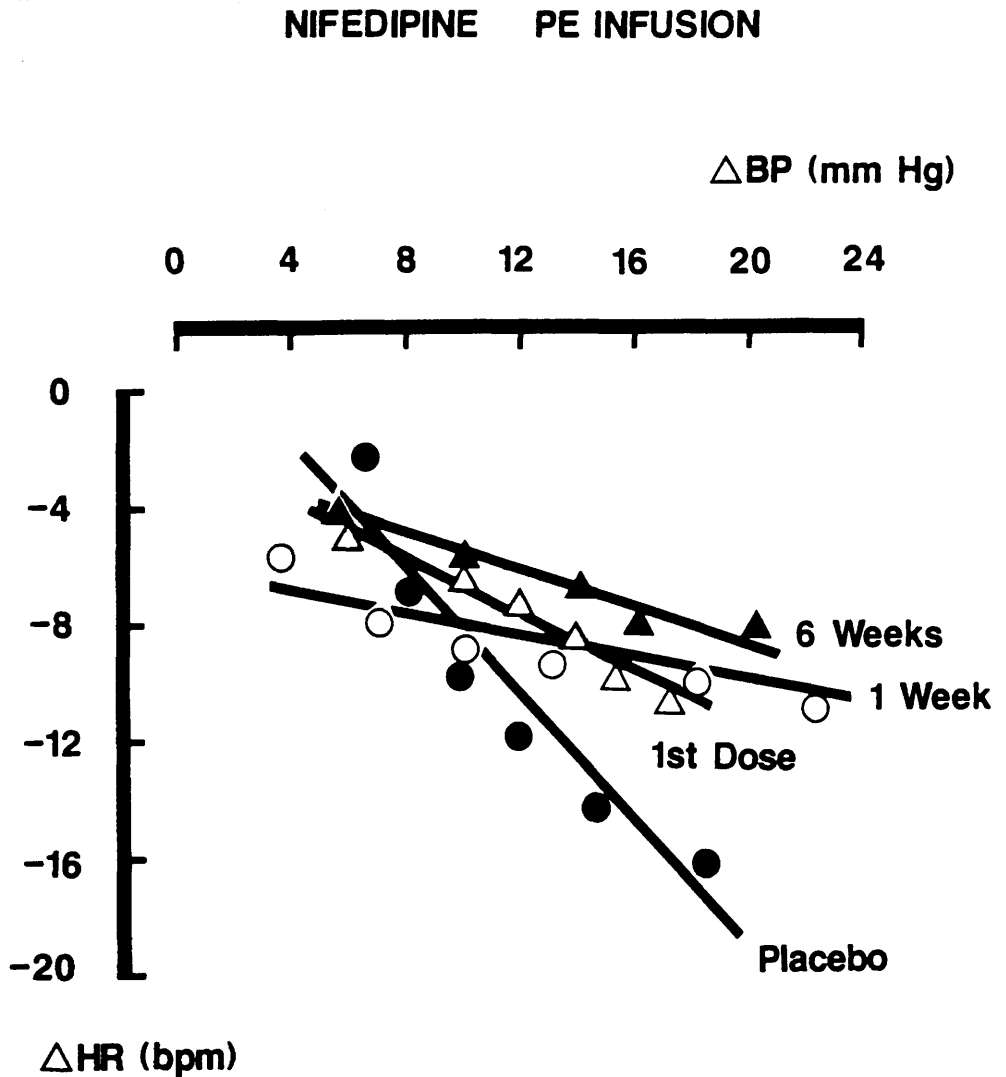


Figure 6.5.
Nifedipine study. The mean relationship between changes in blood pressure and heart rate during phenylephrine infusion for all patients, following placebo ( ● ), 1st dose nifedipine ( △ ) and after 1 week ( ○ ) and 6 weeks ( ▲ ) nifedipine treatment.

# 4. DISCUSSION

Haemodynamic responses to vasoactive agents have been widely used to test various aspects of cardiovascular function and the responses to antihypertensive drugs (Beretta-Piccoli et al, 1982; Imai et al, 1982b; Van Brummelen et al, 1986). However, there has been considerable variation in the methodology, not only concerning the techniques for the administration of agonists but also in the analysis of the dose-response data (Sumner and Elliott, 1987). Thus it has proved difficult to make comparative assessments of drug effects which are independent of other factors such as age and starting blood pressure. In this study, a standardised approach for measuring and analysing the responses to vasoconstrictor agents was employed (Sumner et al, 1987; Sumner and Elliott, 1987), and an assessment of baroreflex responses was also incorporated (Smythe et al, 1969).

In terms of blood pressure reduction the "vasodilator" activity of the three drugs was comparable but the effects on vascular pressor responsiveness were significantly different. Consistent with its mechanism of action, doxazosin produced significant alpha antagonism but no antagonism of angiotensin II-mediated vasoconstriction but the different effects of the two "non-adrenergic vasodilators", nifedipine and enalapril, are of particular interest. For nifedipine, there was interference with both "adrenergic" and "non-adrenergic" pressor responsiveness.

This has been reported previously with other dihydropyridine calcium antagonists and also with verapamil (Beretta-Piccoli et al, 1982; Elliott et al, 1985; Pasanisi et al, 1985). Additionally, however, there was a progressive increase in the extent of the attenuation of the angiotensin response during the 6 weeks of this study. In contrast, there was no attenuation of the pressor responsiveness to either angiotensin II or phenylephrine during treatment with enalapril but instead there was increased responsiveness to both pressor agents. Previous studies have produced an inconclusive picture concerning the effects of ACE inhibitors on pressor responses. Increased responsiveness to angiotensin II has been reported (Imai et al, 1982b; Koletsky et al, 1984) although not in all studies (Fruncilo et al, 1983; Kondowe et al, 1987a), whereas increased adrenergic responsiveness has not been reported before. Similar previous studies of adrenergic responsiveness (to noradrenaline) have described either unchanged or reduced responsiveness after ACE inhibitors (Imai et al, 1982b; Fruncilo et al, 1983; Vierhapper et al, 1986; Kondowe et al, 1987b). However, these previous studies have used the non-selective alpha agonist noradrenaline whose vasopressor effect is mediated predominantly by $alpha_2$-adrenoceptors (Timmermans and van Zwieten, 1981) whereas this study used phenylephrine which is selective for $alpha_1$-adrenoceptors.

The vasoconstrictor action of angiotensin II is mediated not only via stimulation of specific receptors on

vascular smooth muscle (Lin and Godfriend, 1970) but also by facilitation of noradrenergic transmission from sympathetic nerves by presynaptic AII receptors (Zimmerman et al, 1984). It is therefore possible that removal of angiotensin II after ACE inhibition leads to up-regulation not only of post-junctional angiotensin II receptors but also of post-junctional adrenergic receptors, the latter as a consequence of reduced neurotransmission. Alternatively, it may be a reflection of altered post-receptor mechanisms since both angiotensin II receptors and $alpha_1$-adrenoceptors activate second messenger pathways involving phosphoinositol hydrolysis (Nahorski, 1985).

Although the antihypertensive effect of ACE inhibitors is essentially due to a reduction in angiotensin II formation (Gavras et al, 1978), the specific mechanism and site of action have not been clearly established. Additional factors, including altered baroreflex function, have been implicated and there is evidence that baroreflex mechanisms are altered by captopril (Mancia et al, 1982; Imai et al, 1982b; Clementini et al, 1986). Such an alteration to baroreflex-mediated counter-regulatory mechanisms might have contributed to the observed increased pressor responsiveness (Koch-Weser, 1974) but there was no corresponding evidence of altered cardiovascular baroreflex activity in this study. However, the blood pressure-heart rate correlation with phenylephrine is clearly a relatively crude index of cardiac baroreflex response and additionally

202

there may be differential effects produced by a pressor
agent, as opposed to a depressor agent.

Doxazosin had no effect on baroreflex function but with
nifedipine there was a significant attenuation of the heart
rate response suggesting "re-setting" of baroreflex
mechanisms.  This has been suggested previously for calcium
antagonists (Bolli et al, 1985) and changes in both the set-
point and sensitivity of baroreceptors have been reported
during chronic treatment with nifedipine (McLeay et al,
1983).

An additional difference between nifedipine and the
other two drugs was a differential effect on "adrenergic" and
"non-adrenergic" responsiveness according to age.  In the
elderly interference with "adrenergic" pressor responsiveness
was more pronounced whereas in the young "non-adrenergic"
responsiveness was altered to a greater extent by
nifedipine.  This may simply reflect an age-dependent
difference in the activity of baroreflex mechanisms and the
possible baroreflex effect of nifedipine, since bradycardia
is an important component of the response to phenylephrine
and this was less in the older subjects.  There are
alternative explanations in terms of age-related differences
in sympathetic activity, plasma renin activity and starting
blood pressure.  There is some evidence that the renin-
angiotensin system is activated particularly in the early
phase of hypertension ie. in younger hypertensives (Buhler
et al, 1981; Buhler and Bolli, 1985), whereas in elderly

hypertensives alpha adrenoceptor mediated vasoconstriction may assume greater importance (Buhler and Bolli, 1985)

There has been recent discussion about the influence which starting blood pressure has on the magnitude of the subsequent fall with treatment (MacGregor et al, 1982b; Erne et al, 1983).  It might be suggested that the magnitude of the response to a pressor agent may similarly be dependent on the starting blood pressure.  In terms of arterial haemodynamics vascular resistance is directly related to vessel diameter (Westerhof and Huisman, 1987) and it has been shown in vitro that an increase in the cross-sectional area of resistance arterioles (i.e. relatively reduced blood pressure) is associated with a decrease in the pressor response to vasoconstrictor stimuli (Folkow, 1975).  In this study there was no relationship between the starting (pre-infusion) blood pressure (and heart rate) and $PD_{20}$, either before or after antihypertensive treatment.

In conclusion, a standardised method has been used to examine the comparative effects of three vasodilator drugs on vascular pressor responses.  For comparable reductions in blood pressure, doxazosin only affected the adrenergic mechanism whereas nifedipine and enalapril affected both "adrenergic" and "non-adrenergic" vascular responses.  The contrasting results for nifedipine and enalapril may reflect baroreflex resetting in the case of the calcium antagonist and receptor up-regulation in the case of the ACE inhibitor.

# CHAPTER 7

## ACUTE AND CHRONIC KETANSERIN IN ESSENTIAL HYPERTENSION: ANTIHYPERTENSIVE MECHANISMS AND KINETIC-DYNAMIC RELATIONSHIPS

## 7.1. INTRODUCTION

Ketanserin is a selective serotonin ($5HT_2$) antagonist (Van Neuten et al, 1981; Leyson et al, 1981) which, either as monotherapy or in combination with a beta-adrenoceptor antagonist (De Cree et al, 1981a; Hedner and Persson, 1985; Hedner et al, 1985), has been shown to lower blood pressure in patients with essential hypertension. There is evidence that the antihypertensive effect of ketanserin is associated with a reduction in peripheral vascular resistance (Fagard et al, 1984) but the principal underlying mechanism remains to be established. Although serotonin is implicated in cardiovascular regulation, both peripherally and centrally, its actions are complex and variable (Page and McCubbin, 1953) and the blood pressure responses to other serotonin antagonists have been inconsistent (Vanhoutte and Van Neuten, 1983; Vanhoutte, 1985; Hosie et al, 1987). Because ketanserin has also been shown to have $alpha_1$ adrenoceptor antagonist activity (Van Neuten et al, 1981) it has been proposed that alpha blockade underlies the antihypertensive effect in man (Reimann and Frolich, 1983). A number of other mechanisms have also been suggested: for example, an inhibitory effect in the CNS (Mylecharane et al, 1985), including arterial baroreflex resetting (Smits et al, 1987); interference with the renin-angiotensin-aldosterone system (Williams et al, 1984; Mantero et al, 1985; Rocco et al, 1986); and impairment of the vasoconstrictor response to angiotensin II (Neuten et al, 1982).

Although the principal metabolite of ketanserin, ketanserinol, is reported to have negligible affinity for arterial $5HT_2$ receptors (Frenken and Kaumann, 1984), a contribution to the clinical pharmacological effects of ketanserin cannot be excluded. Furthermore, there is evidence to suggest that ketanserinol, during continued administration, may influence the disposition of the parent drug (Van Peer et al, 1986).

Clinical studies, using a dosage regimen of 40 mg b.i.d., have shown large interindividual differences not only in blood pressure reduction (Hedner et al, 1985; Kane et al, 1986; Waller et al, 1987) but also in plasma ketanserin concentrations (Heykants et al, 1986). In addition, it has been suggested that the dose-response curve for the antihypertensive effect of ketanserin is relatively flat, whereas the response curve for side effects and drop-out frequency is much steeper (Amery et al, 1985). Although maximal blood pressure reductions have been correlated with peak plasma levels of ketanserin (Persson et al, 1987), no direct relationship between ketanserin concentration and the fall in blood pressure has been described when group data are evaluated (Hedner et al, 1986; Cameron et al, 1987). While this may reflect the dynamic and kinetic variability between subjects, recent evidence for other cardiovascular drugs suggests that the concentration-effect relationship is potentially more useful when individual patients are considered.

This study in patients with essential hypertension investigates some of the possible mechanisms underlying the antihypertensive effect of ketanserin, including adrenergic and non-adrenergic pressor mechanisms, and evaluates the kinetic-dynamic relationships of ketanserin in individual patients, following single and multiple dosing, and some of the factors which might contribute to the intersubject variability in antihypertensive response.

## 7.2.   METHODS

### 7.2.1.  General

Nine patients with essential hypertension gave consent to participate in this study and individual patient details are shown in Table 7.1.  Five males and four females, age range 45-61 years, discontinued any previous medication at least 6 weeks prior to entering the study and at the end of this drug-free run-in period the mean entry blood pressures were 174/102 $\pm$ 12/7 (supine) and 172/102 $\pm$ 12/6 mmHg (erect).   Two weeks treatment with placebo, followed by ketanserin 40 mg b.i.d. for 4 weeks was administered in a single blind design and the patients completed three 8-hour study days in the Clinical Pharmacology Research Unit to evaluate the effects of placebo, first dose ketanserin and steady state (1 month) ketanserin (Figure 7.1.).

208

TABLE 7.1.

## KETANSERIN STUDY. INDIVIDUAL PATIENT DETAILS

| PATIENT | AGE | SEX | WEIGHT (kg) | RELEVANT MEDICAL HISTORY | PREVIOUS ANTI-HYPERTENSIVE THERAPY | CHOLESTEROL | SMOKER | ENTRY BP SUPINE | ERECT |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 58 | F | 75 | Newly diagnosed EH | Nil | 7.3 | - | 195/108 | 192/106 |
| 2 | 62 | M | 74 | EH diagnosed 12 years ago LVH | Propranolol-wheeze Diuretic-tiredness | 6.6 | - | 172/115 | 179/107 |
| 3 | 59 | M | 70 | EH diagnosed 8 years ago LVH | Atenolol-tiredness Diuretic | 6.5 | - | 169/100 | 163/102 |
| 4 | 46 | M | 95 | Newly diagnosed EH | Nil | 6.9 | - | 177/105 | 178/93 |
| 5 | 58 | M | 73 | Newly diagnosed EH | Nil | 6.0 | - | 166/97 | 156/98 |
| 6 | 45 | F | 70 | EH diagnosed 6 years ago | Diuretic-poor BP control Atenolol-tiredness | 5.9 | + | 192/103 | 183/106 |
| 7 | 59 | M | 68 | Newly diagnosed EH | Nil | 7.3 | + | 171/95 | 169/102 |
| 8 | 49 | F | 75 | EH diagnosed 2 years ago Mild IHD | Diuretic Nifedipine-headache | 7.9 | - | 159/91 | 161/94 |
| 9 | 47 | F | 65 | Newly diagnosed EH | Nil | 5.7 | + | 168/105 | 169/108 |
| MEAN ± SD | 53.6 ± 6.7 | | | | | | | 174/102 ± 12/7 | 172/102 ± 12/6 |

Key: EH = essential hypertension; LVH = left ventricular hypertrophy on ECG; IHD = ischaemic heart disease.
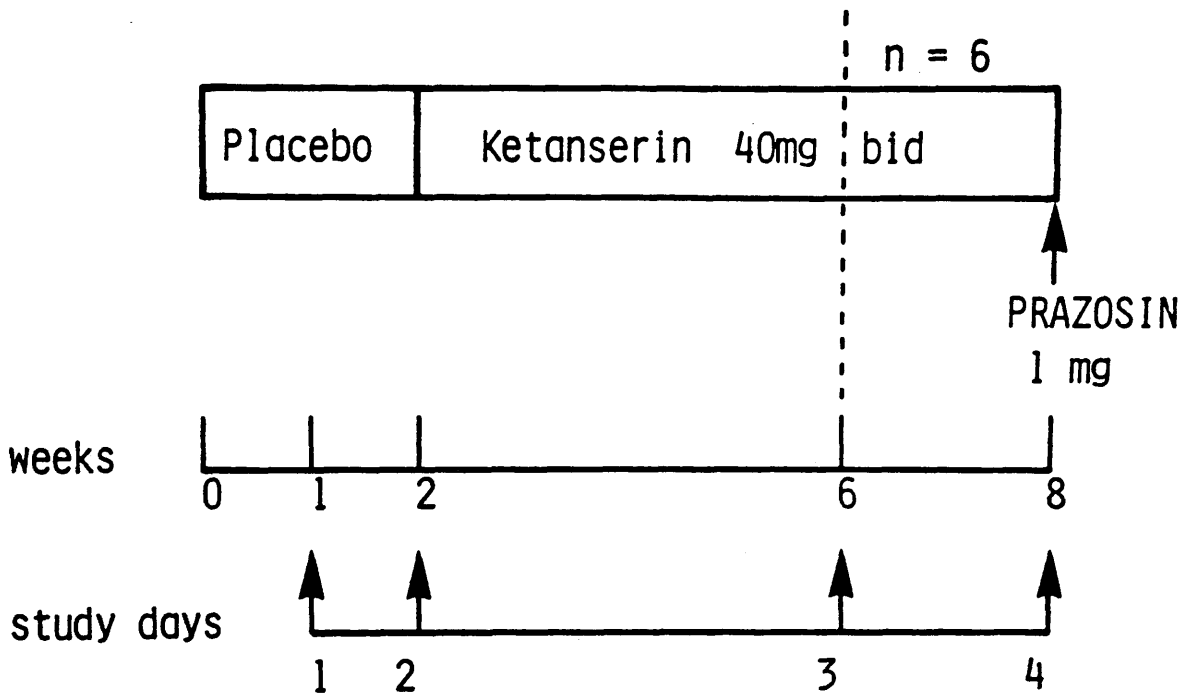
Figure 7.1.
Ketanserin study design. Six of the 9 patients continued
ketanserin therapy for a further 2 weeks and attended a 4th study
day when prazosin was co-administered with ketanserin.

Superimposed treatment with the alpha$_1$ antagonist prazosin.

Six patients (Nos. 1, 2, 4, 5, 6 and 9), randomly selected, continued ketanserin therapy for a further two weeks and completed a 4th study day when prazosin 1 mg was co-administered with ketanserin (Figure 7.1.).

## 7.2.2. Study days

The basic protocol for study days is described in detail in Chapter 2.1. At frequent intervals during each study day, and at 24 hours after dosing, supine and erect blood pressure and heart rate were measured and venous blood samples collected for the measurement of plasma drug and metabolite (ketanserinol) concentrations. Additional blood samples were taken at 1.5 and 5 hours for plasma renin activity, aldosterone and catecholamines. Urine was collected for the 24 hours of each study day.

On each visit to the CPRU patients completed a questionnaire relating to adverse effects and the intensity of specific symptoms was indicated on a self-rating scale.

## Pressor responsiveness

During two periods, 1.5-3 hours (early) and 5-6 hours (late), pressor responses to intravenous infusions of phenylephrine (PE) and angiotensin II (AII) were measured using the protocol described in Chapter 2.2. The relationship between the simultaneous blood pressure and heart rate changes during the infusion of phenylephrine was

used as an index of cardiovascular baroreflex activity
(Chapter 2.2.).

ECG recording

On each study day, at 1 and 5 hours, an ECG recording
from standard chest leads was fed directly to an 'in-house'
computer program for the measurement of heart rate and QT
interval.


7.2.3. Laboratory methods

Plasma concentrations of ketanserin and the metabolite
ketanserinol were measured by reverse phase HPLC with
fluorescence detection (Okonkwo et al, 1983). An alkaline
extraction procedure was used with back-extraction into
sulphuric acid. The extraction efficiency was 80% for
ketanserin and 60% for ketanserinol. The inter and intra-
assay coefficients of variation were 12% and 10%
respectively, and the limits of detection were 2 ng/ml for
ketanserin and 0.5 ng/ml for ketanserinol.

The concentration-time data for ketanserin were most
appropriately fitted to a two-compartment pharmacokinetic
model. Plasma concentrations of prazosin (Yee et al, 1979)
were fitted to a single compartment model.

7.2.4. Concentration-effect analysis

The pharmacokinetic and pharmacodynamic data for
ketanserin were sequentially fitted to the linear
concentration-effect model described in Chapter 2.5. and the
parameters m and $K_{eq}$ derived for individual patients

following the first dose and after 1 month ketanserin. The responsiveness to ketanserin (m) was calculated in terms of the placebo-subtracted change in erect systolic blood pressure per unit change in drug concentration. The first order rate constant of the effect model, $K_{eq}$, describes the removal of drug from the effect compartment and characterises the temporal discrepancy for the plasma concentration-effect relationship.

### 7.2.5. Statistical Analysis

Pressor dose-response relationships for PE and AII were fitted to a quadratic function and the derived $PD_{20}$ values (dose of agonist required to raise mean arterial pressure by 20 mmHg) were compared by repeated measures analysis of variance. QT intervals were corrected for heart rate ($QT_c$) using Bazett's rule (Bazett, 1920) and compared between treatments by Student's paired t test.

### 7.3. RESULTS

### 7.3.1. General

Ketanserin 40 mg b.i.d. was generally well tolerated and no significant adverse effects were reported.

### 7.3.2. Blood Pressure

The first dose of ketanserin was associated with a significant reduction in blood pressure, both supine and erect, after 1 hour ($p < 0.01$): for supine blood pressure

from 178/103 ± 17/11 at baseline to 144/87 ± 13/8 mmHg

following ketanserin, compared with 182/107 ± 13/9 to

168/101 ± 14/11 mmHg following placebo (Figure 7.2.).    A

similar prompt reduction was observed for erect blood

pressure but there was no significant orthostatic component

and there was no associated symptomatic postural

hypotension.    For 6 hours after the first dose supine and

erect blood pressures were significantly lower than with

placebo (p < 0.01), on average 23/14 mmHg supine and 27/13

mmHg erect, but at 24 hours measurements were not

significantly different.    After 1 month of treatment with

ketanserin, the overall antihypertensive effect was

comparable to that following the first dose (Figure 7.2.)

with blood pressures averaging 141/85 supine and 139/87

erect over the 8-hour period.    The addition of 1 mg

prazosin to ketanserin treatment in six patients was

associated with a further significant fall in blood pressure

(Figure 7.3.), for example 11/3 mmHg (supine) and 9/4 mmHg

(erect) on average at 1 hour after dosing.


