Pharmacokinetics and Pharmacodynamics of Conventional and Slow Release Forms of Nifedipine in Essential Hypertensive Patients

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IMAI, Y., ABE, K., SASAKI, S., NIHEI, M., SEKINO, H. and YOSHINAGA, K. Pharmacokinetics and Pharmacodynamics of Conventional and Slow Release Forms of Nifedipine in Essential Hypertensive Patients. Tohoku J. exp. Med., 1986, 148 (4), 421-438 — In patients with essential hypertension, the pharmacokinetics of nifedipine in 2 forms (capsule, 10 mg nifedipine dissolved in an organic solvent; slow release tablet, 20 mg nifedipine) and their pharmacodynamic effectiveness on arterial pressure were studied. The maximum plasma concentration was higher and achieved more rapidly after application of the capsule than after the retard tablet (p <0.01). The plasma half-time of nifedipine in the capsule was shorter than that in the retard tablet (p <0.05). The absorption rate of nifedipine from the capsule tended to be larger than that from the retard tablet. Plasma concentrations of nifedipine, measured 12 hr after the dosing of the retard tablet during chronic treatment, were not different from those after the acute administration of the retard tablet, suggesting that no accumulation of nifedipine occurs. The capsule of nifedipine elicited prompt and profound hypotension with short duration, while the retard tablet produced a hypotensive effect with relatively slow onset and long duration. Arterial pressure reduction was maintained throughout the day using 12 hourly dose of the retard tablet. During the chronic treatment the maximum hypotensive effect was observed 4 weeks after the start of treatment. Twelve hourly administration of the retard tablet is a convenient regimen for the long-term control of mild to severe essential hypertension. ——— nifedipine; slow release form; conventional form; antihypertensive therapy; essential hypertension

Nifedipine is a potent vasodilator, which relaxes vascular smooth muscle probably by its inhibitory effect on the transmembrane influx of calcium (Fleckenstein et al. 1972). It has been demonstrated that this drug exerts a prompt and marked hypotensive effect when administered to hypertensive patients (Murakami et al. 1972; Aoki et al. 1976; Guazzi et al. 1977; Pedersen and Mikkelsen 1978; Imai et al. 1980) and the drug has been accepted as a critical therapeutic for several forms of hypertension (Guazzi et al. 1983; Massie et al. 1984; Mühller et

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Nifedipine is very effective in the treatment of severe hypertension and hypertensive emergency (Imai et al. 1980). When the conventional form of nifedipine (soft capsule containing 10 mg of dissolved nifedipine) was administered orally, there was a rapid hypotensive effect occurring maximally at 1 hr after administration and disappearing within 7 hr (Imai et al. 1980). Therefore, q.i.d. administration of the conventional form of nifedipine is essential for maintenance of a hypotensive effect (Imai et al. 1980). Furthermore, a rapid and profound vasodilation by nifedipine may cause adverse effects such as palpitation, headache, flushing and heat sensation in the face and limbs (Murakami et al. 1972; Aoki et al. 1976; Guazzi et al. 1977; Pedersen and Mikkelsen 1978; Imai et al. 1980). Therefore, it is difficult to use the conventional form of nifedipine for the treatment of mild to moderate hypertensive patients. The slow release form of nifedipine, which may cause much lower incidence of side effects, would be a very valuable therapeutic agent for the treatment of essential hypertension. Recently, the slow release form of nifedipine has been developed by Bayer A.G. In the present study we compared the pharmacokinetics and pharmacodynamics of the slow release form of nifedipine with those of the conventional form in single dosing and in long-term treatment.

Materials and Methods

Subjects

Thirty-four patients with essential hypertension were studied. Secondary hypertension was excluded from this investigation. All patients had mild or moderate hypertension (WHO I or II). The patients had not been treated with any antihypertensive drugs, or antihypertensive therapy had been withdrawn for 4 weeks prior to the study. The purpose and procedure of the study was fully explained, and informed consent was obtained from each patient.

Drug form

Drug forms used in the present study were as follows: 1) soft capsule containing 10 mg of nifedipine dissolved in an organic solvent (conventional form); 2) slow release tablet containing 20 mg of nifedipine (slow release form); 3) nifedipine injectable (solution containing 0.1 mg/ml of organic solvent).

