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PHARMACOKINETICS OF NILVADIPINE AFTER MULTIPLE ORAL DOSING TO STEADY-STATE

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ABSTRACT

Forty-four healthy male volunteers were randomly assigned to receive one of four dosing regimens: placebo or a dose of 6, 8, 10 or 12 mg of nilvadipine administered at 0, 7 and 14 hr each day for 19 doses over seven days. There was a proportional relationship between the maximum plasma concentration of nilvadipine after the first dose and the last dose and the dose administered. There was also a proportional relationship between the area under the plasma concentration-time curve during the last dosing interval and the administered dose. Results showed that there was no accumulation of drug in plasma at steady-state. In addition, there was no dose-dependency in the oral clearance, elimination rate constant or terminal elimination half-life

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values. The pharmacokinetics of nilvadipine are linear upon multiple dosing over the dosing range studied.

Introduction

Nilvadipine (3-Methyl 5-(1-methylethyl) 2-cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate) is a 1,4-dihydropyridine calcium channel blocker structurally similar to nifedipine. The pharmacokinetics of nilvadipine were linear in healthy subjects after receiving single doses of 2, 4 or 6 mg of the drug given as a tablet formulation (1). In another study (2), where subjects received single doses of 4, 8, 12, 16 or 20 mg given as the same tablet formulation as that used in the previous study (1), the pharmacokinetics of nilvadipine appeared to be nonlinear at doses exceeding about 12 mg. In a study where the same dose of nilvadipine (16 mg) was given at different rates as an oral solution, the area under the concentration-time curve (AUC) from time-zero to time-infinity ($AUC_{0\rightarrow\infty}$) in subjects after a single dose 16 mg dose was twice that in subjects receiving the 16 mg oral dose of the drug administered as divided doses (3). The pharmacokinetics of nilvadipine, therefore, may depend on dose and dosing rate. The purpose of this study was to determine the pharmacokinetics of nilvadipine at steady-state using dosing regimens of 6, 8, 10 or 12 mg given three times a day, given as a tablet formulation used in previous single dose studies (1,2).

Materials and Methods

Subjects:

Forty-four male volunteers were enrolled in this study after giving written informed consent, in accordance with the research review and ethics committee at Guy's Drug Research Unit, Guy's Hospital Medical School, London, England. Of the 44 subjects enrolled in this study, 32 were randomized to receive active drug and the other 12 received placebo. The demographic data for the subjects that received nilvadipine and placebo are listed in Table 1. All subjects were confirmed to be in good health by physical examination, medical history and clinical laboratory tests performed on initial entry and just prior to study initiation. They were not on chronic prescription or over-the-counter drug therapy, had no history of alcoholism, and had not participated in another investigational drug research study within the previous 90 days. Subjects were institutionalized from 12 hr before drug administration and until 24 hr after the final dose. All subjects were assessed for safety throughout the study period.

Drug Administration:

The 44 subjects were randomly assigned to one of four groups: 6, 8, 10 or 12 mg of nilvadipine, or placebo, where each treatment was given at time 0, 7 and 14 hr each day for a total of

Table I Demographics and Mean Pharmacokinetic Parameters of Nilvadipine in Subjects Receiving 6, 8, 10 or 12 mg of Nilvadipine Three Times a Day for 19 Doses[a]

	Dose Level			
	6 mg	8 mg	10 mg	12 mg
Demographics[a]				
Age (yr)	22.0 ± 3.0	23.1 ± 2.4	23.3 ± 3.8	23.9 ± 4.4
Weight (kg)	74.9 ± 10.5	70.0 ± 7.7	76.6 ± 11.2	76.9 ± 9.5
Height (cm)	177 ± 8	176 ± 5	179 ± 4	183 ± 9
Pharmacokinetic Parameters				
C_{max} (ng/ml)				
Dose 1	3.59 ± 1.25	7.39 ± 1.96	9.18 ± 6.37	13.5 ± 6.0
Dose 19	3.62 ± 1.90	7.76 ± 5.60	6.69 ± 4.13	9.27 ± 5.18
Ratio (19/1)	1.14 ± 0.68	0.998 ± 0.625	0.808 ± 0.425	0.855 ± 0.647
C_{min} (ng/ml)				
Dose 1	0.290 ± 0.144	0.596 ± 0.180	0.579 ± 0.252	0.836 ± 0.326
Dose 19	0.610 ± 0.252	1.02 ± 0.42	0.843 ± 0.310	1.27 ± 0.51
Ratio (19/1)	2.17 ± 0.30	1.69 ± 0.26	1.53 ± 0.37	1.47 ± 0.37
t_{max} (hr)				
Dose 1	1.71 ± 0.49	1.57 ± 0.53	1.63 ± 0.52	1.75 ± 1.04
Dose 19	1.36 ± 0.63	1.57 ± 0.53	1.31 ± 0.59	1.75 ± 0.46
$AUC_{0\rightarrow7}$ (ng·hr/ml)				
Dose 1	7.11 ± 1.54	16.7 ± 4.7	16.5 ± 6.9	26.4 ± 11.1
Dose 19	10.6 ± 4.0	18.6 ± 8.6	15.7 ± 6.6	25.1 ± 11.8
Ratio (19/1)	1.50 ± 0.51	1.08 ± 0.37	0.952 ± 0.256	1.03 ± 0.41
t_{lag} (hr)				
Dose 1	0.50 ± 0.29	0.29 ± 0.27	0.38 ± 0.23	0.25 ± 0.38
$t_{½}$ (hr)	9.76 ± 3.50	10.2 ± 15.9	11.0 ± 3.0	13.9 ± 4.7
$Kx10^4$ (hr^{-1})	831 ± 402	760 ± 421	687 ± 245	544 ± 163
CL_0 (l/hr)	560 ± 270	510 ± 298	745 ± 309	557 ± 195