### 7.3.3. Heart Rate

There were small but significant increases in heart

rate (p < 0.05) at 1-2 hours after the first dose of

ketanserin compared with placebo (Figure 7.4.).    In contrast,

average heart rates during the 8 hours were lower after 1

month's treatment (64.6 ± 3 bpm supine) compared with the

first dose (69.2 ± 5 bpm) and placebo (71.2 ± 4) administrations

# ERECT SYSTOLIC BP
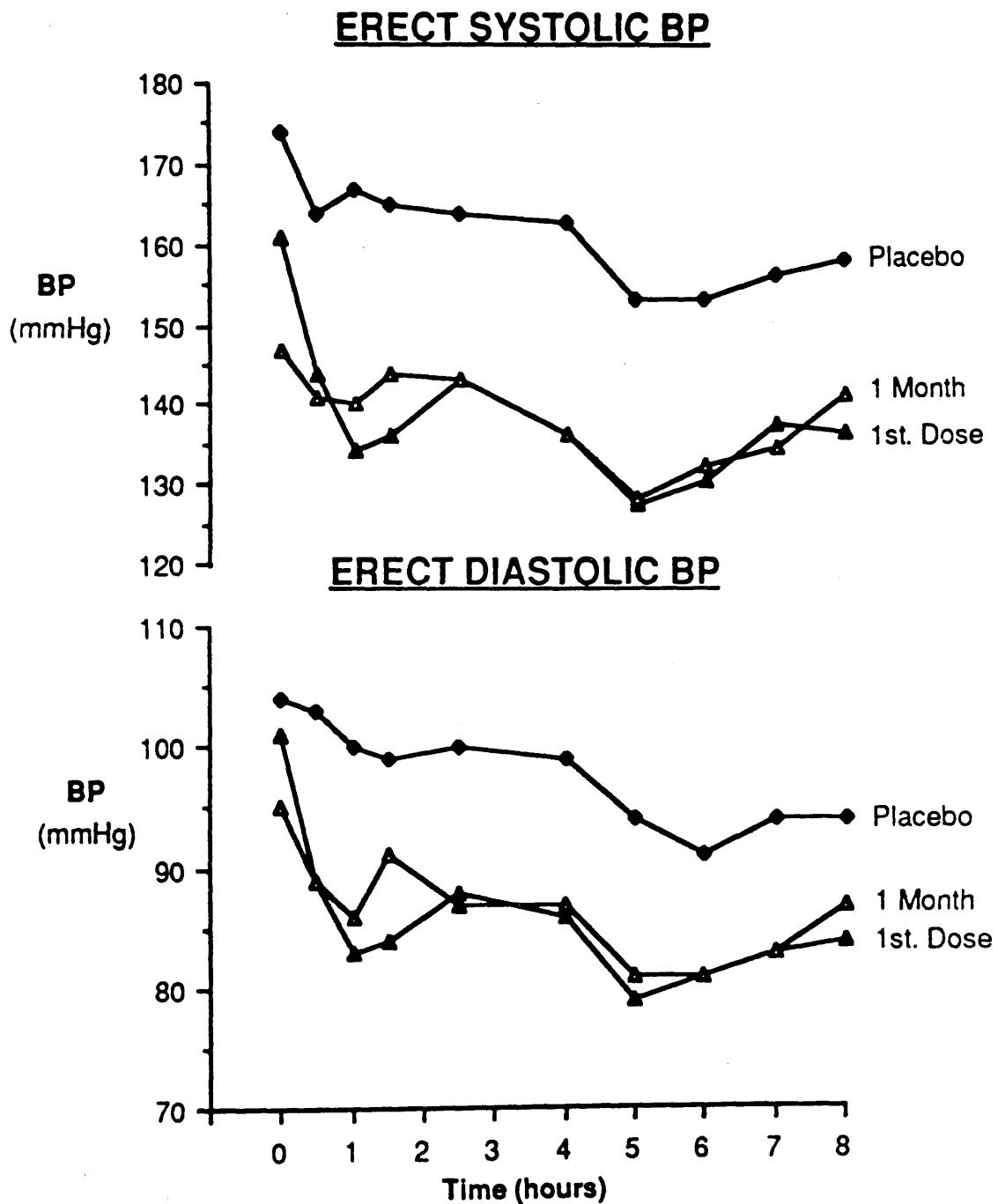


# ERECT DIASTOLIC BP



<u>Figure 7.2.</u>
Mean profiles of erect systolic and diastolic blood pressure after
placebo ( ◆ ), 1st dose ketanserin ( ▲ ) and after 1 month ketanserin
( △ ).
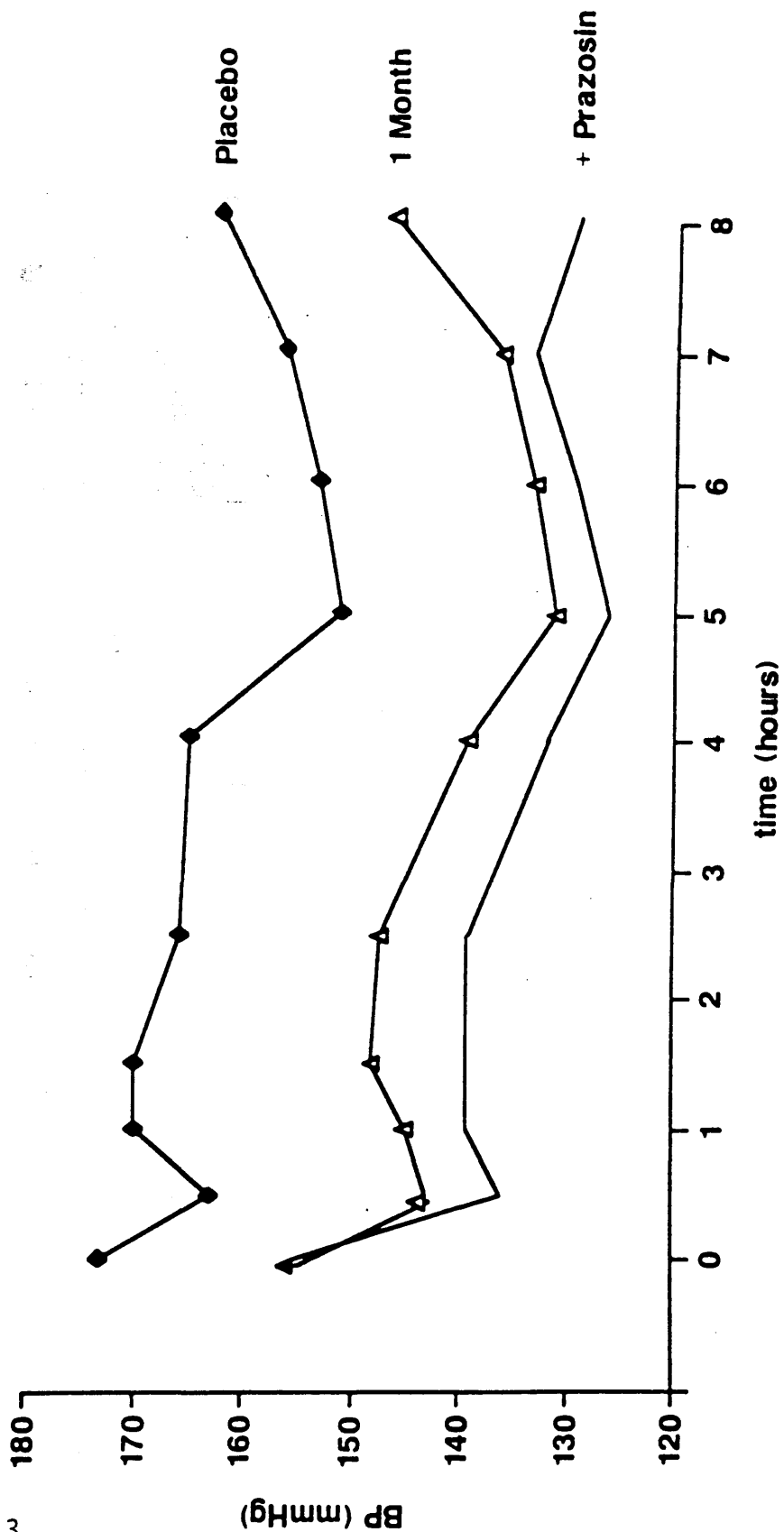
Figure 7.3.
Mean profiles (n=6) of erect systolic blood pressure after
placebo ( ◆ ), 1 month ketanserin ( △ ) and after the addition of
prazosin to ketanserin treatment (————).

# SUPINE HEART RATE
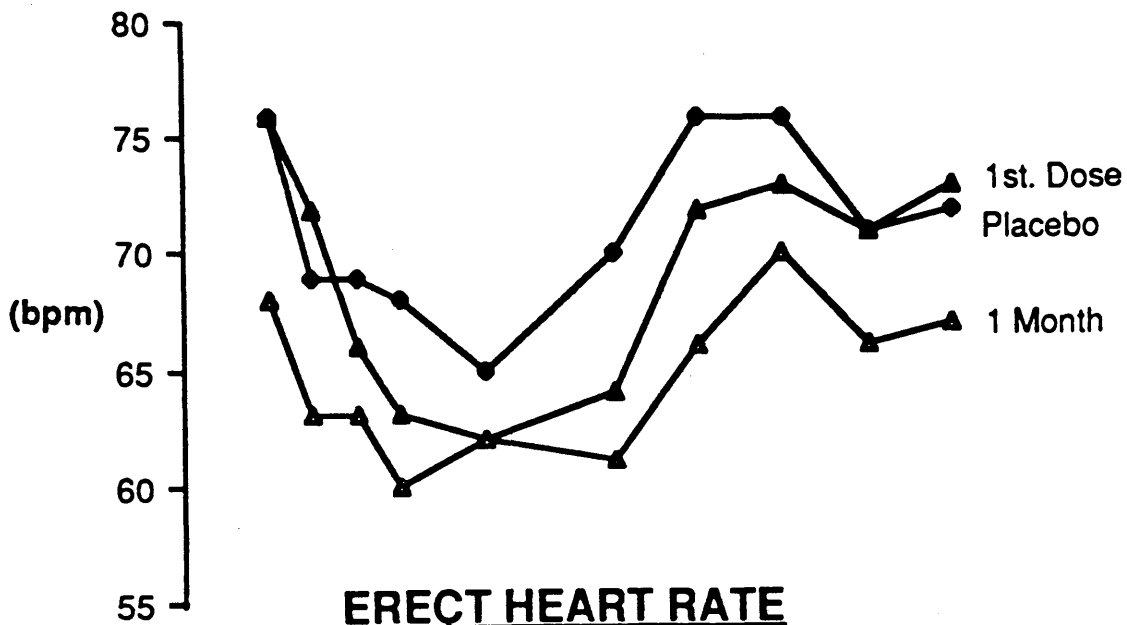


# ERECT HEART RATE
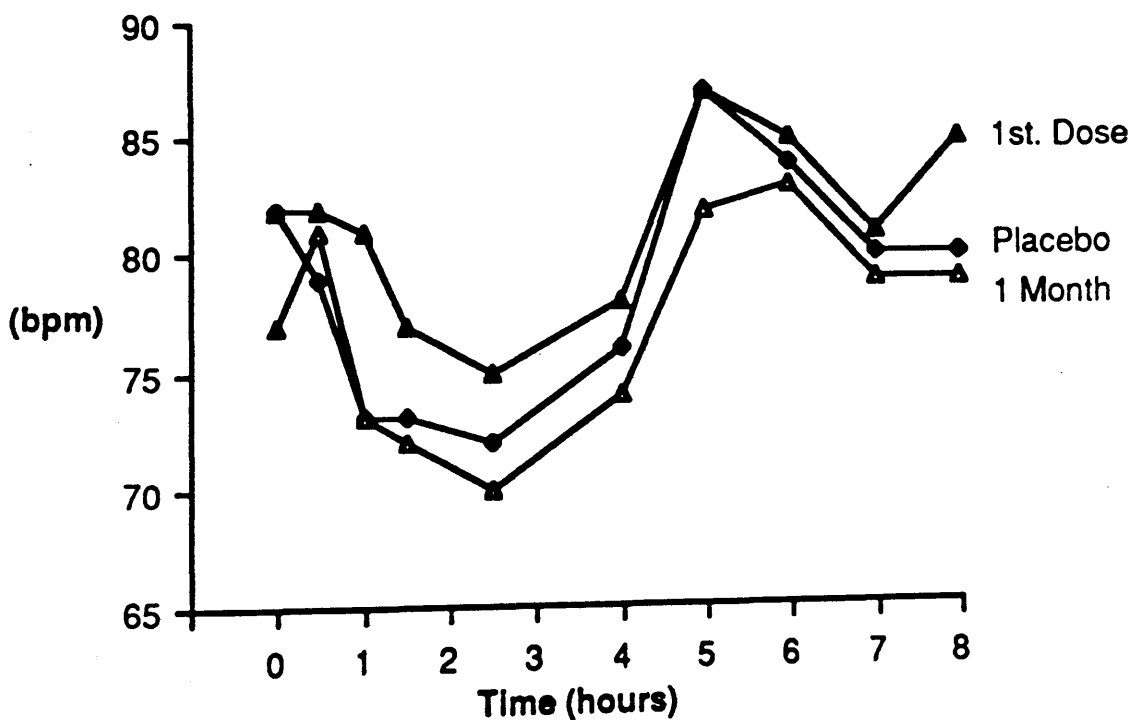


Figure 7.4.
Mean profiles of supine and erect heart rate after placebo ( ◆ ),
1st dose ketanserin ( ▲ ) and after 1 month ketanserin ( △ ).

217

## 7.3.4. Pressor Responsiveness

Ketanserin produced significant (p < 0.05) rightward, parallel shifts of the phenylephrine dose-response curves as illustrated for a representative patient in Figure 7.5. The mean $PD_{20}$ values for PE infusions during both periods were significantly increased by both active treatments: from 1.4 (placebo) to 2.7 following the first dose and 2.4 ug/kg/min after 1 month of ketanserin in the early period (Table 7.2.) and, correspondingly, 1.6 (placebo), 2.2 (1st dose) and 2.3 ug/kg/min (1 month) in the late period (Table 7.3.). On individual study days the differences in pressor responsiveness to PE between the early and late infusions were not significantly different and similarly the responses associated with acute and chronic ketanserin were not significantly different. The addition of prazosin was associated with further rightward shifts of the PE pressor-response curves, and this is shown for a representative subject in Figure 7.5. The increase in mean $PD_{20}$ (n=6) attributable to prazosin (Tables 7.2. and 7.3.) was significantly greater for the PE infusions at the early period, from 2.4 to 7.1 ug/kg/min, compared to 2.3 to 4.6 at the late period. Ketanserin had no effect on the pressor responses to the infusion of AII (Table 7.4.).

Ketanserin had no significant effect on the relationship between the simultaneous blood pressure and heart rate changes during the infusion of phenylephrine (Table 7.5.).
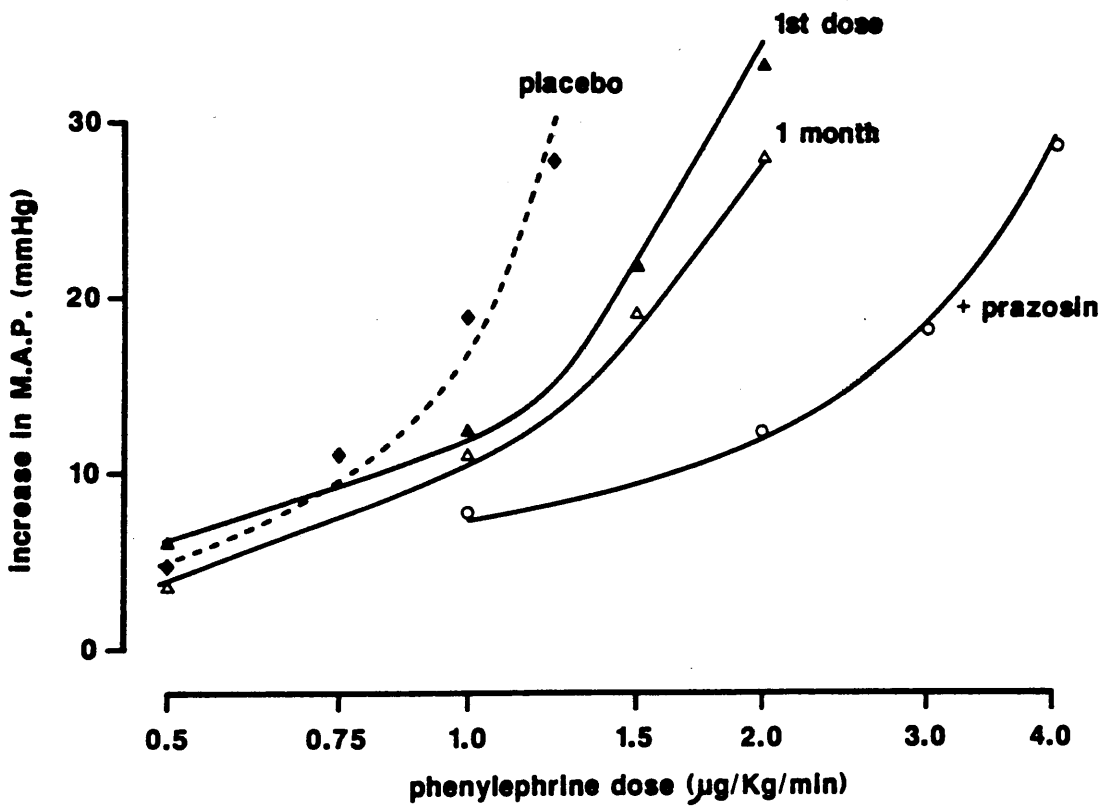
Figure 7.5.
Pressor dose-response curves for phenylephrine in a
representative patient after placebo ( ◆ ), 1st dose ketanserin
( ▲ ), 1 month ketanserin ( △ ) and after the addition of
prazosin ( ○ ).

TABLE 7.2.

KETANSERIN STUDY. PRESSOR RESPONSES TO PHENYLEPHRINE.
EARLY PERIOD.

$PD_{20}$ (ug/kg/min)

| PATIENT | PLACEBO | KETANSERIN 1ST DOSE | 1 MONTH | ADDED PRAZOSIN |
|---------|---------|---------|---------|----------------|
| 1 | 1.3 | 0.9 | 1.7 | 6.3 |
| 2 | 1.6 | 2.0 | 1.0 | 5.8 |
| 3 | 1.1 | 1.9 | 1.6 | - |
| 4 | 0.8 | 1.3 | 1.5 | 5.6 |
| 5 | 2.0 | 3.2 | 3.2 | 6.8 |
| 6 | 1.9 | 4.2 | 3.9 | 9.8 |
| 7 | 1.6 | 3.4 | 3.1 | - |
| 8 | 1.3 | 2.9 | 2.9 | - |
| 9 | 1.3 | 4.3 | 2.3 | 8.5 |
| MEAN ± SD | 1.4 ± 0.4 | 2.7* ± 1.2 | 2.4* ± 1.0 | 7.1** ± 1.7 |

  * $p < 0.03$
 ** $p < 0.00001$

TABLE 7.3.

KETANSERIN STUDY.  PRESSOR RESPONSES TO PHENYLEPHRINE.
LATE PERIOD.

$PD_{20}$ (ug/kg/min)

| PATIENT | PLACEBO | KETANSERIN 1ST DOSE | 1 MONTH | ADDED PRAZOSIN |
|---------|---------|---------------------|---------|----------------|
| 1 | 1.1 | 1.2 | 1.3 | 6.4 |
| 2 | 2.1 | 2.7 | 1.9 | 4.9 |
| 3 | 1.4 | 2.0 | 1.3 | - |
| 4 | 1.0 | 1.2 | 2.8 | 2.5 |
| 5 | 1.7 | 3.1 | 3.1 | 4.0 |
| 6 | 1.6 | 2.4 | 3.5 | 5.9 |
| 7 | 1.5 | 2.5 | 1.9 | - |
| 8 | 2.0 | 2.0 | 2.7 | - |
| 9 | 2.1 | 3.1 | 2.1 | 4.1 |
| MEAN ± SD | 1.6 ± 0.4 | 2.2* ± 0.7 | 2.3* ± 0.8 | 4.6** ± 1.4 |

\*   $p < 0.03$
\*\*  $p < 0.0001$

TABLE 7.4.

KETANSERIN STUDY.  PRESSOR RESPONSES TO ANGIOTENSIN II
MEAN $PD_{20}$ ± SD (ng/kg/min)

|  | PLACEBO | KETANSERIN 1ST DOSE | KETANSERIN 1 MONTH | ADDED PRAZOSIN |
|---|---|---|---|---|
| Early (1.5-3 hrs) | 5.3 ± 1.8 | 4.8 ± 1.8 | 5.7 ± 2.3 | 5.6 ± 3.0 |
| Late (5-6 hrs) | 4.5 ± 1.8 | 6.2 ± 2.1 | 5.0 ± 1.6 | 5.8 ± 3.4 |

TABLE 7.5.

CHANGE IN HR PER UNIT INCREASE IN SYSTOLIC BLOOD PRESSURE
DURING PHENYLEPHRINE INFUSION.    MEAN ± SD

| △ HR/△ BP bpm/mmHg | PLACEBO | KETANERSIN | | ADDED PRAZOSIN |
| | | 1ST DOSE | 1 MONTH | |
|---|---|---|---|---|
| Early (1.5-3 hrs) | -0.41 ± 0.18 | -0.35 ± 0.24 | -0.28 ± 0.21 | -0.35 ± 0.21 |
| Late (5-6 hours) | -0.43 ± 0.22 | -0.33 ± 0.13 | -0.33 ± 0.16 | -0.40 ± 0.12 |

## 7.3.5. QT intervals

After one month's treatment $QT_c$ was significantly increased ($p<0.05$) at 1 hour following drug administration (334 ± 32 msecs) compared with placebo (302 ± 31). Measurements at 5 hours, however, were not significantly different: 329 ± 27 (1 month) and 327 ± 33 (placebo).

## 7.3.6. Pharmacokinetics

The AUC and elimination half-life for both ketanserin and ketanserinol were significantly increased at steady state compared with the first dose (Table 7.6.): for ketanserin, the elimination half-life (hours) and AUC ($ng.h.ml^{-1}$) were respectively 4.3 ± 2.2 and 437 ± 163 (1st dose), and 13.4 ± 6.2 and 830 ± 323 (1 month). There was a proportionately greater increase in ketanserinol AUC which accounted for a reduction in the AUC Drug/AUC metabolite ratio at steady state. Peak plasma concentrations of ketanserin and ketanserinol were achieved within 1.5 hours (Figure 7.6.). The addition of prazosin had no effect on the steady state kinetics of ketanserin or ketanserinol: for ketanserin the elimination half-life was 13.5 ± 1.8 hours and AUC 830 ± 221 $ng.h.ml^{-1}$ (Table 7.6.). There was no significant change in $C_{max}$ or the time to attain $C_{max}$ ($t_{max}$) - Table 7.7.

TABLE 7.6.

PHARMACOKINETICS OF KETANSERIN. DERIVED PARAMETERS AUC AND
ELIMINATION HALF-LIFE.

| PATIENT | AUC $(ng.h.ml^{-1})$ | | | ELIMINATION HALF-LIFE (hours) | | |
|---------|----------|----------|------------------|----------|----------|------------------|
| | 1st DOSE | 1 MONTH | ADDED PRAZOSIN | 1st DOSE | 1 MONTH | ADDED PRAZOSIN |
| 1 | 565 | 1255 | 835 | 3.9 | 8.8 | 11.7 |
| 2 | 496 | 1114 | 567 | 6.9 | 8.1 | 13.0 |
| 3 | 467 | 576 | - | 8.6 | 10.7 | - |
| 4 | 730 | 709 | 835 | 2.4 | 20.6 | 16.8 |
| 5 | 515 | 1076 | 1234 | 2.8 | 11.9 | 12.5 |
| 6 | 289 | 1089 | 730 | 5.3 | 25.6 | 14.2 |
| 7 | 202 | 252 | - | 3.9 | 6.6 | - |
| 8 | 311 | 696 | - | 2.5 | 16.0 | - |
| 9 | 357 | 708 | 780 | 2.9 | 12.5 | 12.6 |
| MEAN ± SD | 437.4 ± 163.0 | 830* ± 323 | 830* ± 221 | 4.3 ± 2.2 | 13.4* ± 6.2 | 13.5* ± 1.8 |

Comparison with 1st dose:  * $p < 0.005$

TABLE 7.7.

PHARMACOKINETICS OF KETANSERIN. DERIVED PARAMETERS $T_{max}$ AND $C_{max}$

| PATIENT | ($\triangle$) $C_{max}$ (ng.h.ml$^{-1}$) | | | $T_{max}$ (hours) | | |
|---|---|---|---|---|---|---|
| | 1st DOSE | 1 MONTH | ADDED PRAZOSIN | 1st DOSE | 1 MONTH | ADDED PRAZOSIN |
| 1 | 184 | 182 | 111 | 0.9 | 1.3 | 0.8 |
| 2 | 116 | 164 | 103 | 0.7 | 0.6 | 0.8 |
| 3 | 43 | 107 | - | 1.0 | 2.2 | - |
| 4 | 278 | 144 | 162 | 0.9 | 0.6 | 0.5 |
| 5 | 164 | 158 | 299 | 0.5 | 0.9 | 0.5 |
| 6 | 91 | 130 | 85 | 0.7 | 1.5 | 1.9 |
| 7 | 47 | 38 | - | 0.8 | 1.5 | - |
| 8 | 72 | 46 | - | 1.6 | 2.4 | - |
| 9 | 101 | 98 | 107 | 1.4 | 0.9 | 1.5 |
| MEAN ± SD | 122 ± 76 | 119 ± 51 | 144 ± 80 | 0.9 ± 0.3 | 1.3 ± 0.6 | 1.0 ± 0.5 |

# Plasma Concentrations (ng/ml)
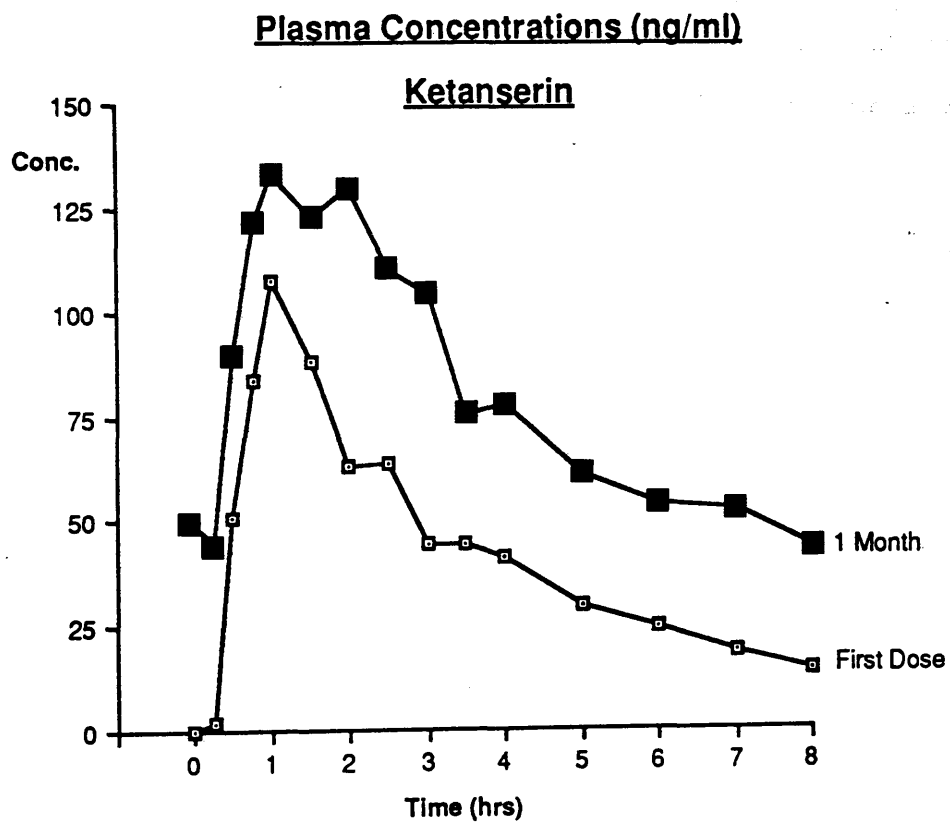
## Ketanserin



**Figure 7.6.**
Mean plasma ketanserin concentration-time profiles for 8 hours after the 1st dose ( ⦿ ) and after 1 month ketanserin ( ■ ).

### 7.3.7. Concentration-effect relationships

When mean data for the group were evaluated there was
no obvious concentration-effect relationship (Figure 7.7.).
Similarly for individual patients, as illustrated for
patient 7 (Figure 7.8.), there was no simple direct
relationship between plasma ketanserin concentration and the
fall in blood pressure.  However, using the effect model,
ketanserin concentrations were well correlated with the
reduction in blood pressure in individual patients and fits
for representative subjects are shown in Figures 7.9. and
7.10.  The concentration-effect parameters, m and $K_{eq}$, and
the goodness of fit (R) for each patient are shown in Table
7.8.  The responsiveness to ketanserin, as the mean of the
group, was -0.47 following the first dose and -0.25
mmHg/ng/ml after 1 month.  This reduction in responsiveness
during chronic compared with single dose administration was
significant ($p < 0.02$).  In addition, there was a
significant increase ($p < 0.01$) in $K_{eq}$ from 0.49 (1st dose)
to 1.86 $h^{-1}$ (1 month).

