Nifedipine: Individual Responses and Concentration-Effect Relationships

RICHARD DONNELLY, HENRY L. ELLIOTT, PETER A. MEREDITH, ANDREW W. KELMAN, AND JOHN L. REID

SUMMARY Dynamic and kinetic variability account for the large intersubject differences in the antihypertensive response to nifedipine, and a clear concentration-effect relationship has not been established. The effects of placebo, first dose, and chronic (1 and 6 weeks) treatment with nifedipine were studied in 14 subjects with essential hypertension using an integrated kinetic-dynamic model to calculate individual subject responsiveness in terms of fall in blood pressure per unit change in drug concentration. Nifedipine concentrations were well correlated with the fall in systolic blood pressure in individual subjects, and the mean responsiveness was -0.48 mm Hg/ng/ml after the first dose, -0.45 mm Hg/ng/ml after 1 week, and -0.49 mm Hg/ng/ml after 6 weeks. The responsiveness to the first dose of nifedipine was significantly correlated with the responsiveness after 1 (r = 0.83) and 6 weeks (r = 0.78) of therapy and with the height of the pretreatment blood pressure (r = 0.6). This study incorporated kinetic as well as dynamic information to characterize the antihypertensive response to nifedipine and identify nifedipine concentration-effect relationships in individual hypertensive subjects. (Hypertension 12: 443–449, 1988)

KEY WORDS • nifedipine • pharmacokinetics • concentration-effect • hypertension

The calcium antagonist drug nifedipine, which is widely used in the treatment of angina pectoris and essential hypertension, shows large interindividual differences not only in drug disposition and dose requirements but also in the magnitude of the antihypertensive response. Attempts to identify a relationship between plasma drug concentration and the fall in blood pressure have produced conflicting reports, and a clear relationship between plasma concentration and blood pressure reduction has not been established. This failure may reflect the wide range of intersubject variability in both kinetic and dynamic parameters when group data are evaluated, but preliminary information suggests that the concentration-effect relationship is potentially more applicable when individual patients are considered. Therefore, the present study was designed to investigate the pharmacodynamics and pharmacokinetics of monotherapy with nifedipine in subjects with essential hypertension and, by integrated pharmacokinetic and pharmacodynamic modeling, to characterize the responses to acute and chronic nifedipine treatment in individual subjects.

Subjects and Methods

Outline of Study

Fourteen subjects (7 men, 7 women) with mild to moderate essential hypertension (160/90–210/115 mm Hg; age range, 33–66 years) gave written consent to participate in this study, which was approved by the Research and Ethical Committee of the Greater Glasgow Health Board (Glasgow, UK). Subjects were either patients with recently diagnosed, untreated hypertension or patients who had discontinued all medication 6 weeks before entering the study.

Following a preliminary assessment period of at least 6 weeks (without treatment), the average entry blood pressure was 181/105 ± 20/8 (SD) mm Hg supine and 183/107 ± 17/5 mm Hg erect. Thereafter, in a single-blind design, subjects received placebo for 2 weeks and then 6 weeks of treatment with nifedipine, 20 mg twice daily, using a delayed-release formulation tablet commercially available in the United Kingdom (Adalat Retard, Bayer). Each subject attended four 8-hour study days in the Clinical Pharmacology Research Unit to evaluate the effects of placebo, the first dose of nifedipine, and then 1 week and 6 weeks of nifedipine therapy.
On each occasion, following an overnight fast, baseline blood pressure and heart rate measurements were recorded, an indwelling cannula was inserted into an antecubital vein, and then nifedipine (20 mg) or placebo was administered orally with 100 ml of water. At frequent intervals during each study day, and 24 hours after dosing, blood pressure and heart rate were measured with the subject supine after not less than 10 minutes’ recumbency and then erect after 1, 3 and 5 minutes’ standing using a semiautomatic sphygmomanometer (Datascope, Accutorr, Paramus, NJ, USA). At corresponding times (i.e., 0, 0.5, 1.0, 1.5, 2.5, 4, 5, 6, 7, 8, and 24 hours) venous blood samples were collected for plasma nifedipine concentrations, and additional samples were obtained at 1.5 hours for plasma renin activity, aldosterone, and catecholamines. A standard light lunch was provided after 4 hours.

