Felodipine population dose-response and concentration-response relationships in patients with essential hypertension

Objectives: To characterize the population dose-response and concentration-response relationships of felodipine and to investigate the influence of patient variables on these relationships.
Methods: We studied 239 evaluable patients with mild to moderate essential hypertension in a multicenter, randomized, double-blind dose-escalation trial, followed by an optional open-label maintenance phase for the remainder of 1 year. Extended-release felodipine (2.5 to 20 mg) monotherapy was given once daily. Felodipine plasma concentration and sitting diastolic blood pressure were measured at approximately 2 and 24 hours after drug administration. Analysis, performed with use of the population approach (NONMEM program), accounted for baseline and placebo effects.
Results: A saturation (E_{max}) model best described both felodipine dose response (only 24-hour postdose data) and concentration response. The maximum effect (E_{max}) characterizing dose response was found to increase linearly with age and was estimated to be 20.6 mm Hg in the typical individual (60 years of age). The dose at which 50% of the maximum effect is achieved (D_{50}) was estimated to be 11.1 mg. The E_{max} characterizing concentration response also increased linearly with age and was estimated to be 27.8 mm Hg for the typical individual. The concentration at which 50% of the maximum effect is achieved (C_{50}) was related to plasma renin activity (PRA) by the following: $(21.6 \cdot PRA)/(0.25 + PRA)$ nmol/L; its value in the typical individual was estimated to be about 16.9 nmol/L. Felodipine (oral) clearance decreased with increasing age, up to 60 years, and was larger in black patients.
Conclusions: The effects of age on felodipine pharmacokinetics and pharmacodynamics lead to a heightened antihypertensive response in the elderly. A starting dose of 2.5 mg daily is recommended, especially in elderly patients. (CLIN PHARMACOL THER 1995;57:569-81.)

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Felodipine, a second-generation dihydropyridine calcium antagonist, has been shown to be effective for the treatment of essential hypertension.[1] The need to define a relationship between exposure and response for any drug is well understood.[2,3] Several studies have shown a close relationship between plasma concentration of felodipine and its antihypertensive effect.[4-6] A meta-analysis of six small studies (10 to 12 patients with hypertension per study) investigated individual felodipine concentration-effect relationships.[7] The authors were only able to model this relationship in 45 of the 67 patients, despite the fact that each patient provided extensive amounts of data. As the authors pointed out, they probably overestimated the maximum drug effect (E_{max}) because it was primarily the patients with low initial diastolic blood pressures whose data could not be modeled. Further, the authors did not find an effect of age on felodipine pharmacodynamics, which is contrary to the predictions of Bühler et al.[8] and Müller et al.[9] A relationship between age and pharmacodynamic response has been documented for other calcium antagonists.[10,11] Schwartz et al.,[11] for example, have shown that both

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pharmacokinetics and pharmacodynamics of verapamil are altered in healthy elderly individuals. The pharmacokinetics of felodipine has, however, been shown to be affected by aging; clearance is decreased and half-life is prolonged.[4] The effect of aging and other covariates on the pharmacodynamics of felodipine, after accounting for their effects on its pharmacokinetics, remains to be shown and characterized.

The population approach is a data analysis tool used to characterize the typical pharmacokinetic and pharmacodynamic profiles, and variability, in target populations.[12] This study was ideally suited for a population analysis, which we implemented using the program NONMEM,[13] because the data were sparse and were derived from a dose-escalation design. Indeed, this approach is particularly appropriate when the amount of data collected per individual is trivial, as is the case with observational studies. Population analysis has also been shown to handle the bias in (non-forced-titration) dose-escalation studies in which only the least-sensitive patients receive the highest dose.[3,14]

The aim of this investigation was to characterize the population dose-response and the population concentration-response relationships of felodipine when administered as an extended-release formulation to patients with hypertension. As part of this study, we considered the effects of demographic and clinical characteristics of the patients (e.g., age and plasma renin activity [PRA]) on these relationships, and we explored the influence of age on the magnitude of interindividual variability.

METHODS

Clinical procedures

This trial was a multicenter (19 centers), randomized, double-blind, placebo-controlled dose-escalation study in 243 men and women who were older than 21 years and who had mild to moderate uncomplicated essential hypertension. At the end of the double-blind phase, patients could enter an optional open-label maintenance phase for the remainder of 1 year.

Patients were required to be otherwise healthy as judged by the investigators. Exclusion criteria included known hypersensitivity to felodipine or other dihydropyridine calcium antagonists, history of multiple drug allergies, myocardial infarction within the last 6 months, unstable angina, history of malignant hypertension or cerebrovascular accident, evidence of significant renal or hepatic disorder as indicated by history or laboratory tests, secondary hypertension of any cause, history of gastrointestinal malabsorption, clinically significant decrease in hematocrit or hemoglobin, uncontrolled diabetes, and receipt of concomitant cimetidine. Women who were not surgically sterilized or postmenopausal were also excluded.

The study consisted of three phases. The baseline phase was a 4-week single-blind placebo phase during which all antihypertensive drugs were discontinued. Patients meeting the criteria for hypertension (sitting diastolic blood pressure [sitDBP] of 95 to 115 mm Hg) entered a 9-week double-blind phase, at the beginning of which they were randomly assigned to receive either 2.5 mg extended-release felodipine or placebo by mouth once daily. Allocation was 3:1 in favor of the felodipine treatment. The dose was titrated to 5 mg and then 10 mg at 3-week intervals if the sitDBP was not ≤90 mm Hg. Patients who received placebo had the number of tablets they received titrated in the same manner. Patients who did not require titration at week 3 or week 6 of the double-blind phase remained on the same dose (or number of placebo tablets) for the duration of the phase. At the end of the double-blind phase, patients could enter an optional open-label maintenance phase, which lasted for the remainder of 1 year. Patients in the maintenance phase could titrate to a maximum of 20 mg extended-release felodipine daily if their sitDBP was not ≤90 mm Hg. Patients who received placebo during the double-blind phase and who entered the maintenance phase started active extended-release felodipine treatment at a dose of 2.5 mg. During the maintenance phase only, doses could be titrated downward and upward. Patients visited the clinic weekly during the baseline phase, every 3 weeks during the double-blind phase, and monthly during the maintenance phase.

