Pharmacodynamic modeling of the antihypertensive response to amlodipine

The distinctive pharmacokinetic characteristics of amlodipine, particularly the long half-life, are presumed to translate directly to a prolonged duration of action, but the concentration-effect relationship for the antihypertensive response has not been clearly established. In this study of 12 patients with essential hypertension, treatment with 5 mg amlodipine once daily has been evaluated with use of an integrated pharmacokinetic-pharmacodynamic model to calculate individual patient responsiveness for the decrease in blood pressure per unit change in drug concentration. Amlodipine concentrations were well correlated with the placebo-corrected reductions in blood pressure in individual patients and responsiveness, for example, for erect systolic blood pressure was -3.1 ± 0.9 mm Hg/ng/ml. By characterizing the concentration-effect relationships in individual patients, this study has confirmed that the plasma concentration–time profile is an appropriate index of the effect-time profile, as reflected by an antihypertensive response that is sustained throughout 24 hours with relatively little trough-to-peak variability. (CLIN PHARMACOL THER 1993;54:303-10.)

Richard Donnelly, PhD, MRCP, Peter A. Meredith, PhD, Stephen H. K. Miller, MSc, Catherine A. Howie, BSc, and Henry L. Elliott, MD, FRCP *Glasgow, Scotland*

Dihydropyridine calcium antagonist drugs are well established in the treatment of hypertension, but clinical studies have shown large interindividual differences not only in drug disposition and dose requirements but also in the magnitude of the antihypertensive response.[1,2] In general, dihydropyridines undergo extensive hepatic metabolism with rapid drug clearance and a relatively short elimination half-life ($t_{1/2}$)[3] and, as a consequence, a protracted antihypertensive effect has been difficult to achieve without pharmaceutical manipulation of the drug formulation.[4] These observations suggest that the time course (and magnitude) of the antihypertensive response are directly dependent on the pharmacokinetic characteristics of the drug and its formulation. Recent studies with nifedipine and felodipine,[5-7] for example, have shown that the plasma drug concentration–time profile is a direct index of the antihypertensive response.

Amlodipine is a dihydropyridine derivative with pharmacokinetic characteristics that are distinctly different from other dihydropyridines, with a protracted elimination $t_{1/2}$ and, at steady state, with a relatively smooth concentration-time profile that shows relatively little trough-to-peak variability across a dosing interval.[8,9] The relationship between the magnitude and time course of the antihypertensive effect of amlodipine and its pharmacokinetics and plasma concentration profile remains to be clearly established. Correlations between mean plasma amlodipine concentrations and change in blood pressure have been reported for groups of young and elderly patients with hypertension,[10] but there is increasing evidence that kinetic-dynamic relationships can be more clearly defined when *individual* subjects are considered and when repeated measurements are obtained throughout a dosing interval.[11-13] With the individualized approach there is potential for wider applicability, particularly in the prediction of the change in response when dosage is altered or omitted.

The principal aims of this study were to characterize the concentration-effect relationship for the antihypertensive response to amlodipine and to assess whether or not the characteristics of the time course of the antihypertensive response (at steady state) is a direct reflection of the pharmacokinetic characteristics.

From the Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary.
Received for publication Feb. 11, 1993; accepted April 22, 1993.
Reprint requests: Henry L. Elliott, MD, Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT, Scotland.

0009-9236/93/$1.00 + 0.10 **13/1/48206**

METHODS

Outline of study. Twelve patients (six men and six women; age range, 25 to 64 years) with mild to moderate essential hypertension (160/90 to 210/115 mm Hg) gave written informed consent to participate in this study, which was approved by the Research and Ethics Committee of the Western Infirmary, Glasgow, Scotland. Subjects either had a recent diagnosis (untreated) of essential hypertension or were patients in whom previous unsatisfactory antihypertensive therapy had been discontinued for at least 6 weeks.

After the preliminary assessment period of at least 6 weeks (without treatment), the average entry blood pressure was 175/103 ± 24/5 mm Hg. Thereafter, in a single-blind design, patients began a placebo (single-dose) period of 3 weeks followed by a treatment period with 5 mg amlodipine once daily for 6 weeks. During the placebo period, in a double-blind randomized manner, single doses of 5 mg amlodipine and matching placebo were administered at the end of weeks 1 and 3 with each patient attending the Clinical Investigation and Research Unit (CIRU) for detailed pharmacokinetic and pharmacodynamic measurements up to 48 hours after administration. After completion of the placebo/single-dose period, patients were established on 5 mg amlodipine as monotherapy and asked to return after 6 weeks for an identical third pharmacokinetic-pharmacodynamic study in the CIRU.

