The bioavailability and pharmacokinetics of slow release nifedipine during chronic dosing in volunteers

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- 1 Eight healthy volunteers received slow release nifedipine 20 mg 12 hourly, for six doses.
- 2 A nifedipine pharmacokinetic profile was performed after the fifth dosing interval using 12 sampling times over 12 h. A specific high pressure liquid chromatography (h.p.l.c.) nifedipine assay was used.
- 3 Six of the volunteers subsequently received an i.v. infusion of 3.5 mg of nifedipine after an identical period (five dosing intervals) of chronic oral dosing with slow release nifedipine 20 mg 12 hourly. An identical pharmacokinetic profile was performed after the infusion.
- 4 Bioavailability, clearance (CL), apparent volume of distribution (V), apparent half life ($t_{1/2}$) and area under the curve (AUC) were calculated.
- 5 The geometric mean apparent $t_{1/2}$ for the slow release preparation was 6.3 ± 2.0 h. In the six volunteers, the mean bioavailability was 46% (range 29–86%), the mean CL was 588.0 ± 67.1 ml min⁻¹, the mean apparent V was 160.1 ± 61.7 l.
- 6 The pharmacokinetics of slow release nifedipine during chronic dosing appear similar to those derived from single dose studies.

Keywords slow release nifedipine pharmacokinetics bioavailability volunteers

Introduction

There are very few data concerning the pharmacokinetics of slow release nifedipine (Taburet *et al.*, 1983; Raemisch & Sommer, 1983). Some of these studies have used a gas liquid chromatography (g.l.c.) assay which is not specific for nifedipine. Waller *et al.* (1984), using a discriminative h.p.l.c. assay have compared the pharmacokinetics of single doses of nifedipine given i.v. and orally as biphasic release tablets. These tablets contain both conventional (fast) release and slow release nifedipine.

We have studied the pharmacokinetics of slow release nifedipine during chronic dosing for several reasons. First, chronic dosing is used clinically. Second, for other calcium antagonists such as verapamil, a marked change in pharmacokinetics is seen during chronic dosing (Buhler *et al.*, 1982). Finally, with a slow release preparation, apparent $t_{1/2}$ is in part determined by sampling

time and therefore, during chronic dosing studies, sampling over only 12 h should yield longer apparent $t_{1/2}$ values which could be more relevant to the clinical situation where dosing occurs every 12 h than values calculated from sampling over 32 or 48 h (Taburet *et al.*, 1983; Waller *et al.*, 1984).

Methods

Eight healthy volunteers (four males) aged 21–34 years and weighing 52–86 kg received slow release nifedipine at a dose of 20 mg, 12 hourly for a total of six doses (up to and including 09.00 h on day 4) as part of a theophylline/nifedipine interaction study (Jackson *et al.*, 1986). On the day of the study, starting at 09.00 h, blood samples were taken at 0, 10, 20, 40 min, 1, 1.5, 2,

3, 4, 6, 8, and 12 h after dosing for determination of serum nifedipine concentrations.

Six of the eight volunteers (four males) were subsequently given an i.v. infusion of 3.5 mg of nifedipine (0.1 mg ml^{-1} , 35 ml over 3.5 min) after an identical period of chronic oral dosing (five doses of 20 mg slow release nifedipine). The infusion was given using opaque tubing and syringes. Blood samples were taken before and at 0, 5, 10, 20, 40 min and 1, 1.5, 2, 3, 4, 6, 8 and 12 h after the end of the infusion.

Aliquots of plasma (2 ml) were transferred to glass vials, $50 \mu\text{g l}^{-1}$ internal standard (nitrendipine, $3 \mu\text{g l}^{-1}$ in ethanol), 1 ml of 1 M sodium hydroxide and 5 ml of hexane/diethyl ether (1:1) were added to each sample. The tubes were capped and placed on a blood mixer for 15 min and then centrifuged for 10 min. The ether layer was removed to another vial and evaporated to dryness at 45°C under a stream of nitrogen. The residue was dissolved in $200 \mu\text{l}$ of methanol/water (60/40) and transferred to an h.p.l.c. vial. Separation of nifedipine, nitrendipine and B4759 was carried out using a $\mu\text{bondapak C18}$ column ($30 \text{ cm} \times 4.6 \text{ mm}$) with a mobile phase of methanol/water (45/55) and a flow rate of 2 ml min^{-1} . The retention times were 6, 12 and 4 min, respectively. The compounds were detected at 236 nm using a Kratos 773 u.v. detector set at 0.004 AU full scale deflection. All manipulations and standards were carried out under sodium or gold fluorescent light. The concentration of nifedipine in the plasma was determined by measurement of the peak height ratio of nifedipine to nitrendipine, and comparison to known standards added to control plasma and analysed with each batch of samples.