At the end of the baseline phase, PRA was determined and the patient's height, age, and race were recorded. Blood for PRA determination was collected in tubes containing ethylenediaminetetraacetic acid after the patient had been supine for 30 minutes. Evaluations made at each visit included blood pressure, pulse, weight, and assessment of any possible adverse reactions. Three blood pressure readings were taken at 1-minute intervals after the patient had been sitting for at least 5 minutes. The average of the three readings was used in the analysis. During the double-blind and maintenance phases, patients were seen approximately 24 hours after they had taken their previous doses. Clinic evaluations were made and patients then took their doses of extended-release felodipine. Some patients remained at the clinic for 2 hours after taking their doses, and their sitDBP measurements were repeated at this time.

In 128 patients, blood samples (14 ml) for determination of felodipine plasma concentration were collected in heparinized tubes before and 2 hours after dosing (after blood pressure measurements) at weeks 3, 6, and 9 during the double-blind phase and at weeks 24, 36, and 52 during the maintenance phase. The plasma was separated and stored at −20° C until analysis. Not all of the 128 patients who had blood samples taken for pharmacokinetic analysis had samples taken at every "pharmacokinetic" visit or had both the predose and 2-hour sample taken at each "pharmacokinetic" visit.

Chemical analysis

Plasma samples were assayed for felodipine by use of a gas chromatographic method.[15,16] The lower limit of detection of the assay was 0.5 nmol/L. Mean interassay variability was 5.9% at 2 nmol/L and 2.0% at 40 nmol/L. PRA was determined by a commercial laboratory with use of radioimmunoassay. The lower limit of assay sensitivity was 0.1 ng/ml/hr. Interassay variability was 20.0% at 2 ng/ml/hr and 13.7% at 6.5 ng/ml/hr.

Data analysis

The primary investigation was performed on the relevant data obtained from all phases and involved characterization of the population dose response, population pharmacokinetics, individual and visit-specific pharmacokinetics, and population concentration response of felodipine (Fig. 1). All analyses were done with a nonlinear mixed-effects model, first-order conditional estimation (FOCE) method, with use of the program NONMEM (version IV).[13] The reader is referred to several publications for a detailed description of the theory and application of nonlinear mixed-effects modeling.[12,13,17]

In brief, each of the population models included parameters to describe the basic shape of the model (structural parameters, such as clearance or E_{max}), covariates (fixed effects) and their associated parameters that influence the structural parameters, and parameters that account for interpatient and intrapatient variabilities (random effects). For our analyses, the structural models were developed first, with use of reasonable models for variability. The covariates (and associated parameters) were then tested by their stepwise addition into the model. Once a full model was developed, the covariates were retested with use of stepwise deletion. The models for variability were retested at the end of, and sometimes during the course of, the analyses. The criterion for selecting a fuller model (more parameters), or a different variability model, was based on the likelihood ratio test. During exploratory stages (e.g., stepwise addition of covariates), our criterion for a significant change in the −2ln(likelihood) was the value that corresponds to $p < 0.05$; for final selection of the model and parameters (e.g., stepwise deletion), we used a stricter criterion ($p < 0.01$).

Because the maintenance phase was open-label, did not include a placebo group, and included the additional dose of 20 mg, the analysis was essentially repeated without data from this phase. The results of this secondary analysis, relative to the primary analysis, are provided in the Discussion section.

The specific models tested in our investigation are described in the three following sections.

Dose-response model. The population dose-response model, which was applied to the 24-hour sitting diastolic blood pressure (sitDBP) measurements only, involved the following general form:

$$\text{sitDBP} = \text{sitDBP}_{\text{baseline}} - \text{placebo effect} - \text{felodipine effect}$$

The model was built in a stepwise fashion, beginning with $\text{sitDBP}_{\text{baseline}}$ (using the baseline phase data only), then placebo effect (using the baseline data and double-blind data of the placebo individuals only) and, last, the felodipine effect (using all data). The final forms (but not the parameter estimates) of the models for $\text{sitDBP}_{\text{baseline}}$ and placebo effect were carried forward to each subsequent step.

The structural model for $\text{sitDBP}_{\text{baseline}}$ involved a single parameter only. The structural models tested for placebo effect included a step model (effect is constant at all times after the baseline phase), a linear model (effect related linearly to time after the baseline phase), and an E_{max} model (effect graded as a function of time just after the baseline phase, but at later times approaches saturation). The structural models tested for felodipine effect were the same as those for the placebo effect, except that "dose" replaces the element "time." The covariates in this study (age, weight, height, PRA, race, and gender) were tested on each component of the dose-response model. In addition, the average baseline sitDBP was tested as a covariate for the placebo and felodipine effects. The continuous covariates were initially introduced in the form of a simple linear function; attempts to refine the models for covariate effects were made by testing other functions (e.g., power, saturable, and piecewise-linear). Additive, constant coefficient of variation, and exponential models for interpatient variability of