Laboratory Methods

Blood and plasma samples were placed in tubes wrapped with aluminum foil to prevent photodegradation of nifedipine. Blood samples for hormone measurements were collected into chilled tubes containing lithium heparin (for plasma aldosterone and catecholamines) and potassium EDTA (for plasma renin activity). Plasma nifedipine concentrations were measured by a modified high performance liquid chromatography technique11 using ultraviolet detection, with interassay and intra-assay coefficients of variation of 8 and 5%, respectively, and a limit of detection of 5 ng/ml. Plasma aldosterone concentrations and plasma renin activity were measured by radioimmunoassay,12-13 and plasma catecholamines were measured by radioenzymatic assay.14 The interassay and intra-assay coefficients of variation were respectively 7.0 and 5.5% for plasma renin activity (normal range, 0–12 ng angiotensin I/ml/hr), 11.0 and 7.3% for plasma aldosterone (normal range, 12–125 pg/ml), and 15 and 13% for plasma norepinephrine (normal range, 0.3–7.5 nmol/L).

Pharmacokinetics and Concentration-Effect Analysis

Plasma nifedipine concentration-time profiles for individual subjects on each study day were most appropriately described by an open one-compartment pharmacokinetic model with first-order input and elimination and inverse weighting of the drug concentrations. The equation defining the model is

\[ C_p = A(e^{-k_{ae}} - e^{-k_{oe}}) \]

where \( C_p \) is the drug concentration in plasma and the pharmacokinetic parameters are the coefficient \( A \) and the first-order rate constants of absorption and elimination, \( k_{ae} \) and \( k_{oe} \). Measurements derived from fitting this model to the data were the apparent elimination half-life, area under the concentration-time curve, maximum concentration (\( C_{max} \)), and time to reach \( C_{max} \) (\( t_{max} \)).

For the concentration-effect analysis the standard pharmacokinetic model was augmented by an ‘effect’ compartment as described previously.10 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 model**
  \[ E = \frac{E_{max} \cdot C_e}{C_{e50} + C_e} \]

where \( E \) 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. However, in clinical studies most data points are usually obtained within a relatively restricted concentration-response range; therefore, the simpler linear model is often more appropriate than the Langmuir \( E_{max} \) equation. The advantage of the linear model is that the slope of the relationship, \( m \), represents the responsiveness to the drug in terms of effect (in mm Hg) per unit of change in drug concentration in the effect compartment, while for the Langmuir model \( E_{max} \) is the maximum possible effect and \( C_{e50} \) is the concentration required to produce 50% of \( E_{max} \).

The first-order rate constant of the effect model, \( K_{oe} \), describes the removal of drug from the effect compartment and characterizes the phase lag between the change in blood pressure and plasma drug concentration. \( K_{so} \) is derived from the concentration-effect analysis, and it is related to the rate of change in the amount of drug in the effect compartment10:

\[ \frac{dX_e}{dt} = K_{oe}X_c - K_{so}X_e \]

where \( X_c \) and \( X_e \) are the drug amounts in the central and effect compartments and \( K_{oe} \) determines the transfer of drug from the central to the effect compartment.

After the pharmacokinetic model and the appropriate parameters in individual subjects were defined, the pharmacodynamic data were then fitted to both effect models using a nonlinear least-squares fitting procedure. In all cases, both acutely and chronically, the data were most appropriately described by the linear model on the basis of the general linear test. The responsiveness to nifedipine was calculated for individual subjects in terms of the placebo subtracted change in erect (5 minutes) systolic blood pressure per unit of change in drug concentration.

Statistical Analysis

Measurements throughout are expressed as means ± SD. Blood pressure and heart rate measurements were evaluated by repeated-measures analysis of variance. The pharmacokinetic and concentration-effect parameters and the measurements of plasma...
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renin activity, aldosterone, and catecholamines were compared between treatments by repeated-measures analysis of variance.