Study design

Acute hypotensive effect and pharmacokinetics of nifedipine administered parenterally (Study I). Five patients with essential hypertension, aged 44.2 ± 8.7 (s.d.) years, 4 males and 1 female, were studied. All patients received an intravenous test dose of nifedipine (0.6 mg) dissolved in 10 ml of physiological saline. The drug was injected over 2 min. Nifedipine was protected from light during the injection. Arterial pressure and heart rate were measured at 1-min intervals for 15 min before and after drug administration and then at 5-min intervals for 2 hr. Blood samples for determination of nifedipine were obtained before injection (0) and at 3, 6, 9, 14, 45, 75, 105 and 135 min after the injection.

Acute hypotensive effect of 20 mg of the conventional form and its pharmacokinetics (Study II). Seven patients, aged 37.7 ± 10.1 years, 5 males and 2 females, were studied. Two capsules of the conventional form of nifedipine were administered orally with 100 ml water. Arterial pressure and heart rate were measured every 5 min for 1 hr before and 2.5 hr after
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the dosage, and then every 30 min for 6 hr. Plasma samples for blood concentration of nifedipine were obtained before administration (0) and 0.5, 1, 1.5, 2.5, 4.5, 6.5 and 8.5 hr after the dosage.

Acute hypotensive effect of 20 mg of the slow release form and its pharmacokinetics (Study III). The subjects of Study II were again investigated in Study III. One week before or after Study II the slow release tablet was administered orally with 100 ml water. Arterial pressure and heart rate were measured every 5 min for 1 hr before and 2.5 hr after the dosage, and then every 30 min for 10 hr. Blood samples for plasma concentration of nifedipine were obtained before administration (0) and 0.5, 1, 1.5, 2.5, 4.5, 8.5, 10.5 and 12.5 hr after the dosage.

Pharmacokinetics of 40 mg of the slow release form (Study IV). Seven patients with essential hypertension, aged 48.0±2.2 years, 4 males and 3 females, were studied. The procedure for drug administration and the times for blood sampling were the same as Study III. In this study blood samples were also taken at 19.5 and 24.5 hr after the ingestion of 40 mg of the slow release form of nifedipine.

Measurement of plasma concentration of nifedipine during long-term treatment with the slow release form (b.i.d., 20 mg each) (Study V). Six patients with the essential hypertension, aged 54.7±13.2 years, 3 males and 3 females, were treated with the slow release form (b.i.d., 20 mg each) for 4 weeks. A placebo was given for 4 weeks before the treatment. All patients received nifedipine in the morning (between 6:00 and 8:00 a.m.) and in the evening (between 6:00 and 8:00 p.m.). The drug compliance was carefully checked. Blood samples for plasma concentration of nifedipine, arterial pressure and heart rate were obtained before, and 1 and 2.5 hr after the first dose. For measurement of plasma concentration of nifedipine 12 hr after ingestion of the drug at the 2nd and 4th week during treatment, patients were requested to ingest the drug at 9 p.m. in the fasting condition on the previous evening of the clinic visit. The patients visited the clinic in the next morning until 8:30 a.m. without drug ingestion and meal. Thus, the blood samples were obtained 12 hr after the final dose at the 2nd and 4th week. At the 2nd week, blood samples were also obtained 1 and 2.5 hr after the drug ingestion.

Long-term hypotensive effect of the slow release form (b.i.d., 20 mg each) (Study VI). Nine patients with essential hypertension, aged 42.3±7.5 years, 6 males and 3 females, were treated with the slow release form (b.i.d., 20 mg each) for 20 weeks. A placebo was given for 4 weeks before the treatment. All patients received nifedipine 30 min after breakfast (between 6:00 and 8:00 a.m.) and the evening meal (between 6:00 and 8:00 p.m.). As a rule, patients visited the clinic every second week and were checked 3 to 5 hr after the morning dose. The drug compliance was also carefully checked. The time interval between the final intake of drug and arterial pressure measurement was carefully recorded. In 8 of these 9 patients arterial pressure was measured at home by themselves. A well calibrated aneroid sphygmomanometer (Apollo, Matsuyoshi & Co., Ltd., Tokyo) had been given to each patient at the beginning of the placebo period. The patients were trained to measure their arterial pressure accurately by skilled nurses. These patients were requested to measure their arterial pressure every morning in a sitting position in bed before taking medication. The sphygmomanometers were checked again after the study.

