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ANTIHYPERTENSIVE DRUGS: INDIVIDUALIZED ANALYSIS AND CLINICAL RELEVANCE OF KINETIC–DYNAMIC RELATIONSHIPS

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Abstract—Individualized approaches to antihypertensive therapy are being widely advocated. Ideally these should incorporate rational prospective methods for drug and dosage selection but progress has been hampered by the paucity of information about dose– (and plasma concentration–) response relationships. However, in several recent clinical studies, concentration–effect analysis has been used to characterize kinetic–dynamic relationships in *individual* patients for a range of antihypertensive drugs. This approach provides an integrated mathematical description of drug response which has potential utility for quickly identifying poor or nonresponders and for determining individual dose requirements for optimum longterm blood pressure control.

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1. INTRODUCTION

Observational studies from as early as 1940 have shown that strokes, cardiac failure, coronary heart disease (CHD) 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 within the normotensive range. Thus, many patients are prescribed longterm antihypertensive treatment, usually based upon thiazide diuretics and beta adrenoceptor antagonists, but recent overviews have highlighted some important limitations of traditional therapeutic policies particularly the disappointing impact on CHD mortality, an average reduction in blood pressure overall of only 6 mmHg, and a significant incidence of drug-related adverse events (Isles *et al.*, 1986; MacMahon *et al.*, 1990).

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At least some of these shortcomings may be related to practical difficulties with antihypertensive treatment which are well recognized in clinical practice; for example, (1) large inter- and intrasubject differences in antihypertensive drug response which are difficult, or often impossible, to predict; (2) decisions about the most appropriate drug or the optimum dose regimen for an individual patient are largely empirical—treatment is usually based on a 'trial and error' approach to drug selection, with dosage adjustments based upon a retrospective appraisal of the preceding response; and (3) the paucity of basic information about dose (–concentration) –response relationships for the common antihypertensive drugs.

In an attempt to improve the overall efficiency of antihypertensive therapy there has been a tendency to adopt a more individualized approach to treatment rather than continuing with pragmatic stepped-care regimens (Menard *et al.*, 1988; Reid, 1988). Thus, there is the longterm goal that antihypertensive therapy might be tailored to the needs of individual patients using rational *prospective* methods for selecting the most suitable agent and optimum dose regimen from four or five alternative first-line drugs (Donnelly *et al.*, 1991). Although this raises many practical problems, individualized treatment policies have been introduced with some success in other areas of therapeutics e.g. with anticonvulsant and bronchodilator drugs; whether this approach can be used successfully in hypertension depends, in part, upon the application of clinical pharmacokinetic techniques to integrate kinetic and dynamic information about antihypertensive therapy in order to guide the choice of drug and dosage regimen and thereby improve both blood pressure control and patient tolerance. The application of individualized dosage schedules should therefore have a favourable effect on the overall risk–benefit relationship.

2. DOSE–CONCENTRATION–RESPONSE RELATIONSHIPS

In general, there is a direct relationship between dose and plasma drug concentration but corresponding, simple relationships between dose (or concentration) and blood pressure response have proved difficult to identify. Several studies have reported 'shallow' or 'flat' dose–response curves for a number of antihypertensive agents, e.g. diuretics (MacGregor *et al.*, 1983), beta blockers (Hansson *et al.*, 1974) and angiotensin converting enzyme (ACE) inhibitors (Gomez *et al.*, 1985), but an important drawback of these experiments has been that many of them used relatively large doses. In classic pharmacological experiments the dose–response relationship is typically represented by a sigmoid-E_{max} curve and it follows that the magnitude of any increment in response is related not only to the magnitude of the change in dose (or concentration) but also to the portion of the dose–response curve covered for that drug (Fig. 1). It seems highly likely, therefore, that those antihypertensive drugs which have long been pronounced to have 'flat' dose–response curves have been administered in relatively high doses which have consistently produced drug concentrations at the top plateau of the dose–response curve and so it has not proved possible to identify clear dose-related effects.