The height of the nifedipine peak approximated to 1.5 mm ng^{-1} and 95% confidence limits for day-to-day variation were better than $\pm 5\%$ for values above $10 \mu\text{g l}^{-1}$ and $\pm 1 \mu\text{g l}^{-1}$ for values less than $10 \mu\text{g l}^{-1}$. The detection limit was $2 \mu\text{g l}^{-1}$ and blank plasma contained only traces of interfering material below the detection limit.

Blank plasma samples frequently contained peaks which interfered with B4759 and no attempt was made to quantify this metabolite (Wickham Laboratories, Winchester Road, Wickham, Sareham, Hampshire PO17 5AU).

All blood and serum samples were handled in sodium light or in foil wrapped containers when exposed to daylight or tungsten light. $\text{AUC}(0-12 \text{ h})$ after oral dosing and $\text{AUC}(0-\infty)$ after i.v. dosing were calculated using the trapezoidal rule. This latter value was corrected for nifedipine present at the start of the infusion using the equation $\text{AUC}(0-\infty) \text{ corrected} = \text{AUC}(0-\infty) \text{ calculated} - \text{Co}/\lambda_z$, where $\text{Co} =$

serum concentration of nifedipine at the start of the infusion and $\lambda_z =$ elimination rate constant (i.v.). The use of the i.v. λ_z may underestimate the portion of AUC attributable to the oral preparation and therefore, underestimate the bioavailability of the formulation. However, we did not feel justified in using the theoretically more correct λ_z oral to correct the i.v. AUC since the measurement of λ_z was based only on 12 h sampling and should be viewed with caution. From these concentration time profiles bioavailability, clearance, apparent $t_{1/2}$, apparent V and $\text{AUC}(0-12)$ were calculated using STRIPE, an interactive curve stripping program (Johnston & Woollard, 1983). In order to reduce further the sum of squares for the pharmacokinetic model, nifedipine concentration time profiles were subsequently analysed using a non-linear regression program (SIMP) (Johnston, 1985) to optimise the parameters in the equation that had been derived using STRIPE. Student's paired t -test was used to compare the serum concentrations of the drug at time 0 and 12 h.

Results

The mean peak serum concentration of nifedipine was $61.4 \pm 21.9 \mu\text{g l}^{-1}$ and occurred at a median time of 90 min (range 40 min–3.0 h) after oral dosing (Figure 1). Trough concentrations at 0 h and 12 h were 10.6 ± 7.8 and $13.5 \pm 13.3 \mu\text{g l}^{-1}$, respectively. They were not statistically different ($t = 0.83$, $P > 0.4$). Marked interindividual variation was seen in all the derived pharmacokinetic variables (Table 1). This was particularly so for apparent $t_{1/2}$. In the six subjects who had an i.v. infusion, the mean bioavailability was $46 \pm 21\%$.

Discussion

This is the first report of the pharmacokinetics of slow release nifedipine tablets during chronic dosing. After single doses of 20 mg of a biphasic mixture of conventional and slow release nifedipine in six volunteers a bioavailability of $43 \pm 10\%$ has recently been reported (Waller *et al.*, 1984). Our mean $\text{AUC}(0-12)$ ($300.1 \pm 146.4 \mu\text{g l}^{-1} \text{ h}$) was very similar to the single dose $\text{AUC}(0-\infty)$ of $298 \pm 137 \mu\text{g l}^{-1} \text{ h}$ reported by Waller *et al.* (1984). This suggests that bioavailability is similar during chronic dosing and after single doses. A previous report of a mean $\text{AUC}(0-\infty)$ value of $537 \pm 105 \mu\text{g l}^{-1} \text{ h}$ after a single dose of 20 mg of slow release nifedipine in eight hypertensives (Taburet *et al.*, 1983) suggests that the g.l.c. assay method used was not specific and was measuring total nifedipine and B4759.

