Br. J. clin. Pharmac. (1986), **22**, 565–570

The effects of food and posture on the pharmacokinetics of a biphasic release preparation of nifedipine

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1 The pharmacokinetics of a novel 20 mg biphasic release tablet of nifedipine were compared with the conventional 10 mg capsule and 20 mg sustained release preparations in healthy volunteers. The influence of food and posture on the pharmacokinetics of the biphasic tablet were studied.

2 In the fasting state, the time to peak concentration of nifedipine was not significantly different between the 20 mg biphasic and 20 mg sustained release tablets, but plasma concentrations were higher between 2 and 4 h after the biphasic tablet. The terminal elimination half-lives of the two formulations were similar.

3 In subjects who fed prior to nifedipine administration there was no significant difference between either the peak plasma concentration or terminal half-life of the biphasic tablet and two 10 mg capsules of nifedipine.

4 When the biphasic preparation was given after a standard breakfast, the time to peak plasma concentration was significantly longer and the terminal half-life shorter than when given in the fasting state.

5 The dissolution characteristics of the biphasic tablet were influenced by prior administration of food to an extent which may be of clinical significance during twice daily administration.

Keywords nifedipine pharmacokinetics food

Introduction

We have previously reported the pharmacokinetics of a novel 20 mg biphasic release formulation of nifedipine (Waller *et al.*, 1984). This formulation contains 5 mg rapid release and 15 mg sustained release components. We report here its comparative pharmacokinetics with existing 10 mg rapid and 20 mg sustained release formulations of nifedipine. The initial studies were carried out in two centres using different protocols and demonstrated discrepant results. Subjects studied in Dundee were fed prior to oral dosing and remained recumbent for longer periods than the subjects in Southampton who were studied fasting. Food may influence drug pharmacokinetics in several ways: drug absorption may be altered and compounds which undergo extensive first-pass extraction may show enhanced bioavailability if their liver metabolism is blood flow rate-limited (Melander & McLean, 1982). Adoption of an upright posture and exercise may both reduce hepatic blood flow, although the effects of these factors on the pharmacokinetics of drugs with hepatic blood flow dependent kinetics are not well understood (George, 1979). A further study was, therefore, carried out to determine the effects of food and

posture on the pharmacokinetics of the biphasic formulation.

Methods

Approval for the studies was obtained from the local ethics committee and each subject gave informed consent to the study. All subjects were male and had not received any medications for at least 2 weeks prior to the study. Four studies were undertaken and the treatments within each study were administered in a restricted randomised order.

(a) Six non-smoking subjects received single doses of a 20 mg sustained release tablet (Adalat Retard) and, on a separate occasion, the 5 + 15 mg biphasic tablet. For this study, carried out in Southampton, the subjects fasted for 12 h prior to and for 3 h after receiving the dose. The subjects lay on the right side for 1 h after administration of nifedipine, following which normal activity was permitted. Blood (10 ml) was withdrawn at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 30 h after dosing.

(b) Eight subjects, seven of whom were non-smokers, received the biphasic tablet and six of these, on another occasion, received two 10 mg capsules of nifedipine. In this study, performed in Dundee, subjects ate a light breakfast 30 min before administration of nifedipine. Subjects remained lying against the backrest on a bed for 4 h after dosing. Sampling times were as for study (a) but with the addition of a sample at 15 min.

(c) Eight subjects, six of whom were non-smokers, received an initial dose of the biphasic tablet and subsequently took twice daily doses of this preparation for 7 days with pharmacokinetic analyses being undertaken after the initial dose and the first dose on the morning of the seventh day. This study was also undertaken in Dundee using a similar protocol to (b) but with an additional blood sample taken at 10 h.