There was no correlation between the responsiveness to
ketanserin and patient age, or plasma renin activity, or the
degree of peripheral alpha blockade (Figure 7.11).  There
was a trend towards a relationship between the
responsiveness and the pretreatment blood pressure (Figure
7.12.) but this did not achieve statistical significance ($p
< 0.07$).
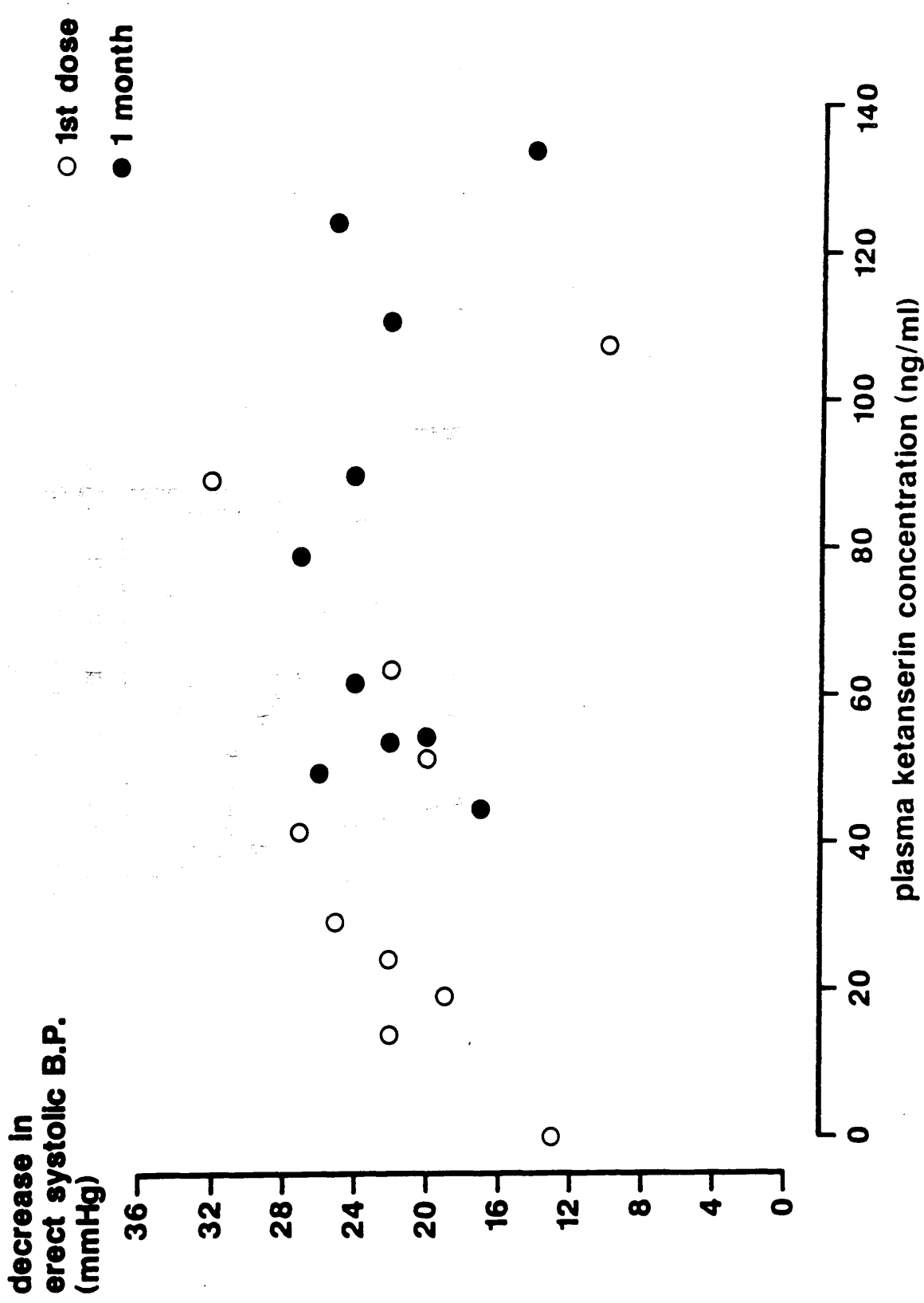
Figure 7.7.
A conventional group approach to concentration-effect analysis
for ketanserin. The mean plasma ketanserin concentration is
plotted against the mean (placebo-subtracted) reduction in erect
systolic BP at different times after drug administration
following the 1st dose ( ○ ) and after 1 month ketanserin ( ● ).

229
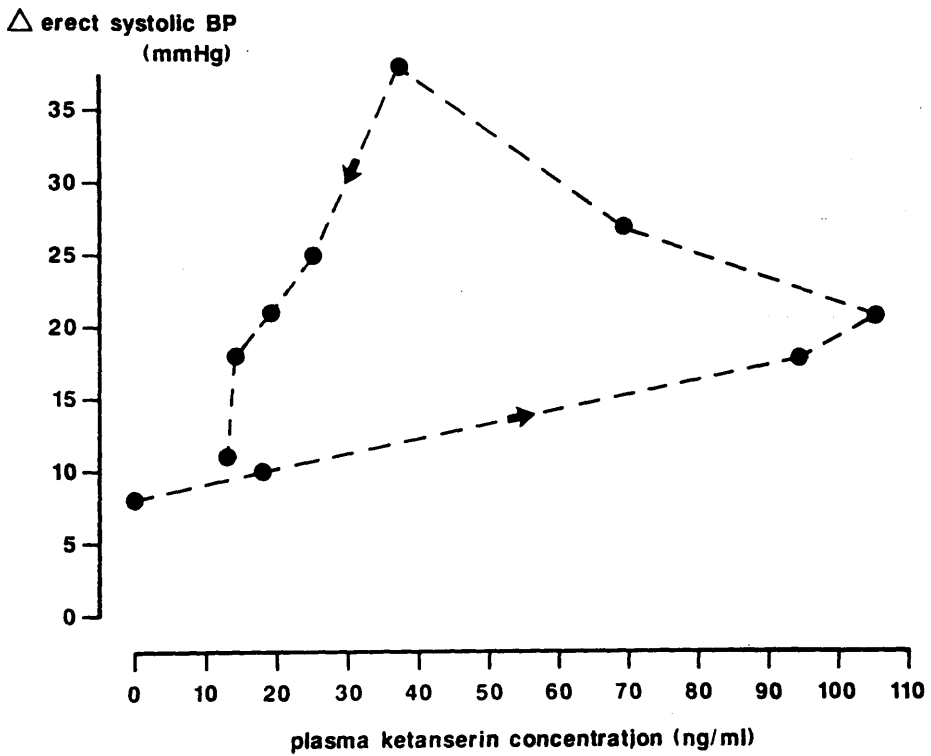
**Patient 7**



Figure 7.8.
The relationship between plasma ketanserin concentration and the placebo-subtracted fall in erect systolic BP in an individual patient after the 1st dose of ketanserin.

**PATIENT 7**

**FIRST DOSE**

m = -0.96 mmHg/ng'ml
$K_{eq} = 0.45$ $h^{-1}$

m = -0.43 mmHg/ng/ml
$K_{eq} = 2.75$ $h^{-1}$
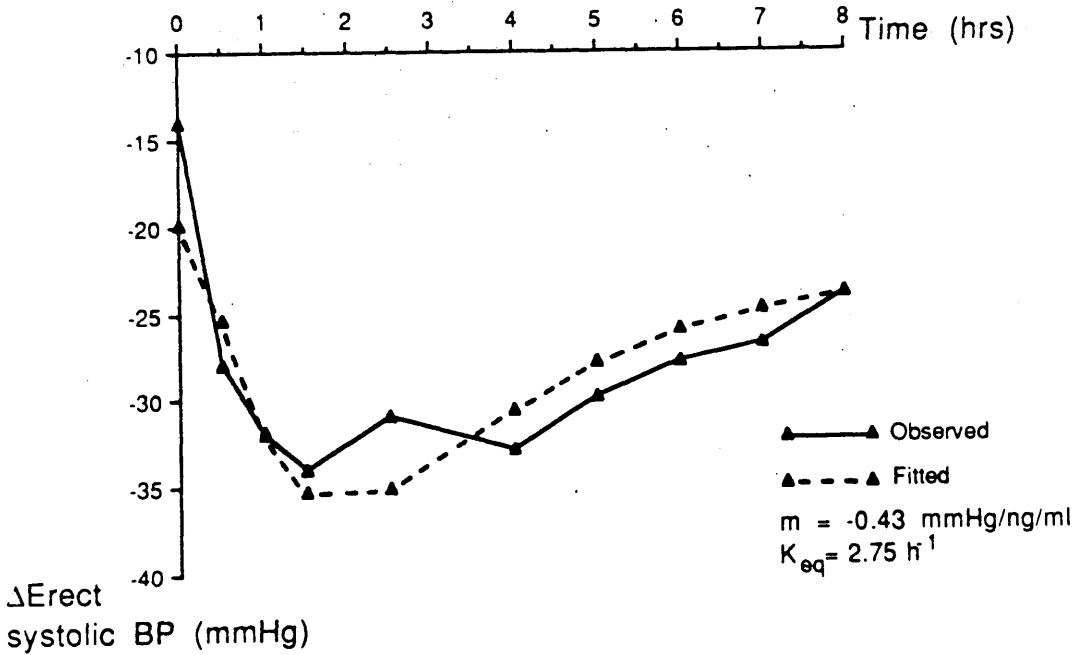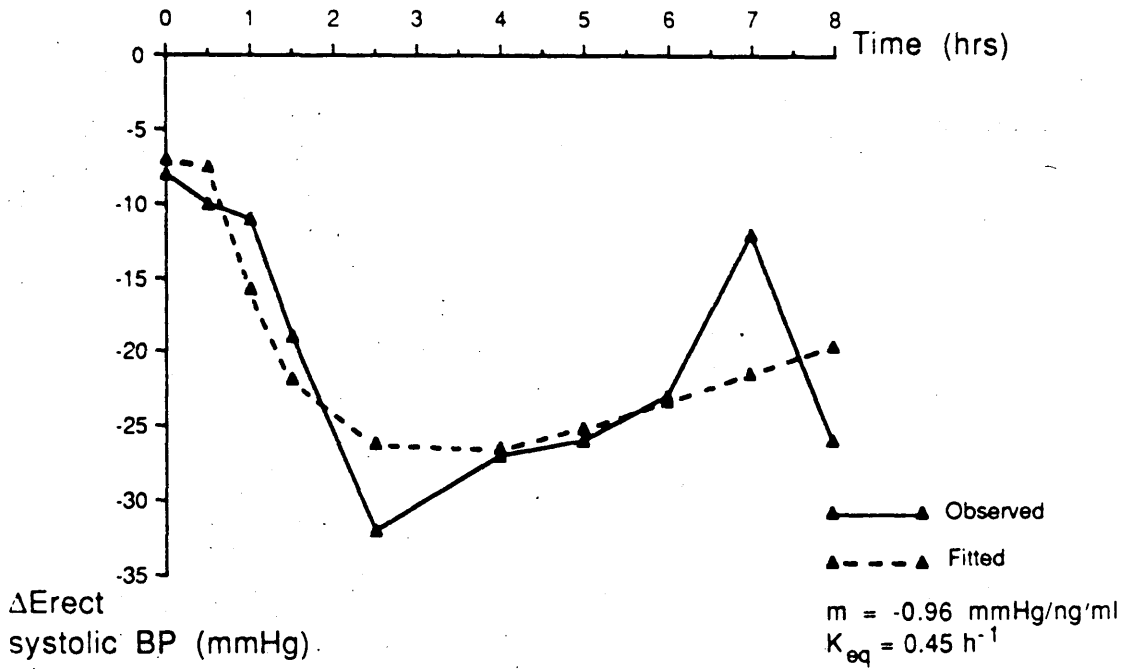
Figure 7.9.
Ketanserin concentration-effect analysis. The observed
( ▲——▲ ) and fitted ( ▲-----▲ ) effect of ketanserin on erect
systolic blood pressure after the 1st dose (Top) and after 1
month (Bottom) in a representative patient, illustrating above
average goodness of fit.

**PATIENT 3**

**FIRST DOSE**

m = -0.36 mmHg·ng/ml
$K_{eq}$ = 0.33 h$^{-1}$

m = -0.26 mmHg/ng/ml
$K_{eq}$ = 0.49 h$^{-1}$
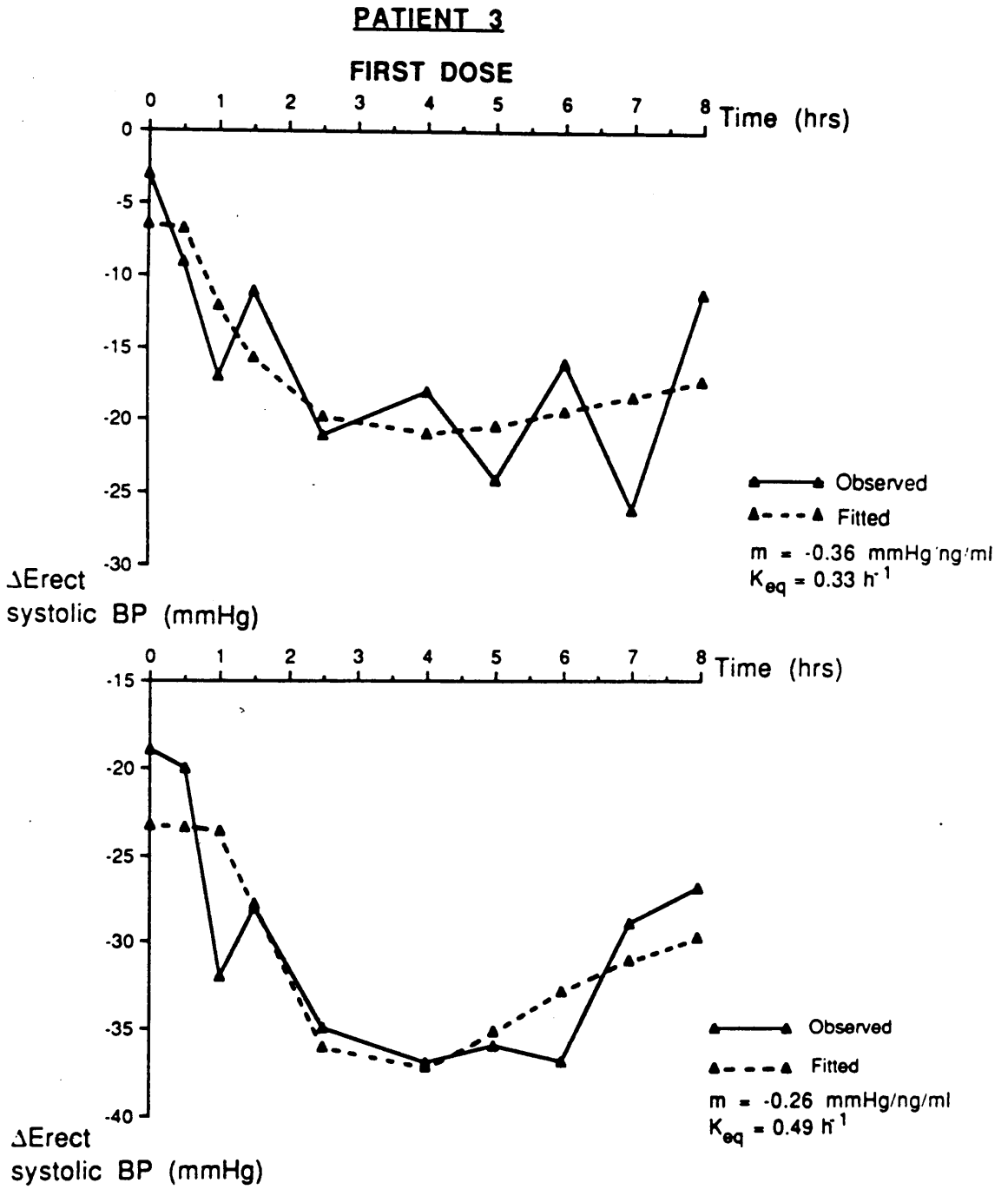
Figure 7.10.
Ketanserin concentration-effect analysis. The observed
( ▲——▲ ) and fitted ( ▲-----▲ ) effect of ketanserin on erect
systolic blood pressure after the 1st dose (Top) and after 1
month (Bottom) in a representative patient (patient 3),
illustrating below average goodness of fit.

TABLE 7.8.

CONCENTRATION-EFFECT PARAMETERS m (mmHg/ng/ml) AND $K_{eq}$
($h^{-1}$), AND THE GOODNESS OF FIT R (AS A FRACTION
OF UNITY) FOR CHANGES IN ERECT SYSTOLIC BLOOD PRESSURE.

| PATIENT | FIRST DOSE | | | ONE MONTH | | |
|---|---|---|---|---|---|---|
| | m | $K_{eq}$ | R | m | $K_{eq}$ | R |
| 1 | -0.26 | 0.66 | 0.87 | -0.12 | 3.60 | 0.89 |
| 2 | -0.58 | 0.49 | 0.74 | -0.12 | 0.90 | 0.88 |
| 3 | -0.36 | 0.33 | 0.75 | -0.26 | 0.49 | 0.82 |
| 4 | -0.23 | 0.24 | 0.79 | -0.29 | 0.40 | 0.78 |
| 5 | -0.41 | 0.46 | 0.89 | -0.19 | 2.30 | 0.82 |
| 6 | -0.72 | 0.31 | 0.59 | -0.30 | 0.45 | 0.75 |
| 7 | -0.96 | 0.45 | 0.83 | -0.43 | 2.75 | 0.86 |
| 8 | -0.29 | 1.01 | 0.69 | -0.25 | 5.40 | 0.86 |
| 9 | -0.44 | 0.43 | 0.79 | -0.30 | 0.41 | 0.87 |
| Mean | -0.47 | 0.49 | 0.77 | -0.25* | 1.86$^X$ | 0.84 |
| ± SD | ± 0.24 | ± 0.23 | ± 0.09 | ± 0.10 | ± 1.80 | ± 0.05 |

Comparison with 1st dose:  * p < 0.02
                           x p < 0.01

# First Dose Ketanserin

**PE dose ratio**

*(scatter plot with y-axis "PE dose ratio" ranging from 0.5 to 3.3 and x-axis "responsiveness (mmHg/ng/ml)" ranging from 0.2 to 1.0)*

**responsiveness (mmHg/ng/ml)**
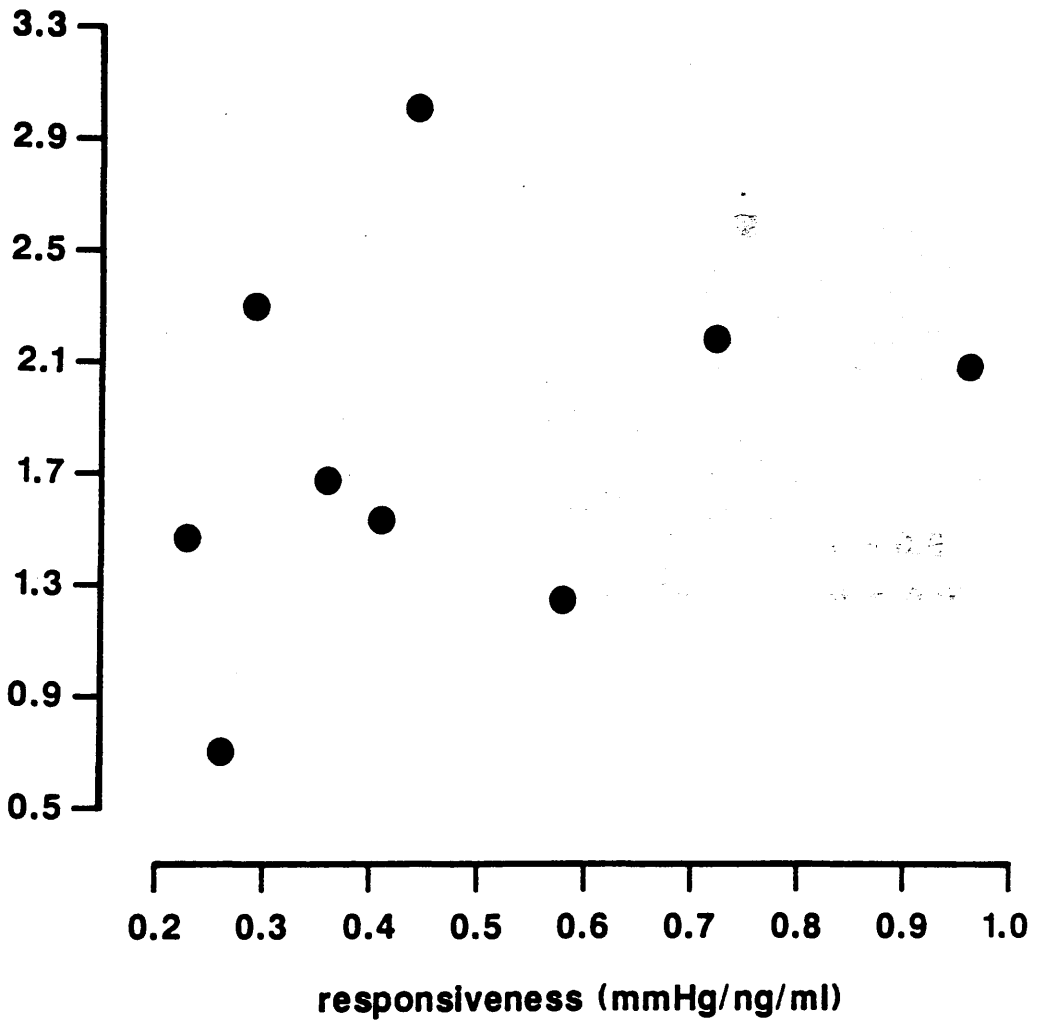
Figure 7.11.
The relationship between responsiveness to ketanserin (1st dose)
and the degree of peripheral $alpha_1$ adrenoceptor antagonism (i.e.
the phenylephrine dose ratio).

# First Dose Ketanserin

**Baseline BP (mmHg)**
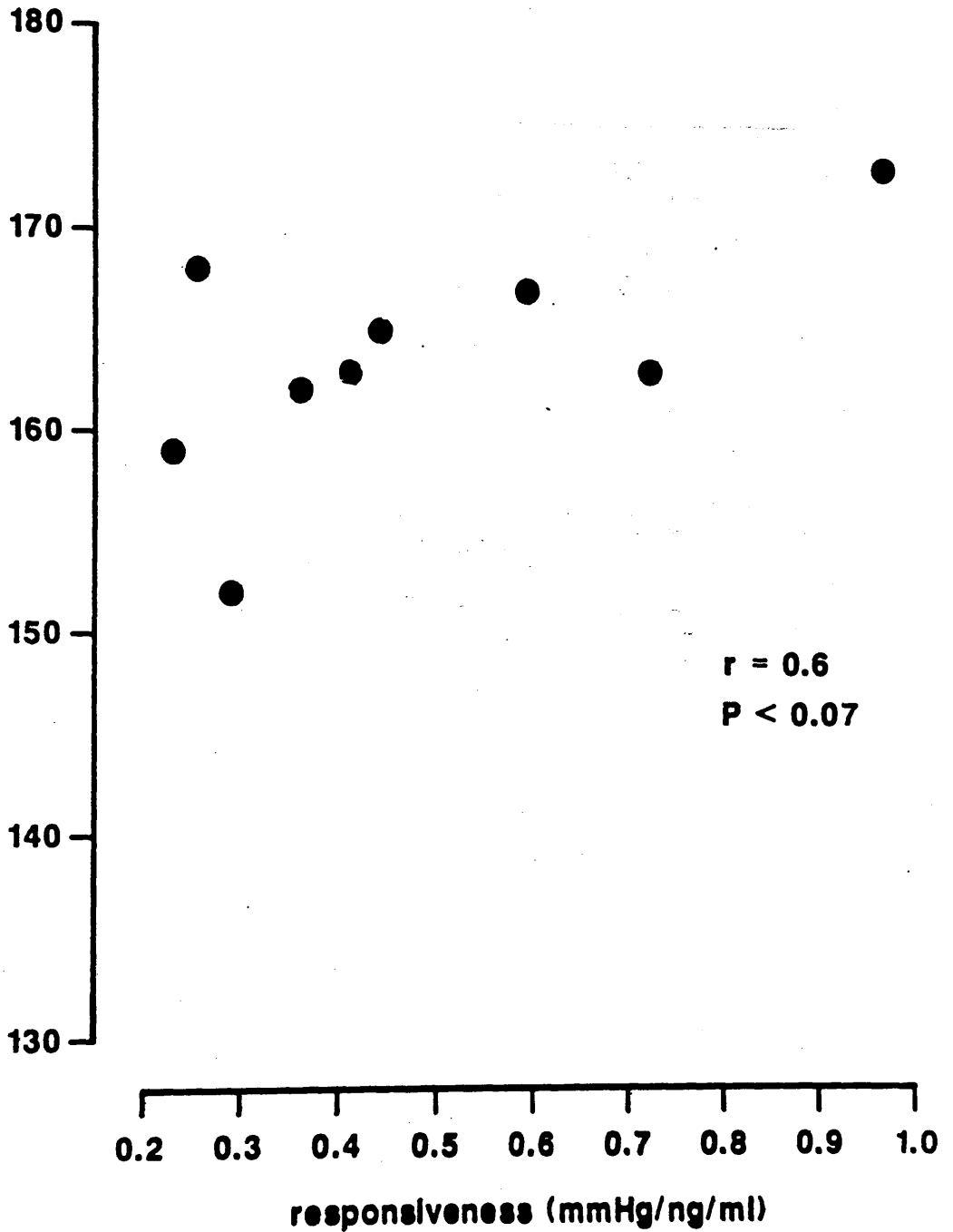


Figure 7.12.
The relationship between responsiveness to the 1st dose of
ketanserin and the pretreatment systolic blood pressure. Not
significant - r = 0.6, p < 0.07.

TABLE 7.9.

KETANSERIN STUDY.  PLASMA RENIN ACTIVITY, ALDOSTERONE
AND NORADRENALINE (AT 1.5 HRS), AND 24-HOUR URINARY VOLUME
AND SODIUM EXCRETION.  MEAN ± SD.

| | PLACEBO | KETANSERIN | |
| | | 1ST DOSE | 1 MONTH |
| --- | --- | --- | --- |
| Plasma renin activity (ngA1/ml/hr) | 1.0 ± 0.5 | 1.9 ± 1.7 | 1.7 ± 1.6 |
| Plasma aldosterone (pg/ml) | 83 ± 29 | 79 ± 26 | 67 ± 23 |
| Plasma noradrenaline (nM/L) | 2.4 ± 1.3 | 2.7 ± 1.4 | 3.2 ± 1.6 |
| Urine Vol (ml) | 1843 ± 732 | 1848 ± 621 | 1739 ± 636 |
| Urinary $Na^+$ (mmol) | 184 ± 43 | 176 ± 71 | 174 ± 66 |

### 7.3.8. <u>Hormone measurements and urinary electrolyte excretion</u>

Measurements of plasma renin activity, aldosterone and catecholamines, and 24-hour urinary volume and electrolyte excretion were not significantly different after ketanserin compared with placebo (Table 7.9.).

