Pharmacokinetics of Nicardipine following Intravenous and Oral Administration to the Same Human Subject

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Summary: The pharmacokinetic study of nicardipine in the same human after intravenous and oral administration was examined. The profile of nicardipine after bolus 1.05 mg injection fit well to a bi-exponential curve. Plasma nicardipine concentrations for constant rate infusion at 1.27 mg/hr for 3 hr declined from 3 to 7 hr with the same pattern as the bolus injection, but exhibited another slope after 7 hr that declined more gently. The $\gamma$-value was 0.0463 hr$^{-1}$, 1/5 the $\beta$-values. On the other hand, absolute bioavailability values for Perdipine LA® sustained-release capsule containing 40 mg nicardipine as hydrochloride salt after single and multiple doses were calculated by dividing $\text{AUC}_{\text{PO}}$ by $\text{AUC}_{\text{IV}}$, correcting for administered dose. Bioavailability values calculated based on the bolus injection (about 20%) represented a 2-fold difference when compared to values derived from constant rate infusion data. Consequently, differences in bioavailability values must be considered carefully to calculate bioavailability accurately. When the $\gamma$-phase is detected as in the case of nicardipine disposition, we need to select the intravenous administration for detecting $\gamma$-phase.

Key words: Nicardipine, $\gamma$-phase, Bioavailability, Human

Introduction

Nicardipine is a dihydropyridine calcium channel inhibitor possessing antihypertensive and arterial vasodilator properties. Pharmacokinetic studies for intravenous administration in man reported a biphasic decline with a terminal half life of 1-5 hr. A sustained-release capsule (Perdipine LA®) has gained widespread clinical use. However, terminal rate constants for the oral administration of uncoated tablets or sustained-release capsules, are much smaller than for intravenous administration.

Different rate constants during the terminal phase may be due to the sensitivity of the assay procedures for each sampling period, which in turn provide data to determine the area under the concentration-time curve (AUC). Since it would be useful to determine the pharmacokinetics of nicardipine using standard techniques, the terminal phase of orally and intravenously administered nicardipine was examined to confirm the existence of a similar small rate constant. Differences in the terminal decay of nicardipine have a seriously affect measurement of its bioavailability. This paper describes the determination of the constants for nicardipine after bolus injection and constant infusion and gives accurate estimates on the bioavailability after oral administration by $\text{AUC}_{\text{PO}}$/\text{AUC}_{\text{IV}}$ correcting for dose which exhibits the linear pharmacokinetics.

Methods

Subject

One healthy subject (32-year-old woman) was used in this study on receipt of her informed consent. No other medication was taken at least 2 weeks prior to and during the study. Subject had normal renal and liver function.

Materials

Nicardipine was obtained from Yamanouchi Pharmaceuticals (Japan) as the hydrochloride salt in either a sustained-release capsule (Perdipine LA®) containing 40 mg or in an intravenous solution (Perdipine solution) containing 1 mg/ml.

Study Protocol

Perdipine solution for bolus injection was diluted with saline to yield a volume of 9 ml, which contained 1.05 mg nicardipine. This diluted solution was ad-
ministered over 2 min. Venous blood samples were collected from the arm in heparinized glass tubes at 0.12, 0.23, 0.37, 0.73, 1.1, 1.9, 3.0 and 4.0 hr after infusion.

After washout interval of one week, a Perdipine LA® 40 mg capsule was administered with 100 ml water at AM 9 : 00 after the subject fasted for 10 hr. Blood samples were collected in heparinized glass tubes at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hr.

After a lapse of two weeks, a Perdipine LA® 40 mg capsule was given twice daily (at AM 9 : 00 and PM 9 : 00) with 100 ml water for 10.5 days, and the multiple doses were consisted of the 21st dosing. Blood samples were collected at AM 9 : 00 right before each dosing. At the 8th and the 20th dosing interval during this multiple dosing, the additional blood samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 10 and 12 hr after the 8th and 20th dosing. Blood samples were collected at 12, 14, 15, 18, 20 and 36 hr after the last dose.