Study days. On each study day, after an overnight fast, patients attended the CIRU at 8 AM. After 20 minutes of supine rest, baseline blood pressure and heart rate measurements were recorded, an indwelling cannula was inserted into an antecubital vein, and 5 mg amlodipine or placebo was administered orally with 100 ml water. At frequent intervals during each study day (i.e., 0, ½, 1, 1½, 2, 2½, 3, 3½, 4, 5, 6, 7, 8, 9, 10, and 12 hours), blood pressure and heart rate were recorded after not less than 10 minutes of supine rest and erect after 2 and 4 minutes of standing by use of an Accutorr semiautomatic sphygmomanometer (Datascope Corp., Paramus, N.J.). These sphygmomanometers are routinely serviced on a monthly basis by the hospital Medical Physics Department and calibrated against a standard column of mercury. At corresponding times, venous blood samples were collected for plasma drug concentrations. A standard light lunch was provided after 5 hours. Patients returned to the CIRU at 24, 32, and 48 hours after drug administration for further measurements of blood pressure and heart rate, as well as for venous sampling for drug concentration analysis.

Ambulatory blood pressure monitoring. In a randomly selected subgroup of six patients (patients 2, 4, 5, 9, 10, and 11), 24-hour ambulatory blood pressure monitoring was performed at the end of the placebo phase and after 6 weeks of treatment with amlodipine with use of a Spacelabs ambulatory blood pressure recorder (Spacelabs International, Inc., Berkshire, England).

Laboratory methods. Blood and plasma samples were placed in tubes wrapped with aluminium foil to prevent photodegradation of amlodipine. Plasma amlodipine concentrations were measured by gas liquid chromatography with electron capture detection,[14] with interassay and intra-assay coefficients of variation of 8% and 6.5%, respectively, and a limit of detection of 1 ng/ml.

Pharmacokinetics and concentration-effect analysis. Plasma amlodipine concentration data were evaluated with use of both model-independent and model-dependent methods. The linear trapezoidal rule was applied in calculating the area under the concentration-time curve (AUC), and log-linear regression analysis was used to obtain measurements of the elimination $t_{1/2}$. A hierarchy of pharmacokinetic models were fitted independently and simultaneously to the amlodipine plasma concentration data after first-dose and steady-state administration. The most appropriate model was selected on criteria of goodness of fit, including the coefficient of determination, the z values of runs in residuals, and application of the general linear (*F* ratio) test to the sum of squares values. In all subjects the most appropriate model was a one-compartment model with first-order input simultaneously fitted to single-dose and steady-state data. The fitted parameters derived from this model were V/F (liters), k_e ($hours^{-1}$), and k_a ($hours^{-1}$). These respectively represent the volume of distribution and the first-order rate constants describing elimination and absorption.

For the concentration-effect analysis, the standard pharmacokinetic model was augmented by an "effect" compartment as described previously.[15] The effect, in this case, blood pressure reduction, was then related to the drug concentration in the effect compartment by means of both linear and nonlinear models, which define the relationship between drug concentration and effect as follows:

Linear model:

$$E = mC_e + i$$

Langmuir E_{max} model:

$$E = \frac{E_{max} \cdot C_e}{C_{e(50)} + C_e}$$

in which E is the measured effect and C_e is the drug concentration in the effect compartment. The principal

disadvantage of the linear model is that it does not define a maximum effect, but in clinical studies most data points are usually obtained within a relatively restricted concentration-response range. Thus, under physiologic conditions, the simpler linear model is often more appropriate than the Langmuir E_{max} equation. The main advantage of the linear model is that the slope of the relationship (m) represents the responsiveness to the drug, that is, blood pressure reduction (in millimeters of mercury) per unit drug concentration in the effect compartment, whereas for the Langmuir model E_{max} is the theoretic possible effect and $C_{e(50)}$ is the concentration required to produce 50% of E_{max}.[15]