[a] The mean age, weight and height for subjects who received placebo were 22.6 ± 2.3 yr, 73.4 ± 12.5 kg and 177 ± 8 cm, respectively.

19 doses. In each group, eight subjects received nilvadipine and three received placebo. Ten mL blood samples were collected into heparinized tubes prior to (0 hr) and at 0.5, 1, 2, 4 and 7 hr following the morning dose on days one and seven. On day seven following the last (19th) dose, additional blood samples were taken at 12, 15, and 24 hr. In addition, trough (predose) blood samples were taken on days 2, 3, 4, 5 and 6. The harvested plasma was stored frozen at -20°C until analysis. All subjects were re-evaluated for safety at the end of the study on day seven.

Analytical Methods:

Plasma concentrations of nilvadipine were determined using a high resolution capillary gas chromatographic method with electron-capture detection (4). Linearity of this assay method was observed over the plasma concentration range of 0.1 to 20.0 ng/ml with coefficients of variation always less than 10%. All plasma samples found upon initial assay to exceed 20 ng/ml were diluted with drug-free human plasma and reassayed.

Pharmacokinetic Analysis:

Pharmacokinetic parameters were determined using classical model-independent methods (5). The pharmacokinetic parameters determined included: the area under the plasma concentration-time

curve (AUC) from time-zero to 7 hr ($AUC_{0\rightarrow 7}$), the rate constant for the terminal phase (K), the terminal elimination half-life ($t_{\frac{1}{2}}$), the lag time (t_{lag}), the peak plasma concentration (C_{max}) for the first and final doses, the time to C_{max} (t_{max}), the plasma concentration at seven hours after each morning dose (C_{min}) and the oral clearance (CL_o) during the last dosing interval.

Plasma concentrations of nilvadipine observed after the last dose on day seven were compared to those predicted for the same subject using a simulation method employing the superposition principle (5). In this analysis, plasma concentrations observed after the first dose were used to predict those for the first seven hour for the subsequent 18 doses.

Statistical analysis:

Pharmacokinetic parameters for nilvadipine for the four dosing regimens studied were compared, where appropriate, using analysis of variance methods with $P<0.05$ levels taken for significance.

Results

Nilvadipine was safe and well tolerated by most subjects at doses up to 12 mg. Two subjects were withdrawn from the study because of adverse experiences that were considered to be drug-

related. One subject (6 mg Group) had light-headedness and headache during the first day of dosing, and another subject (8 mg Group) experienced some chest tightness and tachycardia after the first dose. Both subjects recovered rapidly with no sequelae. The most common drug related adverse events included headache, flushing, light-headedness, palpitations and transient ECG and laboratory changes. All were mild and resolved quickly without the need for any medication.

Mean concentrations of nilvadipine for each Group are shown in Fig. 1. After the 19th dose, there was a distinct distribution phase after attaining the C_{max} value. This phenomenon was also observed in the data from each subject (not shown). Mean pharmacokinetic parameters for nilvadipine are listed in Table 1. The C_{max} and $AUC_{0\rightarrow 7}$ values after the first and last dose (Dose 19) increased proportionally with dose (Fig. 2 and Table 1). The dose-adjusted $AUC_{0\rightarrow 7}$ after the first dose in the 6 mg Group was significantly ($P<0.05$) smaller than for the 8, 10 or 12 mg Groups. There was no apparent accumulation of nilvadipine in plasma at steady-state as indicated by the ratio of C_{max}, C_{min} or $AUC_{0\rightarrow 7}$ values after dose 19 to the respective parameters after dose 1. There was no dose-dependency in CL_O, K or $t_{\frac{1}{2}}$ at any of the dose levels studied. There was only a small t_{lag} in the absorption of nilvadipine after each dose level.