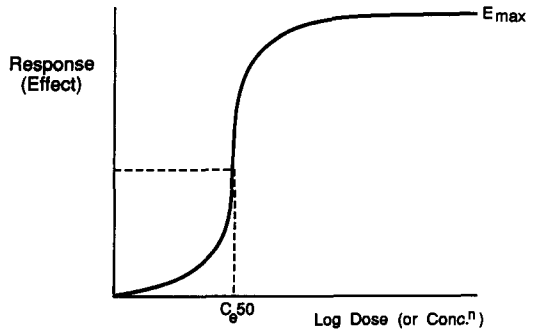

FIG. 1. The classic pharmacological relationship between drug dose (or concentration) and response, which defines a maximum possible effect, E_{max}, and the drug concentration required to produce 50% of E_{max} (C_e50).

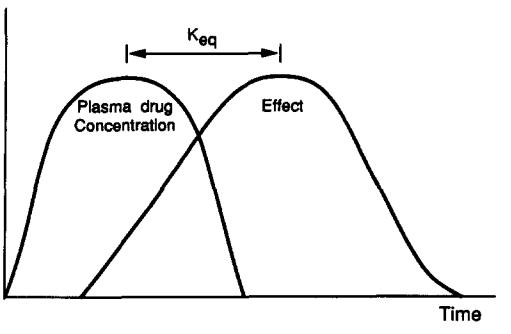

FIG. 2. For most drugs there is a temporal dissociation, or time lag, between the time course of plasma drug concentration and the measured response. In the extended model (Fig. 3), K_{eq} defines this phase discrepancy with units of hr^{-1}.

For some drugs there is a simple direct correlation between the time-course both for plasma drug concentration and for the measured response; this implies a rapid equilibration between the drug concentration in plasma and that at the site of action. For many drugs, however, the relationship is not simple and the time-course of drug effect is out of phase with the plasma drug concentration profile, i.e. delayed (Fig. 2). This time lag or temporal discrepancy between drug concentration and response is variable. It may simply reflect the time taken for the drug–receptor interaction to produce its effect or it may be due to the delayed penetration of drug into a deep tissue compartment; or occasionally it may reflect the formation of an active metabolite.

Because of the apparent dissociation of kinetic and dynamic time profiles, conventional wisdom has been that no predictable concentration–effect relationship exists for most, if not all, antihypertensive drugs. There have been many unsuccessful attempts to identify kinetic–dynamic relationships but most of these studies have sought correlations between drug concentrations and the fall in blood pressure in groups of subjects, not in individuals (Biollaz *et al.*, 1982; Larochelle *et al.*, 1982; de Leeuw *et al.*, 1987; Kleinbloesem *et al.*, 1987). When group data are considered, however, the wide range of intersubject variability in both pharmacokinetic and pharmacodynamic parameters is likely to compromise the consistent identification of concentration–effect relationships. Generally, concentration–effect relationships are identified more readily and more consistently when *individual* subjects are considered (Kelman *et al.*, 1983; Pasanisi and Reid, 1983).

2.1. Concentration–Effect Analysis

In the last 20 years considerable attention has been devoted to refining mathematical models for characterizing drug disposition in the body, i.e. pharmacokinetics, but the time course of drug concentration cannot in itself predict the time course or magnitude of drug effect. More recently, however, there has been greater interest in the application of modelling of the inter-relationship between the effect of a drug and its concentration in plasma, i.e. 'concentration–effect analysis' or 'pharmacodynamic modelling' (Whiting and Kelman, 1980). Using this technique, the pharmacodynamic effects of a number of drugs have been correlated with their pharmacokinetic properties: for example, the prolongation 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). More recently, this integrated approach has been used successfully in clinical studies of hypertension to characterize relationships between drug concentration and antihypertensive response in individual patients (Meredith *et al.*, 1987; Vincent *et al.*, 1983; Donnelly *et al.*, 1988a,b, 1989, 1990; Elliott *et al.*, 1989).