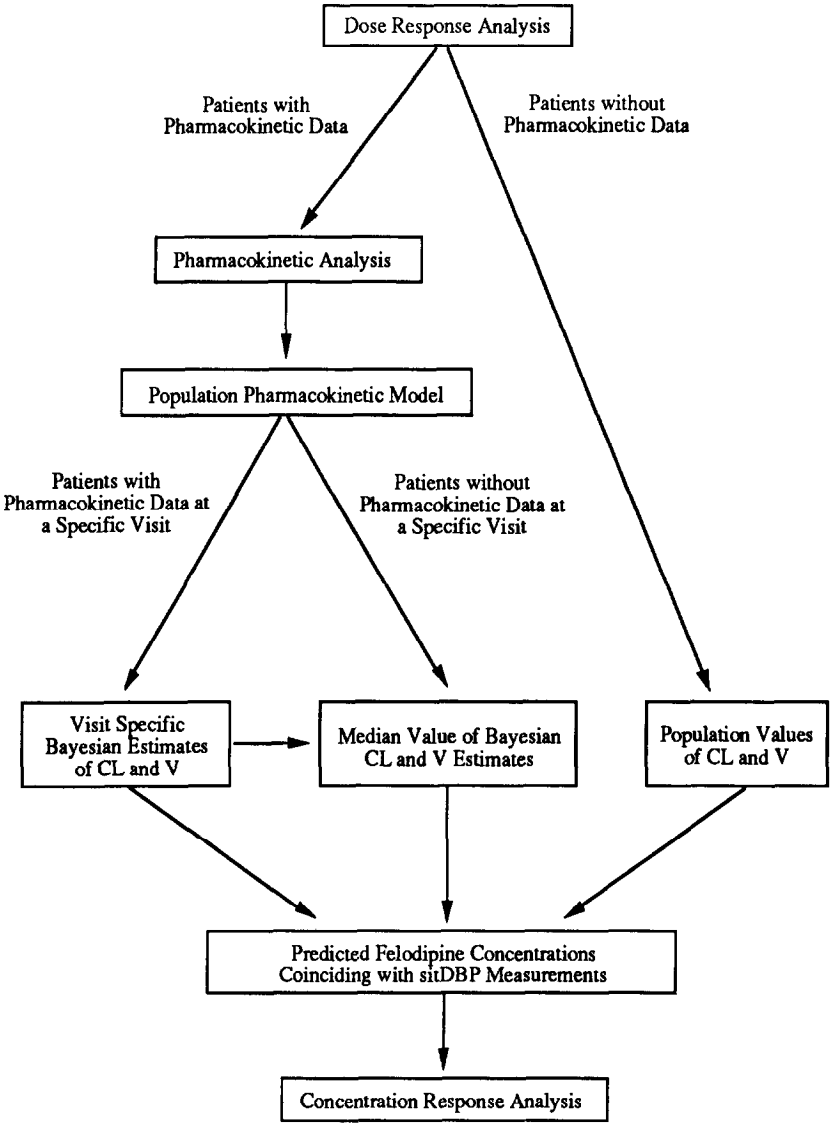

Fig. 1. Algorithm used for population analysis of felodipine dose-response, dose-concentration, and concentration-response relationships.

the dose-response parameters were tested. The interpatient variability of felodipine effect was tested further to see if older patients (>60 years of age) and younger patients (<60 years of age) differed. Additive and constant coefficient of variation models of intrapatient (residual) variability of sitDBP measurements were tested.

Pharmacokinetic model. A pharmacokinetic model was developed, principally to predict plasma concentrations at time points at which sitDBP was measured. The predicted concentrations were subsequently used in the concentration-effect analysis. Because the main focus of this investigation was pharmacodynamics rather than pharmacokinetics, a simple one-compartment instantaneous input, steady-state model, parameterized by clearance (CL) and volume of distribution (V), sufficed for obtaining these predictions. Furthermore, it is unlikely that the data would have supported a larger model. Because felodipine has been described previously with a model consisting of as many as three compartments (after intravenous administration),[18] the values of CL, and particularly V, estimated here should be thought of as "relative" among individuals, rather than "absolute." As such, it is fair to assume that this measure of CL (particularly as it relates to drug exposure) may vary between individuals as a result of identifiable patient characteristics. Thus the available covariates were tested for their in-

fluence on CL. The approaches for studying the covariates and the random effects were as described for the dose-response analysis.

We obtained visit-specific values of CL and V for each individual by treating all visits for any one patient as though each visit was made by a separate individual, followed by use of a bayesian approach (POSTHOC feature of NONMEM). When a patient had at least one felodipine concentration measured at a specific visit, then that patient's visit-specific estimates of CL and V were used to obtain the predicted felodipine concentrations that coincided with the sitDBP measurements at that visit (Fig. 1). For patients in whom pharmacokinetic data were collected, but not at a particular visit, individual median values of CL and V were used to predict felodipine concentrations at that visit. For patients in whom pharmacokinetics were not assessed, the population (mean) estimates of CL and V were used for the predictions.

Concentration-response analysis. The population concentration-response model, which was applied to both the 2-hour and 24-hour postdose data, involved the same general form as the population dose-response model. As with the dose-response model, the concentration-response model was built in a stepwise fashion, with the same approach taken for estimating $sitDBP_{baseline}$ and for modeling the placebo effect. The structural models tested for (pure) felodipine effect—the step, linear, and E_{max} models—were also similar to those in the dose-response model, except that (predicted) felodipine concentration was the independent variable. Consistent with other analyses of felodipine concentration-effect relationship,[4,5,19] preliminary analysis of these data indicated that (pure) felodipine effect was directly related to the (predicted) felodipine concentration (i.e., modeling an "effect" compartment was not required).[20]

As with the dose-response model, the available covariates were tested on each component of the concentration-response model. The approaches to studying the covariates and the random effects were also as described for the dose-response analysis.

