The pharmacokinetics of oral nifedipine – a population study

A. G. RENWICK, D. R. C. ROBERTSON, B. MACKLIN, V. CHALLENGOR, D. G. WALLER & C. F. GEORGE

Clinical Pharmacology Group, University of Southampton, Medical and Biological Sciences Building, Bassett Crescent East, Southampton SO9 3TU

- 1 The pharmacokinetics and metabolism of nifedipine have been studied in a population of 59 young male volunteers following administration of a 10 mg capsule.
- 2 The area under the plasma concentration-time curves (AUC) for nifedipine demonstrated a skewed but not a bimodal distribution (mean $154 \text{ ng ml}^{-1} \text{ h}$; range $54\text{--}306 \text{ ng ml}^{-1} \text{ h}$).
- 3 Calculation of the ratio of the AUC of nifedipine to the AUC of its nitropyridine metabolite did not separate those individuals with high AUC values of nifedipine from the remainder of the population.
- 4 Similarly there was no evidence for bimodality in the excretion of the major urinary metabolite. Those subjects with high plasma AUC values for nifedipine excreted similar amounts to the remainder of the population.
- 5 In contrast to a previous study using a 20 mg oral dose, there was no evidence of polymorphism in the pharmacokinetics or metabolism of nifedipine following a single 10 mg oral dose.

Keywords nifedipine metabolism pharmacokinetics population polymorphism

Introduction

Nifedipine is a dihydropyridine calcium channel blocker which undergoes extensive first pass metabolism in man following oral administration (Foster *et al.*, 1983; Waller *et al.*, 1984). Metabolism is apparently via a single pathway involving initial oxidation to the pyridine analogue, followed by conversion to acid metabolites which are excreted in the urine (Horster *et al.*, 1972; Figure 1). The nitropyridine analogue is a major circulating metabolite which is present at concentrations approaching those of the parent drug after oral but not intravenous administration (Waller *et al.*, 1984). The liver is involved in the first pass metabolism of nifedipine since patients with liver cirrhosis show a reduced systemic clearance and an increased bioavailability compared with normal subjects (Kleinbloesem *et al.*, 1986). Direct evidence of extensive trans-hepatic extraction of nifedipine in man (Challenor *et al.*,

1987b) has confirmed that the liver is the principal site of first pass metabolism.

The initial oxidation of dihydropyridines in rat liver has been shown to occur by the cytochrome P-450 system (Baarnhielm *et al.*, 1984; Baarnhielm & Hansson, 1986) and specific forms (designated P-450_{UT-A} and P450_{PCN-E}) with high activity against dihydropyridines have been identified (Guengerich *et al.*, 1986). The report by Kleinbloesem *et al.* (1984a) of a polymorphism in the oxidation and pharmacokinetics of nifedipine in man intensified interest in the nature of human cytochrome P-450 involved in this reaction (Guengerich *et al.*, 1986). This form of cytochrome P-450 (designated P-450_{NF}; Guengerich *et al.*, 1986) was purified, and inhibition studies using monoclonal antibodies have shown that it is responsible for more than 90% of nifedipine oxidation in human liver microsomes. The levels

Figure 1 Pathways of metabolism of nifedipine (based on Horster *et al.*, 1972).

of cytochrome P450_{NF} correlated well with the level of nifedipine oxidase activity in microsomal preparations. The authors concluded that the locus determining a phenotypic deficient metaboliser of nifedipine may therefore be at the level of factors involved in transcription rather than the structural gene. Cytochrome P-450_{NF} oxidises a range of dihydropyridines as well as catalysing the 2- and 4- hydroxylation of oestradiol, the 6 β -hydroxylation of testosterone, androstenedione and cortisol, aldrin epoxidation and benzphetamine *N*-demethylation (Guengerich *et al.*, 1987); thus a deficit in the enzyme could affect a number of substrates.

We have not found evidence for polymorphism in the pharmacokinetics of nifedipine following intravenous or oral administration in various studies but these involved a range of oral formulations, (capsule, slow release and biphasic release) and doses (10 to 30 mg) (Waller *et al.*, 1984; Challenor *et al.*, 1986, 1987a; Renwick *et al.*, 1987). The present investigation was designed to extend our observations using the 10 mg capsule formulation in fasting normal healthy volunteers to provide a data base comparable to that of Kleinbloesem *et al.* (1984a) who reported impaired oxidative metabolism in 9 out of 53 subjects studied.