Linear regression analysis was used for the correlation between age and $C_{\text{max}}$, for the correlations between the responsiveness to nifedipine after the first dose and the responsiveness after 1 and 6 weeks of therapy, and for the correlation between responsiveness and starting blood pressure.

**Results**

**Pharmacodynamics**

Nifedipine produced significant reductions ($p < 0.01$) in supine and erect blood pressure, as illustrated by the erect systolic and diastolic blood pressures (Figure 1). The maximum antihypertensive effect of this formulation of nifedipine occurred 5 to 6 hours after drug administration (see Figure 1); for example, 5 hours after the first dose, erect blood pressure had fallen from a baseline of $166/104 \pm 12/10$ to $135/86 \pm 16/8$ mm Hg, compared with $171/105 \pm 16/9$ to $162/97 \pm 9/7$ mm Hg following placebo. The average maximal fall in blood pressure following the first dose (baseline and placebo corrected) was $21/11 \pm 11/8$ mm Hg supine and $27/13 \pm 18/10$ mm Hg erect.

The acute reduction in blood pressure, particularly following the first dose and after 1 week of nifedipine, was associated with significant increases in heart rate and plasma norepinephrine (Table 1). Erect heart rate increased from a baseline of $87 \pm 13$ to $108 \pm 14$ beats/min 5 hours after the first dose, compared with a corresponding change from $86 \pm 14$ to $94 \pm 12$ beats/min following placebo. Plasma renin activity was significantly increased after 1 week but not at 6 weeks (see Table 1).

With continued treatment there was a sustained antihypertensive effect ($p < 0.01$); for example, baseline measurements of supine blood pressure (recorded 12 hours after the last dose) after 1 and 6 weeks were respectively 23/11 and 33/15 mm Hg lower than those observed with placebo.

**Pharmacokinetics**

There were large intersubject differences in plasma nifedipine concentrations, but the intrasubject mean pharmacokinetic parameters were not significantly different across the 3 study days, as assessed by repeated-measures analysis of variance. Following the first dose, after 1 week, and after 6 weeks, the mean values for the area under the concentration-time curve were respectively $824 \pm 327, 813 \pm 282$, and $880 \pm 814$ ng $\cdot$ hr/ml; for apparent elimination half-life, $6.0 \pm 2.8, 10.0 \pm 3.1$, and $7.5 \pm 2.3$ hr; for change in $C_{\text{max}}, 74 \pm 25, 53 \pm 15$, and $77 \pm 68$ ng/ml; for $t_{1/2}$, $2.5 \pm 1.0, 2.0 \pm 0.7$, and $2.0 \pm 0.6$ hr. In addition, there was a significant correlation ($p < 0.03$) between subject age and $C_{\text{max}}$ after the first dose of nifedipine (Figure 2).

**Concentration-Effect Relationships**

In individual subjects there was no simple direct relationship between the plasma nifedipine concentration and the fall in blood pressure. In all subjects, following both acute and steady state treatment, the most appropriate model to describe the effect data was the linear model, and the two representative examples shown in Figures 3 and 4 illustrate above and below average goodness of fit. The derived $m$ and $K_{eq}$ values of individual subjects are shown in Table 2. Responsiveness to nifedipine, as the mean of the group, was $-0.48$ mm Hg/ng/ml following the first dose, $-0.45$ after 1 week, and $-0.49$ after 6

**Table 1. Hormone Measurements at 1.5 Hours on Each Study Day**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>1st dose</th>
<th>1 wk</th>
<th>6 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (ng Ang I/ml/hr)</td>
<td>$1.5 \pm 1.4$</td>
<td>$1.8 \pm 1.0$</td>
<td>$2.6 \pm 1.4^*$</td>
<td>$3.3 \pm 4.9$</td>
</tr>
<tr>
<td>Plasma aldosterone (pg/ml)</td>
<td>$76 \pm 33$</td>
<td>$99 \pm 60$</td>
<td>$110 \pm 58^*$</td>
<td>$106 \pm 79$</td>
</tr>
<tr>
<td>Plasma norepinephrine (nmol/L)</td>
<td>$2.5 \pm 1.3$</td>
<td>$4.2 \pm 2.1t$</td>
<td>$3.9 \pm 1.7^*$</td>
<td>$3.0 \pm 1.6$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD. Ang I = angiotensin I.