## 7.4. DISCUSSION

This study has addressed some of the ill-defined areas relating to the clinical pharmacology and pharmacokinetics of ketanserin.

Ketanserin has previously been shown to lower blood pressure (De Cree et al, 1981a; Hedner et al, 1985) and this study tends to confirm that the antihypertensive effect is sustained for 24-hour blood pressure control with a dosage regimen of 40 mg twice daily. While we are unable to assess the magnitude of the chronic antihypertensive response to ketanserin, it is worth noting that the patients in this study were previously in regular attendance at our hypertension clinic, and additionally they completed a preliminary six week run-in period before the formal placebo assessment. It therefore seems likely that placebo effects were small. On the third study day predosing blood pressures recorded 12 hours after the last dose of ketanserin were less than 150/95 in six out of nine patients, and good blood pressure control was achieved during 8 hours of a 12-hour dosage interval with average blood pressures in 7

patients less than 145/90 supine and 140/90 erect.

The principal mechanism underlying the antihypertensive effect of ketanserin remains uncertain but a number of features of this study suggest that peripheral alpha adrenoceptor antagonism was not the sole mechanism involved. In contrast to the classical alpha$_1$-antagonist drug prazosin, the effects of ketanserin on supine and erect blood pressure were comparable and the first dose was not associated with postural hypotension, marked tachycardia or increased catecholamines. Furthermore, whereas heart rate is usually unchanged during longterm prazosin therapy (Lund-Johansen, 1974), in this and other studies heart rate was significantly reduced with ketanserin (Fagard et al, 1984; Persson et al, 1983). A previous study, which demonstrated weak alpha blocking activity in normotensive subjects, found no reduction in blood pressure (Zabludowski et al, 1985) and the evidence of only modest alpha antagonist activity in this study also suggests that this mechanism is unlikely to account entirely for the antihypertensive effect. There is some dispute about the extent of the reduction in peripheral vascular resistance associated with the antihypertensive effect of ketanserin (Fagard et al, 1984; Omvik and Lund-Johansen, 1983) and in this study ketanserin had no effect on the pressor responses to angiotensin II.

There is good evidence that serotonergic neurones in the CNS are involved in the maintenance of vascular tone and

therefore a central mode of action has been proposed (Kuhn et al, 1980) particularly in relation to baroreflex function (Smits et al, 1987). In this study the relationship between the simultaneous blood pressure and heart rate changes during the infusion of phenylephrine was used as an approximate index of cardiovascular baroreflex activity and ketanserin had no effect on this relationship. However, the reduction in responsiveness (m) to ketanserin during chronic treatment may reflect "resetting" of baroreceptor mechanisms. In addition, the reduction in heart rate observed during chronic therapy may be evidence of a drug-related central effect, perhaps producing an enhancement of vagal tone.

Ketanserin is reported to cause prolongation of the QT interval (Cameron et al, 1986; Stott et al, 1985) and this may have clinical implications with respect to the development of ventricular arrhythmias (Soffer et al, 1982). Our results confirm that QT prolongation occurs during chronic therapy, particularly at 1 hour after dosing when combined drug and metabolite concentrations were highest.

Some aspects of the pharmacokinetics of ketanserin remain to be clearly established. In this study the AUC and the elimination half-life were significantly increased at steady state compared with single dose administration by approximately 2 and 3-fold respectively. Similar 3-fold changes in elimination half-life have been reported by others (Hedner et al, 1986; Persson et al, 1987) and

239

additionally there is some evidence of drug accumulation in a study of elderly subjects (Kurowski, 1985). These changes may reflect alterations in hepatic extraction but, more recently, it has been suggested that reformation of ketanserin from ketanserinol is a determining factor for the elimination half-life of ketanserin (Van Peer et al, 1986).

The haemodynamic effects and pharmacokinetics of ketanserin have been widely reported independently (De Cree et al, 1981a; Hedner and Persson, 1985; Kurowski, 1985) but to date little attention has been paid to the kinetic-dynamic relationships in essential hypertension. Previous studies have sought correlations between ketanserin concentration and effect data for groups of subjects (Hedner et al, 1986; Cameron et al, 1987; Persson et al, 1987) and a clear relationship between plasma concentration and the fall in blood pressure has not been identified. In this study no obvious direct relationship was identified when a group approach was employed but further analysis showed that ketanserin concentrations were well correlated with the fall in blood pressure when individual patients were considered.

There has been some dispute about the usefulness of ketanserin in the clinical management of hypertension (Hedner et al, 1985; Waller et al, 1987; Jennings and Opie, 1987). There is evidence that adequate blood pressure control is only achieved in a small proportion of patients (Waal-Manning et al, 1985) and it has been suggested that ketanserin is particularly effective in the older age group

(Hedner et al, 1985) and in patients with higher pretreatment blood pressures (De Cree et al, 1981b). However, interindividual differences in the therapeutic effect of ketanserin reflect kinetic as well as dynamic variability and many previous studies have failed to take account of differences in plasma ketanserin concentrations when assessing the variability in antihypertensive response (De Cree et al, 1981b; Hedner et al, 1985; Waal-Manning et al, 1985; Waller et al, 1987; Jennings and Opie, 1987). In this study responses to acute and chronic ketanserin were characterised for individual patients in terms of blood pressure reduction per unit change in drug concentration and, albeit across a relatively narrow age range, there was no relationship between age and the responsiveness (m) to ketanserin.

Concentration-effect analysis has provided additional information about the mechanism of action of ketanserin. An acute hypotensive effect has been reported (De Cree et al, 1981b) and in this study the responsiveness to the first dose of ketanserin (in mmHg per unit drug concentration) was significantly greater than that after 4 weeks treatment. There was no relationship between the responsiveness to ketanserin and the degree of alpha blockade, which adds further evidence that the antihypertensive effect of ketanserin is not directly dependent upon its weak peripheral alpha$_1$ antagonist activity (Stokes et al, 1986).

The significance of an increase in the $K_{eq}$ derived from

the concentration-effect analysis during chronic ketanserin treatment is not entirely clear. It reflects a change (i.e. shortening) of the temporal discrepancy between the plasma concentration and effect profiles and such a change in $K_{eq}$ has not been observed in studies of other antihypertensive drugs. While the increase in $K_{eq}$ is unlikely to be solely due to the change in kinetics of ketanserin, it may reflect a change in receptor sensitivity or, alternatively, it may reflect a change in the predominant antihypertensive mechanism of ketanserin during chronic compared with acute administration.

In conclusion, although ketanserin has a useful antihypertensive effect the principal underlying mechanism remains uncertain but is unlikely to involve peripheral alpha blockade, perturbation of the renin-angiotensin-aldosterone system or altered baroreflex sensitivity. There may be a change in the predominant antihypertensive mechanism of ketanserin during chronic compared with acute administration. Ketanserin concentrations are correlated with the fall in blood pressure in individual hypertensive patients and the derived concentration-effect parameters are potentially useful for investigating the intersubject variability in antihypertensive response and the mechanism of action of ketanserin.

# CHAPTER 8

## THE CLINICAL PREDICTION OF ANTIHYPERTENSIVE DRUG RESPONSE

## 8.1. INTRODUCTION

A wider choice of antihypertensive drugs is now available and some of the newer agents such as calcium antagonists, ACE inhibitors and $alpha_1$ adrenoceptor antagonists represent reasonable alternatives to a diuretic or beta blocker as first-line treatments in essential hypertension. An individualised approach to treatment is a laudable goal but, since the factors which determine the response to antihypertensive therapy are not clearly understood, at present we are unable to identify which patients will respond to which drugs. In practice, therefore, the choice of a drug and its appropriate dose is largely empirical and clinical decisions are usually based on 'trial and error'. Attempts to identify demographic, racial and biochemical factors which influence drug response have produced conflicting and often misleading statements, for example about variations in responsiveness related to age or ethnic origin (Breckenridge , 1987) and overall the results have been disappointing both theoretically and practically. For instance, two widely quoted studies have drawn opposite conclusions about the relationship between age and the fall in blood pressure with a calcium antagonist (Buhler et al, 1982; Ferrara et al, 1985).

A significant problem with such studies, and a problem which is often underestimated, is that the 'response' to an antihypertensive drug is difficult to define because it is not a discrete finite end-point. Even the effect - fall in

blood pressure - is not easy to assess although blood pressure may be readily measurable, but a qualitative or quantitative assessment of drug response also requires consideration of several other factors: for example, drug dose and variations in plasma drug concentration and blood pressure in relation to the dosage interval. Thus pharmacokinetic as well as pharmacodynamic factors account for the inter and intra-subject variability in blood pressure response. More recently, as illustrated in the earlier chapters, it has been possible to define concentration-effect relationships for several groups of drugs and to thereby describe the antihypertensive responses of individual patients in terms of both kinetic and dynamic parameters.

Having established a method which integrates kinetic and dynamic information, having characterised the responses to acute and chronic treatment in individual hypertensive patients and thereby having an index which is comparable and reproducible, it is now feasible to start to address the more difficult task of identifying factors which may account for the inter and intra-subject variability in responsiveness. This study investigates the relationship between responsiveness to the calcium antagonists, nifedipine and verapamil, the ACE inhibitor enalapril, the $5HT_2$-antagonist ketanserin and the alpha blockers prazosin and doxazosin, and various haemodynamic, demographic, biochemical and neuro-endocrine parameters.

## 8.2. PATIENTS AND METHODS

### 8.2.1. General

'The description and prediction of antihypertensive response' has been the subject of several clinical research studies. In addition to the four principal drug studies presented here, acute and chronic responses to verapamil (Meredith et al, 1987) and prazosin (Elliott et al, 1988c) have also been examined. For the purposes of this chapter, the combined data for all six drugs will be considered.

In a series of single-blind studies a total of 69 patients with mild to moderate essential hypertension received treatment with placebo for 2 weeks then nifedipine retard 20 mg bid (n=14), or verapamil 120 mg bid (n=14), or enalapril 20 mg o.d (n=13), or ketanserin 40 mg bid (n=9), or prazosin 1 mg bid (n=9), or doxazosin 2 mg o.d (n=10). Each drug was administered as monotherapy for 4-6 weeks and patients attended for a sequence of 8-hour study days in the Clinical Pharmacology Research Unit to evaluate the effects of placebo, first dose and chronic (1-6 weeks) treatment. The clinical protocol is described in detail in Chapter 2.1. and the same method was used in all six studies.

### 8.2.2. The description of antihypertensive response

Using concentration-effect analysis (Chapter 2.5.), which integrates both kinetic and dynamic measurements, the responses of individual patients on each study day were characterised by the parameters m (in mmHg/ng/ml) or

$E_{max}$ (in mmHg).  The responsiveness (m) of individual patients to verapamil and prazosin is shown in Tables 8.1. and 8.2.  In the studies of nifedipine, enalapril and doxazosin (Chapters 3-5) responses were described in terms of the placebo-subtracted fall in both systolic and diastolic blood pressure.

### 8.2.3. Statistical analysis

In each individual study a number of haemodynamic, demographic, biochemical and neuro-endocrine parameters which may influence the inter and intra-subject variability in responsiveness were identified:

(i)    Haemodynamic variables

- starting (pretreatment) blood pressure

- response to the first dose

- reflex increases in heart rate and plasma catecholamines

(ii)   Demographic variables

- age

- sex

- cigarette smoking

(iii)  Biochemical variables

- plasma renin activity

- plasma noradrenaline

- serum cholesterol

(iv)   Neuro-endocrine variables

- vascular pressor responsiveness to

247

TABLE 8.1.

THE RESPONSIVENESS (m) TO PRAZOSIN 1 mg bid AFTER THE
1ST DOSE AND AFTER 1 WEEK AND 4 WEEKS TREATMENT

mmHg fall in systolic blood pressure/ng/ml

| PATIENT | 1ST DOSE | 1 WEEK | 4 WEEKS |
|---------|----------|--------|---------|
| 1 | -17.0 | -15.0 | -12.8 |
| 2 | - 8.9 | - 7.8 | - 7.0 |
| 3 | -19.9 | -15.2 | -17.3 |
| 4 | -21.1 | -14.5 | -11.2 |
| 5 | -13.6 | - 9.1 | - 7.8 |
| 6 | -18.2 | - 8.6 | -10.9 |
| 7 | - 3.8 | - 2.4 | - 2.2 |
| 8 | - 4.8 | - 2.3 | - 3.2 |
| 9 | - 7.0 | - 4.1 | - 4.0 |
| MEAN ± SD | -11.5 ± 6.7 | - 8.7* ± 5.2 | - 8.5* ± 5.0 |

Comparison with 1st dose  * $p < 0.02$.

TABLE 8.2.

THE RESPONSIVENESS (m) TO VERAPAMIL 120 mg bid
AFTER THE 1ST DOSE AND AFTER 4 WEEKS TREATMENT

mmHg fall in erect systolic blood pressure/ng/ml

| PATIENT | 1ST DOSE | 4 WEEKS |
|---------|----------|---------|
| 1 | -0.05 | -0.07 |
| 2 | -0.06 | -0.05 |
| 3 | -0.08 | -0.05 |
| 4 | -0.09 | -0.08 |
| 5 | -0.10 | -0.07 |
| 6 | -0.11 | -0.12 |
| 7 | -0.11 | -0.10 |
| 8 | -0.13 | -0.12 |
| 9 | -0.15 | -0.15 |
| 10 | -0.16 | -0.15 |
| 11 | -0.16 | -0.15 |
| 12 | -0.18 | -0.14 |
| 13 | -0.21 | -0.26 |
| 14 | -0.27 | -0.21 |
| MEAN ± SD | -0.13 ± 0.06 | -0.12 ± 0.06 |

phenylephrine and angiotensin II.

The relationship between these variables and
responsiveness was investigated at two levels.
Firstly, for individual drugs by simple linear regression
analysis of the form:

$$y = AX + Z$$

where X is the independent variable being examined, e.g.
starting blood pressure or age, and y is the responsiveness
to the drug represented by m or $E_{max}$ in terms of systolic
blood pressure.   Then, stepwise multiple linear regression
analysis was performed for each drug to investigate the
relative contributions of 4 variables - starting blood
pressure, age, pretreatment plasma renin activity and (where
appropriate) the reflex heart rate response - in accounting
for the intersubject variability in drug responsiveness to
the first dose.

The approach of multiple regression analysis involved
fitting a hierarchy of linear models to the distribution of
values for responsiveness.   Thus, responsiveness is the
dependent variable and the 4 independent variables are
modelled separately and then in all combinations with each
other to find the best fit.   The $R^2$ value obtained for each
model represents the percentage variability in
responsiveness which can be accounted for by the independent

variables incorporated in the model. One, 2, 3 and 4-variable models were fitted to the data:

$$y = AX_1 + Z \tag{1}$$

$$y = AX_1 + BX_2 + Z \tag{2}$$

$$y = AX_1 + BX_2 + CX_3 + Z \tag{3}$$

$$y = AX_1 + BX_2 + CX_3 + DX_4 + Z \tag{4}$$

where y is the responsiveness; $X_1$, $X_2$, $X_3$ and $X_4$ are the independent variables, i.e. starting blood pressure, age, pretreatment plasma renin activity and heart rate increase; and A, B, C and D are the coefficients.

To evaluate differences between nifedipine, enalapril and doxazosin in their relative effects on systolic and diastolic blood pressure, the ratios of m or $E_{max}$(systolic)/(diastolic) for individual patients were compared between treatments by unpaired t test with appropriate correction for multiple comparisons.

## 8.3. RESULTS

### 8.3.1. Starting blood pressure

For each of the individual drugs and for all treatments as a whole there was a significant positive correlation between the responsiveness to the first dose and the

baseline (pretreatment) blood pressure. This relationship
was more evident with systolic than diastolic blood pressure
and was particularly significant for the calcium antagonists,
nifedipine (Figure 3.10.) and verapamil (Figure 8.1.), with
regression coefficients of 0.60 and 0.80 respectively.

8.3.2. The first dose response

In each of the individual studies except ketanserin,
there was a significant correlation between the
responsiveness to the first dose and the responsiveness
after 1-6 weeks treatment. With the ACE inhibitor
enalapril and with the calcium antagonists, nifedipine and
verapamil, there was no significant reduction in
responsiveness during chronic compared with acute
administration: for example, responsiveness to verapamil as
the mean of the group was -0.13 mmHg/ng/ml after the first
dose and -0.12 after 4 weeks (Figure 8.2.). In contrast,
however, with both prazosin and doxazosin and with the
serotonin antagonist ketanserin, there was a significant
reduction in responsiveness in translation from acute to
steady state therapy: for example, the mean responsiveness
to doxazosin was -2.1 mmHg/ng/ml after the first dose and -
1.5 and -1.4 after 1 and 6 weeks respectively (Table 5.9).
Although, on average, there was a 20-30% fall in
responsiveness during chronic treatment, for individual
patients there was a significant correlation between the
responsiveness to the first dose and the responsiveness

**VERAPAMIL
First Dose**

Systolic BP
(mmHg)

r = 0.80
(P < 0.001)

responsiveness (mmHg/ng/ml)
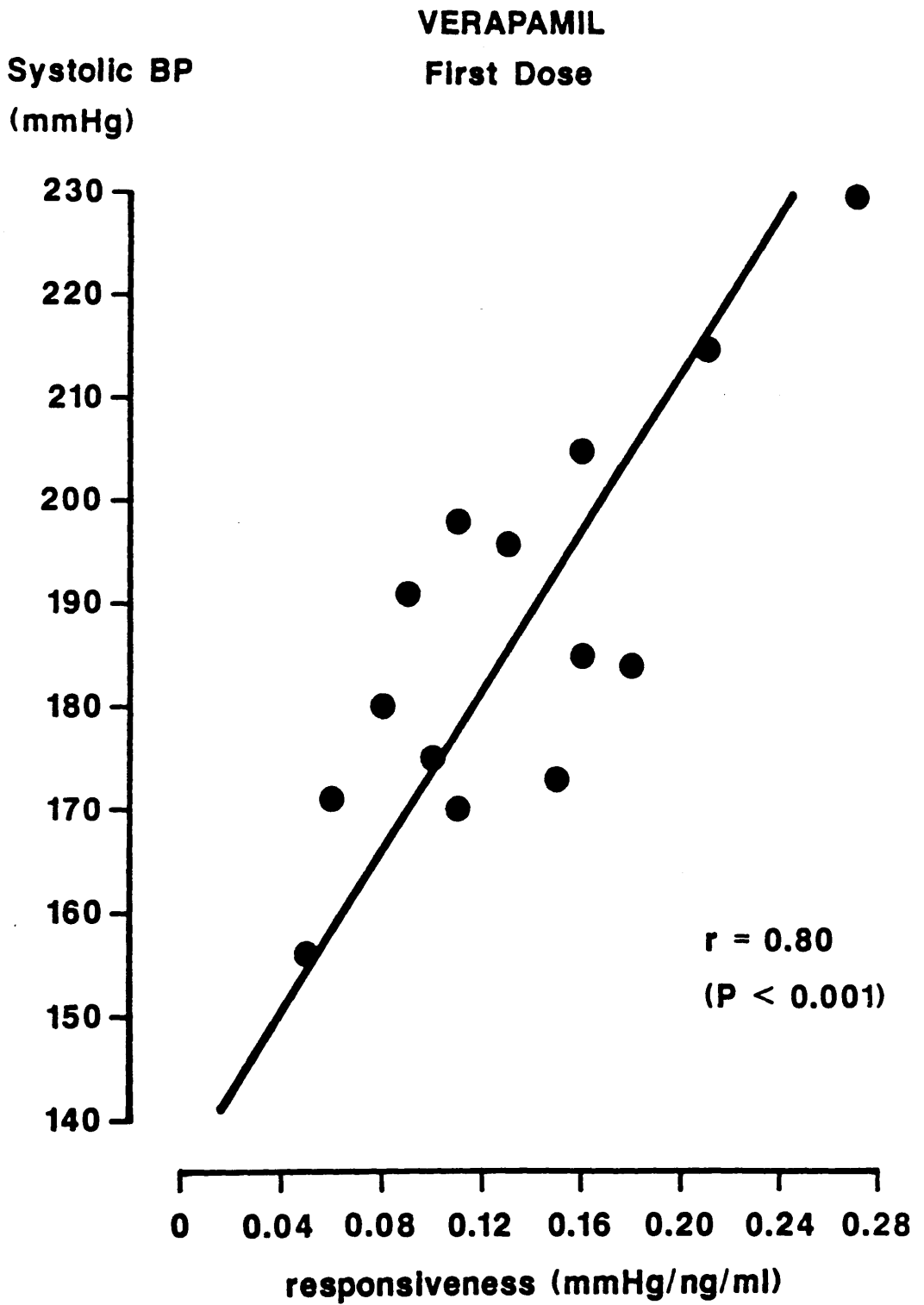
Figure 8.1.
Correlation between the responsiveness to verapamil (1st dose) and the
height of the pretreatment systolic blood pressure (n=14).

**ACUTE AND CHRONIC RESPONSE TO VERAPAMIL**
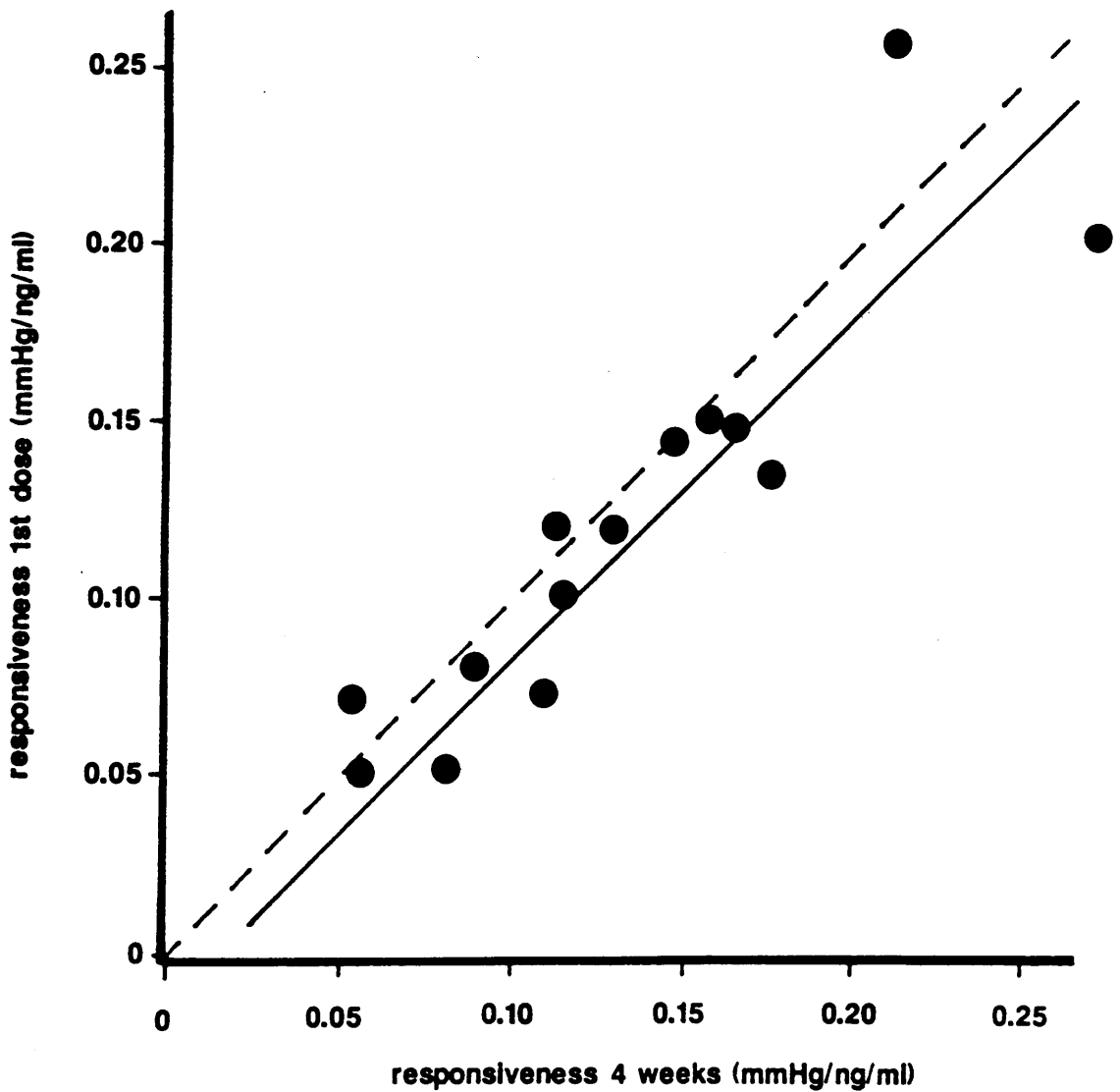
Figure 8.2.
Correlation between the responsiveness to the 1st dose of
verapamil and the responsiveness after 4 weeks verapamil
treatment (n=14), and the line of identity (------); r = 0.90.

after 6 weeks, as illustrated for doxazosin in Figure 5.7.
In the case of ketanserin there was no relationship between
responsiveness acutely and the responsiveness after 4 weeks.

### 8.3.3. Counter-regulatory effects

The fall in blood pressure after the first doses of
nifedipine, prazosin and doxazosin, but not verapamil or
enalapril, was associated with a significant reflex increase
in heart rate (Figures 3.2. and 5.2.) and plasma
noradrenaline.  Tachycardia was particularly marked with
the alpha blockers and there was a significant negative
correlation between the responsiveness to the first dose of
doxazosin and the maximal (placebo-corrected) change in
heart rate (Figure 5.11).  A similar inverse relationship
was observed with nifedipine (Figure 3.10.) although it did
not achieve statistical significance.  There was no
relationship between patient age and the reflex rise in
heart rate as illustrated for nifedipine (Figure 8.3.).

### 8.3.4. Demographic factors

There was no significant relationship between age and
responsiveness either for individual drugs or collectively
in the 69 patients.  In particular, neither the
responsiveness to the calcium antagonists, nifedipine
(Figure 3.11) and verapamil (Figure 8.4.), nor the
responsiveness to enalapril (Figure 4.7.) was significantly
related to patient age.