Other experimental procedure

All patients, except for Study VI, were studied while fasting in the morning, and they remained supine in bed for at least 1 hr before study. In Studies II, III and IV, patients received a light meal 2.5 hr after the drug administration. In all studies except Study VI arterial pressure and heart rate were measured in the recumbent position with an Arteriosonde (Type 1225, Roche Medical Electronics, Cranvury, NJ, USA) and a cardiotachometer (RT-5, Nihon Kohden, Tokyo), respectively. Five readings of arterial pressure and heart rate before drug administration were averaged in each patient and taken as control (0). In Study VI arterial pressure and heart rate in the sitting position were measured with a
mercury sphygmomanometer and palpation of radial pulse, respectively, and 3 readings of arterial pressure and heart rate in 3 different placebo periods were averaged and taken as control (0). In all studies blood samples were taken by venipuncture. Syringes for blood sampling were protected from light using aluminium foil. Separation of blood was carried out under a sodium lamp. Plasma was immediately frozen after separation and stored at \(-20^\circ C\).

**Measurement of plasma nifedipine**

Plasma concentrations of nifedipine were determined by high performance liquid chromatography. Briefly, plasma samples (3 ml) were made alkaline (pH 12) with sodium hydroxide solution and extracted with chloroform. The organic layer was evaporated to dryness under nitrogen gas and nifedipine was oxidized to its pyridine analogue by adding an aqueous solution of hydrochloric acid and sodium nitrite. After re-extraction with chloroform, the organic layer was evaporated to dryness and an internal standard (aminopyrine) was added to the residue. Aliquots (50 \(\mu l\)) were injected into a high performance liquid chromatography. The amount of nifedipine in each sample was calculated by measuring the peak height ratio and referring to the standard curve. The detection limit of nifedipine in plasma was 4 ng/ml. The mean recovery of nifedipine from plasma was 92.6\% when control plasma samples containing 50 ng/ml of nifedipine were measured.

**Data analysis**

The data obtained from intravenous administration were fitted to the two-compartment open model and the data obtained from oral administration were fitted to the one compartment open model. The data concerning plasma concentration of nifedipine were analyzed using a computer, HITAC II. The post injection concentration-time curve is 

\[ \text{Cp}(t) = Ae^{-at} + Be^{-bt} \]

The following parameters were assessed for pharmacokinetic analysis using data on plasma nifedipine concentration: volume of the central compartment (\(v_1\)), plasma elimination half-time of elimination phase (\(t_{1/2}\)), total body clearance (\(Cl\)) and area under the plasma concentration-time curve from 0 to infinity (\(AUC_{\infty}\)). The total body clearance was determined by the relation: 

\[ Cl = D/v \cdot AUC_{\infty} \]

The plasma concentration-time curve after oral administration is: 

\[ C(t) = C_0 \left( e^{-kt_a} - e^{-kt_b} \right) \]

Fraction of dose absorbed (systemic availability, \(F\)) was determined from the experimental data using: 

\[ F = \frac{AUC_o \cdot D_0}{AUC_i \cdot D_o} \]

where \(D_0\) is the dose administered intravenously and \(D_o\) is the dose administered orally. The area under the plasma concentration-time curve obtained from the parenteral study (\(AUC_{iv}\) in Study I) was used for the calculation of \(F\) in Studies II, III and IV. Total body clearance was determined by the relationship: 

\[ Cl = F \cdot D_0 / AUC_o \]

Plasma concentration of nifedipine during chronic administration was simulated using the pharmacokinetic parameters obtained from a single oral dose of conventional and slow release forms of nifedipine.