*$p < 0.03$, $t_p < 0.006$, compared with values for placebo.

**Figure 1.** The effects of placebo, first dose nifedipine, and nifedipine for 1 and 6 weeks on erect systolic and diastolic blood pressure (BP) for all subjects. Values are means $\pm$ SD.
weeks. There were no significant differences in $K_{eq}$ among the 3 study days. For individual subjects there were significant correlations ($p < 0.001$) between the responsiveness to the first dose of nifedipine and the responsiveness after 1 week ($r = 0.83$) and after 6 weeks of treatment ($r = 0.78$), as illustrated in Figure 5, the slope of both these regression lines being not significantly different from unity.

There was a significant positive correlation ($p < 0.02$) between the responsiveness to the first dose of nifedipine and the baseline blood pressure ($r = 0.6$; Figure 6A). There was no significant correlation between responsiveness and the maximal change in heart rate, although there was a trend toward an inverse relationship (Figure 6B). Finally, there was no significant relationship between the responsiveness to nifedipine and subject age, pretreatment plasma renin activity (Figure 7), or plasma norepinephrine.

**Discussion**

Reliable assays for measuring nifedipine in plasma have only recently become available, and there is still a relative paucity of detailed information about
TABLE 2. Concentration-Effect Variables for Changes in Erect Systolic BP

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>1st dose (mm Hg/ng/ml)</th>
<th>1 wk</th>
<th>6 wk</th>
<th>1st dose (1/hr)</th>
<th>1 wk</th>
<th>6 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.29</td>
<td>-0.24</td>
<td>-0.24</td>
<td>49.6</td>
<td>12.5</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>-0.79</td>
<td>-0.95</td>
<td>-0.87</td>
<td>2.1</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>-0.63</td>
<td>-0.55</td>
<td>-0.61</td>
<td>1.9</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>-0.84</td>
<td>-0.58</td>
<td>-0.56</td>
<td>0.8</td>
<td>3.7</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>-0.34</td>
<td>-0.34</td>
<td>-0.37</td>
<td>12.2</td>
<td>12.5</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>-0.39</td>
<td>-0.46</td>
<td>-0.51</td>
<td>2.0</td>
<td>46.9</td>
<td>2.4</td>
</tr>
<tr>
<td>7</td>
<td>-0.18</td>
<td>-0.25</td>
<td>-0.27</td>
<td>1.1</td>
<td>7.6</td>
<td>0.6</td>
</tr>
<tr>
<td>8</td>
<td>-0.43</td>
<td>-0.42</td>
<td>-0.46</td>
<td>1.8</td>
<td>1.3</td>
<td>4.7</td>
</tr>
<tr>
<td>9</td>
<td>-0.43</td>
<td>-0.50</td>
<td>-0.48</td>
<td>0.5</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>-0.55</td>
<td>-0.39</td>
<td>-0.46</td>
<td>0.6</td>
<td>3.8</td>
<td>0.1</td>
</tr>
<tr>
<td>11</td>
<td>-0.52</td>
<td>-0.37</td>
<td>-0.36</td>
<td>0.3</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>-0.57</td>
<td>—</td>
<td>-0.48</td>
<td>0.9</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>13</td>
<td>-0.18</td>
<td>-0.25</td>
<td>-0.39</td>
<td>9.3</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>14</td>
<td>-0.67</td>
<td>-0.54</td>
<td>-0.78</td>
<td>29.1</td>
<td>1.5</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Mean ± SD: -0.48 ± 0.20, -0.45 ± 0.19, -0.49 ± 0.17, 8.0 ± 14.3, 7.2 ± 12.6, 0.9 ± 1.2

\( m \) = responsiveness to the drug in terms of effect per unit of change in drug concentration (linear model); \( K_{eq} \) = first-order rate constant of the effect model.