# △HR versus Age

△HR (1st dose)



age (years)
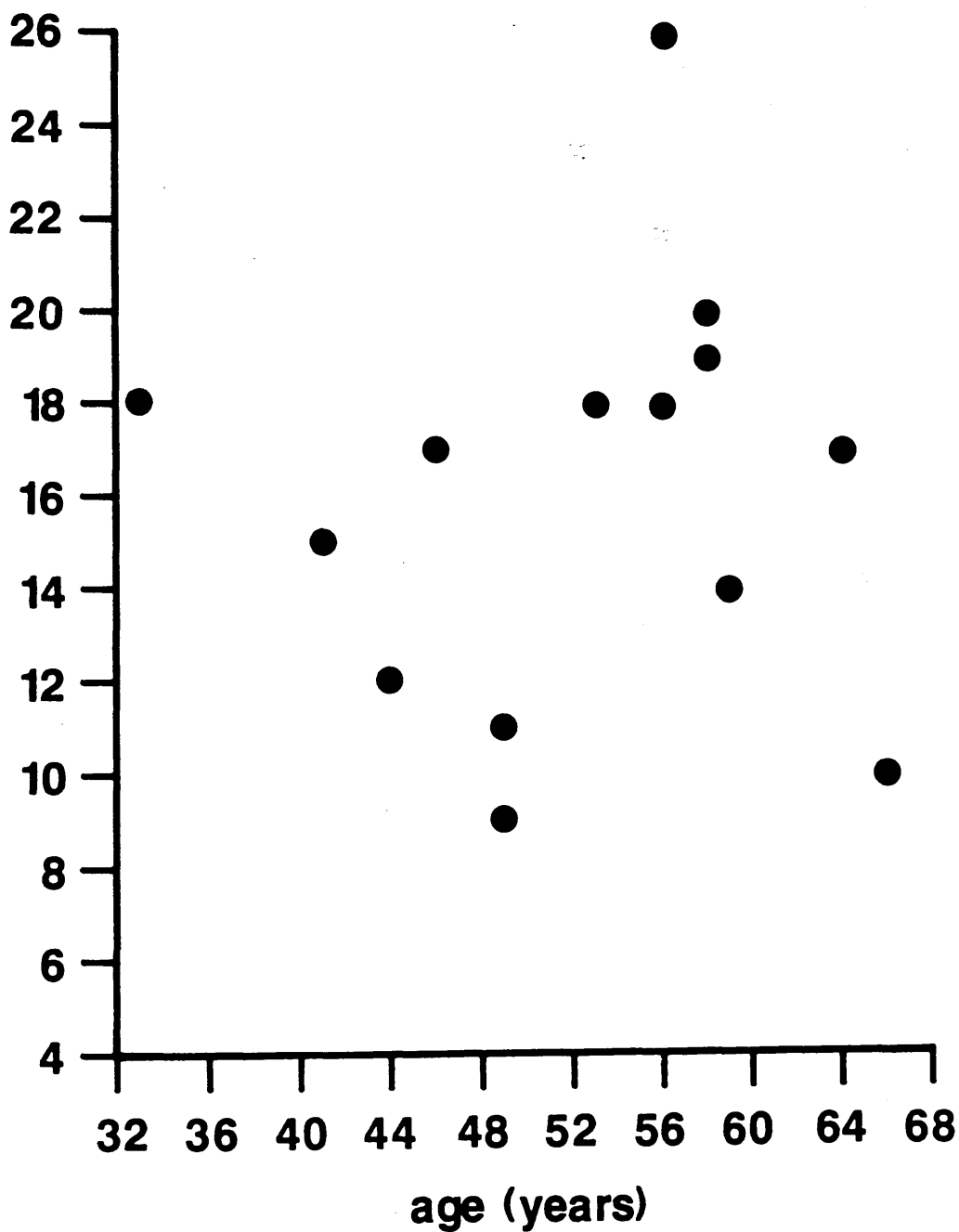
Figure 8.3.
Nifedipine study. Relationship between patient age and the
maximal (placebo and baseline subtracted) change in erect heart
rate following the 1st dose of nifedipine.
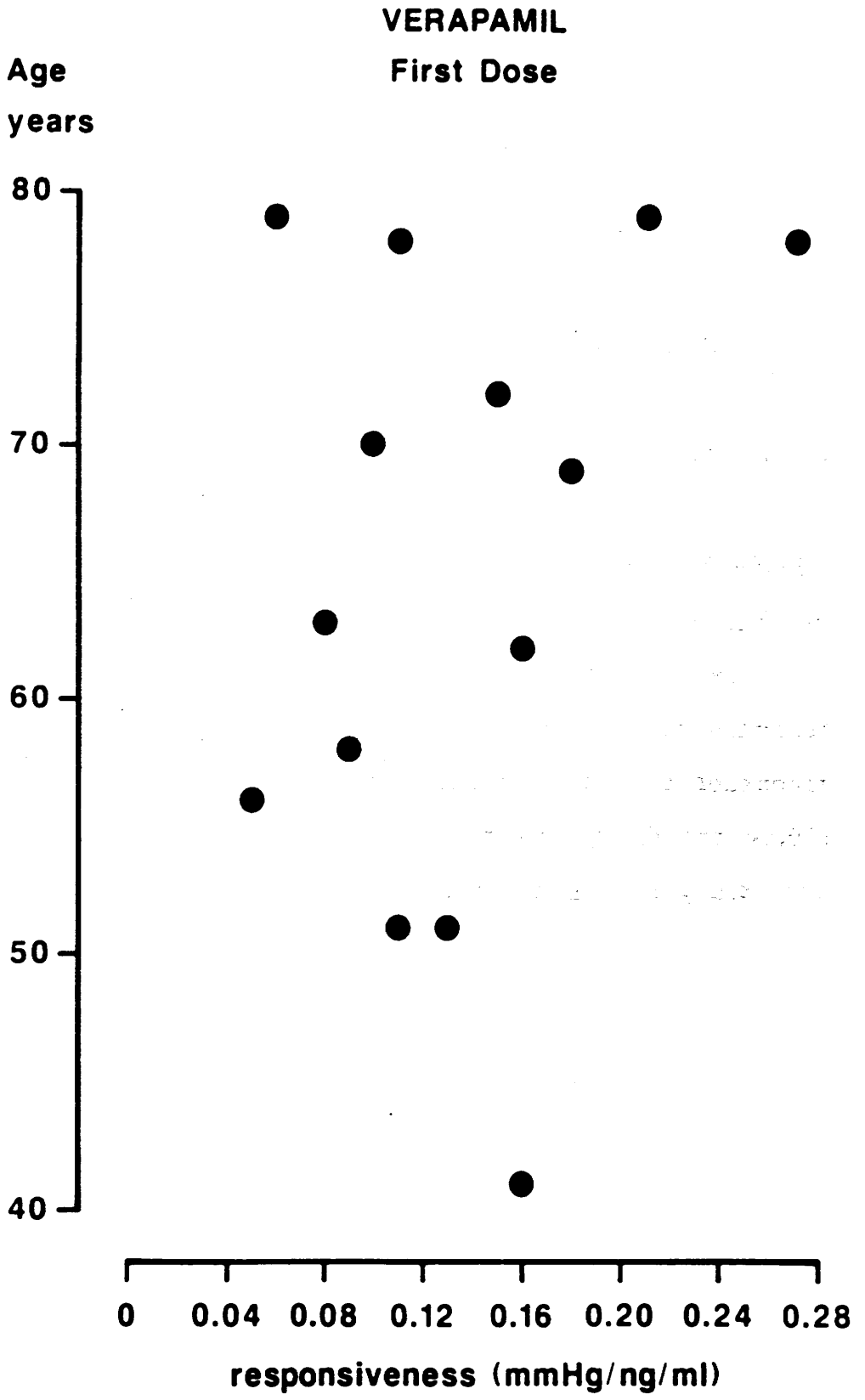
Figure 8.4.
The relationship between responsiveness to verapamil (1st dose)
and patient age (n=14).

The number of cigarette smokers in our group of
patients (26%) was too small to allow any formal statistical
analysis.   However, in the nifedipine study there were 5
smokers and 9 non-smokers (Table 3.1.).   Interestingly, the
responsiveness to nifedipine among smokers was greater than
non-smokers, both acutely and chronically, and was well
above the average for the group:   for example, the mean
responsiveness after the first dose and after 6 weeks among
smokers was -0.56 $\pm$ 0.17 and -0.62 $\pm$ 0.20 mmHg/ng/ml
respectively, compared with corresponding values of -0.43 $\pm$
0.21 and -0.42 $\pm$ 0.11 for the non-smokers and -0.48 $\pm$ 0.20
and -0.49 $\pm$ 0.17 mmHg/ng/ml for the group as a whole.

There was no clear sex difference in the responsiveness
to treatment:   for example, the responsiveness to doxazosin
in males and females respectively was -2.3 $\pm$ 1.1 and -2.0 $\pm$
0.7 after the first dose and -1.6 $\pm$ 1.1 and -1.2 $\pm$ 0.6
mmHg/ng/ml after 6 weeks.


## 8.3.5. Biochemical indices

Doxazosin was the only drug for which there was a
significant relationship between responsiveness and
pretreatment plasma renin activity (Figure 5.12.).   Such a
relationship was not observed with prazosin and additionally
neither the responsiveness to the calcium antagonists
(Figure 3.11.) nor the responsiveness to enalapril (Figure
4.7.) was directly related to plasma renin activity.

There was no significant relationship between drug

responsiveness and plasma levels of noradrenaline and similarly no relationship between responsiveness and serum cholesterol.

### 8.3.6. Vascular pressor responsiveness

There was no significant relationship between vascular pressor sensitivity ($PD_{20}$) before active treatment (i.e. on placebo) and the subsequent responsiveness to antihypertensive therapy. However, consistent with the mechanism of action of doxazosin, there was a trend towards a relationship between responsiveness and the degree of peripheral $alpha_1$ adrenoceptor blockade (Figure 5.9.). In contrast, the responsiveness to ketanserin appeared to be independent of its weak $alpha_1$ antagonist activity (Figure 7.11.). There was no significant relationship between the responsiveness to nifedipine and the attenuation in pressor sensitivity to angiotensin II and phenylephrine.

### 8.3.7. Multiple linear regression analysis

For each of the drugs, the responsiveness to the first dose was modelled with 4 independent variables - starting blood pressure, pretreatment plasma renin activity, age and the maximal (placebo-subtracted) reflex increase in heart rate - using stepwise least squares linear regression analysis. The $R^2$ values obtained from fitting a hierarchy of linear models to the data represent the percentage variability in responsiveness which can be accounted for by

the variable, or variables, incorporated in the model.

The results are summarised in Table 8.3, showing the $R^2$ values for each of the 1-variable analyses and identifying for the different drugs which independent variable, or combination of variables, was most appropriate for predicting the intersubject differences in responsiveness.

Thus, for enalapril, starting blood pressure was singularly the best predictor of responsiveness to the first dose, accounting for 48% of the variability in $E_{max}$, while age and plasma renin activity accounted for only 8% and 10.4% respectively (Table 8.3.). The 1-variable model with starting blood pressure was the most appropriate fit to the data and incorporating additional variables in more complex models did not significantly improve the correlation. The 1-variable model for enalapril was defined by the equation:

$$E_{max} = -0.62 \text{ (starting BP)} + 61.3 \quad : R^2 = 48\%$$

Similarly, for both prazosin and verapamil, starting blood pressure alone was the best predictor of response, accounting for 64% and 65% of the variabilities respectively (Table 8.3.). In both cases, age and plasma renin activity accounted for less than 10%, and more complex models, for example with 2 or 3 variables, were inferior to the 1-variable models with starting blood pressure which were defined by the equations:

m (prazosin)  = -0.3 (starting BP) + 38.8    : $R^2$ = 64%


m (verapamil) = -0.0025 (starting BP) + 0.3  : $R^2$ = 65%


For nifedipine, 1-variable analyses showed that starting blood pressure accounted for 37.1% of the variability in responsiveness;  the reflex increase in heart rate accounted for 25%;  and age accounted for only 0.9% (Table 8.3.).   However, the most appropriate model to describe the variability in responsiveness to nifedipine was a 3-variable model incorporating starting blood pressure, age and the heart rate increase.   This model accounted for 87.3% and was defined by the equation:


m (nifedipine) = -0.02 (BP) - 0.02 (Age) + 0.01 (HR) - 1.8


Starting blood pressure, plasma renin activity and the reflex heart rate response were all important determinants of the responsiveness to the first dose of doxazosin.   When fitted separately these variables accounted for 43%, 59.4% and 52% of the variability in responsiveness respectively. In contrast, age could explain only 0.6% of the variability (Table 8.3.).   The most appropriate model for doxazosin was a 3-variable model incorporating plasma renin activity, starting blood pressure and the reflex heart rate response ($R^2$ = 85%), and this was defined by the equation:

TABLE 8.3.

MULTIPLE LINEAR REGRESSION ANALYSIS USING FOUR INDEPENDENT
VARIABLES:  STARTING BP, PLASMA RENIN ACTIVITY (PRA), AGE
AND REFLEX HR INCREASE.  $R^2$ REPRESENTS THE PERCENTAGE OF THE
VARIABILITY IN RESPONSIVENESS TO THE FIRST DOSE WHICH CAN BE
ACCOUNTED FOR BY THE VARIABLES IN THE MODEL

| | $R^2$ FOR 1-VARIABLE MODELS | | | | BEST MODEL ($R^2$) |
|---|---|---|---|---|---|
| | AGE | BP | PRA | $\triangle$ HR | |
| Doxazosin | 0.6% | 43% | 59.4% | 52% | 3-variable: PRA + BP + $\triangle$ HR (85%) |
| Nifedipine | 0.9% | 37.1% | 4% | 25.5% | 3-variable: PRA + BP + $\triangle$ HR (87.3%) |
| Enalapril | 8% | 48% | 10.4% | - | 1-variable: BP (48%) |
| Prazosin | 10.3% | 64% | 5.3% | - | 1-variable: BP (64%) |
| Verapamil | 7% | 65% | 9% | - | 1-variable: BP (65%) |

TABLE 8.4.

THE COMPARATIVE EFFECTS OF THREE TREATMENTS ON SYSTOLIC
VERSUS DIASTOLIC BP EXPRESSED AS THE RATIO RESPONSIVENESS (m
or $E_{max}$) SYSTOLIC/DIASTOLIC BP. MEAN ± SD AFTER ACUTE AND
CHRONIC ADMINISTRATION.

|  | FIRST DOSE | 6 WEEKS |
| --- | --- | --- |
| Nifedipine: | 2.23 ±<br>1.20 | 1.92 ±<br>0.56 |
| Doxazosin: | 1.47 ±<br>0.30 | 1.51 ±<br>0.43 |
| Enalapril: | 2.39* ±<br>1.0 | |

\* $E_{max}$ values derived from fitting the data sets for
all 3 study days simultaneously (see Chapter 4.3.5.).

m (doxazosin) = -0.4 (PRA) - 0.02 (BP) + 0.03 (HR) + 0.9

### 8.3.8. Differential effects on systolic and diastolic blood pressure

Responsiveness to nifedipine, enalapril and doxazosin was characterised in terms of the fall in both systolic and diastolic blood pressure (Chapters 3-5). In each study there were significant correlations between the responsiveness ($\dot{m}$ or $E_{max}$) in terms of systolic and diastolic blood pressure. The mean ratios of systolic/diastolic response are shown in Table 8.4. and there was no significant difference between treatments in their relative effects on systolic versus diastolic blood pressure.

### DISCUSSION

Many studies during the last fifteen years have investigated the inter and intra subject variability in response to different antihypertensive drugs and produced a number of conflicting and often misleading statements, for example about variations in responsiveness related to age (Buhler et al, 1982; Ferrara et al, 1985; Ram, 1987; Bidiville et al, 1988; M'Buyamba-Kabangu et al, 1988), ethnic origin (Seedat and Reddy, 1971) and biochemical parameters such as plasma renin activity (Buhler et al, 1982; Cody et al, 1983; Bidiville et al, 1988). Much of the confusion that has arisen is a direct result of the

inconsistent and often unsatisfactory methods used for describing antihypertensive response: for example, in most previous studies response has been quantified on the basis of pharmacodynamics alone - usually single measurements of blood pressure recorded on one or two separate occasions - and no account has been taken of interindividual or time related differences in plasma drug concentration. A good example of this is the widely quoted study by Buhler and colleagues (1982) which over the last few years has formed the basis of an over-stated and probably misconceived argument that calcium antagonists are significantly more effective in the elderly. Buhler investigated a group of patients receiving different doses of verapamil and showed that the fall in blood pressure was directly proportional to age (Figure 1.1.) but the study took no account of placebo effects, starting blood pressure or, more importantly, plasma verapamil concentrations which may have been higher in the elderly. Since kinetic as well as dynamic variability accounts for interindividual differences in blood pressure rsponse, it is possible that the observations of Buhler may have been due to age-related differences in pharmacokinetics rather than increased responsiveness per se. Similar criticism may be extended to the study by Ferrara et al (1985) which purported to show an opposite relationship between age and the antihypertensive response to nitrendipine.

Another example which illustrates the need for

integrated pharmacokinetic-pharmacodynamic analysis concerns the relationship between smoking and antihypertensive drug response. One of the conclusions from the MRC Trial (1985) was that the fall in blood pressure with propranolol was less in cigarette smokers than non-smokers, whereas no such difference occurred with bendrofluazide. Similar findings were also reported in the IPPPSH study with the non-selective beta blocker oxprenolol (IPPPSH study group, 1985). While this may reflect a difference in smokers to the haemodynamic effects of beta blockade, it is also possible that a pharmacokinetic basis seems more likely since smoking has been shown to increase the clearance of propranolol (Dawson and Vestal, 1981). Thus, the fall in blood pressure per unit drug concentration may have been similar in smokers compared with non-smokers.

The present study has highlighted the importance of considering pharmacokinetic as well as pharmacodynamic variability when investigating interindividual differences in blood pressure response. The measurements of responsiveness derived from the concentration-effect analysis incorporate both kinetic and dynamic data for individual patients and additionally take account of placebo effects and variations in blood pressure and drug concentration during the dosage interval. A number of haemodynamic, demographic and biochemical markers were examined in relation to the responsiveness to different drugs and by far the most important determinants of

antihypertensive response during longterm treatment were the height of the pretreatment blood pressure and the response to the first dose.

The relationship between starting blood pressure and the magnitude of the fall with treatment has been described previously with calcium antagonists (MacGregor et al, 1982b; Erne et al, 1983).  However, there are statistical problems in correlating two dependent variables (Gill et al, 1985), i.e. BP and $\triangle$ BP, and it is probably more appropriate to seek correlations which also take account of interindividual differences in drug concentrations and in the extent of the blood pressure fall associated with placebo (Sumner et al, 1988a).  In this study there were significant positive correlations not only with the calcium antagonists but also with the other four drugs between responsiveness and the baseline (pretreatment) blood pressure.  The relationship was seen most clearly with systolic blood pressure and this probably reflects the wider range of systolic blood pressures observed.  The slope of the correlation was greatest for nifedipine and verapamil and this may partly explain why calcium antagonists are reported to be particularly effective in severe or resistant hypertension (Bayley et al, 1982;  Dean and Kendall, 1983).

It has been suggested that the acute fall in blood pressure with a given antihypertensive drug is not a good predictor of the response obtained during longterm therapy (Bidiville et al, 1988).  In this study, however, which

considered kinetics as well as dynamics in individual
patients, there were significant correlations between the
responsiveness to the first dose and the responsiveness
after 4-6 weeks, which suggests that the first dose response
may be used to forecast the steady state effect for an
individual patient.  Additionally, with the exception of
ketanserin, this relationship applied irrespective of
treatment and was independent of any reduction in
responsiveness in translation from acute to chronic therapy.
Clearly this has potential application in clinical practice
as a means of quickly identifying poor or non-responders and
for determining individual dose requirements for optimum
longterm blood pressure control.  During the first week of
treatment with nifedipine and with the alpha blockers,
prazosin and doxazosin, there was evidence that the fall in
blood pressure was associated with reflex sympathetic
activation but it is noteworthy that this did not perturb
the correlations with the responses obtained at 6 weeks,
when baroreflex mechanisms had apparently "reset".

Since the early 1970s when Laragh (1973) proposed a
volume-vasoconstrictor hypothesis to account for some of the
pathophysiological abnormalities in hypertension, there has
been considerable interest in the effects of age and plasma
renin activity on the response to antihypertensive drugs.
Initial optimism about the potential value of renin
profiling was quickly removed when it soon became clear that
in clinical practice plasma renin activity alone could not

268

predict the response to a beta blocker or diuretic (Hansson et al, 1974; Zanchetti, 1985). More recently, the haemodynamic effects of some of the newer antihypertensive agents such as calcium antagonists (Buhler et al, 1982; M'Buyamba-Kabangu et al, 1988), ACE inhibitors (Gavras et al, 1978; Case et al, 1981; Cody et al, 1983) and alpha blockers (Bolli et al, 1981) have been shown to be partly related to the activity of the renin-angiotensin system and there has been revived interest in the role of plasma renin as a predictive marker of drug response (Cody et al, 1983). While extremes of sodium intake may influence the haemodynamic effects of these drugs, this study has shown that in a typical group of hypertensive patients on a normal diet calcium antagonists, ACE inhibitors and alpha blockers are generally far more effective than can be usefully predicted by age or measurements of plasma renin activity.

The multiple linear regression analysis showed that for all drugs age and plasma renin activity each accounted for less than 10% of the variability in responsiveness to the first dose. The exception to this was the somewhat surprising relationship between PRA and responsiveness to doxazosin but, since no such relationship was seen with prazosin, the significance of this result should be interpreted cautiously. The most important observation from the multivariant analysis was that for each of the drugs, including doxazosin, starting blood pressure alone could explain over 50% of the variability in responsiveness

to the first dose. Furthermore, the only additional variable which produced a clinically significant improvement in the correlation between starting blood pressure and responsiveness was the reflex increase in heart rate associated with nifedipine and doxazosin.

There is some evidence with the dihydropyridine calcium antagonist nicardipine that the antihypertensive effect is dependent on baseline sympathetic nervous activity (Ryman et al, 1987). In this study, and in another study with nifedipine and verapamil (Schwietzer et al, 1983), there was no relationship between responsiveness and plasma levels of noradrenaline but the limitations of this method as an index of sympathetic activity are well recognised. In addition, it has been shown that impairment of the pressor response to noradrenaline is not a prerequisite for the antihypertensive action of calcium antagonists (Schwietzer et al, 1983) and in this study there was no relationship between responsiveness to nifedipine (m) and the attenuation in pressor sensitivity to angiotensin II and phenylephrine.

Although not specifically measured in this study, intracellular electrolyte concentrations have also been proposed as important biochemical determinants of antihypertensive response (Breckenridge, 1987). Lymphocyte $Na^+$ and $K^+$ levels have been directly correlated with the antihypertensive effects of captopril (Costa et al, 1985) and nifedipine (M'Buyamba-Kabangu, 1988) but it demands great extrapolation to conceive of this becoming a useful

step in selecting antihypertensive drugs.

Because of the apparent failure of antihypertensive therapy to improve coronary heart disease mortality, it has become important that we gain greater understanding of the inter-relationship between hypertension and other coronary risk factors (Reid, 1988). The number of patients in the present study was too small to gain any useful insight into the effects of cigarette smoking and cholesterol on responsiveness to different antihypertensive drugs but similar studies with selected patient groups are warranted in the future.

The relative importance of systolic and diastolic blood pressures in predicting risk and likely benefit from treatment remains controversial (Fisher, 1985; Ramsay and Waller, 1986). Although systolic and diastolic blood pressures are closely correlated (r=0.80), there is considerable discord in the relationship: for example, 20% of men aged 40-59 years with systolic blood pressures greater than 180 mmHg have a diastolic blood pressure less than 90 mmHg and similarly about 20% of men with diastolic blood pressures greater than 100 mmHg have a systolic blood pressure of less than 160 mmHg (Shaper et al, 1987). In this study the responsiveness to nifedipine, enalapril and doxazosin was characterised in terms of the fall in both systolic and diastolic blood pressure and there was no significant difference between treatments in their relative effects on the two parameters. In particular, there was no

evidence to support previous suggestions that the ACE inhibitor enalapril is particularly effective in lowering systolic more than diastolic blood pressure (O'Connor et al, 1984; Beevers et al, 1984).

In summary, an integrated method for describing antihypertensive response, which incorporates both pharmacokinetic and pharmacodynamic information, forms a useful basis for investigating factors which determine inter and intra-subject differences in blood pressure response. A number of haemodynamic, demographic and biochemical parameters have been examined in relation to the responsiveness to calcium antagonists, alpha blockers, the ACE inhibitor enalapril and the serotonin antagonist ketanserin. The most important determinants of response during longterm treatment are the height of the pretreatment blood pressure and the response to the first dose. This has important and encouraging implications for developing an individualised approach to antihypertensive treatment.

# CHAPTER 9

## GENERAL DISCUSSION

273

# DISCUSSION

The scope for improvement in antihypertensive therapy has been highlighted by some of the recent major trials in mild to moderate hypertension, which have exposed important limitations of pragmatic 'stepped-care' policies and advocated instead a more flexible individualised approach to treatment. However, in contrast to developments in other areas of therapeutics, for example with anticonvulsant, antiarrhythmic and bronchodilator drugs, little attempt has been made to apply developments in clinical pharmacokinetics to improve drug selection and dosage in hypertension. An understanding of dose-response and concentration-effect relationships and of factors which determine the response to antihypertensive drugs constitutes a basis for optimising drug therapy prospectively in individual patients but so far such information has been scarce and ill-defined.

It has been suggested that for a number of antihypertensive drugs no predictable concentration-effect relationship exists but this probably reflects the negative findings of those previous studies which considered the response for groups of patients rather than for individuals. This series of studies has shown that drug concentrations are correlated with the reductions in blood pressure in individual hypertensive patients and has extended some preliminary observations (Pasanisi and Reid, 1983; Kelman et al, 1983) by defining individual concentration-response relationships which are applicable during chronic treatment.

274

The linear concentration-effect model was better than the Langmuir ($E_{max}$) model for describing the kinetic-dynamic relationships of nifedipine, doxazosin and ketanserin and the same was found with verapamil (Meredith et al, 1987) and prazosin (Elliott et al, 1988c).  In contrast, the individual data sets for enalapril were fitted most appropriately by the $E_{max}$ relationship and this has been reported previously with other ACE inhibitors (Kelman et al, 1983;  Francis et al, 1987).  The significance of this observation is not entirely clear but it may reflect the non-linear kinetics of ACE inhibitors and their binding properties to plasma and tissue ACE.  Additionally, it may partly explain why ACE inhibitors have been reported to have flat dose-response curves (Davies et al, 1984), since previous studies may have used doses which produce drug levels at the top end of the concentration-effect curve.