**Statistical analysis**

Results are given as mean\(\pm\)s.e. The Student’s \(t\)-test was employed for comparison of paired data. The \(t\)-test for independent means was used for comparison of groups. When the variance of different distribution was not equal, approximation of Cochran-Cox was used for statistical analysis.
RESULTS

Pharmacodynamics of nifedipine

Acute effects of parenteral nifedipine

An intravenous dose of nifedipine, 0.6 mg, caused rapid changes in arterial pressure and heart rate. Three min after the injection the decrease in arterial pressure and increase in heart rate reached the maximum. The effect on arterial pressure and heart rate waned rapidly in the first 9 min and thereafter the initial levels recovered slowly (Fig. 1). Two of the 5 subjects complained of slight vascular pain. Heat sensation in the face and limbs and palpitation were transiently observed in each subject.

Acute effect of oral nifedipine

Fig. 2 shows the time course of change in arterial pressure and heart rate caused by 20 mg of both conventional and slow release forms. Both forms caused a significant decrease in arterial pressure. The appearance of the hypotensive effect of the conventional form was more rapid than that of the slow release form. The maximum decrease in arterial pressure was observed 1 hr after the administration of the conventional form and thereafter the hypotensive effect attenuated gradually. The arterial pressure returned to the initial levels 8.5 hr after the ingestion. The maximum decrease in arterial pressure was also observed 1 hr after the administration of the slow release form and this hypotensive effect remained constant for 5 hr and thereafter arterial pressure gradually returned to

![Fig. 1. The effects of single parenteral dose of nifedipine (0.6 mg) on mean arterial pressure (a) and heart rate (b) in essential hypertensive patients. *p < 0.05, **p < 0.01 against controls.](image)
the initial level. The fall in arterial pressure was still significant up to 10.5 hr after the dosing. As shown in Fig. 2(a), the hypotensive effect of the conventional form at 0.5, 1, and 1.5 hr after ingestion was significantly more remarkable than that of the slow release form. The hypotensive effect of the slow release form at 4.5 hr after the administration was significantly more remarkable than that of the conventional form. As shown in Fig. 2(b), both forms of nifedipine significantly increased heart rate. The appearance of tachycardia caused by the conventional form was more rapid than that caused by the slow release form. The increase in heart rate at 1 and 1.5 hr after the conventional form was more remarkable than that after the slow release form. Five of the 7 subjects complained of palpitation when the conventional form was administered. Palpitation was also observed in 3 of the 7 subjects when the slow release form was administered, but this side effect was not so severe as that after the conventional form and was well tolerated. A mild or moderate degree of heat sensation in the face and limbs, or facial flushing was observed in every patient when the conventional form was administered, while these symptoms were observed only in 3 of the 7 patients given the slow release form. Throbbing headache was observed in 1 case when the conventional form was administered.

Fig. 2. The effects of single oral dose of nifedipine (20 mg) on mean arterial pressure (a) and heart rate (b) in essential hypertensive patients. (●) Slow release form. (○) Conventional form. *p < 0.05, **p < 0.01, against controls 'p < 0.05, ''p < 0.01 against conventional form.
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Fig. 3. The effects of the slow release form of nifedipine (20 mg b.i.d.) on mean arterial pressure (a) and heart rate (b) during chronic treatment obtained at outpatient clinic (●) and at home (▲). *p < 0.05, **p < 0.01 against control. *p < 0.05, **p < 0.01 against values at the 20th week. Every mean arterial pressure at home during chronic treatment was significantly lower than that in placebo period (p < 0.01).

Fig. 4. Plot of plasma nifedipine concentration versus time following a 0.6 mg intravenous dose.
Table 1. Pharmacokinetic parameters of parenteral nifedipine