(d) Due to a discrepancy found in the data for the biphasic tablet in studies (a) and (b), an additional study was undertaken to investigate the influences of food and recumbency on its pharmacokinetics. In this study, which was performed in Southampton, eight non-smoking subjects were given a single dose of the biphasic formulation on three separate days, at least 1 week apart, either:
  (i) Fasting followed by 1 h recumbency
  (ii) Fasting followed by 4 h recumbency
  (iii) After a standard light breakfast followed by 4 h recumbency. Blood samples were taken as described under study (a).

Blood samples (10 ml) were anticoagulated with lithium heparin 10 u ml^{-1}, centrifuged immediately and the plasma was separated and stored at −20° C (protected from light) until analysis. Nifedipine analyses were carried out (with precautions to prevent photodegradation) in Southampton using an h.p.l.c. assay which allows measurement of both the parent drug and its nitropyridine metabolite (Waller *et al.*, 1984).

Due to the unusual absorption characteristics of the biphasic formulation, the data did not fit first order absorption into either a one- or two-compartment open model using the non-linear least squares regression analysis programme, NONLIN. Pharmacokinetic analysis of the data was restricted, therefore, to linear least squares regression analysis of the terminal phase of the plasma drug concentration-time curve, for calculation of the terminal half-life. The decision of the number of points incorporated into the terminal phase was made without knowledge of the treatment group. (An average of five points were included and gave an average log-linear correlation coefficient of 0.990). This apparent terminal half-life was largely derived from data up to 12 h, since in many cases the concentration at 24 h was close to or less than the limit of detection of the assay (0.5 ng ml^{-1}). The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule with extrapolation to infinity using the last data point and the slope derived by linear regression analysis. An average of only 5% of the AUC was derived from the period calculated by extrapolation. The peak concentration (C_{max}) and times to peak (t_{max}) are the observed values. Results are expressed as the mean ± s.d. Statistical analysis was by Wilcoxon's rank sum and signed rank tests and in study (d) also by the method of paired differences, according to Hills & Armitage (1979), to examine for treatment and order effects and for treatment-order interactions.

Results

Study (a) (Table 1) (Figure 1)

The plasma concentration-time curves for nifedipine were similar after both the sustained release and biphasic formulations. Despite wide interindividual differences, the plasma concentrations after the biphasic tablet were significantly higher at 2 and 3 h after administration but there

Table 1 Study (a) Comparative pharmacokinetics after 20 mg sustained release and 20 mg biphasic release formulation of nifedipine (mean ± s.d., $n = 6$)

	Sustained release	*Biphasic release*
C_{max} (ng ml^{-1})	37.9 ± 15.6	63.5 ± 36.6*
t_{max} (h)	1.8 ± 1.2	1.6 ± 0.2
AUC (ng ml^{-1} h)	255 ± 109	311 ± 155
Terminal half-life (h)	6.1 ± 3.0	4.3 ± 2.4

*$P < 0.02$
For abbreviations in this and subsequent Tables, see under Methods.

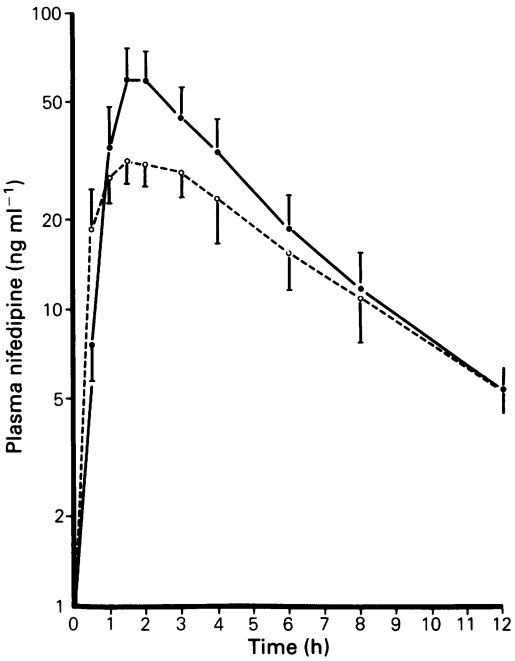

Figure 1 Plasma concentration-time curve for 20 mg sustained release (○) and 20 mg biphasic release (●) formulations of nifedipine in fasting subjects (mean ± s.d., $n = 6$).