For concentration–effect analysis the conventional compartmental pharmacokinetic model is extended 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 (Holford and Sheiner, 1981; Fig. 3). The measured effect (e.g. the placebo-subtracted reduction in blood pressure) is then related to the drug concentration in the effect compartment (C_e) at each time point by means

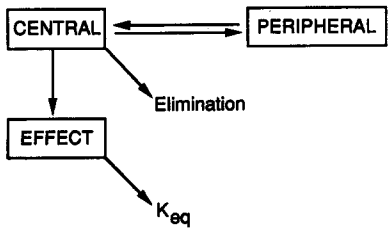

FIG. 3. Pharmacodynamic modelling is based upon an extension to the usual pharmacokinetic compartmental model, with central and peripheral compartments, in which there is an additional effect compartment (Sheiner *et al.*, 1979).

of either a linear or a nonlinear (E_{max}) model:

$$E = mC_e + i \qquad \text{Linear Model (eqn 1)}$$

$$E = \frac{E_{max} \cdot C_e}{C_e 50 + C_e} \qquad \text{Nonlinear Model (eqn 2)}$$

where E is the effect, m is the slope of the relationship, i is the intercept and C_e the drug concentration in the effect compartment. On theoretical grounds, the relationship between a continuously changing drug concentration and the corresponding response should be described most accurately by an E_{max} equation (eqn 2) where E_{max} is the maximum possible effect and $C_e 50$ the concentration required to produce 50% of E_{max}. In clinical studies however, where data points are usually collected over a restricted (central) portion of the concentration–response curve, the kinetic–dynamic relationships are often adequately described by the simpler linear model (eqn 1). The advantage of the linear model is that the slope of the relationship (m) represents the effect per unit change in drug concentration. Thus, from integrated analysis using a linear model, m quantifies the 'responsiveness' of an individual in mmHg per ng/ml. The first-order rate constant (K_{eq}) derived from the concentration–effect analysis, which has units of hr^{-1}, can be used as an index of the temporal discrepancy in the plasma concentration–effect relationship (Figs 2 and 3).

3. KINETIC–DYNAMIC RESPONSES TO ANTIHYPERTENSIVE THERAPY

In a series of clinical studies, this integrated approach has been successfully applied to characterize relationships between drug concentration and hypotensive response in individual subjects (Table 1). Each study followed a similar basic design in which pharmacokinetic and pharmacodynamic profiles were measured over 8–10 hr for individual patients on a series of study days to evaluate the effects of placebo, first dose administration and chronic (1–6 weeks) treatment. Concentration–effect relationships were described for each individual in terms of the reduction in systolic as well as diastolic blood pressure using either the linear model or the nonlinear (E_{max}) model.

The attraction of this approach is that the parameters derived from the concentration–effect analysis—either m or E_{max} and $C_e 50$—provide a simple numerical end-result which characterizes antihypertensive responsiveness in the individual patient. Moreover, this measurement is standardized to take account of the variability in pharmacokinetics, the magnitude of the blood pressure response, placebo effects and time-related changes in blood pressure and plasma drug concentration during the dosage interval.

3.1. CALCIUM ANTAGONISTS

Acute and chronic responses to nifedipine 20 mg bid and verapamil 120 mg bid have been characterized most appropriately using a linear model (Meredith *et al.*, 1987; Donnelly *et al.*, 1988a). For example, the values for responsiveness (m) to nifedipine (as the mean of the group) in terms of systolic and diastolic blood pressure respectively were -0.48 and -0.25 mmHg/ng/ml following the first dose; -0.45 and -0.24 after treatment for 1 week; and -0.49 and -0.26 after 6 weeks therapy (Table 1). As a marker of the constancy of the concentration–effect relationships within each individual, there were significant correlations between acute and chronic responsiveness (nifedipine, $r = 0.78$; verapamil, $r = 0.90$) and the slopes of these relationships were not significantly different from unity.

3.2. ALPHA ADRENOCEPTOR BLOCKERS

Concentration–effect analysis has been used to characterize responses in both normotensive and hypertensive subjects to a range of quinazoline derivatives, e.g. prazosin (Elliott *et al.*, 1989), doxazosin (Vincent *et al.*, 1983; Donnelly *et al.*, 1989) and trimazosin (Meredith *et al.*, 1983). As with the calcium antagonists, the kinetic–dynamic relationships were best described by a linear model and Vincent *et al.* (1983) showed that doxazosin concentrations after a single dose i.v. administration were correlated not only with reductions in blood pressure but also with changes in pressor sensitivity to the alpha 1 agonist phenylephrine.