<table>
<thead>
<tr>
<th>Case No.</th>
<th>A</th>
<th>B</th>
<th>$\alpha$ min$^{-1}$</th>
<th>$\beta$ min$^{-1}$</th>
<th>$K_{pl}$ min$^{-1}$</th>
<th>$t_{1/2}$ hr</th>
<th>$V_1$ L</th>
<th>AUC_{iv} ng ml$^{-1}$ hr</th>
<th>AUC_{iv/mg}</th>
<th>Cl ml min$^{-1}$</th>
<th>$V_{d\beta}$ L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.7</td>
<td>15.6</td>
<td>0.007</td>
<td>0.0062</td>
<td>0.0125</td>
<td>1.86</td>
<td>13.9</td>
<td>47.8</td>
<td>79.7</td>
<td>209.1</td>
<td>38.5</td>
</tr>
<tr>
<td>2</td>
<td>21.0</td>
<td>4.7</td>
<td>0.164</td>
<td>0.0045</td>
<td>0.0220</td>
<td>2.57</td>
<td>23.4</td>
<td>19.4</td>
<td>32.3</td>
<td>515.7</td>
<td>128.8</td>
</tr>
<tr>
<td>3</td>
<td>38.1</td>
<td>15.1</td>
<td>0.096</td>
<td>0.0054</td>
<td>0.0166</td>
<td>2.14</td>
<td>11.3</td>
<td>51.9</td>
<td>86.4</td>
<td>192.8</td>
<td>39.7</td>
</tr>
<tr>
<td>4</td>
<td>18.0</td>
<td>26.0</td>
<td>0.050</td>
<td>0.0100</td>
<td>0.0148</td>
<td>1.15</td>
<td>13.6</td>
<td>49.4</td>
<td>82.3</td>
<td>202.5</td>
<td>23.1</td>
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<tr>
<td>5</td>
<td>177.5</td>
<td>16.0</td>
<td>0.282</td>
<td>0.0102</td>
<td>0.0881</td>
<td>1.13</td>
<td>3.1</td>
<td>36.7</td>
<td>61.1</td>
<td>272.9</td>
<td>37.5</td>
</tr>
<tr>
<td>Mean</td>
<td>56.5</td>
<td>15.5</td>
<td>0.134</td>
<td>0.0073</td>
<td>0.0313</td>
<td>1.77</td>
<td>13.1</td>
<td>41.0</td>
<td>68.4</td>
<td>278.6</td>
<td>53.5</td>
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<td>s.e.</td>
<td>30.5</td>
<td>3.4</td>
<td>0.042</td>
<td>0.0012</td>
<td>0.0142</td>
<td>0.21</td>
<td>3.2</td>
<td>6.0</td>
<td>8.9</td>
<td>54.5</td>
<td>19.1</td>
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</table>

$A$, $B$, $\alpha$ and $\beta$ are constants of the following equation: $C_p(t) = Ae^{-\alpha t} + Be^{-\beta t}$.
$K_{pl}$, elimination constant; $t_{1/2}$, plasma elimination half-time of elimination phase; $V_1$, distribution volume of central compartment; AUC_{iv}, area under the plasma concentration-time curve; Cl, total body clearance; $V_{d\beta}$, distribution volume for $\beta$-phase.

Table 2. Pharmacokinetic parameters of oral nifedipine, 20 mg of the conventional form (A), 20 mg (B) and 40 mg (C) of the slow release form (A):

<table>
<thead>
<tr>
<th>Case No.</th>
<th>$C_0$ ng ml$^{-1}$</th>
<th>$k_a$ min$^{-1}$</th>
<th>$k_{el}$ min$^{-1}$</th>
<th>$t_{1/2}$ hr</th>
<th>$t_{max}$ hr</th>
<th>$C_{max}$ ng ml$^{-1}$</th>
<th>AUC_{0} ng ml$^{-1}$ hr</th>
<th>AUC_{0/mg}</th>
<th>F</th>
<th>$V_{d/F}$</th>
<th>Cl ml$^{-1}$</th>
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<td>0.36</td>
<td>249.8</td>
<td>672</td>
<td>33.6</td>
<td>0.49</td>
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<tr>
<td>Mean</td>
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$C_0$, concentration at time 0; $k_a$, absorption rate constant; $k_{el}$, elimination rate constant; $t_{1/2}$, plasma elimination half-time; $t_{max}$, time to maximum concentration; $C_{max}$, maximum concentration; AUC_{0}, area under plasma concentration-time curve; F, fraction of dose absorbed; $V_{d/F}$, apparent distribution volume; Cl, total body clearance.
### B:

<table>
<thead>
<tr>
<th>Case No.</th>
<th>$C_0$ (ng ml$^{-1}$)</th>
<th>$k_a$ (min$^{-1}$)</th>
<th>$k_{el}$ (min$^{-1}$)</th>
<th>$t_{1/2}$ (hr)</th>
<th>$t_{max}$ (hr)</th>
<th>$C_{max}$ (ng ml$^{-1}$)</th>
<th>AUC$_0$ (ng ml$^{-1}$ hr)</th>
<th>AUC$_{0-24}$ (ng ml$^{-1}$ hr)</th>
<th>$F$</th>
<th>$V_{cl/F}$</th>
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Abbreviations are the same as in Table 2A.