were no significant differences in the time to reach maximum concentrations or the AUC values. The terminal half-life after the biphasic preparation (mean 4.3 h) was not significantly different from the sustained release formulation (mean 6.1 h) although the concentration at 24 h was significantly higher for the sustained release (3.0 ± 1.3 ng ml^{-1}) compared to the biphasic formulation (1.2 ± 0.2 ng ml^{-1}) ($P < 0.05$).

Study (b) (Table 2) (Figure 2)

The peak plasma concentration after the two capsules occurred earlier and was higher than

Table 2 Study (b) Comparative pharmacokinetics after two 10 mg capsules and 20 mg biphasic formulation of nifedipine (mean ± s.d.)

	Capsules (n = 6)	*Biphasic release* (n = 8)
C_{max} (ng ml^{-1})	96.7 ± 42.0	67.6 ± 21.4
t_{max} (h)	1.8 ± 1.1	2.7 ± 0.8
AUC (ng ml^{-1} h)	343 ± 98	269 ± 86
Terminal half-life (h)	2.6 ± 0.4	2.2 ± 0.4

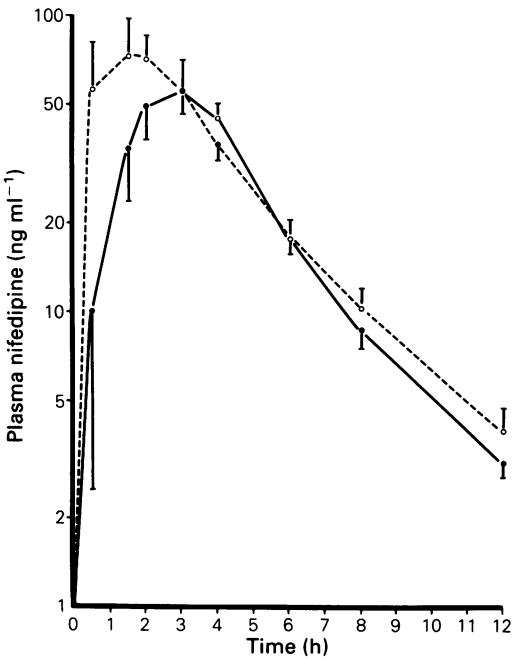

Figure 2 Plasma concentration-time curve for two 10 mg capsules (○) ($n = 6$) and 20 mg biphasic release (●) formulations ($n = 8$) of nifedipine following a light breakfast.

that seen with the biphasic formulation but the differences were not statistically significant. There were no significant differences in AUC after the two formulations.

Unexpectedly, the terminal half-life after the biphasic formulation was slightly shorter than after the capsules (mean 2.2 h and 2.6 h respectively). Comparison of the data in studies (a) and (b) showed that the half-life after the biphasic tablet was significantly ($P < 0.05$) shorter in study (b) than in study (a).

Study (c) (Table 3)

(i) Single dose of the biphasic tablet. The plasma concentration-time curves and pharmacokinetic data were similar to those found in the other study conducted in Dundee, i.e. study (b) and again the terminal half-life was shorter than in study (a).

(ii) After multiple dosing with the biphasic tablet. There were measurable concentrations of nifedipine in the pre-dose sample and the maximum concentration and AUC values calculated to infinity (295 ± 117 ng ml^{-1} h) were about 15% greater than after the single dose, although these differences were not statistically significant. The AUC calculated for the dosage interval (0–12 h) was similar to the AUC to infinity for the single dose. Thus, there was no evidence of induction or inhibition of nifedipine clearance due to chronic administration.