RESULTS

Patients. Four of the 243 patients enrolled were not included in this analysis because of suspect compliance ($n = 2$) and apparent incorrect dosing information ($n = 2$). SitDBP measurements obtained in the presence of other antihypertensive medication were also not used. The evaluable data included 3001 sitDBP measurements and 457 felodipine plasma concentrations collected from 239 patients. The mean age of the evaluable patients was 58 years (age range, 26 to 77 years), mean weight was 83.4 kg (weight range, 49.5 to 124.3 kg), mean height was 172.5 cm (height range, 134.6 to 193.0 cm), and mean PRA was 1.0 ng/ml/hr (PRA range, 0.1 to 8.2 ng/ml/hr); 161 patients were men, 195 patients were white, 32 were black, and 12 were other races.

Eleven of the 239 patients contributed only baseline phase data because they discontinued the study before starting the next phase. Fifty-one patients received placebo and 177 received extended-release felodipine in the double-blind phase of the study. Sixty-four percent of the patients who entered the double-blind phase continued into the maintenance phase of the study. Parameter estimates throughout this article are presented as their values and 95% confidence intervals (CI).

Dose response. Of the 3001 sitDBP measurements, only the 2088 taken at 24 hours after drug administration were included in the dose-response analysis (Fig. 2). The parameter estimates of the dose-response model are summarized in Table I. The $sitDBP_{baseline}$ was estimated to be 101 mm Hg (95% CI, 100 to 102 mm Hg) and had very little interpatient or intrapatient variability. The step model (which states that all the effect attributable to placebo was present immediately on entry into the double-blind phase) was found to best describe the placebo effect. The placebo effect in the typical patient was estimated to be 3.8 mm Hg (95% CI, 2.7 to 4.8 mm Hg). The interpatient variability for both the baseline and placebo effects were described with constant coefficient of variation (CV) models.

The E_{max} model was found to best describe the (pure) felodipine effect in sitDBP ($p < 0.001$ compared with the next best model, a linear model). The estimate of E_{max} in the typical individual (who was 60 years of age in this study) was 20.6 mm Hg (95% CI, 16.0 to 25.2 mm Hg), and that of the dose at which 50% of the maximum drug effect is achieved (D_{50}) was 11.1 mg (6.1, 16.1 mg). Thus the highest dose studied (20 mg) is predicted to achieve 67% of the maximal reduction in sitDBP in the typical patient. Interpatient variability in both E_{max} and D_{50} was not supported by the data; the interpatient variability for the (pure) felodipine effect was therefore modeled in E_{max} only. With use of a constant CV model, its magnitude was estimated to be 41.7% and was not found to differ significantly between older and younger patients.

No covariate significantly influenced $sitDBP_{baseline}$ or placebo effect. Age was the only covariate that sig-

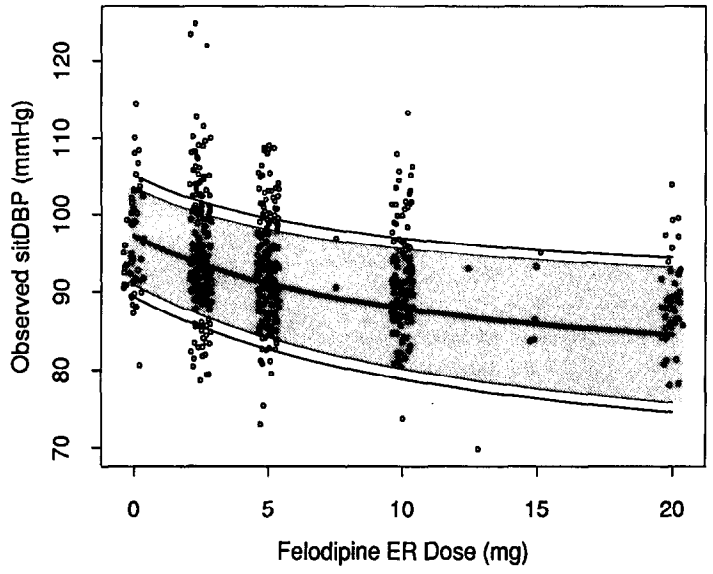

Fig. 2. Felodipine extended-release (ER) dose versus sitting diastolic blood pressure (sitDBP; 24 hours after drug administration). The data *(points)* have been slightly displaced (randomly) along the *x*-axis for greater resolution. The *bold line* is the dose-response curve predicted in the typical individual, based on a saturation (E_{max}) model before the inclusion of covariates. The *shaded area* includes ±1 SD of interpatient variability. The *outer lines* bound ±1 SD of interpatient plus intrapatient variability of the response. Population predictions below the mean of the responses at higher doses are expected, because patients who do not contribute data at these doses *do* contribute to the parameter estimates for the *entire* dose-response curve.

Table I. Parameter estimates of the felodipine population dose-response model

Parameter	*Estimate*	
	Mean	*95% Confidence interval*
Structural parameters		
$sitDBP_{baseline}$ (mm Hg)	101.0	100.3 to 101.7
Placebo effect (mm Hg)	3.8	2.7 to 4.8
Felodipine E_{max} (mm Hg)*	20.6	16.0 to 25.2
Felodipine D_{50} (mg)	11.1	6.1 to 16.1
Covariate parameters		
Age effect on felodipine E_{max} (mm Hg/yr)*	0.4	0.2 to 0.6
Random effects parameters		
Interpatient variability in $sitDBP_{baseline}$ (%, CV)	4.0	3.5 to 4.5
Interpatient variability in placebo effect (%, CV)	55.3	NE
Interpatient variability in felodipine E_{max} (%, CV)	41.7	25.2 to 53.3
Intrapatient variability (mm Hg, SD)	4.7	4.5 to 4.9

$sitDBP_{baseline}$, Baseline sitting diastolic blood pressure; E_{max}, maximum effect; D_{50}, dose at which 50% of the maximum drug effect is achieved; CV, coefficient of variation; NE, not estimated.
*The final model for felodipine E_{max} was: E_{max} (mm Hg) = 20.6 + (Age − 60) · 0.4.

nificantly influenced ($p < 0.001$) the effect of felodipine (Fig. 3). E_{max} is predicted to increase (decrease) by about 4 mm Hg (95% CI, 2 to 6 mm Hg) per decade.