The first-order rate constant of the effect model (k_{eo}) describes the removal of drug from the effect compartment and characterizes the phase lag between the change in blood pressure and plasma drug concentration. The k_{eo} is derived from the concentration-effect analysis and is related to the rate of change in the amount of drug in the effect compartment.[15]

After the pharmacokinetic model and the appropriate parameters in individual subjects were defined, the pharmacodynamic data (i.e., the profiles of [placebo-corrected] reduction in erect systolic blood pressure) were fitted to both effect models by use of a nonlinear least-squares fitting procedure. In all patients, when both study days were fitted simultaneously, the data were most appropriately described by the linear model on the basis of the general linear test. The responsiveness (m) to amlodipine was calculated for individual patients for the placebo-subtracted change in erect (3 minutes) systolic blood pressure per unit change in drug concentration.

Statistical analysis. Measurements throughout are expressed as mean value ± SD. Blood pressure and heart rate measurements were evaluated by repeated-measures ANOVA. Linear regression analysis was used for the correlation between responsiveness and pretreatment blood pressure.

RESULTS

Pharmacodynamics. For the group as a whole there was no statistically significant decrease in blood pressure during the 10-hour study day after first-dose administration of amlodipine, as illustrated for erect blood pressure (Fig. 1). However, reductions in blood pressure were significant at 24 and 48 hours after the first dose ($p < 0.001$). For example, supine blood pressures at 24 and 48 hours were 154/97 ± 20/11 and 154/94 ± 17/4 mm Hg, respectively, compared with 161/98 ± 18/9 and 165/98 ± 13/6 mm Hg after placebo.

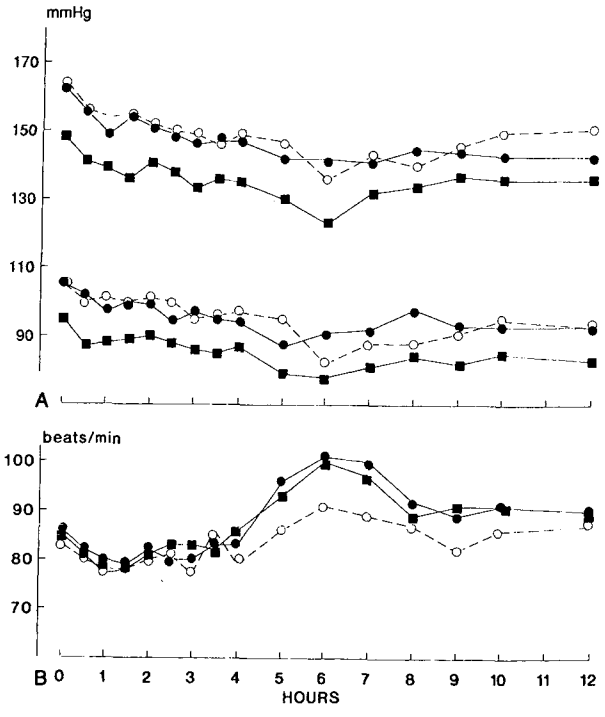

Fig. 1. Mean profiles for erect blood pressure and heart rate after placebo *(open circles)*, first dose of amlodipine *(solid circles)*, and steady-state amlodipine *(squares)*.

After 6 weeks, there were significant reductions in baseline (predose) blood pressure ($p < 0.001$) and further reductions in supine blood pressure and in erect blood pressure (Fig. 1) during the third study day ($p < 0.001$). Thus baseline blood pressures (recorded 24 hours after the previous dose) were 145/94 ± 16/8 mm Hg for supine and 148/94 ± 18/8 mm Hg for erect, compared with 165/103 ± 20/6 and 164/105 ± 18/8 after placebo. Average blood pressures during the third study day (from 0 to 10 hours) were 135/83 mm Hg for supine and 136/85 mm Hg for erect; these values represent reductions of 12/9 and 15/12 mm Hg, respectively, compared with the corresponding blood pressures after placebo.

Ambulatory blood pressure monitoring in six patients confirmed the significant reductions in blood pressure with steady-state dosing ($p < 0.001$). Overall average values for ambulatory blood pressure were 131/82 ± 15/11 mm Hg (0 to 24 hours) and 131/82 ± 12/5 mm Hg (0 to 16 daytime hours) after amlodipine, compared with corresponding values of 141/88 ± 11/7 mm Hg and 144/90 ± 13/11 mm Hg after 3 weeks treatment with placebo.