Table 1 Pharmacokinetics of nifedipine (10 mg) in a young healthy population

	<i>n</i>	Mean	<i>s.d.</i>	Median	Min	Max
<i>Nifedipine</i> (plasma)						
$C_{\max}$ (ng ml ⁻¹)	59	79	44	81	16	198
AUC (ng ml ⁻¹ h)	59	154	61	141	54	306
$t_{1/2}$ (h)	59	2.5	1.3	2.2	1.0	9.9
<i>Nitropyridine metabolite</i> (plasma)						
$C_{\max}$ (ng ml ⁻¹)	59	41	24	34	7	105
AUC (ng ml ⁻¹ h)	59	71	28	67	32	181
$t_{1/2}$ (h)	59	1.6	0.8	1.4	0.6	4.9
<i>Acid metabolite</i> ^a (urine)						
0–8 h (% dose)	50	48	9	47	33	73
0–24 h (% dose)	48	55	14	54	35	106
$t_{1/2}$ (h)	51	3.3	1.3	3.2	0.7	6.6

 $C_{\max}$ – maximum observed plasma concentration

AUC – area under the plasma concentration-time curve

 $t_{1/2}$ – terminal half-life

a – incomplete urine collections prevented measurement of % recovered in some subjects

Methods

A total of 59 male volunteers aged 19–35 years (mean $\pm$ s.d.; 22 ± 3) and body weights 55–94 kg (mean $\pm$ s.d. 73 ± 8) took part in the study which had been approved by the local Ethics Committee. None of the subjects had received any medication for a period of 2 weeks prior to the study but 11 of them were regular smokers. Following an overnight fast each subject was given a single capsule containing 10 mg of nifedipine (Adalat) with 50 ml of water. They remained semi-recumbent and continued to fast for a period of 4 h. Venous blood samples (10 ml) were withdrawn prior to the dose and at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after the dose. The samples were centrifuged immediately and the plasma separated and stored at -20°C prior to analysis. In 51 of the subjects, urine was collected prior to the dose and at 2 hourly intervals to 8 h after the dose and then from 8–24 h. (The plasma data for the eight subjects who did not collect urine were from a previous study, Challenor *et al.*, 1987a). The plasma samples were analysed for nifedipine and its nitropyridine metabolite, taking precautions to prevent photodecomposition, by the method described previously (Waller *et al.*, 1984). The principal acid metabolite in urine was determined by a published modification (Renwick *et al.*, 1987) to the method of Kleinbloesem *et al.* (1984b).

The terminal half-life was derived by least squares regression analysis applied to the post-peak, log-linear part of the plasma concentration-time curve. The area under the plasma concentration-time curve (AUC) was determined by the linear trapezoidal method with extrapolation to infinity by dividing the last measurable plasma concentration by the terminal slope. The area under the curve to the last measurable plasma concentration represented $95 \pm 3\%$ of the AUC to infinity for nifedipine and $92 \pm 6\%$ of the total AUC for the metabolite. The terminal half-life of the acid metabolite was determined by linear least squares regression analysis applied to the amount remaining to be excreted (sigma-minus method; Gibaldi & Perrier, 1982; using the last 3 to 5 data points which gave regression coefficients of at least 0.99).

Results

The overall pharmacokinetic data for the population are given in Table 1. The difference between the mean and median for the AUC of nifedipine indicated that the data were not normally distributed. This is shown in Figure 2a but the values represent a skewed distribution with no clear evidence of bimodality. Five subjects had AUC values equivalent to the lower end of

Figure 2 Frequency distributions of the pharmacokinetic indices of nifedipine; a) area under the plasma concentration-time curve; b) maximum plasma concentration; c) terminal half-life. ■ individuals with AUC values for nifedipine $> 240 \text{ ng ml}^{-1} \text{ h}$; ▨ individuals with AUC values for nifedipine $200\text{--}240 \text{ ng ml}^{-1} \text{ h}$.