Pharmacokinetics. Samples were collected at mean (±SE) times of 1.97 ± 0.15 and 24.4 ± 0.73 hours after an extended-release felodipine dose. The parameter estimates of the pharmacokinetic model are given in Table II.

Age and being a black patient (versus a patient who was not black) were found to influence CL ($p < 0.01$ and $p < 0.001$, respectively). CL is predicted to decrease linearly with increasing age until 60 years and then remain constant. Thus, CL in a typical 60-year-

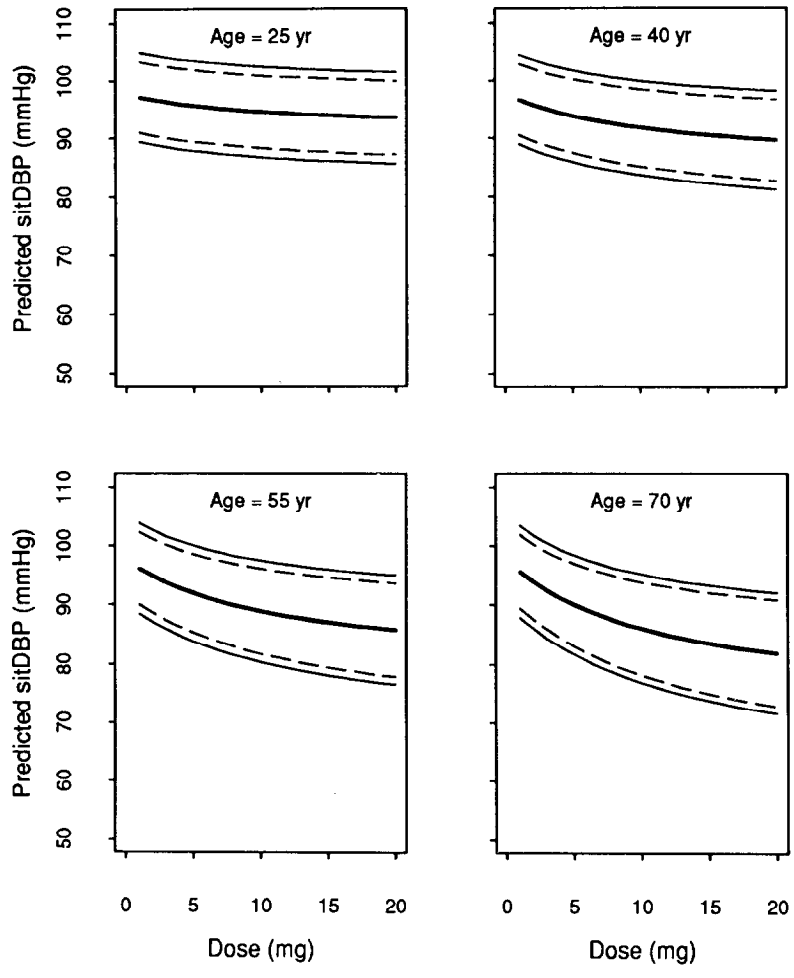

Fig. 3. Felodipine dose versus sitDBP (24 hours after drug administration) curves predicted for various ages. The *bold lines* are the predictions for the typical individual at the ages indicated. The *broken lines* bound ±1 SD of interpatient variability of the response. The *outer lines* bound ±1 SD of interpatient plus intrapatient variability of the response.

old white patient is estimated to be 35% lower than in a typical 30-year-old white patient. The typical black patient is predicted to have a CL value that is higher than the typical patient of the same age who is not black. For a 30-year-old, this difference is about 27%; for a 60-year-old it is about 38%. An exponential model best described the interpatient variability for both CL and V, the estimates of which were 33.9% and 35.4%, respectively. Again, no difference in interpatient variability was found between older and younger patients.

Preliminary analysis of the pharmacokinetic data suggested that it was invalid to assume that CL did not vary within an individual (among visits). The need to model visit-to-visit variability was considered because initially, the CL of felodipine was found to relate to the length of time in the study, and to dose (which varies with time), neither of which have been reported previously for this drug. Karlsson and Sheiner[21] have shown that when CL varies from visit to visit (i.e., contains significant interoccasion variability) but is not accounted for, false period effects may arise. When our model was altered to include interoccasion variability, both length of time in the study and dose were no longer found to be significant. The estimate of interoccasion variabilities for CL and V were 33.3% and 45.3%, respectively.

Concentration response. All of the available 3001 sitDBP measurements (490 of which were collected during the baseline phase) were used in the concentration-response analysis (Fig. 4). Approximately two-thirds of these measurements were taken at 24.5 ±