Both effect models provide an integrated method for quantifying the antihypertensive response of an individual in terms of kinetic as well as dynamic parameters and for characterising the temporal discrepancy for the plasma concentration-effect relationship ($K_{eq}$).  Clearly there are potentially numerous applications of this approach both in research and in clinical practice.  The study of ketanserin illustrates the use of concentration-effect analysis in clinical investigations of antihypertensive mechanisms. Responsiveness to the first dose of ketanserin was significantly greater than that after 4 weeks and there was

no relationship between responsiveness and the degree of peripheral alpha blockade. Additionally, in contrast to the other drugs, there was no relationship between acute and chronic responsiveness and there was a significant change in the parameter $K_{eq}$ in translation from acute to steady state therapy. The increase in $K_{eq}$ reflects an alteration to the temporal relationship between the profiles of plasma concentration and blood pressure reduction and it is my suggestion that this change in $K_{eq}$, together with the lack of a direct relationship between the acute and chronic responses, reflects a change in the relative contributions of different components of the antihypertensive mechanism of ketanserin. Thus, peripheral $alpha_1$ antagonism may make a relatively greater contribution after the first dose whereas a centrally-mediated effect may predominate during longterm treatment.

The studies presented in this thesis have illustrated the feasibility of using concentration-effect analysis to examine various aspects of the clinical pharmacology of antihypertensive drugs. This work forms the basis for a number of further investigations, which are already planned, to test the application of this approach in clinical practice and to refine pharmacokinetic techniques for improving drug use in hypertension. Having identified concentration-effect relationships for a number of vasodilator drugs, it would be appropriate to investigate conventional drugs like beta blockers and diuretics using a similar approach. A

preliminary study with the beta blocker flusoxolol has shown that in normotensive subjects the concentration-effect relationship is defined most appropriately by an $E_{max}$ model (Sumner et al, 1988b). This would be consistent with the conventional wisdom that beta blockers have flat dose-response curves but would again suggest that previous studies have used doses which produce drug levels at the top end of the $E_{max}$ curve. In contrast, beta blockers with additional vasodilator properties, for example medroxalol and labetalol, appear to have concentration-effect relationships which are described more appropriately by a linear model (Elliott et al, 1984).

So far we have only characterised responses to drug treatment as monotherapy but a large proportion of patients require treatment with more than one drug. A study to investigate concentration-effect relationships with combination treatments is therefore warranted and may provide additional information about drug interactions. As an introduction to this step, we have established the efficacy and patient acceptability of two relatively novel combinations: the combination of a calcium antagonist with an ACE inhibitor (Donnelly et al, 1987) and the combination of a calcium antagonist with an alpha blocker (Elliott et al, 1988b). Using concentration-effect analysis, it may be possible to identify favourable drug interactions: for example, to compare the effects of an alpha blocker and an ACE inhibitor on the responsiveness to additional treatment

with a calcium antagonist.

Large studies are required to further investigate factors responsible for interindividual differences in blood pressure response. However, in this project, with a relatively small number of patients, it has been possible to identify two important determinants of response during longterm treatment, the height of the starting blood pressure and the response to the first dose. Additionally, it has been shown that in a typical group of salt replete hypertensive patients on a normal diet calcium antagonists and ACE inhibitors are far more effective than can be usefully predicted by age or measurements of plasma renin activity.

An individualised approach to treatment is a laudable goal. Ideally this would involve an initial selection, from 4 or 5 alternative first-line drugs, based on clinical and demographic information about the individual; a rapid assessment, ideally following the first dose, that the patient is likely to have a satisfactory response; and then the selection of the optimum dosage for longterm treatment. The present study has raised the possibility that the response during longterm treatment for an individual patient may be forecast on the basis of the response to the first dose. Clearly this would be useful in clinical practice as a means of quickly identifying poor or non-responders and for determining individual dose requirements for optimum blood pressure control. However, the relationships between

acute and chronic response were identified retrospectively and further work is planned to attempt to predict and thereby optimise the longterm response prospectively from single dose experiments.

If concentration-effect analysis is to find a place in routine clinical practice it must become possible to characterise individual patient responses using much fewer measurements of blood pressure and drug plasma concentration. In the present studies we have measured the full kinetic and dynamic profiles over 24 hours but with retrospective analysis it may be feasible to derive reliable estimates of the concentration-effect parameters using one or two important data points, for example peak or trough concentrations and the associated blood pressure effects. An alternative approach may be to use population pharmacokinetic analysis, which takes one or two measurements per individual from a large group of subjects and derives population estimates of pharmacokinetic parameters (Whiting et al, 1986). Additionally, this technique can incorporate data on efficacy and toxicity, allowing the development of a more rigorous approach to the concept of the 'therapeutic range'.

In conclusion, this project has identified drug concentration-effect relationships in individual hypertensive patients using recently developed methods of clinical pharmacokinetic analysis. The derived concentration-effect parameters are potentially useful not

only for identifying factors responsible for intersubject
variability in response but also for optimising drug therapy
in individual patients.

REFERENCES

Adlin, E.V., Marks, A.D. & Channick, B.J. (1972)
Spironolactone and hydrochlorthiazide in essential
hypertension. Archives of Internal Medicine, **130**, 855-858.

Ajayi, A.A., Campbell, B.C., Meredith, P.A., Kelman, A.W. &
Reid, J.L. (1985) The effect of captopril on the reflex
control of heart rate: possible mechanisms. British Journal
of Clinical Pharmacology, **20**, 17-25.

Amann, F.W., Bolli, P., Kiowski, W. & Buhler, F.R. (1981)
Enhanced alpha adrenoceptor mediated vasoconstriction in
essential hypertension. Hypertension, 3 (Suppl.1), 119-123.

Amery, A., Fagard, R., Fiocchi, P., Lijnen, J., Staessen,
J. & Vanhees, L. (1985) Ketanserin: a new hypotensive
drug? Journal of Cardiovascular Pharmacology, **7(Suppl.7)**,
S176-S182.

Andrews, G., MacMahon, S.W., Austin, A. & Byrne, D.G.
(1982) Hypertension: comparison of drug and non-drug
treatments. British Medical Journal, **284**, 1523-1526.

Antman, E., Miller, J. & Goldberg, S. (1980) Nifedipine
therapy for coronary artery spasm. New England Journal of
Medicine, **302**, 1269-1273.

Aoki, K., Sato, K., Kawaguchi, Y. & Yamamoto, M. (1982)
Acute and longterm hypotensive effects and plasma
concentrations of nifedipine in patients with essential
hypertension. European Journal of Clinical Pharmacology, **23**,
197-201.

Atkinson, A.B., Brown, J.J., Lever, A.F. & Robertson,
J.I.S. (1980) Combined treatment of severe intractible
hypertension with captopril and diuretic. Lancet, **ii**, 165-
168.

Australian Therapeutic trial in mild hypertension (1980).
Report by the management committee. Lancet, **i**, 1261-1267.

Bach, D., Blevins, R., Kerner, M., Ruberfire, M. & Edwards,
D.J. (1986) The effect of verapamil on antipyrine
pharmacokinetics and metabolism in man. British Journal of
Clinical Pharmacology, **21**, 655-659.

Baez, M.A., Garg, D.C., Jallad, N.S. & Weidler, D.J.
(1986) Antihypertensive effect of doxazosin in hypertensive
patients: comparison with atenolol. British Journal of
Clinical Pharmacology, **21**, 63s-68s.

Bateman, D.N., Hobbs, D.C., Twomey, T.M., Stevens, E.A. &
Rawlins, M.D. (1979) Prazosin, pharmacokinetics and

concentration-effect. European Journal of Clinical Pharmacology, 16, 171-181.

Bauer, J.H., Brooks, C.A.S., Weinstein, I., Wilcox, H.H., Heimberg, M., Burch, R.N. & Barkley, R. (1981) Effects of diuretic and propranolol on plasma lipoprotein lipids. Clinical Pharmacology and Therapeutics, 30, 35-43.

Bayley, S., Dobbs, R.J. & Robinson, B.F. (1982) Nifedipine in the treatment of hypertension: report of a double-blind controlled trial. British Journal of Clinical Pharmacology, 14, 509-512.

Bazett, H.C. (1920) An analysis of the time-relations of electrocardiograms. Heart, 7, 353-370.

Beevers et al (1984) Enalapril Hypertension Study Group. Enalapril in essential hypertension: a comparative study with propranolol. British Journal of Clinical Pharmacology, 18, 51-56.

Bendall, M.J., Baloch, K.H. & Wilson, P.R. (1975) Side effects due to treatment of hypertension with prazosin. British Medical Journal, 2, 727-728.

Beretta-Piccoli, C., Bianchetti, M.G., Weidmann, P., Boehringer, K., Link, L. & Morton, J. (1982) Effects of acute mild hypercalcaemia or of the calcium antagonist nifedipine on cardiovascular responsiveness to norepinephrine or angiotensin II in normal humans. Journal of Cardiovascular Pharmacology, 4, S306-S312.

Berglund, G. & Andersson, O. (1981) Beta blockers or diuretics in hypertension? A six-year follow-up of blood pressure and metabolic side effects. Lancet, i, 744-747.

Bevington, P.R. (1969) Data reduction and error analysis for the physical sciences. McGraw-Hill, New York, p235-236.

Bidiville, J., Nussberger, J., Waeber, G., Porchet, M., Waeber, B. & Brunner, H.R. (1988) Individual responses to converting enzyme inhibitors and calcium antagonists. Hypertension, 11, 166-173.

Biollaz, J., Schelling, J.L., Jacot Des Combes, B., Brunner, D.B., Deponds, G., Brunner, H.R. & Gomez, H.J. (1982) Enalapril maleate and a lysine analogue (MK521) in normal volunteers; relationship between plasma drug levels and the renin angiotensin system. British Journal of Clinical Pharmacology, 14, 363-368.

Bolli, P., Amann, F.W. & Buhler, F.R. (1981) Antihypertensive response to post-synaptic alpha blockade with prazosin in low and normal renin. Journal of Cardiovascular Pharmacology, 2, 399-400.

282

Bolli, P., Kiowski, W., Erne, P., Hulthen, L.U. & Buhler, F.R. (1985) Haemodynamic and antihypertensive treatment responses with calcium antagonists. Journal of Cardiovascular Pharmacology, 7, S126-S130.

Boomsma, F., De Bruyn, J.H.B., Derkx, F.H.M., Schalekamp, M.A.D.H. (1981) Opposite effects of captopril on angiotensin I converting enzyme 'activity' and 'concentration'; relation between enzyme inhibition and longterm blood pressure response. Clinical Science, 60, 491-498.

Braunwald, E. & Epstein, F.H. (1982) Mechanism of action of calcium channel blocking agents. New England Journal of Medicine, 26, 1618-1627.

Breckenridge, A. (1987) Factors in the choice of antihypertensive therapy. British Journal of Clinical Pharmacology, 23, 5s-8s.

Brouwer, R.M., Bolli, P., Erne, P., Conen, D., Wolfgang, K. & Buhler, F.R. (1985). Antihypertensive treatment using calcium antagonists in combination with captopril rather than diuretics. Journal of Cardiovascular Pharmacology, 7 (suppl.1), S88-S91.

Brunner, H.R., Gavras, H., Waeber, B., Textor, S.C., Turini, C.A. & Wauters, J.P. (1980) Clinical use of an orally active converting enzyme inhibitor: captopril. Hypertension, 2, 558-566.

Brunner, D.B., Desponds, G. & Biollaz, J. (1981) Effect of a new angiotensin converting enzyme inhibitor, MK421, and its lysine analogue on the components of the renin system in healthy subjects. British Journal of Clinical Pharmacology, 11, 461-467.

Brunner, H.R., Waeber, B., Nussberger, J., Schaller, M.D. & Gomez, H.J. (1983) Longterm clinical experience with enalapril in essential hypertension. Journal of Hypertension, 1(Suppl.1), 103-107.

Bruun, N.E., Ibsen, H., Nielsen, F., Nielson, M.D., Molbak, A.G. & Hartling, O.J. (1985) The influence of nifedipine treatment on counter-regulatory mechanisms in essential hypertension. Journal of Hypertension, 3 (Suppl.3), S223-S225.

Buhler, F.R., Laragh, J.G., Baer, L., Vaughan, E.D. & Brunner, H.R. (1972) Propranolol inhibition of renin secretion. New England Journal of Medicine, 287, 209-214.

Buhler, F.R., Kiowski, W., Landmann, R., van Brummelen, P., Amann, F.W., Bolli, P. & Bertel, O. (1981) Changing role of beta and alpha adrenoceptor mediated cardiovascular responses in the transition from a high cardiac output into

a high peripheral resistance phase in essential
hypertension. In <u>Frontiers</u> <u>in</u> <u>Hypertension</u> <u>Research</u>, ed.
Laragh, J.H., Buhler, F.R., Seldin, D.W. pp316-324. New
York: Springer.

Buhler, F.R. & Hulthen, L. (1982) Calcium channel blockers:
a pathophysiologically based antihypertensive treatment
concept for the future. <u>European</u> <u>Journal</u> <u>of</u> <u>Clinical</u>
<u>Investigation</u>, **12**, 1-3.

Buhler, F.R., Hulthen, D.L. & Kiowski, W. (1982) The place
of the calcium antagonist verapamil in antihypertensive
therapy. <u>Journal</u> <u>of</u> <u>Cardiovascular</u> <u>Pharmacology</u>, **4**, 5350-
5357.

Buhler, F.R. & Bolli, P. (1985) Changes in cardiovascular
responsiveness caused by age and high blood pressure:
implications for therapy. <u>Journal</u> <u>of</u> <u>Cardiovascular</u>
<u>Pharmacology</u>, **7** (Suppl.3), S206-S215.

Bulpitt, C.J., Beevers, D.G., Butler, A., Coles, E.C., Hunt,
D., Munro-Faure, A.D. et al. (1986) The survival of treated
hypertensive patients and their causes of death:  a report
from the D.H.S.S. Hypertensive Care Computing Project
(DHCCP). <u>Journal</u> <u>of</u> <u>Hypertension</u>, **4**, 93-99.

Burris, J.F., Notargiacomo, A.V., Papademetriou, V. & Freis,
E.D. (1982) Acute and short-term effects of a new calcium
antagonist in hypertension. <u>Hypertension</u>, **4**(Suppl.II), 32-
35.

Cameron, H.A., Waller, P.C. & Ramsay, L.E. (1986) The effect
of ketanserin on the QT interval. <u>British</u> <u>Journal</u> <u>of</u>
<u>Clinical</u> <u>Pharmacology</u>, **23**, 630p.

Cameron, H.A., Waller, P.C. & Ramsay, L.E. (1987) Ketanserin
in essential hypertension: use as monotherapy and in
combination with a diuretic or beta-adrenoceptor antagonist.
<u>British</u> <u>Journal</u> <u>of</u> <u>Clinical</u> <u>Pharmacology</u>, **24**, 705-711.

Cappuccio, F.P., Markandu, N.D. & MacGregor, G.A. (1987)
Nifedipine blunts the blood pressure lowering effect of a
thiazide diuretic in hypertensive patients. <u>Journal</u> <u>of</u>
<u>Cardiovascular</u> <u>Pharmacology</u>, (Suppl.), in press.

Carlson, L.A. & Roessner, S. (1979) Risk factors for
myocardial infarction in the Stockholm Prospective Study.
<u>Acta</u> <u>Medica</u> <u>Scandinavica</u>, **206**, 351-360.

Case, D.B., Atlas, S.A., Laragh, J.H. (1981) Position paper:
Physiologic effects and diagnostic relevance of acute
converting enzyme blockade. In: <u>Frontiers</u> <u>in</u> <u>Hypertension</u>
<u>Research</u>, edited by Laragh, J.H., Buhler, F.R. and Seldin,
D.W. New York: Springer Verlag, 541-550.

Chiknas, S.G. (1979) Liquid chromatography assisted assay for angiotensin converting enzyme in serum. Clinical Chemistry, 25(7), 1259-1262.

Chobanian, A.R. (1986) Antihypertensive therapy in evolution. Editorial. New England Journal of Medicine, 314, 1701-1702.

Chu, D. & De Gori, D. (1982) Antihypertensive effect of tiapamil, a calcium antagonist. Cardiology, 69(Suppl.1), 99-104.

Clement, D.L. (1978) Effect of indoramin on finger blood flow in vasospastic patients. European Journal of Clinical Pharmacology, 14, 331-333.

Clementini, W., Durst, N.L., McNay, J.L. & Keeton, T.K. (1986) Captopril modifies the haemodynamic and neuroendocrine responses to sodium nitroprusside in hypertensive patients. Hypertension, 8, 229-237.

Cody, R.J., Tarazi, R.C., Bravo, E.L. & Fouad, F.M. (1979) Haemodynamics of an orally active converting enzyme inhibitor (captopril) in hypertensive patients. Clinical Science and Molecular Medicine., 55, 453-459.

Cody, R.J., Laragh, J.H., Case, D.B. & Atlas, S.A. (1983) Renin system activity as a determinant of response to treatment in hypertension and heart failure. Hypertension, 5, (Suppl.III), 36-42.

Cohen, M.L. & Kurz, K.D. (1982) Angiotensin converting enzyme inhibition in tissues from spontaneously hypertensive rats after treatment with captopril or MK421. Journal of Pharmacology and Experimental Therapeutics, 220, 63-69.

Coleman, A.J. (1981) Evidence for increase in peripheral blood flow by indoramin in man. British Journal of Clinical Pharmacology, 12, 79s-83s.

CONSENSUS Trial Study Group (1987) Report. New England Journal of Medicine, 316, 1429-1435.

Costa, F.V., Borghi, C., Boschi, S. & Ambrosioni, E. (1985) Differing doses of captopril and hydrochlorthiazide in the treatment of hypertension. Journal of Cardiovascular Pharmacology, 7, 570-576.

Cox, D.A., Leader, J.P., Milson, J.A. & Singleton, W. (1986) The antihypertensive effects of doxazosin: a clinical overview. British Journal of Clinical Pharmacology, 21, 83s-90s.

Cubeddu, L.X., Fuenmayor, N., Caplan, N. & Ferry, D. (1987) Clinical Pharmacology of doxazosin in patients with

essential hypertension. <u>Clinical Pharmacology and Therapeutics</u>, **41**, 439-449.

Dale, J., Landmark, K.M. & Myhre, E. (1983) The effects of nifedipine, a calcium antagonist, on platelet function. <u>American Heart Journal</u>, **105**, 103-105.

Da Prada M. & Zurcher, G. (1976) Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtamole range. <u>Life Sciences</u>, **19**, 1161-1174.

Davies, R.O., Gomez, H.J., Irvin, J.D. & Walker, J.F. (1984) An overview of the clinical pharmacology of enalapril. <u>British Journal of Clinical Pharmacology</u>, **18**, 215s-229s.

Dawson, G.W. & Vestal, R.E. (1981) Smoking and drug metabolism. <u>Pharmacology and Therapeutics</u>, **15**, 207-222.

Dean, S. & Kendall, M.J. (1983) Nifedipine in the treatment of difficult hypertensives. <u>Euorpean Journal of Clinical Pharmacology</u>, **24**, 1-5.

De Cree, J., Leempoels, J., Geukens, H., De Cock, W. & Verhaegen, H. (1981a). The antihypertensive effects of ketanserin, a novel 5-hydroxytryptamine-blocking agent, in patients with essential hypertension. <u>Clinical Science</u>, **61**, 473s-476s.

De Cree, J., Verhaegen, H., Symoens, J. (1981b) Acute blood pressure lowering effect of ketanserin. <u>Lancet</u>, **i**, 1161.

de Leeuw, P.W., Hoogma, R.P.L.M., van Soest, G.A.W., Tchang, P.T., Birkenhager, W.H. (1983) Humoral and renal effects of MK 421 (enalapril) in hypertensive subjects. <u>Journal of Cardiovascular Pharmacology</u>, **5**, 731-736.

Derkx, F.H.M., Boomsma, F., Tan-Tjiong, H.L. & Schalekamp, M.A.D.H. (1972) Role of plasma kallikrein in the proteolytic activation of the renin-angiotensin system. <u>Clinical and Experimental Hypertension</u>, **2 (3 & 4)**, 575-592.

Desch, C.E., Magorien, R.D., Triffon, D.W., Blanford, M.F., Unverferth, D.V. & Leier, C.V. (1979) Development of pharmacodynamic tolerance to prazosin in congestive heart failure. <u>American Journal of Cardiology</u>, **44**, 1178-1182.

Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. (1987) An evaluation of the pharmacodynamics and pharmacokinetics of nicardipine combined with enalapril in essential hypertension. <u>Journal of Cardiovascular Pharmacology</u>, **10**, 723-727.

Doyle, A.E. (1983) Comparison of beta-adrenoceptor blockers and calcium antagonists in hypertension. <u>Hypertension</u>, **5**

(II), 103-108.

Dunn, F.G., Oigman, W., Ventura, H.O., Messerli, F.H., Kobrin, I. & Frohlich, E.D. (1984) Enalapril improves systemic and renal haemodynamics and allows regression of left ventricular mass in essential hypertension. American Journal of Cardiology, 53, 105-108.

Dunstan, H.P., Tarazi, R.C. & Bravo, E.L. (1972) Dependence of arterial pressure on intravascular volume in treated hypertensive patients. New England Journal of Medicine, 286, 861-866.

Echizen, H. & Eichelbaum, M. (1986) Clinical pharmacokinetics of verapamil, nifedipine and diltiazem. Clinical Pharmacokinetics, 11, 425-449.

Edwards, C.R.W. & Padfield, P.L. (1985) Angiotensin converting enzyme inhibitors: past, present and bright future. Lancet, 1, 30-34.

Eggertsen, R. & Hansson, L. (1982) Effects of treatment with nifedipine and metoprolol in essential hypertension. European Journal of Clinical Pharmacology, 21, 389-390.

Elliott, H.L., McLean, K., Sumner, D.J., Meredith, P.A. & Reid, J.L. (1981) Immediate cardiovascular responses to oral prazosin - effects of concurrent beta-blockers. Clinical Pharmacology and Therapeutics, 29, 303-309.

Elliott, H.L., Meredith, P.A., Sumner, D.J., McLean, K. & Reid, J.L. (1982) A pharmacodynamic and pharmacokinetic assessment of a new alpha-adrenoceptor antagonist, doxazosin, in normotensive subjects. British Journal of Clinical Pharmacology, 13, 699-703.

Elliott, H.L., Meredith, P.A., Sumner, D.J. & Reid, J.L. (1984) Comparison of the clinical pharmacokinetics and concentration-effect relationships for medroxalol and labetalol. British Journal of Clinical Pharmacology, 17, 573-578.

Elliott, H.L., Pasanisi, F., Sumner, D.J. & Reid, J.L. (1985) The effect of calcium channel blockers on $alpha_1$ and $alpha_2$ adrenoceptor mediated vascular responsiveness in man. Journal of Hypertension, 3 (Suppl.3), S235-S237.

Elliott, H.L., Meredith, P.A. & Reid, J.L. (1987) Pharmacokinetic overview of doxazosin. American Journal of Cardiology, 59, 78G-81G.

Elliott, H.L., Meredith, P.A., Logue, C. & Reid, J.L. (1988a) The interaction between nisoldipine and beta adrenoceptor antagonists. British Journal of Clinical Pharmacology, in press.

287

Elliott, H.L., Meredith, P.A., Campbell, L. & Reid, J.L. (1988b) The combination of prazosin and verapamil in the treatment of essential hypertension. Clinical Pharmacology and Therapeutics, 43, 554-560.

Elliott, H.L., Donnelly, R., Meredith, P.A. & Reid, J.L. (1988c) Antihypertensive responsiveness and alpha$_1$ adrenoceptor antagonism during longterm treatment with prazosin: application of concentration-effect analysis. Clinical Pharmacology and Therapeutics, in press.

Epstein, F.H. (1982) Mechanism of action of calcium channel blocking agents. New England Journal of Medicine, 307, 1618-1627.

Erne, P., Bolli, P., Bertel, O., Hulthen, U.L., Kiowski, W., Muller, F. & Buhler, F. (1983) Factors influencing the hypotensive effects of calcium antagonists. Hypertension, 5 (Suppl.2) 97-102.

Fagard, R., Amery, A., Lijnen, P. & Staesen, J. (1980) First dose effect of the oral angiotensin converting enzyme inhibitor captopril: factors determining adverse hypotension. Archives Internationales de Pharmacodynamie et de Therapie, 245 (Suppl.1), 178-187.

Fagard, R., Fiocchi, R., Lijnen, P., Staesen, J., Momman, E., de Schaepdryver, A. & Amery, A. (1984). Haemodynamic and humoral responses to chronic ketanserin treatment in essential hypertension. British Heart Journal, 51, 149-156.

Feely, J. (1984) Nifedipine increases and glyceryl trinitrate decreases apparent liver blood flow in normal subjects. British Journal of Clinical Pharmacology, 17, 83-85.

Ferguson, R.K., Irvin, J.D., Swanson, B.N., Vlasses, P.H., Bergquist, B.S., Till, A.E. and Feinberg, J.A. (1983) Food does not alter the absorption of enalapril maleate as measured by the disposition of its active metabolite. Clinical Pharmacology and Therapeutics, 33, 254.

Ferrara, L.A., Fasano, M.L. & Soro, S. (1985) Age related antihypertensive effect of nitrendipine, a new calcium entry blocking agent. European Journal of Clinical Pharmacology, 28, 473-474.

Fisher, C.M. (1985) The ascendancy of diastolic blood pressure over systolic. Lancet, ii, 1349-1350.

Fleckenstein, A. (1983) History of calcium antagonists. Circulation Research, 52(Suppl.II), 1-16.

Fleckenstein, A. (1984) Calcium antagonism: history and prospects for a multifaceted pharmacodynamic principle. In

Calcium Antagonists and Cardiovascular Disease. Ed. Opie, L.H. pp9-28. New York: Raven Press.

Folkow, B. (1975) Relationship between physical vascular properties and smooth muscle function: its importance for vascular control and reactivity. Clinical Experimental Pharmacology and Physiology, 2 (Suppl.), 55-61.

Folkow, B. (1978) Cardiovascular structural adaptation: its role in the initiation and maintenance of primary hypertension. Clinical Science, 55 (Suppl.4), 3s-22s.

Folkow, B. (1982) Physiological aspects of primary hypertension. Physiological Reviews, 62, 347-504.

Francis, R.J., Brown, A.N., Kler, L, Fasanella d'Amore, T., Nussberger, J., Waeber, B. & Brunner, H.R. (1987) Pharmacokinetics of the converting enzyme inhibitor cilazipril in normal volunteers and the relationship to enzyme inhibition: Development of a mathematical model. Journal of Cardiovascular Pharmacology, 9, 32-38.

Freedman, S.B., Richmond D.R., Ashley, J.J. & Kelley, D.T. (1981) Verapamil kinetics in normal subjects and patients with coronary artery spasm. Clinical Pharmacology and Therapeutics, 30, 644-652.