the slow metaboliser range reported by Kleinbloesem *et al.* (1984a) (i.e. with AUC values greater than $25 \text{ ng ml}^{-1} \text{ h}$ per mg dosed), but these were not clearly separated from the rest of the population (Figure 2a). These individuals and those with AUC values greater than $20 \text{ ng ml}^{-1} \text{ h}$ per mg dosed have been identified in all figures to show relationships with other para-

eters. The maximum observed plasma concentration ($C_{\max}$) showed a wide interindividual variability (Table 1) which was inversely related to the time since dosing ($r = -0.644$; $P < 0.001$). Although there was a significant positive correlation between the AUC and $C_{\max}$ ($r = 0.487$; $P < 0.001$) over the whole population, this relationship did not correlate well for those individuals with the highest AUC values (Figure 2b). Similarly the high AUC values for nifedipine did not relate to long terminal half-lives (Figure 2c). The single individual with the prolonged terminal half-life was not unusual in other respects and his values for all other parameters discussed were very close to the median of the population.

The plasma concentration-time curves for the nitropyridine metabolite were similar to those of the parent compound. In 53 of the 59 subjects the time of the peak concentration of the metabolite was the same as that of nifedipine (overall correlation: $r = 0.811$; $P < 0.001$). There was also a highly significant positive correlation between the maximum concentrations of nifedipine and of its metabolite ($r = 0.769$; $P < 0.001$). The AUC for the nitropyridine metabolite showed a skewed distribution (Figure 3a) but there was no apparent trend for subjects with a high AUC for nifedipine to show a reduced AUC for the metabolite. In consequence calculation of the ratio of the AUC of nifedipine to that of the nitropyridine metabolite, as suggested by Schmid *et al.* (1986), did not result in a clearer separation of those individuals with higher AUC values of nifedipine (Figure 3b).

The excretion of the major urinary metabolite accounted for 48% of the dose within 8 h and 55% within 24 h (Table 1). There was no evidence of bimodality in the 0–8 h data, as reported by Kleinbloesem *et al.* (1984a) but none of the individuals excreted less than 25% of the dose, which corresponded to the poor metaboliser group in that study (Figure 4a). Those individuals who showed the highest AUC values for nifedipine did not show lower excretion of the urinary metabolite, and were evenly distributed. Calculation of the terminal half-life of the acid metabolite did not separate out those individuals with high AUC values for nifedipine (Figure 4b).

Discussion

The data in the present study do not confirm the report of a polymorphism in the disposition of nifedipine following oral administration (Kleinbloesem *et al.*, 1984a). Although there was a wide variability in the AUC values of nifedipine there was no clearly separated group equivalent to the poor metabolisers in the latter study.

Figure 3 Frequency distributions of the pharmacokinetic indices of the nitropyridine metabolite of nifedipine: a) area under the plasma concentration-time curve; b) metabolite ratio calculated from areas under the plasma concentration-time curve. ▨ individuals with AUC values for nifedipine $> 240 \text{ ng ml}^{-1} \text{ h}$; ▩ individuals with AUC values for nifedipine $200 - 240 \text{ ng ml}^{-1} \text{ h}$.

Whereas eight out of the nine poor metabolisers identified by Kleinbloesem *et al.* (1984a) in their study on 53 subjects had AUC values greater than $30 \text{ ng ml}^{-1} \text{ h}$ per mg dosed, this value was exceeded by only one subject in the present study. The incidence of poor metabolisers in the present study (incidence 0/59–95% confidence limits 0–6%) was significantly different from the results of Kleinbloesem *et al.* (1984a) (incidence 9/53–95% confidence limits 8–30%). In addition, there was no evidence of the inverse relationship between the AUC of nifedipine and the % of the dose recovered in the urine as the acid metabolite that was found in the previous study; but again

Figure 4 Frequency distributions of the pharmacokinetic indices of the acid metabolite of nifedipine: a) percentage of dose excreted in 8 h; b) terminal half-life. ▨ individuals with AUC values for nifedipine $> 240 \text{ ng ml}^{-1} \text{ h}$; ▩ individuals with AUC values for nifedipine $200 - 240 \text{ ng ml}^{-1} \text{ h}$.

the exceptional values of the poor metabolisers (less than 25% in 8 h) were not detected.