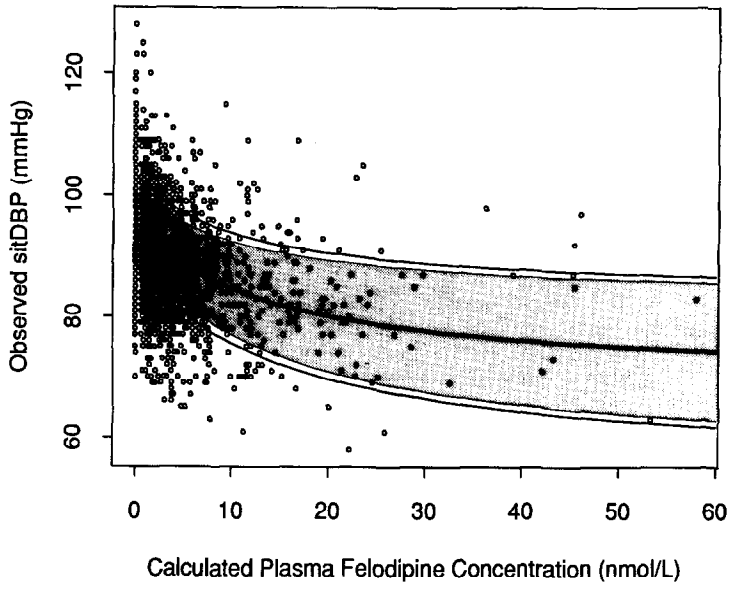

Fig. 4. Felodipine concentration versus sitDBP. The *points* are the felodipine plasma levels predicted from the population pharmacokinetic model. The *bold line* is the concentration-response curve predicted in the typical individual, based on the E_{max} model before the inclusion of covariates. The *shaded area* includes ±1 SD of interpatient variability. The *outer lines* bound ±1 SD of interpatient plus intrapatient variability of the response.

Table II. Parameter estimates of the felodipine population pharmacokinetic model

Parameter	*Estimate*	
	Mean	*95% Confidence interval*
Structural parameters		
CL (L/hr)*	1,260	1,128 to 1,392
V (L)	33,100	4,900 to 61,300
Covariate parameters		
Race effect on CL (L/hr)*	477	159 to 795
Age effect on CL (L/hr/yr)*	16.8	2.8 to 32.5
Random effects parameters		
Interpatient variability in CL (%, CV)	33.9	27.3 to 39.4
Interpatient variability in V (%, CV)	35.4	23.6 to 44.1
Interoccasion variability in CL (%, CV)	33.3	28.1 to 37.8
Interoccasion variability in V (%, CV)	45.3	38.3 to 51.3

CL, Clearance; V, volume of distribution; CV, coefficient of variation.
*The final model for CL was: CL (L/hr) = 1260 + (Q · 477) + R · (60 − Age) · 16.8, in which Q = 1 if race is black, else Q = 0; and R = 1 if age <60 years, else R = 0.

1.2 hours after drug administration and the remaining one-third at 2.0 ± 0.5 hours after administration.

The parameter estimates of the concentration-response model are given in Table III. The estimate of $sitDBP_{baseline}$ at approximately 2 hours after drug administration was allowed to differ from that at approximately 24 hours after administration. $SitDBP_{baseline}$ at 2 hours after dosing was estimated to be 99 mm Hg (95% CI, 98 to 100 mm Hg); sitDBP at 24 hours after dosing was estimated to be 101 mm Hg (95% CI, 100 to 102 mm Hg). Even though interpatient variability in the baseline was small, it was best described by an exponential model.

Inclusion of the 2-hour postdose data (in addition to the 24-hour postdose data) enabled the placebo effect to be described by an E_{max} model ($p < 0.01$ compared with the next best model, a step model). The parameter E_{max} of the placebo effect in the typical individual was

Table III. Parameter estimates of the felodipine population concentration-response model

Parameter	*Estimate*	
	Mean	*95% Confidence interval*
Structural parameters		
$sitDBP_{baseline}$ (~2 hr postdose) (mm Hg)	99.3	98.4 to 100.2
$sitDBP_{baseline}$ (~24 hr postdose) (mm Hg)	101.0	100.3 to 101.7
Placebo effect E_{max} (mm Hg)	6.1	4.8 to 7.4
Placebo effect T_{50} (weeks)	2.1	0.9 to 3.3
Felodipine E_{max} (mm Hg)*	27.8	21.6 to 34.0
Covariate parameters		
Age effect on felodipine E_{max} (mm Hg/yr)*	0.4	0.1 to 0.7
PRA E_{max} on felodipine C_{50} (nmol/L)†	21.6	10.7 to 32.5
PRA C_{50} on felodipine C_{50} (ng/ml/hr)†	0.25	~0 to 0.52
Random effects parameters		
Interpatient variability in $sitDBP_{baseline}$ (%, CV)	5.3	4.7 to 5.8
Interpatient variability in placebo E_{max} (%, CV)	47.2	33.0 to 58.9
Interpatient variability in felodipine E_{max} (%, CV)	38.7	27.6 to 47.2
Intrapatient variability (mm Hg, SD)	4.9	4.7 to 5.1

$sitDBP_{baseline}$, Baseline sitting diastolic blood pressure; E_{max}, maximum effect; T_{50}, time at which 50% of the maximum placebo effect is achieved; PRA, plasma renin activity; C_{50}, concentration at which 50% of the maximum drug effect is achieved; CV, coefficient of variation.
*The final model for felodipine E_{max} was: E_{max} (mm Hg) = 27.8 + (Age − 60) · 0.4.
†The final model for felodipine C_{50} was: C_{50} (nmol/L) = (21.6 · PRA)/(0.25 + PRA).

estimated to be 6.08 mm Hg (95% CI, 4.72 to 7.43 mm Hg), and the time at which the placebo effect is half its maximum was estimated to be 2.1 weeks (95% CI, 0.9 to 3.3 weeks). Interpatient variability for the placebo effect was best described by an exponential model and was 47.2% (CV). No covariate significantly influenced $sitDBP_{baseline}$ or placebo effect.