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<th>$k_{el}$ (min$^{-1}$)</th>
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Abbreviations are the same as in Table 2A.
Long-term effect of the slow release form of nifedipine

Fig. 3 shows the long-term effect of the slow release form (b.i.d., 20 mg each). The maximum hypotensive effect was observed 4 weeks after the start of the treatment. Twenty weeks after the start of treatment, hypertension was controlled satisfactorily. One week after the cessation of treatment the arterial pressure returned to the hypertensive level, but it was still significantly lower than the pretreatment control level (0). Heart rate was slightly increased during the chronic treatment. The increase in heart rate reached a significant level in several weeks. Four of the 9 subjects complained of mild palpitation initially. This complaint was temporary and well tolerated. Heat sensation or flushing in the face was observed in 3 of the 9 subjects. These side effects were also temporary and well tolerated. Fig. 3 also shows arterial pressure measured at home every Friday morning 12 hr after taking the drug in the preceding evening. As shown in the figure, arterial pressure measured at home during the control period was slightly lower than that measured at the outpatient clinic, but the difference was not significant. One week after the start of chronic treatment, arterial pressure measured at home in the morning was significantly lower than that during the control period and was satisfactorily controlled during the long-term treatment ($p < 0.01$).

Pharmacokinetics

Pharmacokinetics of parenteral and oral nifedipine administered acutely

Plasma concentrations of nifedipine after a single intravenous dose are shown in Fig. 4. The corresponding pharmacokinetic parameters are listed in Table 1. Plasma concentration-time curves of nifedipine after a single oral dose of the conventional and the slow release forms are shown in Fig. 5. The corresponding pharmacokinetic parameters are listed in Table 2. Plasma concentration of nifedipine increased more slowly after the slow release form than that after the conventional form. The peak plasma concentration of nifedipine after an oral dose of 20 mg of the conventional form was achieved more rapidly than that after the slow release form of 20 mg ($p < 0.01$) or 40 mg ($p < 0.01$). The plasma elimination half-time, $t_{1/2}$, of nifedipine after a 0.6 mg injection was significantly shorter than that after an oral dose of 20 mg and 40 mg of the slow release form ($p < 0.05$). However, $t_{1/2}$ after an oral dose of 20 mg of the conventional form was not significantly different from that after 0.6 mg injection. The plasma elimination half-time of nifedipine after 20 mg of the conventional form was significantly shorter than that after 20 mg ($p < 0.05$) and 40 mg ($p < 0.02$) of the slow release form. There was no significant difference between $t_{1/2}$ after 20 mg and that after 40 mg of the slow release form. The maximum plasma nifedipine concentration ($C_{max}$) achieved by 20 mg of the slow release form was significantly lower than that achieved by 20 mg of the conventional form ($p < 0.01$) and 40 mg of the slow
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Fig. 5. Plots of plasma nifedipine concentration versus time following an oral dose of 20 mg of the conventional form (○), 20 mg of the slow release form (●), and 40 mg of the slow release form (▲).

Fig. 6. Systolic arterial pressure (○), diastolic arterial pressure (△), heart rate (□) and plasma concentration of nifedipine (PCN, ●) during the chronic treatment with the slow release form (20 mg b.i.d.). PCN: plasma concentration of nifedipine.
release form \((p<0.05)\). There was no significant difference between \(C_{\text{max}}\) after 20 mg of the conventional form and 40 mg of the slow release form. The area under the plasma concentration-time curve per mg (AUC/mg) after 0.6 mg injection was higher than that after an oral dose of 20 mg of conventional form \((p<0.01)\), and 40 mg of the slow release form \((p<0.01)\). The AUC/mg after 20 mg of the conventional form tends to be larger than that after 20 mg of the slow release form, but the difference was not significant. The absorption rate constant (\(k_{a}\)) after 20 mg of the conventional form was significantly higher than that after 20 mg \((p<0.05)\) and 40 mg \((p<0.05)\) of the slow release form. There was no significant difference between \(k_{a}\) after 20 mg and 40 mg of the slow release form.