In general, there was an excellent correspondence between observed and predicted $AUC_{0\rightarrow 7}$, C_{max} and C_{min} values (Table 2).

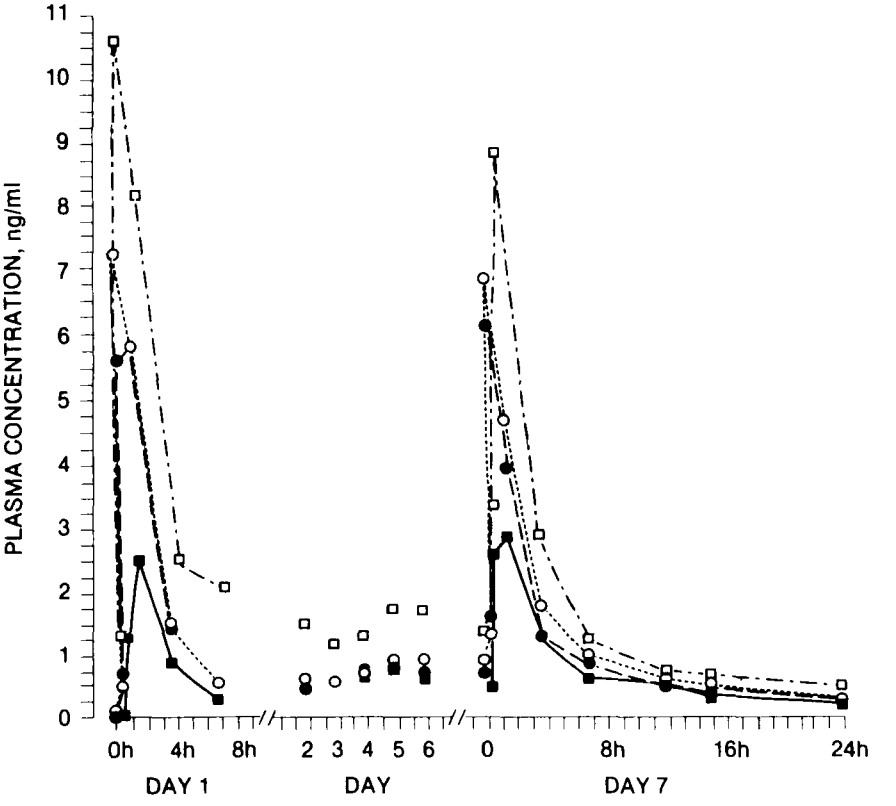

FIGURE 1

Mean plasma concentration-time profiles of nilvadipine in healthy human subjects after receiving 6 (■), 8 (●), 10 (o) or 12 mg (□) doses three times daily for 19 doses.

The predicted $AUC_{0\rightarrow 7}$ values for the 6 mg Group were significantly smaller ($P<0.05$) than the observed $AUC_{0\rightarrow 7}$ values; otherwise, there were no significant differences ($P>0.05$) in $AUC_{0\rightarrow 7}$ values between the predicted and observed values for the 8, 10 or 12 mg Groups. There were no significant differences ($P>0.05$) in C_{max} values between the observed and predicted values for all dose levels