TABLE 1. *Application of Concentration–Effect Analysis in Clinical Studies of Antihypertensive Drug Response*

Drug	Administration	Subjects	Concentration–effect model	Responsiveness ± SD (m or E_{max}/C_e50) in mmHg per ng/ml Acute	Chronic	Reference
(1) *Calcium antagonists*						
Nifedipine	20 mg bid oral	Hypertensives ($n = 14$)	linear	-0.48 ± 0.20	-0.49 ± 0.20	Donnelly *et al.*, 1988a
Verapamil	120 mg bid oral	Hypertensives ($n = 12$)	linear	-0.13 ± 0.06	-0.12 ± 0.06	Meredith *et al.*, 1987
(2) *Alpha 1 adrenoceptor antagonists*						
Prazosin	1 mg bid oral	Hypertensives ($n = 9$)	linear	-11.5 ± 6.7	$-8.5^* \pm 5.0$	Elliott *et al.*, 1989
Doxazosin	1 mg i.v.	Normotensives ($n = 6$)	linear	-2.5 ± 0.35	—	Vincent *et al.*, 1983
Doxazosin	2 mg od oral	Hypertensives ($n = 10$)	linear	-2.1 ± 0.8	$-1.4^* \pm 0.8$	Donnelly *et al.*, 1989
(3) *ACE inhibitors*						
Enalapril	20 mg od oral	Hypertensives ($n = 13$)	E_{max}	-0.64 ± 0.3	-0.96 ± 1.4	Donnelly *et al.*, 1990
(4) *Beta adrenoceptor blockers*						
Labetalol	1 mg/kg i.v.	Normotensives ($n = 4$)	linear	-0.19 ± 0.05	—	Elliott *et al.*, 1984
Labetalol	50 mg i.v.	Pregnant women ($n = 6$)	linear	-0.44 ± 0.26	—	Rubin *et al.*, 1983
Dilevalol	200 mg oral	Hypertensives ($n = 18$)	E_{max}	-3.5 ± 3.0	-2.1 ± 1.3	Macphee *et al.*, 1991

*Significant difference between acute and chronic.

Concentration–effect relationships for both prazosin and doxazosin have been identified during longterm oral treatment in hypertensive patients and there were significant correlations between acute and chronic responsiveness (e.g. doxazosin, $r = 0.63$). However, the slopes of both relationships were significantly less than unity and there was a consistent reduction of approximately 30% in the responsiveness during chronic treatment compared with first dose administration (Donnelly *et al.*, 1989; Elliott *et al.*, 1989). For example, responsiveness to doxazosin in terms of the change in systolic blood pressure fell from -2.1 mmHg/ng/ml after the first dose to -1.5 and -1.4 after 1 and 6 weeks, respectively. Despite reports that tolerance occurs with alpha blockers, particularly in cardiac failure, these findings suggest that the reduction in antihypertensive responsiveness to alpha 1-antagonism occurs early in the course of treatment and is probably not progressive.

Concentration–effect analysis of the response to trimazosin illustrates another application of this approach. The pharmacodynamic profile of trimazosin shows a biphasic response; following i.v. administration the maximum antihypertensive effect is delayed until 4–6 hr, but there is a transient initial reduction in blood pressure within the first hour. Using integrated kinetic–dynamic analysis, evidence emerged to suggest that the biphasic response is related to both drug and metabolite concentrations. Meredith *et al.* (1983) showed that the pharmacodynamic profile of trimazosin could not be satisfactorily described by modelling concentrations of the parent drug alone, but an augmented model incorporating two effect compartments—1 for trimazosin and 1 for the metabolite—fitted the data well. The effect modelling approach suggested that the rapid-onset initial effect is associated with the parent drug, while the subsequent maximal fall in blood pressure is mainly attributable to the metabolite 1-hydroxytrimazosin. Thus, for individual subjects, separate parameters were derived from the concentration–effect analysis to characterize the 2 components of the antihypertensive response to trimazosin (Meredith *et al.*, 1983).

3.3. ACE Inhibitors

The pharmacokinetic features of ACE inhibitor drugs are somewhat unusual, which adds an additional complexity to the concentration–effect analysis. In particular, these drugs do not show conventional and dose-linear pharmacokinetic characteristics (Till *et al.*, 1984), so ordinary compartmental models do not satisfactorily describe all the features of the disposition, particularly the lack of accumulation during chronic therapy. Instead a protein-binding type of model, which is based on the putative saturable binding of the drug to both tissue and circulating ACE, has been shown to be more appropriate for pharmacokinetic analysis (Francis *et al.*, 1987; Lees *et al.*, 1989).