Study (d) (Table 4)

The influences of food and posture on the pharmacokinetics of the biphasic tablet were consistent with the discrepancies found between studies (a) and (b) conducted in the two centres. The mean time to the peak plasma nifedipine concentration was significantly longer after food (3.8 ± 2.2 h) when compared to the fasting state with 1 h recumbency (1.8 ± 0.9 h; $P < 0.05$). The mean differences between these times to peak concentration were also significant by the method of paired differences ($P < 0.01$). The elimination half-life was also reduced from 4.1 ± 1.3 h to 3.0 ± 1.4 h when the tablet was given after food (Table 4). The mean values were not significantly different by Wilcoxon's rank sum or signed rank tests but a treatment related effect was demonstrated ($P < 0.05$) using the method of paired differences.

In contrast, food and posture did not influence the peak plasma concentration or the AUC for nifedipine or its nitropyridine metabolite.

Table 3 Study (c) Pharmacokinetic parameters for nifedipine during single dose and chronic administration of a 5 + 15 mg formulation (mean ± s.d., $n = 8$)

	First dose	*Final dose*
C_0 (ng ml^{-1})	0.0	10.4 ± 5.2
C_{max} (ng ml^{-1})	54.7 ± 19.0	63.2 ± 26.1
t_{max} (h)	3.6 ± 0.7	3.4 ± 0.7
AUC (ng ml^{-1} h)†	259 ± 86	267 ± 104
Terminal half-life (h)	2.8 ± 0.7	3.3 ± 1.9

C_o initial concentration present prior to dose
† The AUC was calculated to infinity for the first dose and to 12 h (the dose interval) for the final dose

Table 4 Study (d) Influence of food and posture on the pharmacokinetics of a biphasic formulation of nifedipine (mean ± s.d., $n = 8$)

	Fasting + 1 h supine	*Fasted + 4 h supine*	*Fed + 4 h supine*
Nifedipine			
C_{max} (ng ml^{-1})	61 ± 19	45 ± 13	84 ± 58
t_{max} (h)	1.8 ± 0.9	2.4 ± 1.8	3.8 ± 2.2*
$AUC_{(0-\infty)}$ (ng ml^{-1} h)	299 ± 91	274 ± 67	328 ± 167
$t_{½}$ (h)	3.7 ± 1.2	4.1 ± 1.2	3.0 ± 1.3†
Nitropyridine metabolite			
C_{max} (ng ml^{-1})	34 ± 12	26 ± 9	37 ± 20
t_{max} (h)	1.7 ± 0.9	2.4 ± 1.8	3.8 ± 2.2*
$AUC_{(0-\infty)}$ (ng ml^{-1} h)	131 ± 57	121 ± 42	138 ± 52
$t_{½}$ (h)	3.3 ± 1.7	3.2 ± 2.6	2.4 ± 1.4

*compared with fasting + 1 h supine, $P < 0.05$ Wilcoxon signed rank sum test, $P < 0.01$ method of paired differences
†compared with fasting + 4 h supine; $P < 0.05$ method of paired differences

Discussion

The pharmacokinetic profile of the 10 mg nifedipine capsules (study b) was similar to previous reports (Raemsch, 1981; Raemsch & Sommer, 1983; Foster *et al.*, 1983) although the time to the peak nifedipine plasma concentration was somewhat longer. As reported previously, there were wide inter-individual differences in the plasma drug concentration-time curves. The 20 mg sustained release (retard) preparation (study a) also showed pharmacokinetics similar to those obtained by most other workers (Raemsch, 1981; Raemsch & Sommer, 1983; Banzet *et al.*, 1983; Ochs *et al.*, 1984). In some of these earlier studies, however, the assay technique did not separate nifedipine from a major nitropyridine metabolite (see Waller *et al.*, 1984).