After the first dose of amlodipine, there were small but significant increases in both supine and erect heart

Table I. Pharmacokinetics of amlodipine

	*Model-independent analysis**				*Model-dependent analysis†*		
	AUC (ng · hr · ml^{-1})		*Elimination $t_{1/2}$*				
Patient No.	*First dose*	*6 Weeks*	*First dose*	*6 Weeks*	*V/F (L)*	*k_e (hr^{-1})*	*k_a (hr^{-1})*
1	210	245	48.2	46.1	2350	0.011	0.26
2	132	199	29.8	28.9	1150	0.021	0.18
3	125	182	52.6	69.3	1450	0.026	0.26
4	163	155	63.4	58.4	1650	0.024	0.28
5	236	238	36.1	44.1	1000	0.031	0.43
6	125	—	38.9	—	1400	0.027	0.31
7	172	250	53.6	39.7	1600	0.024	0.21
8	80	90	55.5	67.8	1450	0.008	0.19
9	160	215	37.2	35.1	850	0.019	0.18
10	106	118	46.2	45.0	1900	0.028	0.17
11	169	192	39.7	49.8	1950	0.011	0.88
12	210	300	48.2	52.4	1600	0.014	0.19
Mean ± SD	152 ± 45	194 ± 62	45.6 ± 10	49.0 ± 13	1550 ± 400	0.020 ± 0.008	0.29 ± 0.20

AUC, Area under the plasma concentration–time curve; $t_{1/2}$, half-life; V/F, volume of distribution; k_e and k_a, first-order rate constants describing elimination and absorption.

*The model-independent parameters, AUC and elimination $t_{1/2}$, were calculated for individual patients on each study day.

†The model dependent variables were obtained by means of simultaneous fitting to both drug concentration–time profiles for each subject.

rate ($p < 0.001$), on average, 2.5 and 4 beats/min, respectively, which were maximal between 5 to 9 hours after drug administration (Fig. 1), but no significant increases were observed after steady-state dosing.

Pharmacokinetics. Model-independent analysis of the pharmacokinetic data showed an elimination $t_{1/2}$ at steady state of 49 ± 13 hours (Table I). After steady-state dosing, there was an approximately fourfold increase in plasma amlodipine concentrations, which is wholly consistent with the factorial accumulation predicted from such a long terminal $t_{1/2}$.

With use of a model-dependent approach, in all patients the plasma concentration–time profiles after single-dose and steady-state administration were most appropriately described by fitting a one-compartment model simultaneously to the plasma concentration data derived in individual patients on both study days. The derived parameters are shown in Table I and the fits for three representative patients are shown in Fig. 2. These profiles represent the best, worst, and "average" (of the group) fits characterized by coefficients of determination of 0.992, 0.834, and 0.935, respectively, with corresponding Akaike information criterion values of 18.2, 68.8, and 54.3, respectively.

Concentration-effect relationships. In individual patients there was no simple relationship between plasma amlodipine concentrations and the decrease in blood pressure (Fig. 3). In all subjects, however, the most appropriate model to describe the pharmacodynamic data was the linear model; drug concentrations in individual patients were well correlated with the (placebo-subtracted) reduction in erect systolic blood pressure, as shown for three representative patients (Fig. 4). The best, worst, and "average" fits were characterized by coefficients of determination of 0.970, 0.752, and 0.850, respectively, and by Akaike information criterion values of 162.4, 285.4, and 217.9, respectively. The derived m and k_{eo} values are summarized in Table II and, as the mean of the group, responsiveness to amlodipine was −3.1 ± 0.9 mm Hg/ng/ml for erect systolic blood pressure.

There was no relationship between responsiveness (m) and patient age or pretreatment plasma renin activity, but there was a significant positive correlation between responsiveness (m) and the pretreatment (baseline) blood pressure ($r = 0.71$).

DISCUSSION

The antihypertensive efficacy and disposition characteristics of amlodipine are well documented,[8,16] but there is a paucity of detailed information about the relationship between the pharmacokinetic characteristics (i.e., the plasma drug concentration–time profile) and the antihypertensive response.