Frenken, M. & Kaumann, A. (1984) Interaction of ketanserin and its metabolite ketanserinol with $5HT_2$ receptors in pulmonary and coronary arteries of calf. Naunyn Schmiedeberg's Archives of Pharmacology, 326, 334-339.

Frick, H.M., Halttunen, P., Himanen, P., Huttunen, M., Porsti, P., Pitkajarvi, T., Poyhonen, L. et al (1986) A longterm double-blind comparison of doxazosin and atenolol in patients with mild to moderate essential hypertension. British Journal of Clinical Pharmacology, 21, 55s-62s.

Fruncilo, R.J., Tomensch, H.H., Vlasses, P.H., Koplin, J.R., Monsell, K., Clementini, R.A. & Fergusson, R.A. (1983) Effects of captopril and hydrochlorthiazide on the pressor responses to norepinephrine and angiotensin II in hypertensives. Clinical Pharmacology and Therapeutics, 33(2), 226-229.

Fyhrquist, F., Gronhagen-Riska, C., Hortling, L., Forslund, T. and Tikkanen, I. (1983) Regulation of angiotensin converting enzyme. Journal of Hypertension, 1(Suppl.1), 25-30.

Gavras, H., Brunner, H.R., Turini, G.A., Kershaw, G.R., Tifft, C.P., Cuttelod, S., Gavras, I. et al. (1978) Antihypertensive effect of the oral angiotensin converting enzyme inhibitor SQ14225 in man. New England Journal of Medicine, 298, 991-995.

Gavras, H., Biollaz, J., Waeber, B., Brunner, H.R., Gavras, I., Davies, R.O. (1981) Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor, MK421. Lancet, 2, 543-547.

Gill, J.S., Beevers, D.G., Zezulka, A.V. & Davies, P. (1985) Relationship between initial blood pressure and its fall with treatment. Lancet, i, 567-569.

Giudicelli, J.F., Berdeaux, A., Edouard, A., Richer, C. & Jacalot, D. (1985) The effect of enalapril on baroreceptor mediated reflex function in normotensive subjects. British Journal of Clinical Pharmacology, 20, 211-218.

Glossman, H., Ferry, D.R., Goll, A. & Rombusch, M. (1984) Molecular pharmacology of the calcium channel: evidence for subtypes, multiple drug-receptor sites, channel sub-units and the development of a radio-iodinated 1,4-dihydropyridine c-c label, [$^{125}$I] iodipine. Journal of Cardiovascular Pharmacology, 6, S608-S621.

Gomez, H.J., Sromovsky, J., Kristianson, K., Cirillo, V.J., Wilhelmsson, C.E. and Berglund, G. (1985) Lisinopril dose-response in mild to moderate hypertension. Clinical Pharmacology and Therapeutics, 37, 198-201.

Graham, R.M. (1984) Selective alpha$_1$ adrenergic antagonists: therapeutically relevant antihypertensive agents. American Journal of Cardiology, 53, 16A-20A.

Grahnen, A., Seideman, P., Lindstrom, B., Haglund, K. & von Bahr, C. (1981) Prazosin kinetics in hypertension. Clinical Pharmacology and Therapeutics, 30, 439-446.

Guazzi, M., Olivari, M.T., Polese, A., Fiorentini, C., Magini, F. & Moruzzi, P. (1977) Nifedipine, a new antihypertensive with rapid action. Clinical Pharmacology and Therapeutics, 22, 528-532.

Hamilton, M., Thompson, E.N. & Wisniewski, T.K.M. (1964) The role of blood pressure control in preventing complications of hypertension. Lancet, i, 235-238.

Hamilton, C.A. & Reid, J.L. (1981) Changes in alpha-adrenoceptors during longterm treatment of rabbits with prazosin. Journal of Cardiovascular Pharmacology, 3, 977-985.

Hansson, L., Zweifler, A.J., Julius, S., Ellis, C.N. (1974) Propranolol therapy in essential hypertension: observations on predictability of therapeutic response. International Journal of Clinical Pharmacology, 10, 79.

Hansson, L. (1985) Assessment of the patient's response.

_Journal of Hypertension_, 3 (Suppl.2), 565-569.

Harington, M., Kincaid-Smith, P. & McMichael, J. (1959) Results of treatment in malignant hypertension. A seven-year experience in 94 cases. _British Medical Journal_, 2, 969-979.

Hedner, T., Persson, B. & Berglund, G. (1985) A comparative and long-term evaluation of ketanserin in the treatment of essential hypertension. _Journal of Cardiovascular Pharmacology_, 7(Suppl.7), S148-S153.

Hedner, T. & Persson, B. (1985) Antihypertensive properties of ketanserin in combination with beta-adrenergic blocking agents. _Journal of Cardiovascular Pharmacology_, 7 (Suppl.7), S161-163.

Hedner, T., Pettersson, A. & Persson, B. (1986) Blood pressure reduction and pharmacokinetics of ketanserin in hypertensive patients. _Journal of Hypertension_, 4(Suppl.1), S91-S93.

Heykants, J., Peer Van, A., Woestenborghs, R., Gould, S. & Mills, J. (1986) Pharmacokinetics of ketanserin and its metabolite ketanserinol in man after intravenous, intramuscular and oral administration. _European Journal of Clinical Pharmacology_, 31, 343-350.

Hichens, M., Hand, E.L. & Mulcahy, W.S. (1981) Radioimmunoassay of angiotensin converting enzyme inhibitors. _Ligand Quarterly_, 4, 43.

Hockings, N., Ajayi, A.A. & Reid, J.L. (1986) Age and the pharmacokinetics of angiotensin converting enzyme inhibitors enalapril and enalaprilat. _British Journal of Clinical Pharmacology_, 21, 341-348.

Hodsman, G.P., Brown, J.J. & Davies, D.L. (1982) Converting enzyme inhibitor enalapril in treatment of hypertension with renal artery stenosis. _British Medical Journal_, 285, 1697-1699.

Holford, N.H.G. & Sheiner, L.B. (1981) Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. _Clinical Pharmacokinetics_, 6, 429-453.

Holford, N.H.G., Coates, P.E., Guentest, T.W., Riegelman, S. & Sheiner, L.B. (1981) The effect of quinidine and its metabolites on the electrocardiogram and systolic time intervals: concentration-response relationships. _British Journal of Clinical Pharmacology_, 11, 187-195.

Hollifield, J.W., Shearman, K., Swagg, R.K. & Shand, D.G. (1976) Proposed mechanism of propranolol's antihypertensive effect in essential hypertension. _New England Journal of Medicine_, 295, 68-73.

Holme, I., Helgeland, A., Hjermann, I., Leren, P. & Lund-Larsen P.G. (1984) Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. Journal of the American Medical Association, 251, 1298-1299.

Hornung, R.S., Gould, B.A., Jones, R.I., Tansukh, N., Sonecha, T.M. & Raftery, E.B. (1983) Nifedipine tablets for systemic hypertension: a study using continuous ambulatory intra-arterial recording. American Journal of Cardiology, 51, 1323-1327.

Hosie, J., Stott, D.J., Robertson, J.I.S. & Ball, S.G. (1987) Does serotonergic Type-2 antagonism reduce blood pressure? Journal of Cardiovascular Pharmacology, 10(Suppl.3), S86-S88.

Hypertension Detection and Follow-up Program Co-operative Study Group (1982) Effect of treatment on mortality in mild hypertension. New England Journal of Medicine, 307, 976-980.

Ibsen, H., Egan, B. & Julius, S. (1983) Baroreflex sensitivity during converting enzyme inhibition with enalapril in normal man. Journal of Hypertension, 1(Suppl.2), 222-224.

Imai, Y., Abe, K., Seino, M., Haruyama, T., Tajima, U., Yoshinaga, K. & Seikino, H. (1982a) Captopril attenuates pressor responses to noradrenaline and vasopressin through depletion of endogenous angiotensin II. American Journal of Cardiology, 49, 1537-1539.

Imai, Y., Abe, K., Seino, M., Haruyama, T., Tajima, J., Sato, M., Goto, T. et al (1982b) Attenuation of pressor responses to norepinephrine and pitressin and potentiation of pressor response to angiotensin II by captopril in human subjects. Hypertension, 4, 444-451.

IPPPSH Collaborative Group (1985) Cardiovascular risk and risk factors in a randomised trial of treatment based on the beta blocker oxprenolol: The International Prospective Primary Prevention Study in Hypertension. Journal of Hypertension, 3, 379-392.

Jennings, A.A. & Opie, L.H. (1987) Effects of intravenous ketanserin on severely hypertensive patients with double-blind crossover assessment of central side effects. Journal of Cardiovascular Pharmacology, 9, 120-124.

Johnston, C.I., McGrath, B.P., Millar, J.A. & Mathews, P.G. (1979) Longterm effects of captopril on blood pressure and hormone levels in essential hypertension. Lancet, ii, 493-495.

Johnston, C.I., Jackson, B., McGrath, B., Mathews, G. & Arnolda, L. (1983) Relationship of antihypertensive effect of enalapril t

Voogd, P.J. & Breimer, D.D. (1984a) Nifedipine: kinetics and dynamics in healthy subjects. Clinical Pharmacology and Therapeutics, 35, 742-749.

Kleinbloesem, C.H., van Brummelen, P., Faber, H., Danhof, M., Vermeulen, N.P.E. & Breimer, D.D. (1984b) Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. Biochemical Pharmacology, 33, 3721-3724.

Kleinbloesem, C.H., van Brummelen, P. & Breimer, D.D. (1987a) Nifedipine. Relationship between pharmacokinetics and pharmacodynamics. Clinical Pharmacokinetics, 12, 12-29.

Kleinbloesem, C.H., van Brummelen, P., Faber, H. & Breimer, D.D. (1987b) Pharmacokinetics and haemodynamic effects of longterm nifedipine treatment in hypertensive patients. Journal of Cardiovascular Pharmacology, 9, 202-208.

Koch-Weser, J. (1974) Vasodilator drugs in the treatment of hypertension. Archives of Internal Medicine, 133, 1017-1027.

Kokubu, T., Itoh, I., Kurita, H., Orchi, T., Murata, K. & Yuba, I. (1982) Effect of prazosin on serum lipids. Journal of Cardiovascular Pharmacology, 14 (Suppl.2), S228-S232.

Koletsky, R.J., Gordon, M.B., Le Boff, M.S., Moore, T.J., Dluhy, R.G., Hollenberg, N.K. & Williams, G.H. (1984) Captopril enhances vascular and adrenal responsiveness to angiotensin II in essential hypertension. Clinical Science, 66, 299-305.

Kondowe, G.B., Kelly, J.G., Copeland, S. & Johnston, G.D. (1987a) The effect of chronic captopril therapy on platelet angiotensin II receptor density and vascular responsiveness to angiotensin II infusion. European Journal of Clinical Pharmacology, 31, 525-530.

Kondowe, G.B., Copeland, S., Passmore, A.P., Leahey, W.J. & Johnston, G.D. (1987b) The effect of chronic captopril therapy on adrenergic receptors, plasma noradrenaline and the vascular responses to infused noradrenaline. European Journal of Clinical Pharmacology, 32, 229-235.

Krebs, R. (1983) Adverse reactions with calcium antagonists. Hypertension, 5II (Suppl.2), 125-129.

Kubo, S.H. & Cody, R.J. (1985) Clinical pharmacokinetics of the angiotensin converting enzyme inhibitors. A review. Clinical Pharmacokinetics, 10, 377-391.

Kuhn, D.M., Wolf, W.A. & Lovenberg, W. (1980). Review of the role of the central serotonergic neuronal system in blood pressure regulation. Hypertension, 2, 243-255.

Kurowski, M. (1985) Bioavailability and pharmacokinetics of ketanserin in elderly subjects. <u>European</u> <u>Journal</u> <u>of</u> <u>Clinical</u> <u>Pharmacology</u>, 28, 411-417.

Lancet Editorial (Anonymous) (1982) Diuretics or beta blockers for hypertension? <u>Lancet</u>, 2, 1316-1317.

Landmark, K. (1985) Antihypertensive and metabolic effects of longterm therapy with nifedipine slow-release tablets. <u>Journal</u> <u>of</u> <u>Cardiovascular</u> <u>Pharmacology</u>, 7, 12-17.

Lant, A. (1985) Diuretics: clinical pharmacology and therapeuti use. <u>Drugs</u>, 29, 57-87 (Part I), 162-188 (Part II).

Laragh, J.H. (1973) Vasoconstrictor-volume analysis for understanding and treating hypertension. The use of renin and aldosterone profiles. <u>American</u> <u>Journal</u> <u>of</u> <u>Medicine</u>, 55, 261-274.

Laragh, J.H., Case, D.B., Atlas, S.A. & Sealey, J.A. (1980) Captopril compared with other antirenin system agents in hypertensive patients: its triphasic effects on blood pressure and its use to identify and treat the renin factor. <u>Hypertension</u>, 2, 586-593.

La Rochelle, P., Genest, J., Kuchel, O., Boucher, R., Gotkowska, Y. & McKinstry, D. (1979) Effect of captopril on blood pressure, plasma renin activity and angiotensin converting enzyme activity. <u>Canadian</u> <u>Medical</u> <u>Association</u> <u>Journal</u>, 121, 209-213.

La Rochelle, P., Sonich, P.D., Hamlet, P., Lorocque, P. & Armstrong J. (1982) Prazosin plasma concentration and blood pressure reduction. <u>Hypertension</u>, 4, 93-101.

Lederballe-Pedersen, O., Mikkelsen, E., Christensen, N.J., Kornerup, H.J. & Pedersen, E.B. (1979) Effect of nifedipine on plasma renin, aldosterone and catecholamines in arterial hypertension. <u>European</u> <u>Journal</u> <u>of</u> <u>Clinical</u> <u>Pharmacology</u>, 15, 235-240.

Lederballe-Pedersen, O., Christensen, C.K., Mikkelsen, E. & Ramsch, K.D. (1980) Relationship between the antihypertensive effect and steady-state plasma concentration of nifedipine given alone or in combination with a beta adrenoceptor blocking agent. <u>European</u> <u>Journal</u> <u>of</u> <u>Clinical</u> <u>Pharmacology</u>, 18, 287-293.

Lederballe-Pedersen, O. (1981) Calcium blockade as a therapeutic principle in arterial hypertension. <u>Acta</u> <u>Pharmacologica</u> <u>et</u> <u>Toxicologica</u>, 49 (Suppl.), 1-31.

Lees, K.R. & Reid, J.L. (1987) Age and the pharmacokinetics and pharmacodynamics of chronic enalapril treatment. <u>Clinical</u> <u>Pharmacology</u> <u>and</u> <u>Therapeutics</u>, 41(6), 597-602.

Lefkowitz, R.J. (1978) Identification and regulation of
alpha- and beta-adrenergic receptors. Federation
Proceedings: Federation of American Societies for
Experimental Biology, 37, 123-129.

Lehtonen, A., Kleimola, T. & Kanto, J. (1977) Plasma
concentrations of propranolol in patients with essential
hypertension. European Journal of Clinical Pharmacology, 11,
155-157.

Leonetti, G., Sala, C., Bianchini, C., Terzoli, L. &
Zanchetti, A. (1980) Antihypertensive and renal effects of
orally administered verapamil. European Journal of Clinical
Pharmacology, 18, 375-382.

Leren, P., Eide, I., Foss, O.P., Helgeland, A., Hjermann,
I., Holme, I. & Lund-Larsen, P.G. (1982) Antihypertensive
drugs and blood lipids:  the Oslo Study. Journal of
Cardiovascular Pharmacology, 4 (Suppl.2), S222-S224.

Lewis, G.R.J., Morley, K.D., Lewis, B.M. & Bones, P.J.
(1978) The treatment of hypertension with verapamil. New
Zealand Medical Journal, 84, 351-354.

Leyson, J.E., Awouters, V. & Kennis, L. (1981).  Receptor
binding profile of ketanserin, a novel antagonist of $5HT_2$
receptors.  Life Sciences, 28, 1015-1022.

Lin, S.Y. & Godfriend, T.L. (1970) Angiotensin receptors.
American Journal of Physiology, 218(5), 1319-1328.

Lindholm, L., Ejlertsson, G. & Schersten, B. (1984) High risk o
cerebrovascular morbidity in well treated male hypertensives. A
retrospective study of 40-59 year old hypertensives in a Swedis
primary care district. Acta Medica Scandinavica, 216, 251-259.

Lithell, H., Waern, U. & Vessby, B. (1982) Effect of
prazosin on lipoprotein metabolism in premenopausal,
hypertensive women. Journal of Cardiovascular Pharmacology,
4 (Suppl.2), S242-S244.

Littler, W.A., Young, M.A. & Smith, S.A. (1986) The acute
and chronic effects of nicardipine on blood pressure, heart
rate, neurocirculatory reflexes and renal function in
hypertensive patients. British Journal of Clinical
Pharmacology, 22 (Suppl.3), 239s-242s.

Lund-Johansen, P. (1974) Haemodynamic changes at rest and
during exercise in long-term prazosin therapy of essential
hypertension.  In: Evaluation of a new antihypertensive
agent. Ed. Cotton, D.W.K. pp43-53. New York:  Excerpta
Medica.

Lund-Johansen, P., Omvik, P. & Haugland, H. (1986) Acute

and chronic haemodynamic effects of doxazosin in hypertension at rest and during exercise. British Journal of Clinical Pharmacology, 21, 45s-54s.

Lund-Johansen, P. (1986) Effects of antihypertensive therapy on the haemodynamics of hypertension: Clinical implications. Clinical Therapeutics, 8(4), 382-397.

Lynch, P., Dargie, H., Krikler, S. & Krikler, D. (1980) Objective assessment of antianginal treatment: a double-blind comparison of propranolol, nifedipine, and their combination. British Medical Journal, 281, 184-187.

McAllister, R.G. (1982) Clinical pharmacokinetics of calcium channel antagonists. Journal of Cardiovascular Pharmacology, 4, S340-S345.

McAreavey, D., Ramsay, L.E. & Latham, L. (1984) "Third drug" trial: comparative study of antihypertensive agents added to treatment when blood pressure remains uncontrolled by a beta blocker plus thiazide diuretic. British Medical Journal, 288, 106-111.

MacCarthy, E.P., Frost, G.W., Monaghan, J.C., Mennie, B.A. & Stokes, G.S. (1980) Prediction of response to antihypertensive therapy with prazosin. Medical Journal of Australia, 2 (Suppl.), 12-14.

MacGregor, G.A., Markandu, N.D., Banks, R.A., Bayliss, J., Roulston, J.E. & Jones, J.C. (1982a) Captopril in essential hypertension: contrasting effects of adding hydrochlorthiazide or propranolol. British Medical Journal, 284, 693-696.

MacGregor, G.A., Rotellar, C., Markandu, N.D., Smith, S. & Sagnella, G.A. (1982b) Contrasting effects of nifedipine, captopril and propranolol in normotensive and hypertensive subjects. Journal of Cardiovascular Pharmacology, 4, S358-S362.

MacGregor, G.A., Banks, R.A., Markandu, N.D., Bayliss, J. & Roulston, J. (1983) Lack of effect of beta-blocker on flat dose-response to thiazide in hypertension: efficacy of low dose thiazide combined with beta-blocker. British Medical Journal, 286, 1535-1538.

MacMahon, S.W., Cutler, J.W., Furberg, C.D. & Payne, C.H. (1986) The effects of drug treatment for hypertension on morbidity from cardiovascular disease: a review of randomised controlled trials Progress in Cardiovascular Diseases, 29(Suppl.3), 99-118.

Mancia, G., Parati, G. & Pomidossi, G. (1982) Modification of arterial baroreflexes by captopril in essential hypertension. American Journal of Cardiology, 49, 1415-1419.

Man in't Veld, A.J., Schicht, I.M., Derkx, F.H.M. and Schalekamp, M.A.D.H. (1980) Effects of an angiotensin converting enzyme inhibitor (captopril) on blood pressure in anephric subjects. British Medical Journal, 1, 288-290.

Mantero, F., Rocco, S., Opocher, G., Armanini, D., Boscaro, M. & D'Agostino, D. (1985) Effect of ketanserin in primary aldosteronism. Journal of Cardiovascular Pharmacology, 7 (Suppl.7), 172-175.

Marlin, G.E., Thompson, P.J., Reddel, H.K., Chow, C.M. & Cheng, S. (1982) Bronchodilator activity of prazosin in patients with allergic rhinitis and asthma. British Journal of Clinical Pharmacology, 13, 445-448.

M'Buyamba-Kabangu, J.R., Lepira, B., Lijnen, P., Tshiani, K., Fagard, R. & Amery, A. (1988) Intracellular sodium and the response to nitrendipine or atenolol in African Blacks. Hypertension, 11, 100-105.

McKenzie, J.K. & Clements, J.A. (1974) Simplified radioimmunoassay for serum aldosterone utilising increased antibody specificity. Journal of Clinical Endocrinology and Metabolism, 38, 622-627.

McLeay, R.A.B., Stallard, T.J., Watson, R.D.S. & Littler, W.A. (1983) The effect of nifedipine on arterial pressure and reflex cardiac control. Circulation, 67, 1084-1090.

McLenachan, J.M., Henderson, E., Morris, K.I. & Dargie, H.J. (1987) Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. New England Journal of Medicine, 317 (13), 787-792.

McNamara, P.J., Levy, G. & Gibaldi, M. (1979) Effect of plasma protein and tissue binding on the time course of drug concentration in plasma. Journal of Pharmacokinetics and Biopharmaceutics, 7, 195-206.

McNeil, J.J., Drummer, O.H., Conway, E.L., Workman, B.S. & Louis, W.J. (1987) Effect of age on pharmacokinetics of and blood pressure responses to prazosin and terazosin. Journal of Cardiovascular Pharmacology, 10, 168-175.

Medical Research Council working party on mild to moderate hypertension (1981) Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Lancet, ii, 539-543.

Medical Research Council working party (1985) Trial of treatment of mild hypertension: principal results. British Medical Journal, 291, 97-104.

Meredith, P.A., Kelman, A.W., Elliott, H.L. & Reid, J.L.

(1983) Pharmacokinetic and pharmacodynamic modelling of trimazosin and its major metabolite. Journal of Pharmacokinetics and Biopharmaceutics, 11 (4), 323-335.

Meredith, P.A., Elliott, H.L., Pasanisi, F., Kelman, A.W., Sumner, D.J. & Reid, J.L. (1985a) Verapamil pharmacokinetics and apparent hepatic and renal blood flow. British Journal of Clinical Pharmacology, 20, 101-106.

Meredith, P.A., Pasanisi, F., Elliott, H.L. & Reid, J.L. (1985b) The effect of nisoldipine on apparent liver blood flow and effective renal plasma flow. British Journal of Clinical Pharmacology, 20, 235-237.

Meredith, P.A., Elliott, H.L., Ahmed, J.A. & Reid, J.L. (1987) Age and the antihypertensive efficacy of verapamil: An integrated pharmacokinetic-pharmacodynamic approach. Journal of Hypertension, 5 (Suppl.5), S219-S221.

Midtbo, K., Hals, O. & ven der Meer, J. (1982) Verapamil compared with nifedipine in the treatment of essential hypertension. Journal of Cardiovascular Pharmacology, 4, S363-S368.

Millar, J.A., McLean, K. & Reid, J.L. (1981) Calcium antagonists decrease adrenal and vascular responsiveness to angiotensin II in normal man. Clinical Science, 61, 655-685.

Millar, J.A., Derkx, F.H.M., McLean, K. & Reid, J.L. (1982a) Pharmacodynamics of converting enzyme inhibition: the cardiovascular, endocrine and autonomic effects of enalapril and MK521. British Journal of Clinical Pharmacology, 14, 347-355.

Millar, J.A., Derkx, F.H.M., McLean, K. & Reid, J.L. (1982b) Absence of reflex tachycardia during converting enzyme inhibition: evidence against impairment of autonomic reflexes. British Journal of Clinical Pharmacology, 14, 129-130.

Miller, N.E. (1982) Coronary atherosclerosis and plasma lipoproteins: epidemiology and pathophysiologic considerations. Journal of Cardiovascular Pharmacology, 4 (Suppl.2), S190-S195.

Mimran, A. & Ribstein, J. (1985) Effect of chronic nifedipine in patients inadequately controlled by a converting enzyme inhibitor and a diuretic. Journal of Cardiovascular Pharmacology, 7 (Suppl.1), S92-S95.

Mizuno, K., Nakamaru, M., Higashimori, K. & Inagami, T. (1988) Local generation and release of angiotensin II in peripheral vascular tissue. Hypertension, 11, 223-229.

Mooy, J., Shols, M., van Baak, M., van Hoof, N. & Muytjens, A. (1985) Pharmacokinetics of verapamil in patients with renal failure. European Journal of Clinical Pharmacology, 208, 405-410.

Moser, M. (1978) How to treat essential hypertension. In: Freis, E.D. ed. The Treatment of Hypertension. pp 93-114. Lancaster: MT Press,

Muiesan, G., Agabiti-Rosei, M., Castellano, C.L., Alicandri, L. & Corea, R. (1982) Antihypertensive and humoral effects of verapamil and nifedipine in essential hypertension. Journal of Cardiovascular Pharmacology, 4, S325-S329.

Multiple Risk Factor Intervention Trial (1982) Risk factor changes and mortality results. MRFIT Research Group. Journal of the American Medical Association, 248, 1465-1469.

Mylecharane, E.J., Phillips, C.A., Markus, J.M. & Shaw, J. (1985) Evidence for a central component to the hypotensive action of ketanserin in the dog. Journal of Cardiovascular Pharmacology, 7 (Suppl.7), 114-116.

Nahorski, S.R. (1985) Inositol phospholipid hydrolysis as a primary response to receptors not linked to adenylate cyclase. Drug Research, 35(II), 1886-1390.

Nayler, W.G. & Ferrari, R. (1979) The use of nifedipine in the protection of the ischaemic heart. Excerpta Medica International Congress Series, 516, 197-206.

Nelson, E.B., Chrysant, S.G., Gradman, A.H., Leon, A.S., McCarthy, E.P. & Rush, J. (1985) Dose-response study of lisinopril efficacy in hypertension. British Journal of Clinical Pharmacology, 25, 470.

Neuten, J.M., Janssen, P.A.J., De Ridder, W. & Vanhoutte, P.M. (1982). Interaction between 5-hydroxytryptamine and other vasoconstrictor substances in the isolated femoral artery of the rabbit; effect of ketanserin. European Journal of Pharmacology, 77, 281-287.

O'Connor, D.T., Mosley, C.A., Cervenka, J. & Bernstein, K.N. (1984) Contrasting renal haemodynamic responses to the angiotensin converting enzyme inhibitor enalapril and the beta-adrenergic antagonist metoprolol in essential hypertension. Journal of Hypertension, 2(Suppl.2), 89-92.