The elimination rate constant (\(k_{e1}\)) after 20 mg of the slow release form tends to be lower than that of the conventional form, but the difference was not significant. There was no significant difference between \(K_{e1}\) after 20 mg and 40 mg of the slow release form. The fraction of the dose absorbed (\(F\)) after 20 mg of the slow release form showed a tendency to be lower than that after 20 mg of the conventional form and 40 mg of slow release form, but the difference was not significant. No significant difference was found between the total body clearance (\(Cl\)) among 4 types of treatment.

**Plasma concentration of nifedipine during chronic treatment**

Plasma concentrations of nifedipine 1 and 2.5 hr after the first dose of the slow release form (20 mg) were 33.0±5.2 and 49.8±3.9 ng/ml, respectively. These values were slightly higher than those obtained in Study III (28.0±4.5 and 40.8±7.1 ng/ml, respectively), though the differences were not statistically

\[\text{Fig. 7. Plasma concentration of nifedipine obtained at the first dose of the slow release form [20 mg (A)] and during the chronic treatment with the slow release form [20 mg b.i.d; at the 2nd week (B) and 4th week (C)].} \quad *p<0.05 \text{ against values in the corresponding period in the 2nd week.} \]
As shown in Fig. 6, plasma concentrations of nifedipine 12 hr after the dose at the 2nd and 4th weeks were 10.8±0.7 and 10.3±1.1 ng/ml, respectively. These values were not significantly different from those obtained by the first dose in Study III (12.0±3.3 ng/ml). Arterial pressure 12 hr after the dose in each period remained significantly lower than the control.

Fig. 8. Relation between plasma concentrations of nifedipine and the percent changes in mean arterial pressure obtained at the first dose of the slow release form of nifedipine.

Fig. 9. Simulation of plasma concentration of nifedipine versus time following an oral dose of the conventional form (20 mg t.i.d.).
As shown in Fig. 7, plasma concentrations of nifedipine 1 and 2.5 hr after ingestion at the 2nd week were significantly higher than those obtained at the 1st dose.

Relation between plasma concentration and hypotensive effect of nifedipine

The relation between plasma concentrations of nifedipine and the percent changes in mean arterial pressure obtained from acute administration of the slow release form (Study III) was examined. As shown in Fig. 8, plasma concentration of nifedipine was well correlated with the percent change in mean arterial pressure ($r = -0.66$, $p < 0.01$).

Simulation of plasma concentration-time curve

Fig. 9 shows the simulated plasma concentration-time curve of the conventional form of nifedipine, 20 mg t.i.d. Steady state was obtained by the 4th administration of this form and the maximum plasma concentration in steady state was estimated as 174 ng/ml.

Fig. 10 shows the simulated plasma concentration-time curve of the slow release form of nifedipine, 20 mg b.i.d. Steady state was obtained by the 6th administration of this form and the maximum plasma concentration was estimated as 53 ng/ml. This value was almost identical with that obtained by the actual measurement during chronic treatment.

DISCUSSION

Nifedipine is one of the most potent calcium antagonistic vasodilators (Fleckenstein et al. 1972; Hashimoto et al. 1972). In the present study, both forms of nifedipine (conventional and slow release forms) proved to be very effective in lowering arterial pressure. As reported previously, and confirmed again in the present study, the conventional form showed prompt and remarkable hypotensive effect with short duration. Therefore, frequent administration is required to obtain the sustained hypotensive effect when the conventional form is used. Furthermore, rapid and remarkable hypotension may sometimes bring about headache, palpitation, heat sensation, flushing, etc. These characteristics of the
conventional form may deteriorate the drug compliance and may be disadvantageous for the treatment of asymptomatic hypertension. Therefore, it would be desirable to develop a long-acting form of nifedipine to overcome these disadvantages of the conventional form. As shown in the present study, the slow release form of nifedipine lowered arterial pressure and maintained a hypotensive effect even after 12 hr of the drug administration in chronic treatment. This suggests that twice a day administration of the slow release form can reduce arterial pressure throughout the day.