For the group as a whole, the gradual onset of action after the first dose of amlodipine did not elicit a statistically significant hypotensive response until 24 to 48 hours after drug administration, but the small increases in heart rate provide some evidence of vasodilator activity during the first 10 hours. After 6 weeks

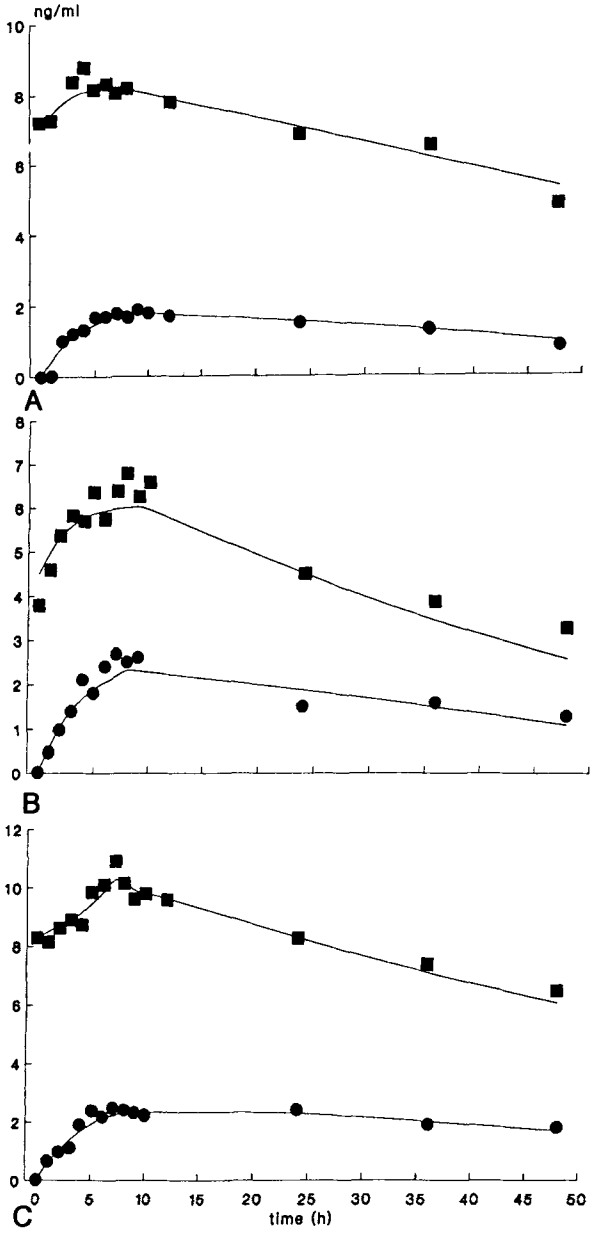

Fig. 2. Representative plasma drug concentration–time profiles for first dose of amlodipine *(circles)* and steady-state amlodipine *(squares)* in three representative patients. **A,** Best fit. **B,** Worst fit. **C,** "Average" fit.

of treatment, there was clear evidence of a sustained antihypertensive response (on average, 12/9 mm Hg supine and 15/12 mm Hg erect), and heart rates were not significantly different from the placebo values.

There was no simple relationship between plasma amlodipine concentrations and the decrease in blood pressure, as shown by the hysteresis pattern, but direct