Figure 1 Mean ($\pm$ s.e. mean) concentration-time profile for eight volunteers during oral chronic dosing with slow release nifedipine 20 mg 12 hourly.

Table 1 Individual, mean and standard deviation (s.d.) values for the derived pharmacokinetic variables: clearance (CL), apparent volume of distribution (V), bioavailability (F) (in six subjects), elimination half-life i.v. ($t_{1/2}$ (iv)) and apparent oral elimination half-life ($t_{1/2}$ (oral)) after nifedipine. Arithmetic means are shown with the exception of $t_{1/2}$ (oral) where the geometric mean is shown

Volunteer	CL (ml min ⁻¹)	V (l)	F	$t_{1/2}$ (iv) (h)	$t_{1/2}$ (oral) (h)
1	536.7	116.2	0.29	2.5	2.9
2	620.0	161.0	0.42	3.0	3.3
3	687.6	261.6	0.46	4.4	3.6
4	552.7	203.8	0.86	4.3	41.0†
5	507.8	121.2	0.45	2.8	5.0
6	63.2	101.8	0.30	1.9	3.4
7	304.0*				10.0
8	634.0*				18.2
Mean	558.3	160.9	0.46	3.2	6.3
s.d.	118.4	61.7	0.21	1.0	2.0

*Subjects 7 and 8: clearance of oral preparation, corrected using mean bioavailability.

†Approximate value.

The apparent elimination half-life for a slow release preparation is governed by the interplay of three main factors: the release characteristics of the preparation, the gastrointestinal transit time and the duration of the blood sampling period. The longer the sampling period, the more likely the apparent $t_{1/2}$ is to approach the true $t_{1/2}$. Thus it would be expected that comparisons of apparent $t_{1/2}$ values derived here with those reported by others using sampling over different time intervals would yield different results. However using a 48 h sampling period (and non specific assay) after a single dose of 20

mg, Taburet *et al.* (1983) derived an apparent $t_{1/2}$ of 10.8 h whereas Waller *et al.* (1984), sampling for 30 h after a single dose of a biphasic preparation of 20 mg derived an apparent $t_{1/2}$ of 5.4 h. The trough concentrations at 0 and 12 h were not significantly different suggesting (but not proving) that steady state had been reached, volunteer compliance was good and that no circadian variation in trough concentrations occurred.

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References

- Buhler, F. R., Hulthen, U. L., Kiowski, W., Muller, F. B. & Bolli, P. (1982). The place of the calcium antagonist verapamil in antihypertensive therapy. *J. cardiovasc. Pharmac.*, **4** (suppl 3), S350-S357.
- Jackson, S. H. D., Shah, K., Debbas, N. M. G., Johnston, A., Peverel-Cooper, C. A. & Turner, P. (1986). The interaction between i.v. theophylline and chronic oral dosing with slow release nifedipine. *Br. J. clin. Pharmac.*, **21**, 389-392.
- Johnston, A. (1985). SIMP. a basic computer program for non linear curve fitting. *J. pharmac. Methods*, **14**, 323-329.
- Johnston, A. & Woollard, R. C. (1983). STRIPE: An interactive computer program for the analysis of drug pharmacokinetics. *J. pharmac. Methods*, **9**, 193-200.
- Raemisch, K. D. & Sommer, J. (1983). Pharmacokinetics and metabolism of nifedipine. *Hypertension*, **5** (suppl. II) II 18-II 24.
- Taburet, A. M., Singlas, E., Colin, J-N., Banzet, O., Thibonnier, M. & Corvol, P. (1983). Pharmacokinetic studies of nifedipine tablet. Correlation with antihypertensive effect. *Hypertension*, **5** (suppl. II) II 29-II 33.
- Waller, D. G., Renwick, A. G., Gruchy, B. S. & George, C. F. (1984). The first pass metabolism of nifedipine in man. *Br. J. clin. Pharmac.*, **18**, 951-954.

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