A linear model was found to be inadequate to characterize the responses to enalaprilat, whereas an E_{max} function described good correlations between enalaprilat concentrations and both blood pressure reduction and plasma ACE inhibition (Donnelly *et al.*, 1990). Similar nonlinear models have been reported with other ACE inhibitors (Kelman *et al.*, 1983; Francis *et al.*, 1987) and this feature may partly explain why ACE inhibitor drugs have often been reported to have shallow or flat dose–response curves (Davis *et al.*, 1984), reflecting the use of relatively high doses producing drug concentrations towards the top end of the E_{max} curve.

The kinetic–dynamic parameters for both blood pressure reduction and ACE inhibition with enalapril again showed a significant correlation between acute and chronic responsiveness (E_{max}, $r = 0.74$) with a slope which did not differ significantly from unity (Table 1; Donnelly *et al.*, 1990). The C_e50 value for ACE inhibition, however, was significantly increased after 6 weeks compared with first dose administration and this would be consistent with induction of ACE during chronic therapy with enalapril.

3.4. Beta Adrenoceptor Blockers

Relationships between dose (or plasma drug concentration) and the degree of beta blockade—assessed by exercise or isoprenaline-induced increases in heart rate—have been identified with a number of beta-adrenoceptor antagonists (Zacest and Koch-Weser, 1972) but no such kinetic–dynamic relationship has been reported for the antihypertensive effects. Concentration–effect analysis has been undertaken only with labetalol (Rubin *et al.*, 1983; Elliott *et al.*, 1984) and the related compound dilevalol (Macphee *et al.*, 1991). In both cases, however, placebo-corrected reductions in blood pressure were consistently correlated with drug concen

trations in individual subjects (Donnelly and Macphee, 1991). Responses to single i.v. doses of labetalol were characterized using a linear model (Elliott *et al.*, 1984) but in hypertensive patients the kinetic–dynamic relationships of dilevalol after chronic oral treatment were best described by the E_{max} equation. An E_{max} model is also more appropriate for responses to another beta blocker, flusoxolol (Sumner *et al.*, 1988).

3.5. Thiazide Diuretics

Although thiazide diuretics have formed the mainstay of antihypertensive therapy for over 20 years, there has been little attempt to identify the optimum dose. Conventional wisdom has always been that these drugs have 'flat' dose–response curves but this assumption stems from early studies that selected inappropriately high doses (Cranston *et al.*, 1963). It is only recently that the kinetic–dynamic relationships of thiazide diuretics have received closer attention and it is now clear that much lower antihypertensive doses are equally effective while avoiding many of the unwanted metabolic effects (McVeigh *et al.*, 1988; Carlsen *et al.*, 1990).

Individualized analysis and pharmacodynamic modelling of diuretic responses have recently been undertaken by Alvan *et al.* (1990, 1992). These authors have shown that an E_{max} model is most appropriate for characterizing the natriuretic effects of frusemide and there is no reason why a similar approach cannot be used to relate drug concentrations of thiazide diuretics to the fall in blood pressure.

3.6. Summary

These studies have shown that with a range of antihypertensive agents drug concentrations are related to the placebo-adjusted fall in blood pressure in *individual* subjects. Moreover, kinetic and dynamic information can be integrated into a single parameter (m or E_{max}/C_e50) which characterizes the individual response; this can be defined after single dose or chronic drug administration; for systolic as well as diastolic blood pressure; and for a range of different patient groups.

4. APPLICATIONS OF INTEGRATED KINETIC–DYNAMIC ANALYSIS

These initial studies have confirmed that concentration–effect analysis can be successfully applied to antihypertensive therapy and that the derived parameters represent a mathematical description of drug response which is comparable and reproducible. Although still at an early stage of evaluation, this approach has been shown to have a number of clinical and research applications.