For many studies on polymorphic drug oxidation clear separation of the phenotypes is achieved best by analysis of the ratio of parent drug to metabolite or metabolite to parent drug (partial clearance) (Jackson *et al.*, 1986). In the case of nifedipine the absence of other major pathways of metabolism or excretion suggests that calculation of the metabolite ratio would not provide any advantage. The appearance of high plasma concentrations of the nitropyridine metabolite after oral but not intravenous administration (Waller *et al.*, 1984; Challenor *et al.*,

1987b), indicates that this is formed during first pass metabolism. The half-life of the metabolite was shorter than that of the parent compound (Table 1). This is probably because the duration of metabolite formation for the rapidly absorbed capsule formulation would be limited and the terminal slope for the metabolite would therefore be elimination not formation (i.e. absorption) rate limited. It has been suggested by Schmid *et al.*, (1986) that calculation of the ratio of the AUC of nifedipine to that of its metabolite may provide a more distinct separation of poor metabolisers. However, calculation of the ratio of AUC for nifedipine to that of the metabolite failed to separate clearly the group corresponding to those with high AUC values for nifedipine (Figure 3b). The reciprocal ratio of the AUC of the metabolite to that of the parent compound similarly failed to separate a 'poor metaboliser' subgroup. This finding is in contrast to that of Schmid *et al.* (1986) who reported data for eight subjects given 10 mg nifedipine orally. One of these had a high AUC for nifedipine ($605 \text{ ng ml}^{-1} \text{ h}$ compared with a mean $\pm$ s.d. of $265 \pm 57 \text{ ng ml}^{-1} \text{ h}$ in the other seven subjects) and a low AUC for the nitropyridine ($42 \text{ ng ml}^{-1} \text{ h}$ compared with a mean $\pm$ s.d. of $88 \pm 23 \text{ ng ml}^{-1} \text{ h}$) such that the ratio of nifedipine to metabolite was 14.2 compared with a mean $\pm$ s.d. of 3.3 ± 1.5 . The authors concluded that calculation of the plasma ratio may provide a clue to the metabolic origin of the polymorphism in nifedipine disposition and a convenient procedure for phenotyping individuals. The very high AUC values for nifedipine in the seven normal subjects are at variance with the data in this paper and, after adjustment for dose, are about double those reported by Kleinbloesem *et al.*, (1984a) and in other studies in normal young volunteers (Foster *et al.*, 1983; Waller *et al.*, 1984; Challenor *et al.*, 1986, 1987a; Lobo *et al.*, 1986; Renwick *et al.*, 1987). In addition, the AUC for nifedipine and the nifedipine to metabolite ratio for the unusual subject in the study of Schmid *et al.* (1986) were about twice the maximum values found in the present population.

The failure of the urinary excretion data to define the polymorphism is consistent with a more recent study on a large Dutch population (Schellens *et al.*, 1986) given a 'cocktail' of polymorphically handled drugs (sparteine, mephentoin and nifedipine). Despite the increased size of the study (172 individuals) the data for the excretion of the acid metabolite of nifedipine were not bimodally distributed. However based on the criteria derived in the previous study (Kleinbloesem *et al.*, 1984a) the authors concluded that the incidence of 'poor metabolism'

of nifedipine was 9.9%.

The discrepancy between the clear evidence of polymorphism shown by Kleinbloesem *et al.* (1984a) and the data in the present paper may have arisen from apparently minor differences in the study designs. Bimodal distribution was found in a Dutch population which showed greater variability e.g. sex (33 males, 20 females) and age (27 ± 9 years), than in the present study. However the two modes in that study did not differ with respect to age, gender, smoking habits and the use of oral contraceptives. Age profoundly alters the pharmacokinetics of nifedipine due to a decrease in clearance (Robertson *et al.*, 1987), but neither gender (Lobo *et al.*, 1986) nor smoking (Renwick *et al.*, 1987) influence the AUC of nifedipine. Steroids may increase the ability of the human liver to metabolise nifedipine (Guengerich *et al.*, 1986) and are thus an unlikely cause for an increase in AUC. Correction of the AUC values for nifedipine in the present study for body weight did not alter the pattern of distribution. The influence of body weight was not discussed in the paper of Kleinbloesem *et al.* (1984a) but could clearly affect data generated when a fixed dose is given to a wide range of body weights. Plasma protein binding may also have influenced the findings, however nifedipine is so strongly bound to both albumin (97%) and