In the initial study in Southampton (study a) the pharmacokinetics of the biphasic formulation resembled those of the retard tablet. The AUC indicated similar bioavailabilities and there was no significant difference between the apparent terminal half-lives. The apparent terminal half-lives for these formulations, when measured up to 24 h after the dose, are absorption rate limited, since they are considerably longer than the half-life following intravenous administration (Waller *et al.*, 1984). The times to peak were also similar with the two preparations but after the biphasic formulation, plasma concentrations were significantly higher at 2 h and 3 h after dosing, consistent with the presence of a more rapid release component. The pharmacokinetics for the biphasic formulation were similar to those found in the previous study (Waller *et al.*, 1984).

In contrast, the comparison of the biphasic tablets with capsules (study b) undertaken in Dundee showed similar pharmacokinetics for these two formulations. The terminal half-life for the biphasic preparation (2.2 h) was significantly shorter than either the mean 4.3 h in study (a) from Southampton or the value published previously (5.4 ± 2.6 h) in different volunteers studied at the same centre. The data for the first and final dose of the chronic dosing study with the biphasic formulation in Dundee (study c) also yielded shorter terminal half-lives of 2.8 and 3.3 h respectively.

The differences between the two centres could have arisen from the differences in food intake with the tablet and posture between the protocols and, therefore, study (d) was designed to evaluate the influence of these factors on the pharmacokinetics of the biphasic tablet. The results suggest that when the tablet is taken after food, there is a delay in time to peak concentration but a shorter apparent elimination half-life. Since the amounts of the first-pass dihydropyridine metabolite were similar in all treatment groups, an effect on first-pass extraction is unlikely and the presence of food was probably delaying gastric emptying and increasing the rate of dissolution of the tablet while retained in the stomach.

The differences in the pharmacokinetics of the biphasic tablets were seen clearly when the data for the 18 different subjects studied using the fasting (Southampton) protocol (Waller *et al.*, 1984; study (a) and study (d(ii)) were compared with those for the 24 different subjects studied using the fed (Dundee) protocol (study b; study c (single dose) and study (d(iii)). The time to peak using the fasting protocol (1.8 ± 0.8 h) was significantly shorter ($P < 0.001$) compared to the fed protocol (3.4 ± 1.4 h), whilst the terminal half-life was significantly ($P < 0.001$) longer (4.4 ± 2.0 h compared with 2.7 ± 0.9 h). Similar values were obtained, using the fasting and fed protocols, for the AUCs (287 ± 109 and 285 ± 115 ng ml^{-1} h respectively) and peak concentrations (60 ± 25 and 68 ± 38 ng ml^{-1} respectively). The effects of food on the pharmacokinetics of the 20 mg sustained release formulation of nifedipine have been examined previously (Ochs *et al.*, 1984). A delay in the time to peak plasma drug concentration was recorded but the apparent terminal half-life was not determined. Since the pharmacodynamic and therapeutic effects of nifedipine appear to relate closely to its plasma concentration (Thibonnier *et al.*, 1980; Aoki *et al.*, 1982; Banzet *et al.*, 1983; Gutierrez *et al.*, 1984), the influence of food on the kinetics of the biphasic preparation may be of clinical significance.

The 10 mg capsule formulation of nifedipine when given in three or four divided doses is effective in the management of both angina (Lynch *et al.*, 1980; Mueller *et al.*, 1981) and hypertension (Aoki *et al.*, 1982). In contrast, the 20 mg sustained release preparation has been shown to be an effective antihypertensive in twice daily dosage (Hornung *et al.*, 1983; Lund-Johansen & Omvik, 1983; Landmark, 1985) but its efficacy in angina is less well documented (Brugmann *et al.*, 1983). The biphasic formulation was designed to provide a single preparation suitable for use in both conditions. Our results suggest that in the fasting state it demonstrates pharmacokinetic characteristics intermediate between the capsule and sustained release formulations. However, the present studies suggest that the biphasic formulation will lose its desirable properties if taken with food.

We are grateful to Bayer (UK) Limited for reference compounds and for financial assistance with these studies.

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(*Received 12 December 1985, accepted 9 July 1986*)