The pharmacokinetics of nifedipine and, more importantly, about kinetic-dynamic relationships in patients with essential hypertension. An interesting feature of the pharmacokinetics of other calcium antagonists, particularly verapamil, which potentially might complicate the concentration-effect relationship, is the observed reduction in drug clearance during chronic compared with single dose administration. A similar finding has been reported with the dihydropyridine nicardipine and with nifedipine itself when the kinetics of intravenous administration have been determined following chronic oral treatment with nifedipine. These changes in clearance have been ascribed to drug-related alterations in hepatic blood flow or enzyme activity. Such a change in pharmacokinetics was not observed in this study, but the use of a delayed release formulation of nifedipine obviously did not permit full characterization of the disposition, particularly the terminal elimination phase of nifedipine.

An age-related decline in the clearance of nifedipine has been reported in healthy, elderly subjects. Across the relatively narrow range of middle-aged hypertensive subjects in this study there was no obvious relationship between age and nifedipine disposition, but there was a significant correlation between age and the first dose \( C_{max} \), which is consistent with an age-related effect on absorption or first-pass hepatic extraction.

It has been suggested that there is no predictable concentration-effect relationship for nifedipine, but this probably reflects the negative findings of those previous studies that considered the response for groups of patients rather than for individual patients. This study has shown that nifedipine concentrations are correlated with the reductions in blood pressure in individual hypertensive subjects and has extended the preliminary findings of Pasanisi and Reid by defining individual concentration-response relationships that are applicable during chronic treatment. Additionally, there were significant correlations between the parameters derived from the first dose and those after 1 and 6 weeks of treatment, which suggests that the first dose response may be used to forecast the steady state effect for an individual patient. Clearly, this finding has potential application in therapeutics as a means of quickly identifying poor or non-responders and for determining individual dose requirements for optimum long-term blood pressure control. During the first week of nifedipine treatment there was evidence...
that the fall in blood pressure was associated with reflex sympathetic activation, but this did not perturb the correlation with the response obtained at 6 weeks, when baroreceptor reflex mechanisms had apparently reset. Despite these changes in sympathetic activity, the responsiveness to nifedipine after 6 weeks showed no significant reduction, and this study has highlighted the importance of considering kinetic as well as dynamic parameters when assessing the constancy of the antihypertensive response.

Changes in heart rate with nifedipine have been correlated with acute reductions in blood pressure in young healthy normotensive subjects. However, in this study of hypertensive subjects, there was an opposite trend, whereby the responsiveness to nifedipine following the first dose tended to be greatest in those showing the smallest increase in heart rate. A possible explanation is that the increase in heart rate is a component of the reflex activity attempting to counteract the acute antihypertensive or vasodilator response to nifedipine, as seen in healthy normotensive subjects, but if the compensatory increase in heart rate and resultant cardiac output is inadequate, then the reduction in blood pressure will tend to be more pronounced. Since reflex mechanisms are blunted in the elderly, this may partly explain why calcium antagonists have been reported to be more effective in the older age group.

The relationship between pretreatment or initial blood pressure and the magnitude of the fall with treatment has been described previously. Care is necessary with the statistical methods used in this type of analysis, and it is probably more appropriate to seek correlations that also take into account interindividual differences in drug concentrations and the extent of the blood pressure fall associated with placebo. In this study, illustrated by the placebo-corrected reduction in erect systolic blood pressure, there was a significant relationship between the baseline (pretreatment) blood pressure and the responsiveness (m) to the first dose of nifedipine. It has also been suggested that plasma renin activity influences the antihypertensive effect of nifedipine, but in this study there was no significant relation-
ship between the pretreatment plasma renin activity and the responsiveness to nifedipine.

In conclusion, this study has evaluated the pharmacokinetics of nifedipine in essential hypertension and characterized the antihypertensive response to nifedipine in individual subjects. The derived concentration-effect parameters provide not only a useful means of evaluating factors that influence the kinetic and dynamic variability of nifedipine but also a potential basis for optimizing long-term treatment in individual patients.

Acknowledgment

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References

Nifedipine: individual responses and concentration-effect relationships.
R Donnelly, H L Elliott, P A Meredith, A W Kelman and J L Reid

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