Like the dose-response model, an E_{max} model best described felodipine's concentration-response relationship ($p < 0.001$ compared with the next best model, a linear model). The E_{max} of felodipine increased linearly with increasing age ($p < 0.001$) and was estimated to be 27.8 mm Hg (95% CI, 21.6 to 34.0 mm Hg) for the typical individual (who was 60 years of age in this study). The concentration of felodipine at which 50% of the maximum drug effect is achieved (C_{50}) was found to be a function of the PRA ($p < 0.001$). The model that characterized the relationship between C_{50} and PRA was also an E_{max} model:

$$C_{50}\ (\text{nmol/L}) = (21.6 \cdot \text{PRA})/(0.25 + \text{PRA})$$

Thus, at the median value of PRA in this study (0.9 ng/ml/hr), C_{50} is predicted to be 16.9 nmol/L. The interpatient variability of the felodipine E_{max} was described by an exponential model and was estimated to be 38.7% (CV) and, again, did not differ between older and younger patients. The effects of age and PRA on the felodipine concentration-response relationship are illustrated in Fig. 5.

DISCUSSION

The magnitude of the E_{max} characterized by the dose-response analysis (mean, 20.6 mm Hg) was smaller than that characterized by the concentration-response analysis (mean, 27.8 mm Hg). This difference was expected because only the trough data were used to characterize dose-response, whereas both peak and trough data were used in the concentration-response analysis. Individual felodipine concentration-response relationships have been described previously[4-7] and, despite the differing study conditions (no correction for placebo effect, presence of concomitant therapy [usually a β-blocker and/or diuretic], and use of supine, rather than sitting, diastolic blood pressure), the values of felodipine E_{max} reported previously were quite similar to those we obtained in our concentration-response analysis.

At present, the recommended initial dose of extended-release felodipine in the United States is 5.0 mg (with no special considerations for this dose in the elderly). In other countries, such as Sweden, the initial dose for all patients is lower—2.5 mg. In this study, approximately 25% of the patients reached the criterion of sitDBP ≤90 mm Hg when receiving 2.5 mg. A recently published study of extended-release felodipine dose-response relationship over the range of 2.5 to 10 mg found that over half of the 286 patients had a good or excellent response after receiving 2.5 mg.[22] These two sets of results suggest that the rec-

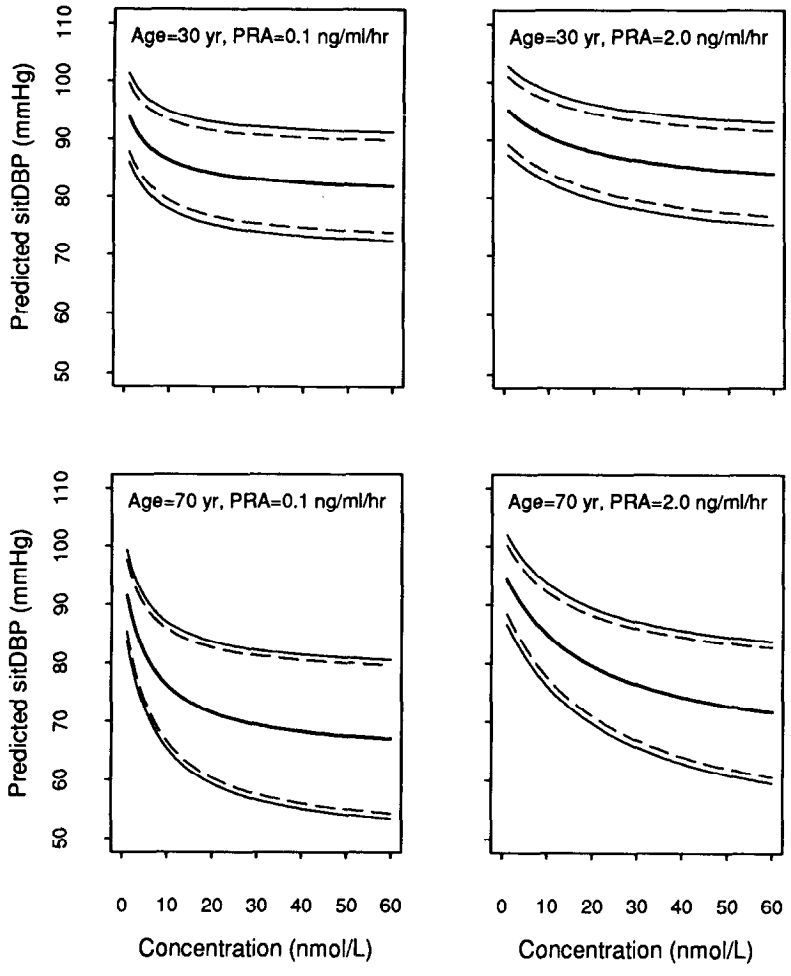

Fig. 5. Felodipine concentration versus sitDBP curves predicted for various ages and plasma renin activity (PRA) levels. The *bold lines* are the predictions for the typical individual at the ages and PRA levels indicated. The *broken lines* bound ±1 SD of interpatient variability of the response. The *outer lines* bound ±1 SD of interpatient plus intrapatient variability of the response.

ommended starting dose should be lowered to 2.5 mg in the United States, especially for the elderly. Our findings predict that 2.5 mg extended-release felodipine will produce a response attributable to the drug (i.e., without placebo effect) that is about 18% of E_{max} (about 4 mm Hg in a typical nonelderly individual and about 5 mm Hg in a typical 75-year-old). In the United States, the highest dose recommended is 20 mg for nonelderly individuals, whereas it is 10 mg in some other countries and in the United States for patients older than 65 years. Our results suggest that increasing the dose from 10 to 20 mg should result in a further reduction in the blood pressure, with a prediction of about 47% of E_{max} (about 10 mm Hg) being attained with 10 mg, and about 64% of E_{max} (about 13 mm Hg) being attained with 20 mg, in nonelderly individuals. Advising against an increase in dose from 10 to 20 mg in elderly individuals (per U.S. labeling) seems to be warranted because these doses are predicted to result in sitDBP reductions of about 12 and 17 mm Hg, respectively.