4.1. Variability in Antihypertensive Drug Response

A wider choice of antihypertensive drugs is now available and ideally individualized therapy might involve a rational selection of the most suitable agent based upon readily available clinical and demographic information about the individual, e.g. age, sex, race, smoking status, obesity and lipids. In practice, however, the factors which determine the response to different antihypertensive drugs are not clearly understood and at present there is no reliable method for identifying which patients will respond to which drugs. 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, ethnic origin or plasma renin activity (Breckenridge, 1987). 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).

Although the magnitude of the hypotensive response is determined, in part, by the 'sensitivity' of the individual to the pharmacological effect, response is also determined by the amount of drug which reaches the site of action. Generally, however, studies of antihypertensive drug response have ignored pharmacokinetic considerations; since there appeared to be no consistent relationship between drug dose or plasma concentration and the fall in blood pressure, kinetic and dynamic variability have usually been addressed separately. This often leads to difficulties with interpretation—for example, the fall in blood pressure with verapamil is greater in the elderly (Buhler *et al.*, 1982) but is this due to an age-related increase in drug 'sensitivity', or do older patients simply achieve higher plasma drug concentrations? Since age may affect both the pharmacodynamic and

pharmacokinetic responses to calcium antagonist drugs (Robertson *et al.*, 1988), measurements of blood pressure alone do not resolve this important question.

Thus, antihypertensive *response* is difficult to define and previous studies have used various criteria for recording blood pressure which may not readily distinguish between peak and trough effects, clinic or ambulatory measurements, and whether the fall in blood pressure is adequately corrected for the placebo response. An accurate quantitative assessment of antihypertensive drug *response*, and its variability, requires that proper account be taken of several important factors—(1) measurement of the placebo-adjusted reduction in blood pressure, (2) measurement of the underlying plasma drug concentrations, and (3) allowances for time factors since kinetics and dynamics change during the dosage interval. In most previous studies antihypertensive 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 differences in plasma drug concentration or of time-related variations in blood pressure or pharmacokinetics. Hence it is no real surprise that little progress has been made over the last 20 years towards identifying which patients (in routine clinical practice) respond best to which drugs.

The big advantage of concentration–effect analysis is that it encompasses the 4 important variables—blood pressure, placebo effect, drug concentration and time—into a single mathematical parameter. Thus, having established a standardized method for describing the antihypertensive drug *response*, it is somewhat easier to tackle the problem of identifying which factors determine the variability in antihypertensive effect. Although this requires large numbers of patients, some preliminary findings have been reported from a series of over 60 patients in whom acute and chronic responses to treatment were characterized using integrated analysis.

4.1.1. *Age and Plasma Renin Activity*

There have been conflicting reports about the effect of age and PRA on antihypertensive drug response. For example, it has been suggested that younger patients and those with high PRA respond better to ACE inhibitors and beta blockers, while elderly, low-renin patients have a greater effect with diuretics and calcium antagonists (Buhler *et al.*, 1972; Adlin *et al.*, 1972; Cody *et al.*, 1983). As mentioned earlier, the influence of age is further complicated by possible effects on pharmacokinetics. In studies that have used concentration–effect analysis with nifedipine and enalapril, age and PRA accounted for less than 10% of the variability in 'responsiveness' (Donnelly *et al.*, 1988a, 1990).

4.1.2. *Starting Blood Pressure*

A relationship between starting blood pressure and the magnitude of the fall with treatment has been reported with several antihypertensive agents (Erne *et al.*, 1983). However, there are statistical problems in correlating two dependent variables, i.e. BP and $\triangle$BP (Gill *et al.*, 1985), 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.*, 1988). The importance of pretreatment blood pressure as a determinant of antihypertensive drug response has been confirmed in several studies where concentration–effect parameters have been correlated with the initial blood pressure (Table 2).

4.2. CONSTANCY AND PREDICTABILITY OF ANTIHYPERTENSIVE DRUG RESPONSE

It has been claimed that the variability in antihypertensive drug response is sufficiently erratic and unpredictable that it represents a major obstacle to the prospective optimization of individual treatment regimens (Menard *et al.*, 1988). For example, there are reports that the first dose response to a calcium antagonist or an ACE inhibitor bears no relationship to the response obtained during longterm treatment (Bidiville *et al.*, 1988) and that the antihypertensive effect of dihydropyridines diminishes after chronic administration (Waller and Ramsay, 1987). However, as mentioned earlier, it is difficult to draw firm conclusions about the constancy of drug response from pharmacodynamic information alone.