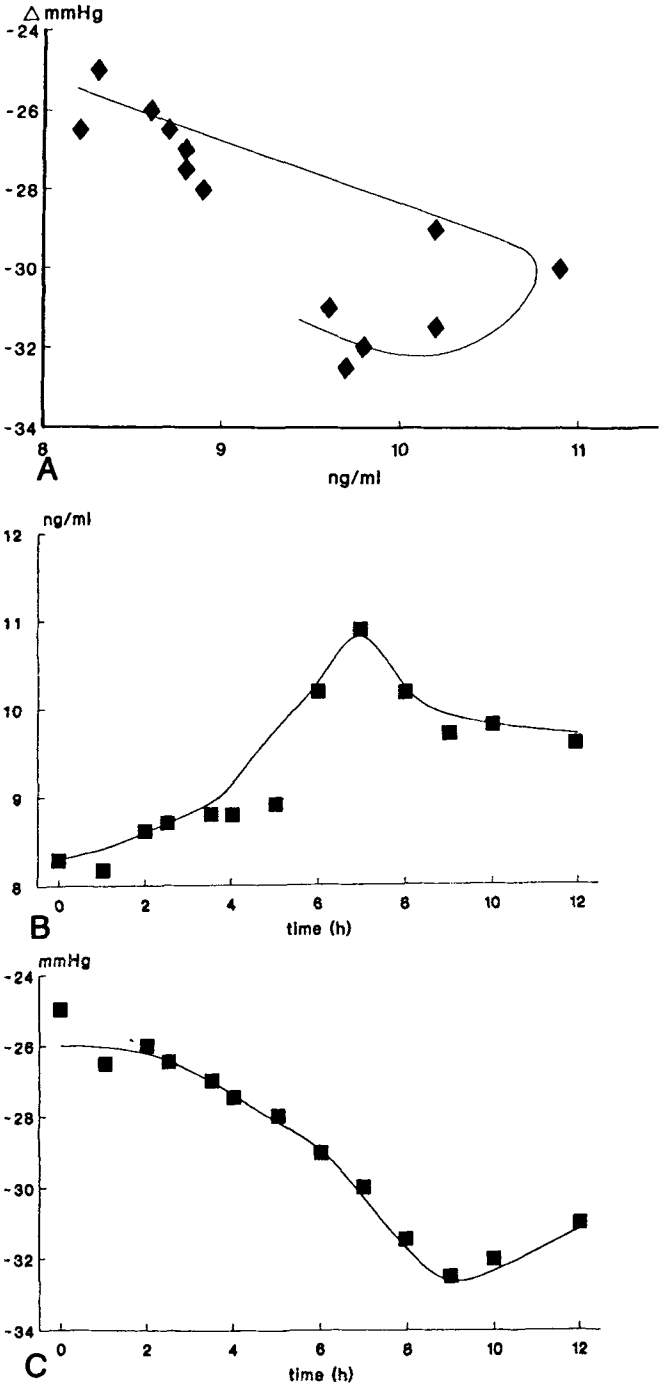

Fig. 3. Hysteresis plot of blood pressure reduction (erect systolic) versus plasma drug concentration in a representative patient **(A).** Also shown are the plasma amlodipine concentration–time profile **(B)** and the effect-time profile (for erect blood pressure at steady state; **C)** in the same representative patient.

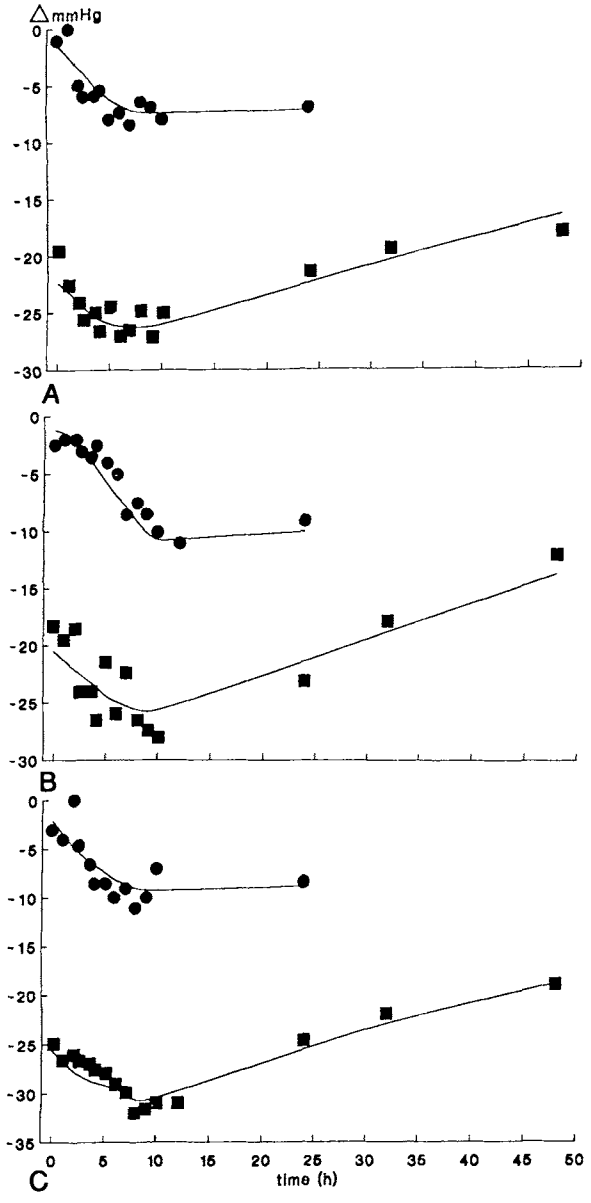

Fig. 4. Integrated pharmacodynamic-pharmacokinetic fits after the first dose of amlodipine *(circles)* and steady state amlodipine *(squares)* in the three representative patients **A**, Best fit. **B**, Worst fit. **C**, "Average" fit.