Figure 5 Frequency distribution of the ratio of the maximum plasma concentration of nifedipine to that of its nitropyridine metabolite. ▨ individuals with AUC values for nifedipine $> 240 \text{ ng ml}^{-1} \text{ h}$; ▩ individuals with AUC values for nifedipine $200 - 240 \text{ ng ml}^{-1} \text{ h}$.

α_1 -acid glycoprotein (51–76%) (Otto & Lesko, 1986) that it is difficult to envisage that the high AUC values arose from an increased binding to plasma proteins.

The only other apparent difference between the studies is the dose of nifedipine given. The present study used a single 10 mg capsule since this is more representative of current clinical practice than the 2×10 mg capsule dose used by Kleinbloesem *et al.* (1984a). The dose cannot explain the failure of Schellens *et al.* (1986) to demonstrate the polymorphism based on urinary data, since they also employed 20 mg. However the co-administration of two other drugs in that study complicates the comparison. It is possible that saturation of first pass metabolism of nifedipine occurs in the 'poor metabolisers' but not the rest of the population after 20 mg, but not 10 mg, in capsule form. Under such circumstances this group may become separated more clearly from the remainder of the population. If this is the case then only transient saturation of the enzyme may occur around the time of maximum absorption following a 10 mg capsule. Evidence supporting this suggestion was found in the present study since calculation of the ratio of the $C_{\max}$ of

nifedipine to that of its metabolite separated three individuals, who had high AUC values for nifedipine, away from the remainder of the population (Figure 5). The other subjects with high AUC values for nifedipine also showed high $C_{\max}$ ratios.

The failure to demonstrate a polymorphism in the present study suggests either that the phenomenon is highly dependent on the dose and therefore the rate of drug delivery to the liver, or that the incidence in the British population is considerably lower than that reported previously. Assessment of the therapeutic implications of the polymorphic oxidation of nifedipine should include the following factors; a) polymorphism was not found at the commonly used dose of 10 mg, b) following 20 mg the interindividual variability in the 'good metaboliser' population (4.5 fold) was almost as great as that in the whole population (8 fold) (Kleinbloesem *et al.*, 1984a) and c) there is a decrease in the metabolism of nifedipine with age, which will shift nearly all elderly subjects into the 'poor metaboliser' range (Robertson *et al.*, 1987). These factors suggest that the polymorphic metabolism of nifedipine may be of academic interest but is of limited clinical importance.