TABLE 2. *Coefficients of Correlation between m or E_{max} and Initial Blood Pressure for a Range of Antihypertensive Drugs*

Drug	Model	No. of subjects	Correlation coefficient
Verapamil	Linear	12	0.82*
Nifedipine	Linear	14	0.60†
Prazosin	Linear	15	0.74*
Doxazosin	Linear	10	0.69†
Endralazine	Linear	8	0.82†
Flusoxolol	E_{max}	8	0.81†
Enalapril	E_{max}	13	0.69*

*$p < 0.01$; †$p < 0.05$.
(Adapted from Sumner *et al.*, 1988.)

A consistent finding in each of the studies listed in Table 1 is that responsiveness to the first dose of a drug was correlated with responsiveness after 1 week and 6 weeks treatment (Fig. 4). This suggests that, for individual patients, the acute hypotensive response may be a useful predictor of the response during chronic therapy. For example, it has been shown that the kinetic and dynamic parameters derived after the first dose of enalapril can be used to predict the blood pressure profiles during chronic treatment for individual patients (Fig. 5; Meredith *et al.*, 1990). 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.

4.3. INDIVIDUALIZED DOSAGE REGIMENS

This constancy of antihypertensive responsiveness in translation from acute to chronic therapy suggests that a concentration–effect modelling approach may have utility in optimizing individual

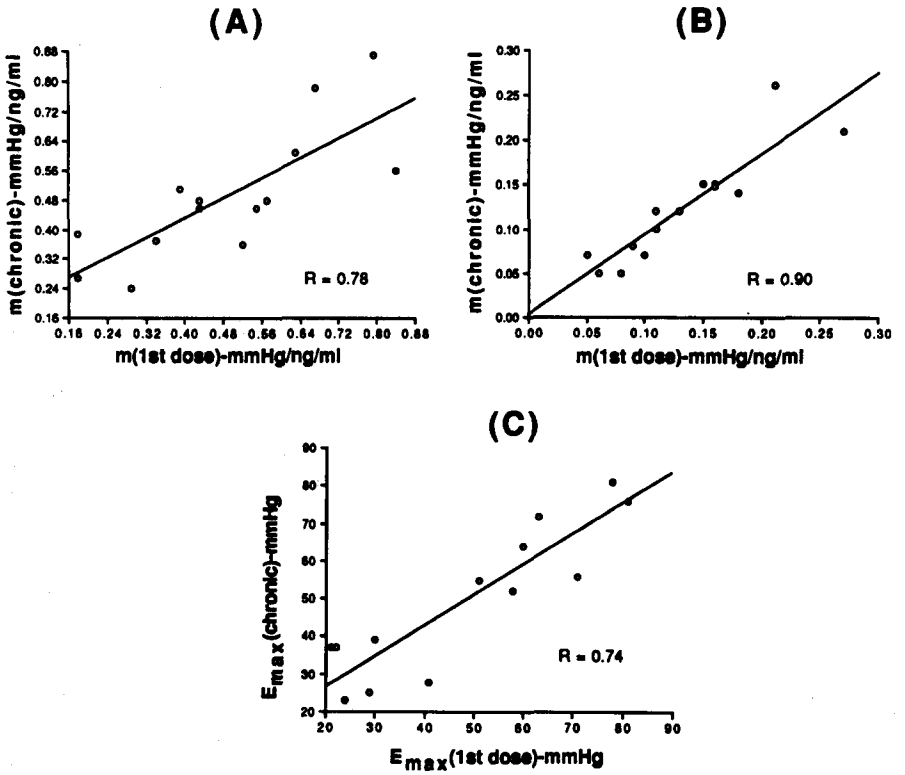

FIG. 4. Responsiveness—expressed either as *m* or E_{max}—to the first dose of an antihypertensive drug was correlated with responsiveness after 4–6 weeks for nifedipine (A), verapamil (B) and enalapril (C).