A constant rate intravenous infusion using a TERUFUSION Syringe Pump (Model: STC 531, TERMO Ltd.) was used to administer a 1.27 mg/hr nicardipine dose for 3 hr into the subject’s left arm. Venous blood samples were collected from the right arm in heparinized glass tubes at 0, 0.2, 0.5, 1.0, 1.5, and 2.0 hr after the start of infusion, and then at 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 10.0, 12.0, 16.0, 20.1, 24.1 and 28.1 hr after stopping infusion.

Plasma was separated from blood by centrifugation, and was kept frozen at −20°C until analysis.

Analytical Method
Plasma concentrations of nicardipine were analyzed by a capillary column GC-ECD procedure11. The sensitivity was 1 ng/ml.

Data Analysis

Intravenous Data
Plasma data were analyzed by a computer program, MULTI12.

1) Bolus infusion Data
The plasma concentrations of nicardipine following bolus injection were fitted to bi-exponential equation (1).

\[ C_t = A_1 \cdot \exp (-\alpha \cdot t) + A_2 \cdot \exp (-\beta \cdot t) \] .................................................. (1)

\( C_t \) represents plasma nicardipine concentration at time \( t \). \( A_1 \) and \( A_2 \) are the hybrid constants, and \( \alpha \) and \( \beta \) are the hybrid constants.

2) Constant rate infusion Data
For constant rate infusion13 plasma concentrations of nicardipine were fitted to tri-exponential equations (2) and (3).

\[ C_t = K_0 [A/\alpha \cdot (1 - \exp (-\alpha \cdot t)) + B/\beta \cdot (1 - \exp (-\beta \cdot t)) + C/\gamma \cdot (1 - \exp (-\gamma \cdot t))] \] .................................................. (2)

During infusion

\[ C_t = K_0 [A/\alpha \cdot (1 - \exp (-\alpha \cdot t)) + B/\beta \cdot (1 - \exp (-\beta \cdot t)) + C/\gamma \cdot (1 - \exp (-\gamma \cdot t))] \] .................................................. (2)

The A, B and C are hybrid constants, and \( \alpha \), \( \beta \) and \( \gamma \) are hybrid constant. \( K_0 \) represents the infusion rate.

Postinfusion

\[ C_t = K_0 [A/\alpha \cdot \exp (-\alpha \cdot t) \cdot (\exp (-\alpha \cdot T) - 1) + B/\beta \cdot \exp (-\beta \cdot t) \cdot (\exp (-\beta \cdot T) - 1) + C/\gamma \cdot \exp (-\gamma \cdot t) \cdot (\exp (-\gamma \cdot T) - 1)] \] .................................................. (3)

with \( T \) the infusion time.

Oral Data
Rate constants were calculated using a semilogarithmic plot of plasma nicardipine concentrations.

Calculation of Absorption Rate and Reconstruction of Plasma Nicardipine Concentration-Time Profile after Single Oral Dosing from Intravenous Data
Bolus intravenous injection data and oral single dose data were analyzed using deconvolution analysis15 to calculate absorption rates. However, long intervals between sampling times are inadequate for this analysis. To make up for these long intervals, the SPLINE function program16 was used and the interval between the sampling points was reassigned as every 0.1 hr. Using the absorption rate during the absorption phase, the convolution analysis program17 was used to reconstruct simulation curve of the protracted rate constant at terminal phase of oral single dose.

Calculation of Bioavailability
AUC was calculated by the trapezoidal rule. Assuming the pharmacokinetics of nicardipine is linear, the absolute bioavailability was calculated using equation (4).

\[ F = \frac{AUC_{PO} \cdot Dose_{IV}}{AUC_{IV} \cdot Dose_{PO}} \] .................................................. (4)

Results and Discussion
The plasma nicardipine concentration vs. time curve after a bolus 1.05 mg injection is shown in Fig. 1. Nicardipine levels in plasma were below the detection limit at 4 hr after administration. A steep log linear decline was obtained from 0.12 to 1 hr. After that, a more protracted decay was observed from 1 to 3 hr. A good fit was obtained to the bi-exponential equation (1) by the Damping–Gauss–Newton method (weighting was 1/Cp²). A value was 2.92 hr⁻¹ for \( \alpha \) and 0.148 hr⁻¹ for \( \beta \). These data are in agreement with other reports6,8.