concentration-effect relationships were described in each individual patient by use of pharmacodynamic modeling. The relationship between continuously changing (increasing) drug concentrations and the hypotensive response should, on theoretic grounds, be described most accurately by an E_{max} equation, but in this study (as has been described in other clinical studies[5,12,17]), in which data points were restricted to a clinically relevant range, the linear model was found to be more appropriate. In practical terms this has the advantage that antihypertensive "responsiveness" is characterized in each individual patient in millimeters of mercury per ng · ml^{-1}, that is, m, the slope of the linear relationship. For example, for erect systolic blood pressure, there was an average reduction of 3.1 mm Hg for each ng · ml^{-1} change in plasma concentration. Thus, concentration-effect analysis provides a mathematic description of drug response that is standardized to take account of kinetic as well as dynamic variability, placebo effects, and time-related differences in drug concentration and blood pressure during a dosing interval.

Table II. Concentration-effect parameters, m and k_{eo}, for changes in erect systolic blood pressure

Patient No.	*Patient age (yr)*	*m (mm Hg/ ng/ml)*	k_{eo} (hr^{-1})
1	62	−3.5	0.74
2	25	−3.0	0.10
3	54	−4.0	0.27
4	57	−3.5	0.13
5	33	−2.7	0.29
6	40	—	—
7	48	−2.8	0.15
8	48	−1.6	1.20
9	53	−2.4	0.46
10	58	−4.9	0.13
11	64	−2.5	1.04
12	41	−2.8	1.23
Mean ± SD		−3.1 ± 0.9	0.52 ± 0.45

m, Responsiveness; k_{eo}, first-order rate constant of the effect model.

In some previous studies the parameters derived from concentration-effect analysis have been used to predict the blood pressure responses to a range of dosing schedules,[18,19] which raises the possibility of optimizing antihypertensive treatment prospectively on an individual basis.[11] However, this potential prospective use of concentration-effect analysis does not appear to be a practical possibility with amlodipine because the onset of the hypotensive effect is too gradual to allow accurate quantification of the initial antihypertensive response. It has often been suggested that the antihypertensive response to calcium antagonists and to other antihypertensive drugs shows no predictable concentration-effect relationships.[20,21] This principally reflects the negative findings of previous studies that have sought correlations between kinetic and dynamic parameters for *groups* of subjects rather than for individuals.[21] The pharmacokinetic analysis in this study

confirmed that, in contrast to other dihydropyridine compounds, steady-state amlodipine shows relatively little fluctuation in plasma concentrations across a dosing interval and, correspondingly, relatively little fluctuation in antihypertensive effect. Thus, in addition to showing that the concentration-time profile is a useful index of the effect-time profile, the unified modeling approach for single and multiple doses emphasises the relative lack of intraindividual pharmacokinetic variability.

An additional but incidental feature of this study relates to those factors that have been implicated as determinants of the antihypertensive response to a calcium antagonist,[22] for example, age, plasma renin activity, and starting blood pressure. In previous studies this type of analysis is often compromised by inconsistent and sometimes inadequate methods for describing drug "response" that take no account of kinetic variability.[11] For example, after a single intravenous dose of amlodipine, the decrease in blood pressure per unit drug concentration was greater in elderly than in young patients with hypertension, but after long-term oral therapy there was no relationship between age and antihypertensive responsiveness.[10] Although not a declared aim of this study, there was no relationship between age (across a relatively narrow range) and the antihypertensive response, but there was a consistent relationship between responsiveness and the height of the pretreatment blood pressure, as has been reported previously.[5,23]

In conclusion, this study has characterized the concentration-effect relationships and individual responses to amlodipine by use of a linear pharmacodynamic model and has shown that the sustained plasma concentration–time profile translates to a sustained antihypertensive effect-time profile.