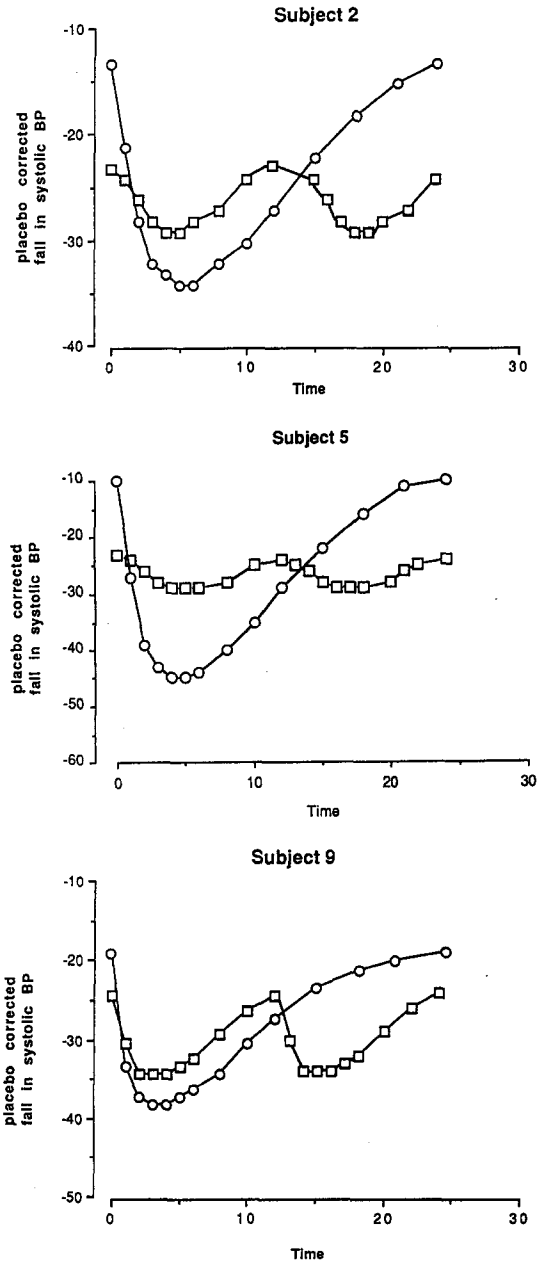

FIG. 5. Kinetic and dynamic parameters following the first dose of enalapril 20 mg, in individual patients, may be used to simulate blood pressure profiles at steady state for a range of alternative dosage regimens. Simulated placebo-corrected systolic blood pressure profiles at steady state for enalapril 20 mg daily (○) and 10 mg bid (□) are shown. Reprinted from Meredith *et al.* (1990), with permission of the copyright holder, *Current Science*, London.

dose regimens prospectively. Thus, not only is there scope to predict the longterm response to a fixed dosage schedule and to identify an individual dose requirement but there is also scope to investigate, by simulation, the response profiles for a range of alternative dosage regimens, e.g. once or twice daily administration (Meredith *et al.*, 1990). For example, the kinetic and dynamic responses to a single dose of enalapril 20 mg have been used to simulate blood pressure profiles during chronic treatment with various alternative dosage regimens (Fig. 5). Furthermore, this approach highlights large interindividual differences in dose requirements and dose interval in order to achieve an optimum ratio of trough to peak response (i.e. >60%) and full 24 hr blood pressure control (Meredith *et al.*, 1990).

5. CONCLUSIONS

In order to maximize the benefits of antihypertensive therapy and improve the overall risk–benefit ratio, particularly in patients with mild hypertension, there are cogent reasons for developing an individualized approach to drug and dosage selection. However, attempts to optimize treatment prospectively have been hampered by the paucity of basic information about dose–concentration–response relationships for the common antihypertensive agents; conventional wisdom has been that for most hypotensive drugs there is no predictable relationship between plasma concentration and effect but previous studies have invariably sought correlations between kinetic and dynamic parameters for groups of subjects rather than for individuals. Studies using integrated kinetic–dynamic analysis have shown that drug concentrations are related to the fall in blood pressure in *individual* patients and this method provides a mathematical description of antihypertensive response which is comparable and reproducible. Moreover, the parameters derived from concentration–effect analysis have potential utility in identifying factors that determine the variability in antihypertensive drug response, identifying poor or nonresponders and determining individual dose requirements for optimum blood pressure control.

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