A plasma profile after a single oral dose of Perdipine LA® 40 mg (as nicardipine hydrochloride) capsule is shown in Fig. 2. This graph was made up for using SPLINE function every 0.1 hr⁻¹. The calculated line represents a good fitting. Two peaks were observed. The first peak appeared at 0.5 hr and the second 4 hr after administration. This phenomenon can be explained by the difference in absorption rates between the two type of granules which are dissolved in either the stomach or intestine14. A semilogarithmic plot of plasma concentrations from 4 to 24 hr displayed a two-phase
The hybrid constants in the terminal phase were 0.264 hr\(^{-1}\) and 0.0221 hr\(^{-1}\). From the reported single dose data\(^{18}\) of Perdipine LA\(^{\circ}\) capsule, the rate constant during the two-decline terminal phase were calculated. The hybrid constants during the terminal phase were 0.868 and 0.0613 hr\(^{-1}\). These parameters are in agreement with our obtained parameters. Using deconvolution analysis, the absorption rate was calculated (Fig. 3). In human studies, it is next to impossible to set up sufficiently frequent blood sampling points in order to get accurate pharmacokinetic parameters, however frequent blood sampling points were obtained. In particular, frequent blood sampling points during absorption phase are very important. These blood sampling points, however, provided insufficient data to use in deconvolution analysis, in spite of such frequent sampling for a human study. Deconvolution analysis also requires constant sampling intervals. Therefore, the SPLINE function was used to make up for the insufficient and irregular blood sampling intervals, and the each assigned time interval was 0.1 hr\(^{-1}\). In the initial phase, two absorption rate peaks were observed. The calculated absorption rate from 8.5 to 10 hr was 0. Thereafter absorption rate appeared to increase again after 10 hr. From in vitro dissolving tests, Perdipine LA\(^{\circ}\) capsules dissolve completely by 8 hr\(^{18}\). Therefore absorption exhibited beginning at 10 hr, was thought to be \(\gamma\)-phase.

A time course curve of the plasma nicardipine concentration vs. time after multiple oral doses is shown in Fig. 4. A plateau level was reached at 4th dose. The steady-state minimum plasma concentrations were maintained at about 4–9 ng/ml. Plasma nicardipine profile within the 8th dosing interval showed one peak of concentration 39.2 ng/ml. For the 20th dose, plasma concentrations showed two peaks: a first peak was 31.6 ng/ml and a second 25.9 ng/ml. Differential absorption due to vary granule signs can explain one peak at a first dosing interval. However, the double peak of the 20th have been due to food effect since no control was made for food for the multiple dose regimen. The semilogarithmic plot of the plasma concentrations vs. time at the last dose from 12 to 36 hr showed a two phase decline and hybrid constants were 0.138 hr\(^{-1}\) and 0.0414 hr\(^{-1}\). The values were closely similar to these obtained for the terminal phase of single oral dose.

Plasma nicardipine concentration at 1.27 mg/hr for 3 hr is shown in Fig. 5. After infusion stopped, the concentrations declined rapidly from 3 to 7 hr as was seen in the bolus injection. Subsequently, a more protracted
A good fit of the data was obtained to the tri-exponential equations (equation (2) and (3)) by Damping–Gauss–Newton method (weighting was 1/Cp^2).

A comparison of hybrid constants after intravenous administration of bolus and constant rate infusion is shown in Table I. The γ-value was about 1/5 that of the average β. In another report at a higher dose of 5 mg/hr for 3 hr reported only a bi-exponential decay was observed. However, that study measured plasma concentrations for only 7 hr which would have been insufficient to detect the γ-phase. Therefore, λ–phase might have been found if more plasma samples had been taken as in our study. This γ-value was very close to the protracted rate constants which were observed after oral administration.

To confirm the γ-phase during the terminal phase after oral dosing, the plasma nicardipine concentration-time profile of single oral dose was reconstructed by convolution analysis. The absorption rate from 0 to 8.5 hr, which was calculated by deconvolution analysis, was used as absorption phase data. In the presence and absence of γ-phase, the profiles were different (Fig. 6).