Okonkwo, P., Reimann, I., Woestenborghs, R. & Klotz, U. (1983) High-performance liquid chromatography assay with fluorescence detection of ketanserin, a new antihypertensive agent and serotonin $S_2$-antagonist in human plasma, blood and urine. Journal of Chromatography, 272, 411-416.

Olivari, M.T., Bartorelli, C. & Polese, A. (1979) Treatment

of hypertension with nifedipine, a calcium antagonist agent. Circulation, 59, 1056-1062.

Omvik, P. & Lund-Johansen, P. (1983). Longterm effects on central haemodynamics and body fluid volumes of ketanserin in essential hypertension: studies at rest and during dynamic exercise. Journal of Hypertension, 1, 405-412.

Opie, L.H. (1980) Drugs and the heart. III: calcium antagonists. Lancet, i, 806-810.

Page, I.M. & McCubbin, J.W. (1953) The variable arterial pressure responses to serotonin in laboratory animals. Clinical Research, 1, 354-362.

Pasanisi, F. & Reid, J.L. (1983) Plasma nifedipine levels and fall in blood pressure in a 53 year old woman. European Journal of Clinical Pharmacology, 25, 143-144.

Pasanisi, F., Elliott, H.L., Meredith, P.A., McSharry, D. & Reid, J.L. (1984) Combined alpha adrenoceptor antagonism and calcium channel blockade in normal subjects. Clinical Pharmacology & Therapeutics, 36(6), 716-723.

Pasanisi, F., Elliott, H.L. & Reid, J.L. (1985) Vascular and aldosterone responses to angiotensin II in normal humans: Effects of nicardipine. Journal of Cardiovascular Pharmacology, 7, 1171-1175.

Persson, B., Hedner, T. & Berglund, G. (1983). Ketanserin in essential hyepertension: effects during rest and exercise. European Journal of Clinical Pharmacology, 25, 307-312.

Persson, B., Pettersson, A., Hedner, T., (1987) Pharmacokinetics of ketanserin in patients with essential hypertension. European Journal of Clinical Pharmacology, 32, 259-265.

Poulter, N., Thompson, A.V. & Sever, P.S. (1987) Do diuretics enhance the hypotensive effect of nifedipine? - a double-blind crossover trial. Journal of Cardiovascular Pharmacology, (Suppl.) (in press).

Prichard, B.N.C. & Owens, C.W.I. (1986) The management of hypertension. British Journal of Clinical Pharmacology, 21, 129s-142s.

Prichard, B.N.C. (1986) Hypertension: current therapeutic practice reviewed. Drugs, 31 (Suppl.1), 67-70.

Ram, C.V.S. (1987) Calcium antagonists as antihypertensives are effective in all age groups. Journal of Hypertension, 5(Suppl.4), S115-118.

Ramsay, L.E. & Waller, P.C. (1986) Strokes in mild hypertension: diastolic rules. Lancet, ii, 854-856.

Rasmussen, S., Damkjaer Nielsen, M. & Giese, J. (1981) Captopril combined with thiazide lowers renin substrate concentration: implications for methodology in renin assays. Clinical Science, 60, 591-593.

Reid, J.L. (1988) Hypertension 1988: present challenges and future strategies. Journal of Hypertension, 6, 3-8.

Reimann, I.W. & Frolich, J.C. (1983) Mechanism of antihypertensive action of ketanserin in man. British Medical Journal, 287, 381-383.

Richer, C., Thuillez, C. & Giudicelli, J.F. (1987) Perindopril, converting enzyme blockade, and peripheral arterial haemodynamics in the healthy volunteer. Journal of Cardiovascular Pharmacology, 9, 94-102.

Robertson, D.R.C., Waller, D.G., Renwick, A.G. & George, C.F. (1988) Age related changes in the pharmacokinetics and pharmacodynamics of nifedipine. British Journal of Clinical Pharmacology, 25(3), 297-305.

Robertson, J.I.S. (1983) Hypertension: primary and secondary prevention. In: Preventive Cardiology, eds. Julian, D.G. & O'Neal, H.J. pp62-85. London, Butterworth & Co.

Robertson, J.I.S. (1984) The risk-benefit equation: when to initiate treatment. British Journal of Clinical Pharmacology, 18, 181s-185s.

Robinson, B.F., Dobbs, R.J. & Kelsey, C.R. (1980) Effect of nifedipine on resistance vessels, arteries and veins in man. British Journal of Clinical Pharmacology, 10, 433-438.

Robinson, B.F., Dobbs, R.J. & Bayley, S. (1982) Response of forearm resistance vessels to verapamil and sodium nitroprusside in normotensive and hypertensive men: evidence for a functional abnormality of vascular smooth muscle in primary hypertension. Clinical Science, 63, 33-42.

Rocco, S., Boscaro, M., D'Agostino, D., Aruanini, D. & Mantero, F. (1986). Effect of ketanserin on the in vitro regulation of aldosterone. Journal of Hypertension, 4 (Suppl), S51-S54.

Rosendorff, C. (1976) Prazosin: severe side effects are dose-dependent. British Medical Journal, 2, 508.

Rowland, E., Evans, T. & Krikler, D. (1979) Effects of nifedipine on atrioventricular conduction as compared with verapamil. British Heart Journal, 42, 124-127.

Rubin, P.C., Brunton, J. & Meredith, P.A. (1980) Determination of the vasodilator UK33274 by HPLC using fluorescence detection. Journal of Chromatography, 221, 193-195.

Rubin, P.C., Scott, P.J.W. & Reid, J.L. (1981) Prazosin disposition in young and elderly subjects. British Journal of Clinical Pharmacology, 12, 401-404.

Ryman, K.S., Spencer, K.H., Shaknovich, A. & Cody, R.J. (1987) Influence of baseline haemodynamic status and sympathetic activity on the response to nicardipine, a new dihydropyridine, in patients with hypertension or chronic congestive heart failure. Clinical Pharmacology and Therapeutics, 41, 483-489.

Sakaguchi, K., Yeen Chai, S., Jackson, B., Johnston, C.I. & Mendelsohn, F.A.O. (1988) Inhibition of tissue angiotensin converting enzyme. Quantitation by autoradiography. Hypertension, 11, 230-238.

Samuelsson, O., Wilhelmsen, L., Elmfeldt, D., Pennert, K., Wedel, H., Wikstrand, J. & Berglund, G. (1985) Predictors of cardiovascular morbidity in treated hypertension: results from the primary preventive trial in Goteborg, Sweden. Journal of Hypertension, 3, 167-176.

Sasaki, J. & Arakawa, K. (1987) Effect of nifedipine on serum lipids, lipoproteins and apolipoproteins in patients with essential hypertension. Current Therapeutic Research, 41(6), 845-851.

Scheidt, S., Frishman, W.H., Packer, M., Mehta, J. & Parodi, O. (1982) Longterm effectiveness of verapamil in stable and unstable angina pectoris. One year follow-up of patients treated in placebo-controlled double-blind randomised clinical trials. American Journal of Cardiology, 50 (Suppl.1), 82-87.

Schwartz, J.B., Taylor, A., Abernethy, D., O'Meara, M., Farmer, J., Young, J. & Mitchell, J. (1985) Pharmacokinetics and pharmacodynamics of enalapril in patients with congestive heart failure and patients with hypertension. Journal of Cardiovascular Pharmacology, 7, 767-776.

Schwietzer, G., Distler, A., Reeck, S., Thiede, H.M. & Philipp, T. (1983) Hypotensive action of calcium antagonists as related to plasma noradrenaline and reactivity to noradrenaline. Journal of Hypertension, 1 (Suppl.2), 102-104.

Scott, M., Castleden, C.M., Adam, H.K., Smith, R.P. & Fitzsimons T.J. (1988) The effect of ageing on the disposition of nifedipine and atenolol. British Journal of Clinical Pharmacology, 25(3), 289-296.

Seedat, Y.K. & Reddy, J. (1971) Propranolol in the South African non-white hypertensive patients. South African Medical Journal, 45, 284-285.

Seideman, P., Grahnen, A., Haghind, K., Lundstrom, B. & Bahr, von C. (1981) Prazosin dynamics in hypertension: Relationship to plasma concentration. Clinical Pharmacology and Therapeutics, 30, 447-454.

Shand, D.G., Hamill, S.C., Aanonsen, L. & Pritchett, E.L.C. (1981) Reduced verapamil clearance during longterm oral administration. Clinical Pharmacology and Therapeutics, 30, 701-703.

Shaper, A.G., Phillips, A.N., Pocock, S.J. & Walker, M. (1987) Systolic and diastolic blood pressures in the prediction of heart attacks and stroke. Journal of Hypertension, 5(6), 763-764.

Sheiner, L.B., Starski, D.R., Vozeh, S., Miller, R.D. & Ham, J. (1979) Simultaneous modelling of pharmacokinetics and dynamics: application of d-tubocurarine. Clinical Pharmacology and Therapeutics, 25, 358-371.

Shionoiri, H., Yasuda, G., Yoshimura, H., Umemura, S., Miyajima, E., Miyakawa, T., Takagi, N. & Kaneko, Y. (1987) Antihypertensive effects and pharmacokinetics of single and consecutive administration of doxazosin in patients with mild to moderate essential hypertension. Journal of Cardiovascular Pharmacology, 10, 90-95.

Singh, B.N. (1986) The mechanism of action of calcium antagonists relative to their clinical applications. British Journal of Clinical Pharmacology, 21 (Suppl.2), 109s-121s.

Smits, J.F.M., van Essen, H., Tijssen, C.M., Struyker-Boudier, H.A.J. (1987) Effects of ketanserin on haemodynamics and baroreflex effects in conscious spontaneously hypertensive rats. Journal of Cardiovascular Pharmacology, 10, 1-8.

Smythe, H.S., Sleight, P. & Pickering, G.W. (1969) Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity. Circulation Research, 24, 109-121.

Soffer, J., Dreifus, L.S. & Michelson, E.L. (1982) Polymorphous ventricular tachycardia associated with normal and long QT intervals. American Journal of Cardiology, 49, 2021-2029.

Somogyi, A., Albrecht, M., Kliems, G., Schafer, K. & Eichelbaum, M. (1981) Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis.

British Journal of Clinical Pharmacology, 12, 51-60.

Sorkin, E.M., Clissold, S.P. & Brogden, R.N. (1985)
Nifedipine: a review. Drugs, 30 (Suppl.3), 182-274.

Staessen, J., Lisnen, P., Fagard, R., Verschoeren, L.J. &
Amery, A. (1981) Rise of plasma aldosterone during longterm
captopril treatment. Journal of Endocrinology, 91, 457-466.

Stanaszek, W.F., Kellerman, D., Brogden, R.N. &
Romankiewicz, J.A. (1983) Prazosin update. A review of its
pharmacological properties and therapeutic use in
hypertension and congestive heart failure. Drugs, 25, 339-
384.


Stokes, G.S., Graham, R.M., Gain, J.M. & Davis, P.R. (1977)
Influence of dosage and dietary sodium on the first-dose
effects of prazosin. British Medical Journal, 1, 1507-1508.

Stokes, G.S., Monaghan, J.C., MacCarthy, E.P. & Oates, H.F.
(1980) Responsiveness of hypertensive subjects to prazosin.
Clinical and Experimental Pharmacology and Physiology, 7,
215-217.

Stokes, G.S. (1984) Prazosin. In: Clinical Pharmacology of
Antihypertensive Drugs. Handbook of Hypertension. pp350-374.
Elsevier.

Stokes, G.S., Mennie, S.R.N., Marwood, J.F. (1986)
Ketanserin and prazosin: A comparison of antihypertensive
and biochemical effects. Clinical Pharmacology and
Therapeutics, 40, 56-63.

Stone, P.H., Antman, E.M., Muller, J.E. & Braunwald, E.
(1980) Calcium channel blocking agents in the treatment of
cardiovascular disorders. Part II: Haemodynamic effects and
clinical applications. Annals of Internal Medicine, 93, 886-
904.

Stott, D.J., McLenachan, J.M. & Ball, S.G. (1985) Ketanserin,
the QT interval and autonomic function testing in normal
subjects. British Journal of Clinical Pharmacology, 21,
84p.

Sumner, D.J., Elliott, H.L., Reid, J.L. (1982) Analysis
of pressor dose response. Clinical Pharmacology and
Therapeutics, 32(4), 450-458.

Sumner, D.J. & Elliott, H.L. (1987) The pressor dose-
response in clinical cardiovascular pharmacology. British
Journal of Clinical Pharmacology, 23, 499-503.

Sumner, D.J., Elliott, H.L., Vincent, J. & Reid, J.L. (1987)
A pragmatic approach to the pressor dose-response as an

index of vascular reactivity and adrenoceptor function in man. British Journal of Clinical Pharmacology, 23, 505-510.

Sumner, D.J., Meredith, P.A., Howie, C.A., Elliott, H.L. & Reid, J.L. (1988a) Initial blood pressure as a predictor of the response to antihypertensive therapy. British Journal of Clinical Pharmacology, in press.

Sumner, D.J., Elliott, H.L., Meredith, P.A. & Reid, J.L. (1988b) Concentration-effect relationships and beta-adrenoceptor antagonist effects of flusoxolol in healthy volunteers. British Journal of Clinical Pharmacology, in press.

Taburet, A.M., Singlas, E., Colin, J.N., Banzet, O., Thibonnier, M. & Corvol, P. (1983) Pharmacokinetic studies of nifedipine tablet: correlation with antihypertensive effects. Hypertension, 5 (Suppl.II), 29-33.

Tarazi, R.C., Bravo, E.L. & Fouad, F.M. (1980) Haemodynamic and volume changes associated with captopril. Hypertension, 2, 576.

Taylor, S.H. (1982) Alpha-adrenoceptor antagonists in hypertension. In: Hypertensive Cardiovascular Disease: Pathophysiology and Treatment. ed. Amery, A. pp 755-782. Martinus Nijhoff Publishers, The Hague.

Thind, G.S. Mahapatra, R.K., Johnson, A. & Coleman, R.D. (1983) Low dose captopril titration in patients with moderate-to-severe hypertension treated with diuretics. Circulation, 67, 1340-1345.

Till, A.E., Gomez, H.J., Hichens, M., Bolognese, M.S. & Lant, H.F. (1984) Pharmacokinetics of repeated single oral doses of enalapril maleate in normal volunteers. Biopharmaceutical Drug Disposition, 5, 273-280.

Timmermans, P.B.W.M. & van Zwieten, P.A. (1981) Mini review: the postsynaptic alpha$_2$ adrenoceptors. Journal of Autonomic Pharmacology, 1, 171-183.

Tocco, D.J., de Luna, F.A., Duncan, A.E.W., Vassil, T.C. & Ulm, E.H. (1982) The physiological disposition and metabolism of enalapril maleate in laboratory animals. Drug Metabolism and Disposition, 10, 15-19.

Ulm, E.H., Hichens, M., Gomez, H.J., Till, A.E., Hand, E., Biollaz, J. & Brunner, H.R. (1982) Enalapril maleate and a lysine analogue (MK-521): disposition in man. British Journal of Clinical Pharmacology, 14, 357-362.

Unger, T., Ganten, D., Lang, R.E. & Scholkens, B.A. (1985) Persistent tissue converting enzyme inhibition following chronic treatment with HOE 498 and MK 421 in spontaneously

hypertensive rats. Journal of Cardiovascular Pharmacology, 7, 36-41.

Van Brummelen, P., Jie, K. & Van Zwieten, P.A. (1986) Alpha adrenergic receptors in human blood vessels. British Journal of Clinical Pharmacology, 21 (Suppl.1), 33s-39s.

Vanhoutte, P.M. & Van Neuten, J.M. (1983) Ketanserin a novel antihypertensive drug. Journal of Pharmacy and Pharmacology, 35, 339-340.

Vanhoutte, P.M. (1985) Can peripheral serotonergic blockade explain the hypotensive effect of ketanserin? Journal of Cardiovascular Pharmacology, 7(Suppl.7), S105-S109.

Van Neuten, J.M., Janssen, P.A.J. & Van Beek, J. (1981). Vascular effects of ketanserin, a novel antagonist of $5HT_2$ serotonergic receptors. Journal of Pharmacology and Therapeutics, 218, 217-230.

Van Peer, A., Woestenborghs, R., Embsechts, L., Heykants, J. (1986) Pharmacokinetic approach to equilibrium between ketanserin and ketanserinol. European Journal of Clinical Pharmacology, 31, 339-342.

Velasco, M., Silva, H., Morillo, J., Pellicer, R., Ramirez, A., Urbina, A. & Gomez, H.J. (1985) Haemodynamic effects of enalapril, a new converting enzyme inhibitor, in hypertensive patients. European Journal of Clinical Pharmacology, 29, 17-20.

Velletri, P. & Bean, B.L. (1981) Comparison of the time course of action of captopril on angiotensin converting enzyme with the time course of its antihypertensive effect. Journal of Cardiovascular Pharmacology, 3, 1068-1081.

Vestal, R.E., Wood, A.J.J. & Shand, D.G. (1979) Reduced beta-adrenoceptor sensitivity in the elderly. Clinical Pharmacology and Therapeutics, 26, 181-186.

Veterans Administration Co-operative Study Group (1967) Effects of treatment on morbidity in hypertension, I. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. Journal of The American Medical Association, 202, 1028-1034.

Veterans Administration Co-operative Study Group (1970) Effects of treatment on morbidity in hypertension, II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. Journal of The American Medical Association, 213. 1143-1152.

Veterans Administration Co-operative Study on Antihypertensive Agents (1982a) Racial differences in response to low dose captopril. British Journal of Clinical

Pharmacology, **14**, 975-979.

Veterans Administration Co-operative Study on Antihypertensive Agents (1982b) Comparison of propranolol and hydrochlorthiazide for the initial treatment of hypertension. Journal of The American Medical Association, **248**, 1996-2003.

Vierhapper, H., Witte, P.U. & Waldhausl, W. (1986) Unchanged pressor effect of norepinephrine in normal man following the oral aministration of two angiotensin converting enzyme inhibitors, captopril and HOE 498. Journal of Hypertension, **4**, 9-11.

Vincent, J., Elliott, H.L., Meredith, P.A. & Reid, J.L. (1983) Doxazosin, an alpha$_1$ adrenoceptor antagonist; pharmacokinetics and concentration-effect relationships in man. British Journal of Clinical Pharmacology, **15**, 719-725.

von Bahr, C., Lindstrom, B. & Seideman, P. (1982) Alpha receptor function changes after the first dose of prazosin. Clinical Pharmacology and Therapeutics, **32**(1), 41-47.

Waal-Manning, H.J., Brown, S.A., Spears, G.F., Simpson, F.O. (1985) Clinical studies with ketanserin in hypertension. Journal of Cardiovascular Pharmacology, **7**(Suppl.7), S154-S158.

Wagner, J.G., Rocchini, A.P. & Vasiliades, J. (1982) Prediction of steady state verapamil plasma concentrations in children and adults. Clinical Pharmacology & Therapeutics, **32**, 172-181.

Waller, D.G., Renwick, A.G., Grunchy, B.S. & George, C.F. (1984) The first pass metabolism of nifedipine in man. British Journal of Clinical Pharmacology, **18**, 951-954.

Waller, P.C. & Ramsay, L.E. (1987) Rapid development of tolerance to the antihypertensive effect of nisoldipine. British Journal of Clinical Pharmacology, **23**(5), 603.

Waller, P.C., Solomon, S.A. and Ramsay, L.E. (1987) Comparison of ketanserin and nifedipine added to thiazide plus beta blocker in hypertension. British Journal of Clinical Pharmacology, **24**(5), 591-598.

Warren, S.E., O'Connor, D.T. & Cohen, I.M. (1983) Autonomic and baroreflex function after captopril in hypertension. American Heart Journal, **105**, 1002-1008.

Webster, J., Newnham, D., Robb, O.J. & Petrie, J.C. (1987) Antihypertensive effect of single doses of enalapril in hypertensive patients treated with bendrofluazide. British Journal of Clinical Pharmacology, **23**, 151-157.

Weidmann, P., Vehlinger, D.E. & Gerber, A. (1985)

Antihypertensive treatment and serum lipoproteins. _Journal of Hypertension_, 3, 297-306.

Westerhof, N. & Huisman, R.M. (1987) Arterial haemodynamics of essential hypertension. _Clinical Science_, **72**, 391-398.

White, W.B., Viadero, J.J., Lane, T.J. & Podesta, S. (1986) Effects of combination therapy with captopril and nifedipine in severe or resistant hypertension. _Clinical Pharmacology and Therapeutics_, **39**, 43-48.

Whiting, B. & Kelman, A.W. (1980) The modelling of drug response. _Clinical Science_, **59**, 311-315.

Whiting, B., Holford, N.H.G. & Sheiner, L.B. (1980) Quantitative analysis of the disopyramide concentration-effect relationship. _British Journal of Clinical Pharmacology_, **9**, 67-75.

Whiting, B., Kelman, A.W., Barclay, J. & Addis, G.J. (1981) Modelling of theophylline response in individual patients with chronic bronchitis. _British Journal of Clinical Pharmacology_, **12**, 481-487.

Whiting, B., Kelman, A.W. & Grevel, J. (1986) Population pharmacokinetics: Theory and clinical application. _Clinical Pharmacokinetics_, **11**, 387-401.

Whitworth, J.A., Walter, N.M.A. & Kincaid-Smith, P. (1982) First dose effects of captopril. _Australian and New Zealand Journal of Medicine_, **12**, 325.

Wilhelmsen, L., Berglund, G., Elmfeldt, D., Fitzsimons, T., Holzgreve, H., Hosie, J. & Hornkvist, P.E. (1987) Beta blockers versus diuretics in hypertensive men:  main results from the HAPPHY Trial. _Journal of Hypertension_, **5**, 561-572.

Williams, B.C., Shaikh, S. & Edwards, C.R.W. (1984) The specificity of ketanserin in the inhibition of serotonin-induced steroidogenesis in the rat adrenal zona glomerulosa. _Journal of Hypertension_, **2** (Suppl.3), 559-561.

Witte, P.U., Irmisch, R., Hajdu, P. & Metzager, H. (1984) Pharmacokinetics and pharmacodynamics of a novel orally active angiotensin converting enzyme inhibitor (HOE 498) in healthy subjects. _European Journal of Clinical Pharmacology_, **27**, 577-581.

Yamakado, T., Oonishi, N., Kondo, S., Noziri, A., Nakano, T. & Takezawa, H. (1983) Effects of diltiazem on cardiovascular responses during exercise in systemic hypertension and comparison with propranolol. _American Journal of Cardiology_, **52**, 1023-1027.

Yee, Y.G., Rubin, P.C. & Mellin, P. (1979).  Prazosin

determination by high pressure liquid chromatography using fluorescence detection.  *Journal of Chromatography*, **172**, 313-318.

Zabludowski, J.R., Ball, S.G. & Robertson, J.I.S. (1985). Ketanserin and alpha$_1$ adrenergic antagonism in humans. *Journal of Cardiovascular Pharmacology*, **7**(Suppl.7), S123-125.

Zacest, R., Gilmore, E. & Koch-Weser, J. (1972) Treatment of essential hypertension with combined vasodilation and beta-adrenergic blockade. *New England Journal of Medicine*, **286**, 617-622.

Zanchetti, A. (1985) Which drug to which patient? *Journal of Hypertension*, **3** (Suppl.2), 557-563.

Zimmerman, B.G., Sybertz, J. & Wong, P.C. (1984) Interaction between sympathetic and renin-angiotensin system. *Journal of Hypertension*, **2**, 581-587.

## COMMUNICATIONS TO LEARNED SOCIETIES

1. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Ketanserin in essential hypertension: haemodynamics, pharmacokinetics and pressor responses. British Pharmacological Society, December 1986. British Journal of Clinical Pharmacology, 23(5), 598p.

2. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Acute and chronic nifedipine in essential hypertension: concentration-effect relationships. Medical Research Society, July 1987. Clinical Science, 73 (Suppl.17), 54p.

3. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Acute and chronic nifedipine in essential hypertension: concentration-effect relationships. $X^{th}$ World Congress of Pharmacology, Sydney, August 1987.

4. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Antihypertensive response and individual concentration-effect relationships. British Hypertension Society, September 1987. Journal of Hypertension, 5(6), 766-767.

5. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Ketanserin in essential hypertension: individual response and concentration-effect relationships. British Pharmacological Society, September 1987. British Journal of Clinical Pharmacology, 25(1), 103p.

6. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Mathematical description and clinical prediction of antihypertensive drug response. Scottish Society of Physicians, October 1987. Scottish Medical Journal, in press.

7. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Vascular pressor responses in treated and untreated essential hypertension. British Pharmacological Society, January 1988. British Journal of Clinical Pharmacology, 25(2), 652-653.

8. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Kinetic-dynamic relationships and antihypertensive mechanisms of ketanserin in essential hypertension. $12^{th}$ Scientific Meeting of the International Society of Hypertension, Japan, May 1988. Journal of Hypertension, in press.

9. Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. Vascular pressor responses in treated and untreated essential hypertension. $12^{th}$ Scientific meeting of the International Society of Hypertension, Japan, May 1988. Journal of Hypertension, in press.

## PUBLICATIONS

1.  Donnelly, R., Elliott, H.L., Meredith, P.A., Kelman, A.W. & Reid, J.L. (1988) Nifedipine: individual responses and concentration-effect relationships. Hypertension, in press.

2.  Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. (1987) Acute and chronic ketanserin in essential hypertension: antihypertensive mechanisms and pharmacokinetics. British Journal of Clinical Pharmacology, 24, 599-606.

3.  Donnelly, R., Elliott, H.L., Meredith, P.A., Hughes, D.M.A. & Reid, J.L. (1988) Ketanserin concentration-effect relationships in individual hypertensive patients. British Journal of Clinical Pharmacology, 26, 61-64.

4.  Donnelly, R., Reid, J.L., Meredith, P.A., Ahmed, J.H. & Elliott, H.L. (1988) Factors determining the response to calcium antagonists in hypertension. Journal of Cardiovascular Pharmacology (Supplement), in press.

5.  Donnelly, R., Elliott, H.L., Meredith, P.A. & Reid, J.L. (1988) Vascular pressor responses in treated and untreated essential hypertension. Clinical Science, submitted.

6.  Donnelly, R. & Elliott, H.L. (1988) Pharmacokinetic-pharmacodynamic relationships of alpha-adrenoceptor antagonists. Review. Clinical Pharmacokinetics, in press.

7.  Elliott, H.L., Donnelly, R., Meredith, P.A. & Reid, J.L. (1988) Antihypertensive responsiveness and alpha$_1$ adrenoceptor antagonism during longterm treatment with prazosin: application of concentration-effect analysis. Clinical Pharmacology and Therapeutics, submitted.