References

1. Bayley S, Dobbs RJ, Robinson BF. Nifedipine in the treatment of hypertension: report of a double-blind controlled trial. Br J Clin Pharmacol 1982;14:509-12.
2. Kiowski W, Bertel O, Erne P, Hulthen UL, Ritz R, Buhler FR. Haemodynamic and reflex responses to acute and chronic antihypertensive therapy with the calcium entry blocker nifedipine. J Hypertens 1983;5(suppl III):170-4.
3. Abernethy DR, Schwartz JB. Pharmacokinetics of calcium antagonists under development. Clin Pharmacokinet 1988;15:1-14.
4. Landmark K. Antihypertensive and metabolic effects of longterm therapy with nifedipine slow-release tablets. J Cardiovasc Pharmacol 1985;7:12-7.
5. Donnelly R, Elliott HL, Meredith PA, Kelman AW, Reid JL. Nifedipine: individual responses and concentration-effect relationships. Hypertension 1988;12: 443-9.
6. Blychert E, Hedner T, Dahlöf C, Elmfeldt D. Plasma concentration effect relationships of intravenous and extended release oral felodipine in hypertensive patients. J Cardiovasc Pharmacol 1990;15:428-35.
7. Blychert E, Edgar B, Elmfeldt D, Hedner T. Plasma concentration-effect relationships for felodipine. A meta analysis. Clin Pharmacol Ther 1992;52:80-9.
8. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. Clin Pharmacokinet 1992;22:22-31.
9. Faulkner JK, McGibney D, Chasseaud LF, Perry JL, Taylor IW. The pharmacokinetics of amlodipine in healthy volunteers after single intravenous and oral doses and after 14 repeated oral doses given once daily. Br J Clin Pharmacol 1986;22:21-5.
10. Abernethy DR, Gutkowska J, Winterbottom LM. Effects of amlodipine, a long-acting dihydropyridine calcium antagonist in aging hypertension: Pharmacodynamics in relation to disposition. Clin Pharmacol Ther 1990;48:76-86.
11. Donnelly R, Meredith PA, Elliott HL. The description and prediction of antihypertensive drug response: an individualised approach. Br J Clin Pharmacol 1991; 31:627-34.
12. Meredith PA, Elliott HL, Ahmed JA, Reid JL. Age and the antihypertensive efficacy of verapamil: an integrated pharmacokinetic-pharmacodynamic approach. J Hypertens 1987;5:S219-21.
13. Reid JL, Meredith PA. Concentration-effect analysis of antihypertensive drug responses. Hypertension 1990; 16:12-8.
14. Beresford AP, Macrae PV, Stopher DA, Wood BA. Analysis of amlodipine in human plasma by gas chromatography. J Chromatogr Biomed Appl 1987;420:178-83.
15. Holford NHG, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet 1981;6:429-53.
16. Murdoch D, Heel RC. Amlodipine: a review of pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. Drugs 1991; 41:478-505.
17. Donnelly R, Elliott HL, Meredith PA, Reid JL. Concentration-effect relationships and individual responses to doxazosin in essential hypertension. Br J Clin Pharmacol 1989;28:517-26.
18. Meredith PA, Donnelly R, Elliott HL. Prediction and optimization of the antihypertensive response to nifedipine. Am J Hypertens [In press].
19. Meredith PA, Donnelly R, Elliott HL, Reid JL. Prediction of response to enalapril. J Hypertens 1990;8:1085-90.
20. Pedersen LO, Mikkelsen E, Christensen NJ, Kornerup HJ, Pedersen EB. Effect of nifedipine on plasma renin,

aldosterone and catecholamines in arterial hypertension. Eur J Clin Pharmacol 1979;15:235-40.

21. Bidiville J, Nussberger J, Waeber G, Porchet M, Waeber B, Brunner HR. Individual responses to converting enzyme inhibitors and calcium antagonists. Hypertension 1988;11:166-73.
22. Erne P, Bolli P, Bertel O, et al. Factors influencing the hypotensive effects of calcium antagonists. Hypertension 1983;5(suppl II):97-102.
23. Sumner DJ, Meredith PA, Howie CA, Elliott HL. Initial blood pressure as a predictor of response to antihypertensive therapy. Br J Clin Pharmacol 1988;26:715-20.