Table I Comparison of rate constants between a bolus injection and constant infusion

<table>
<thead>
<tr>
<th>Dosing Style</th>
<th>A(A1)</th>
<th>B(A2)</th>
<th>C</th>
</tr>
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<tbody>
<tr>
<td>Bolus Injection</td>
<td>39.9±4.59</td>
<td>2.14±1.05</td>
<td>n.d. a)</td>
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<tr>
<td>Constant Infusion</td>
<td>0.0731±0.00603</td>
<td>0.00286±0.00233</td>
<td>0.00108±0.000131</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing Style</th>
<th>α</th>
<th>β</th>
<th>γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus Injection</td>
<td>2.92±0.386</td>
<td>0.148±0.183</td>
<td>n.d. a)</td>
</tr>
<tr>
<td>Constant Infusion</td>
<td>3.61±0.524</td>
<td>0.652±0.331</td>
<td>0.0463±0.00672</td>
</tr>
</tbody>
</table>

Dimensions of A(A1), B(A2), C are ng/ml, and α, β, γ are hr⁻¹.

Figures represent fitting values±S.D.

a) γ–phase was not detected due to the sensitivity.
used. The C value (the hybrid constant for the y-value when assuming tri-exponential decay) was estimated as 0.313 ng/ml by the smallest sum of square division (weight was 0) from the bolus intravenous injection data. Only in the presence of the y-value, the remarkable biphasic terminal phase was observed. This result explained the rate constant which was not observed during the absorption phase.

Nicardipine has an arterial vasodilator properties in the brain\(^1,2\). Slow transfer into the brain and slow back diffusion from cerebrospinal fluid (CSF) might explain the appearance of the y-phase only for the constant rate infusion and for the oral dosing. Nicardipine concentration in CSF have not been reported.

Wagner\(^5\) reported that the elimination phase after oral administration was linear with 30 mg to 120 mg nicardipine a day as a hydrochloride salt. On the other hand it was reported that similar clearance values were obtained at two levels of bolus dose injection (0.01 mg/kg and 0.02 mg/kg)\(^3\). Steady-state average plasma concentrations (40 to 150 mg as hydrochloride salt a day) were shown to exhibit linear kinetics\(^10\). In this study, each a value and b value were roughly equal whether 1.05 mg bolus injection or constant rate infusion at 1.27 mg for 3 hr. The ratio of \(\text{AUC}_{0\rightarrow\infty}\) at a single PO dose to \(\text{AUC}_{\text{Dosing Interval}}\) at multiple doses was about 1. Therefore, the pharmacokinetics of nicardipine was assumed to be linear.

Bioavailability values calculated by equation (4) are listed on Table II. Area values calculated for bolus injection data (about 20%) represented twice those for constant rate infusion data. In the case of nicardipine bolus injection, the low sensitivity of the assay failed to detect the y-phase. In order to detect the y-phase after bolus injection, the dose would have to be high. A high-dose nicardipine bolus injection produces side effects, which are flushing and palpitation\(^4\). Therefore, high dose bolus injection is very dangerous and has to be avoided. It is no report that the presence or absence of a y-phase misleads estimation of bioavailability data. However, when the human bioavailability studies are performed for nicardipine, it is important to administer nicardipine solution using constant rate infusion which can avoid the dangerous side effects of bolus injection yet still provide detection of the "y-phase".

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**Table II** Bioavailability calculated by \(\text{AUC}_{\text{PO}}/\text{AUC}_{\text{IV}}\) correcting for dose

<table>
<thead>
<tr>
<th>Dosing Style</th>
<th>Single Dose</th>
<th>First Interval</th>
<th>Second Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus Injection</td>
<td>20.9%</td>
<td>21.7%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Constant Infusion</td>
<td>11.8%</td>
<td>12.2%</td>
<td>9.81%</td>
</tr>
</tbody>
</table>

Single Dose means \(\text{AUC}_{\text{PO}}(0\rightarrow\infty)\) at a single dose.
First Interval is \(\text{AUC}_{\text{PO}}(\text{Dosing Interval at 1st dose})\) at multiple doses.
Second Interval is \(\text{AUC}_{\text{PO}}(\text{Dosing Interval at 2nd dose})\) at multiple doses.
AUC is calculated by the trapezoidal rule.
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References