References

- Baarnhielm, C., Skanberg, I. & Borg, K. O. (1984). Cytochrome P-450 dependent oxidation of felodipine – a 1,4-dihydropyridine – to the corresponding pyridine. *Xenobiotica*, **14**, 719–726.
- Baarnhielm, C. & Hansson, G. (1986). Oxidation of 1,4-dihydropyridines by prostaglandin synthase and the peroxidic function of cytochrome P-450. *Biochem. Pharmacol.*, **35**, 1419–1425.
- Challenor, V. F., Waller, D. G., Gruchy, B. S., Renwick, A. G., George, C. F., McMurdo, E. T. & McEwen, J. (1986). The effects of food and posture on the pharmacokinetics of a biphasic release preparation of nifedipine. *Br. J. clin. Pharmacol.*, **22**, 565–570.
- Challenor, V. F., Waller, D. G., Gruchy, B. S., Renwick, A. G. & George, C. F. (1987a). Food and nifedipine pharmacokinetics. *Br. J. clin. Pharmacol.*, **23**, 248–249.
- Challenor, V. F., Waller, D. G., Renwick, A. G., Gruchy, B. S. & George, C. F. (1987b). The trans-hepatic extraction of nifedipine. *Br. J. clin. Pharmacol.*, **24**, 473–477.
- Foster, T. S., Hamann, S. R., Richards, V. R., Bryant, P. J., Graves, D. A. & McAllister, R. G. Jr. (1983). Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects. *J. clin. Pharmacol.*, **23**, 161–170.
- Gibaldi, M. & Perrier, D. (1982). In *Pharmacokinetics*, New York: Marcel Dekker. pp. 56–59.
- Guengerich, F. P., Martin, M. V., Beaune, P. H., Kremers, P., Wolff, T. & Waxman, D. J. (1986). Characterisation of rat and human liver microsomal cytochrome P-450 forms involved in nifedipine oxidation, a prototype for genetic polymorphism in oxidative drug metabolism. *J. biol. Chem.*, **261**, 5051–5060.
- Guengerich, F. P., Umbenhauer, D. R., Churchill, P. F., Beaune, P. H., Bocker, R., Knodell, R. G., Martin, M. V. & Lloyd, R. S. (1987). Polymorphism of human cytochrome P-450. *Xenobiotica*, **17**, 311–316.
- Horster, F. A., Duhm, B., Maul, W., Medenwald, H., Patzschke, K. & Wegner, L. A. (1972). Clinical investigations on the pharmacokinetics of radioactively marked 4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester. *Arzneimittel-Forsch.*, **22**, 330–334.
- Jackson, P. R., Tucker, G. T., Lennard, M. S. & Woods, H. F. (1986). Polymorphic drug oxidation: pharmacokinetic basis and comparison of experimental indices. *Br. J. clin. Pharmacol.*, **22**, 541–550.
- Kleinbloesem, C. H., Van Brummelen, P., Faber, H., Danhof, M., Vermeulen, N. P. E. & Breimer, D. D. (1984a). Variability in nifedipine pharmacokinetics and dynamics: a new oxidation polymorphism in man. *Biochem. Pharmacol.*, **33**, 3721–3724.
- Kleinbloesem, C. H., Van Harten, J., Van Brummelen, P. & Breimer, D. D. (1984b). Liquid chromatographic determination of nifedipine in plasma and of its main metabolite in urine. *J. Chromatogr.*, **308**, 209–216.
- Kleinbloesem, C. H., Van Harten, J., Wilson, J. P. H.,

- Danhof, M., Van Brummelen, P. & Breimer, D. D. (1986). Nifedipine: Kinetics and haemodynamic effects in patients with liver cirrhosis after intravenous and oral administration. *Clin. Pharmac. Ther.*, **40**, 21–28.
- Lobo, J., Jack, D. B. & Kendall, M. J. (1986). The intra- and inter-subject variability of nifedipine pharmacokinetics in young volunteers *Eur. J. clin. Pharmac.*, **30**, 57–60.
- Otto, J. & Lesko, L. J. (1986). Protein binding of nifedipine. *J. Pharm. Pharmac.*, **38**, 399–400.
- Renwick, A. G., Le Vie, J., Challenor, V. F., Waller, D. G., Gruchy, B. & George, C. F. (1987). Factors effecting the pharmacokinetics of nifedipine. *Eur. J. clin. Pharmac.*, **32**, 351–355.
- Robertson, D. R. C., Waller, D. G., Renwick, A. G. & George, C. F. (1987). Age related changes in the pharmacokinetics and pharmacodynamics of nifedipine. *Br. J. clin. Pharmac.*, **24**, 244 p.
- Schellens, J. H. M., Danhof, M. & Breimer, D. D. (1986). Incidence of the poor metaboliser phenotype of sparteine, mephentyoin and nifedipine in a Dutch population. *Acta Pharmac. Tox.*, **59**, Supp. V., 217.
- Schmid, B., Penny, H., Feher, M., Sever, P. & Idle, J. (1986). Impaired metabolic dehydrogenation of nifedipine. *Acta Pharmac. Tox.*, **59**, Supp. V, 217.
- Waller, D. G., Gruchy, B. S., Renwick, A. G. & George, C. F. (1984). First pass metabolism of nifedipine. *Br. J. clin. Pharmac.*, **18**, 951–954.

(Received 16 October 1987,
accepted 19 January 1988)