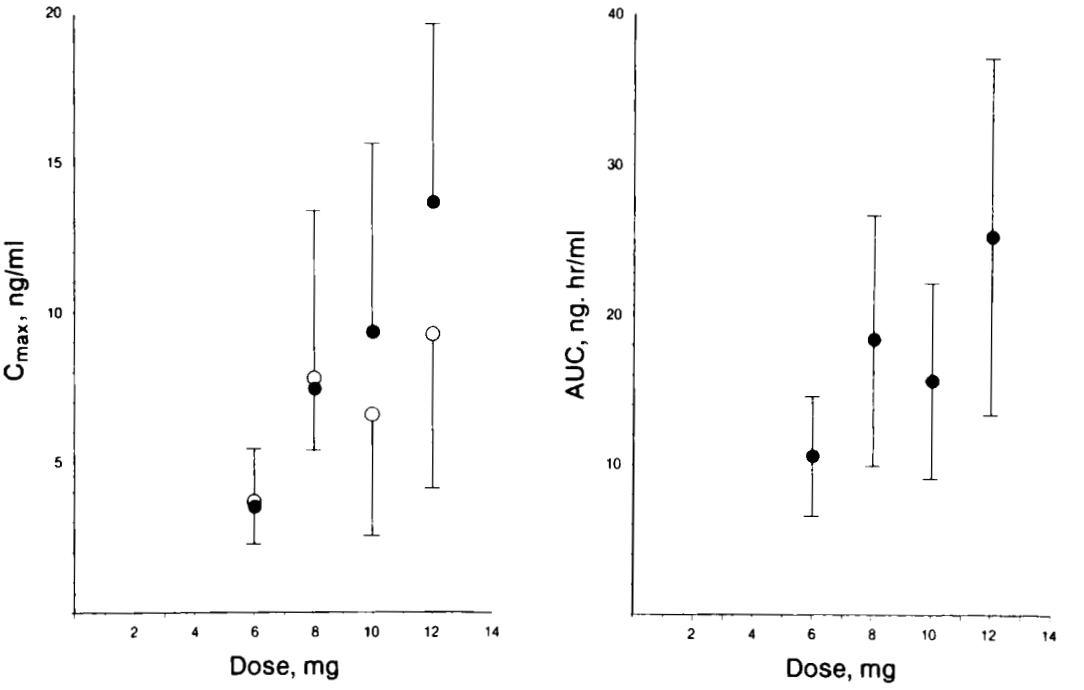

Figure 2

Nilvadipine C_{max} (Left panel) after the first (●) or the last dose (o) as a function of dose and AUC_{0-7} (Right panel) after the last dose as a function of dose.

studied. There was a small but significant ($P<0.05$) difference between predicted and observed C_{min} values for all dosing Groups.

Discussion

Nilvadipine was safe and generally well tolerated at dose levels ranging from 6 to 12 mg given three times a day to steady-state. Although drug-related adverse effects were observed in

Table II Observed and Predicted Ratios of $AUC_{0\rightarrow 7}$, C_{max}, C_{min} Based on Dose 19:Dose 1 Values[a]

	Dose 19/Dose 1 Ratio					
	$AUC_{0\rightarrow 7}$, ng·hr/ml		C_{max}, ng/ml		C_{min}, ng/ml	
Dose mg	Observed	Predicted	Observed	Predicted	Observed	Predicted
6	1.50 ± 0.51[b]	1.08 ± 0.03	1.14 ± 0.68[c]	1.03 ± 0.02	2.17 ± 0.30[b]	1.11 ± 0.01
8	1.08 ± 0.37[c]	1.07 ± 0.01	1.00 ± 0.63[c]	1.03 ± 0.01	1.69 ± 0.26[b]	1.11 ± 0.005
10	0.97 ± 0.25[c]	1.07 ± 0.02	0.81 ± 0.43[c]	1.03 ± 0.01	1.53 ± 0.37[b]	1.11 ± 0.01
12	1.03 ± 0.41[c]	1.07 ± 0.04	0.86 ± 0.65[c]	1.03 ± 0.01	1.31 ± 0.58[b]	0.99 ± 0.39

[a] Predicted from simulated concentration-time profiles based on the principle of superposition.
[b] Statistically different from the predicted value, $p<0.05$.
[c] Not statistically different from the predicted value, $p>0.05$.

some individuals, they were mild, self-limiting, and typical of those seen with other calcium channel blockers like nitrendipine (6), nisoldipine (7), and nifedipine (8-10). The dose-adjusted $AUC_{0\rightarrow 7}$ after the first dose for the 6 mg Group was significantly ($P<0.05$) smaller than for the 8, 10, and 12 mg Groups. However, at steady-state, there were no differences in the dose-adjusted $AUC_{0\rightarrow 7}$ values among the four Groups. The t_{lag} value for the 6 mg Group was significantly longer ($P<0.05$) than that for any of the other Groups. Since the t_{lag} would reduce the AUC value for the first dosing interval but does not affect the AUC during a dosing interval at steady-state (11), the differences in dose normalized $AUC_{0\rightarrow 7}$ values between the 6 mg Group and those of the other Groups could have been due to the somewhat longer t_{lag} in the 6 mg Group.

As shown by the dose 19/dose 1 ratios for $AUC_{0\rightarrow 7}$, C_{max} and C_{min} values in Table 1, there was no substantial accumulation nor any diminution in concentrations of nilvadipine in plasma at steady-state. Since the dosing intervals were different among the three doses administered on each day (0, 7 and 14 hr, respectively), theoretically, the accumulation of drug could not be readily predicted by simple pharmacokinetic equations. Instead, the accumulation of drug at steady-state was reasonably well predicted by simulating the concentrations of drug after dose 19 by using the principle of superposition (5). The simulations suggest that there would be no substantial accumulation of drug in plasma at steady-state based on the predicted dose 19 to dose 1

ratios of $AUC_{0\rightarrow7}$, C_{max} and C_{min} (Table 2). The values of the predicted ratios were comparable to those observed, although predicted C_{min} ratios for all dosing Groups and the predicted $AUC_{0\rightarrow7}$ ratio for the 6 mg Group were statistically significantly smaller ($P<0.05$) than those observed (Table 2). Since the principle of superposition assumes linear pharmacokinetics (5), the good agreement between the observed data and that predicted suggests that the pharmacokinetics of nilvadipine are linear in the dosing range used in the present multiple dose study.

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