This study was the first to show an age effect on felodipine pharmacodynamics, in addition to its effect on pharmacokinetics. One study, by Blychert et al.,[7] found an effect of age on felodipine pharmacokinetics but not on pharmacodynamics. Our ability to detect an age effect on the concentration-response relationship may be in part attributable to greater sensitivity afforded by modeling placebo effect and excluding data associated with concomitant therapy, both of which Blychert et al. did not do.

It has been predicted that patients with low PRA

values will show an increased antihypertensive response when given calcium antagonists.[23] Despite the known negative correlation of PRA and age,[24] the concentration-response analysis was able to detect an effect of PRA beyond that of age alone. The relationship characterized predicts that a typical elderly person who has a lower pretreatment PRA will manifest a greater antihypertensive effect than a person of the same age with a higher pretreatment PRA (Fig. 5), although the effect manifested by the latter individual is still considerable. The finding that felodipine CL is higher in black patients has not been reported or, to our knowledge, studied previously. Indeed, limited research has been done regarding the influence of race on pharmacokinetics in general. Kleinbloesem et al.[25] reported a new oxidative polymorphism for nifedipine and suggested the existence of two phenotypes. Black Americans have been shown to have a lower prevalence of deficient CYP2D6 oxidative drug metabolism phenotypes (1.9% of black individuals are deficient compared with 7.7% of white subjects).[26] These findings, relevant to felodipine because the principal pathway of its metabolism is the same as that of nifedipine, support an overall higher average CL in black patients. The low percentage of the population affected by the deficient phenotype is, however, insufficient to account for the relatively large magnitude (about 30%) of racial difference in CL we observed. The findings might be accounted for by a difference in compliance, bioavailability, or both, because the CL characterized in this analysis was actually CL/F.

It has been postulated that elderly people have greater variability in their response than younger people.[12] A model that allowed interpatient variability to differ in patients older than 60 years was tested during the course of the dose-response, pharmacokinetic, and concentration-response analyses. In all cases, variability did not differ significantly from younger patients, perhaps because the exclusion criteria in this phase III study resulted in the recruitment of "less sick" elderly individuals. This explanation may also account for the fact that we did not observe a higher $sitDBP_{baseline}$ in elderly patients, a phenomenon that is well recognized.

The response variable used in this analysis was the sitting diastolic blood pressure. The analysis could have similarly been applied to systolic blood pressure or mean arterial pressure (these data were not made available to us). A higher prevalence of isolated systolic hypertension has been associated with aging, the black race, and women.[27] Although diastolic blood pressure is generally quite responsive to treatment, isolated systolic hypertension is more difficult to control[28] and optimization of therapy is crucial. To our knowledge, the concentration-response relationship for any treatment of isolated systolic hypertension has never been investigated, and an analysis such as the one described herein could prove to be quite useful.

The field of population analysis as it relates to pharmacodynamics is still relatively new and has been reviewed recently by Sheiner and Ludden.[29] No general guidelines are available yet for population pharmacokinetic-pharmacodynamic modeling, and some new approaches were used during the course of our analysis. Three issues addressed in this analysis specifically were (1) the presence of significant interoccasion variability in pharmacokinetics, (2) the fact that pharmacokinetic data were not available in all patients, and (3) the manner in which pharmacokinetic data and predictions should be linked to response data. The techniques chosen to handle the first two issues are illustrated in Fig. 1.

There are at least two possible methods to handle the third issue—the manner in which pharmacokinetics and pharmacodynamics should be analyzed jointly. One option is to estimate the pharmacokinetic and pharmacodynamic parameters simultaneously. This option probably represents the purist viewpoint and should result in more realistic standard errors associated with the pharmacodynamic parameters, as well as more realistic estimates of interindividual variability.* This option was not, however, available to us because of numerical difficulties encountered with its use. Instead, we used a second option that involves estimating the parameters of the pharmacokinetic model first and then fixing these parameter values in the joint pharmacokinetic-pharmacodynamic analysis. Although either population or individual (bayesian) pharmacokinetic parameter estimates could be used, it seems prudent to take into account unexplained individual pharmacokinetic differences, which the bayesian estimates do.

Our primary analysis included data collected during the open-label maintenance phase, where no placebo data were available, the 20 mg dose was available, and the study was unblinded. To check whether the inclusion of these data affected the results, a second analysis was performed on a reduced data set, consisting of the data collected during the baseline and

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double-blind phases only. The analysis of the reduced data set was able to characterize only a linear model to describe the dose-response relationship. An E_{max} model was still most appropriate for the concentration-response relationship. The fact that a linear model was most appropriate for the reduced dose-response data set is not inconsistent with the results of the analysis of the full data set; the doses included in the reduced data set (2.5 to 10 mg) were all below the D_{50} characterized in the full data set analysis (11.1 mg). The covariates that influenced significantly the parameters of the response models were essentially the same for the reduced and full data sets, with one exception. No effect of PRA was found on the concentration-response model characterized with the reduced data set. It is possible that PRA is a predictor of long-term response, or perhaps more data simply allowed the influence to be detected. The age effect was found in both dose-response analyses but acted on the slope parameter characterized in the reduced data set analysis and the parameter E_{max} in the full data set analysis. Other evidence that the data from the maintenance phase data is reasonably representative of the other data is that response did not change substantially from phase to phase in individuals who received virtually constant doses (either 2.5 mg or 5 mg) throughout the entire study.

In summary, this comprehensive analysis allowed us to both identify important covariates and characterize the nature of their influence. We found that aging influences a patient's response to felodipine and that this influence can be attributed to both pharmacokinetic and pharmacodynamic differences. On the other hand, race was found to influence pharmacokinetics only, and plasma renin activity was found to influence pharmacodynamics only. These results underscore the importance of concentration-response relationships, *in addition to* pharmacokinetics, in considering dosage adjustments and expectations of effect.

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