Although several kinds of vasodilators are used in the treatment of hypertension, the usefulness of these drugs is limited due to their side effects of reflex tachycardia and sodium retention (Koch-Weser 1974). As a matter of fact the slow release form of nifedipine also caused tachycardia. This side effect in the slow release form, however, was far less in degree than that of the conventional form and was well tolerated. These results indicate that the slow release form is preferable for the treatment of hypertension. In a previous study we have shown that combination of nifedipine with β-blocker or clonidine, and diuretic was very useful for the treatment of severe hypertension (Imai et al. 1980). Thus, the hypotensive effect becomes more reliable and the side effect may be less if the hypertension is treated with the slow release form of nifedipine in combination with a β-blocker or clonidine, and diuretic.

The time course of plasma concentration of nifedipine after the conventional form or the slow release form is consistent with the pharmacodynamics and side effects of each drug form. After administration of the conventional form plasma concentration of nifedipine increased rapidly, reached a very high peak level and disappeared quickly. On the other hand, after administration of the slow release form the plasma concentration-time curve showed gentle slope in both absorption and elimination phases with a long elimination half-time. The present study demonstrated that the fractions of dose absorbed (F) in both forms are rather low (0.18–0.63). These values of pharmacokinetic parameters are essentially similar to those reported previously (Brennan et al. 1983; Raemsh and Sommer 1983; Taburet et al. 1983; Kleinbloesem et al. 1984). The values of systemic availability of nifedipine suggest that the absorption is incomplete or this substance is subjected to the first pass effect, or both. It is reported that in rats and dogs more than 90% of orally administered nifedipine was absorbed when labelled compound was administered in a drug form identical to the conventional one (Patzschke et al. 1975). Schloßmann et al. (1975) reported that in rats, metabolism of nifedipine was very rapid and 40% of absorbed nifedipine changed to inactive metabolites within 30 min after oral administration. It is reported that a dihydropyridine derivative such as nicardipine, which is structurally very similar to nifedipine, is highly subjected to the first pass effect (Higuchi and Shiobara 1980). These findings suggest that nifedipine is likely to be subjected to the first pass effect. In the present study the conventional form showed relatively higher
bioavailability than that of the slow release form. The difference of systemic bioavailability may partly be due to the different gastrointestinal releasing rates of the two forms. Patzschke et al. (1975) reported that the bioavailability of nifedipine was influenced by the drug form. It is supposed that excessive load of the drug to the liver before reaching systemic circulation, which is caused by rapid and massive absorption in the case of the conventional form, may saturate and override the metabolic capacity of the liver, causing a higher bioavailability. Excessive load of the drug to the liver may also occur when higher doses of nifedipine, even though in the slow release form, are administered. The higher bioavailability of 40 mg of slow release form than that of 20 mg of the same form may also be explained by this phenomenon.

The plasma concentration of nifedipine, measured 12 hr after the dose of the slow release form during chronic treatment was not different from that after acute administration, suggesting that accumulation does not occur during long-term treatment with the slow release form. In addition during chronic treatment the arterial pressure 12 hr after the dose remained significantly lower than that of the control period, while in acute administration the hypotensive effect disappeared 12 hr after the dose. These results suggest that the factor other than the plasma concentration of nifedipine may affect the arterial pressure during chronic treatment, e.g., tissue binding of nifedipine. Thus, we infer that a minimal effective plasma concentration is 10 ng/ml or less during the chronic treatment.

On the other hand, plasma concentrations of nifedipine in acute administration were well correlated with the percent change in mean arterial pressure, suggesting the dose-dependent effect of the drug. Since plasma concentration of nifedipine during chronic treatment with the slow release form (20 mg, b.i.d.) was well simulated by one compartment open model, we also constructed the simulation during chronic treatment with the slow release form, 20 mg t.i.d. The maximum concentration and the concentration 8 hr after the dosing in the steady state were calculated to be about 70 ng/ml and 40 ng/ml, respectively. Thus, t.i.d. of slow release form, if necessary, would elicit more reliable hypotensive effect.

In conclusion, 20 mg of the slow release form of nifedipine, administered twice a day, is effective in controlling mild to severe essential hypertension without accumulation of the drug in the blood during chronic treatment. Thus, the slow release form of nifedipine is reliable and convenient for the treatment of hypertension.

Acknowledgments

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References
