Br. J. clin. Pharmac. (1991), **31**, 399–403 ADONIS 030652519100077 P

Ethnic differences in the pharmacokinetics of oral nifedipine

C. H. AHSAN, A. G. RENWICK, B. MACKLIN, V. F. CHALLENOR, 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 of a single oral dose of 20 mg nifedipine, given as capsules, has been compared in five South Asian volunteers with data for 27 Caucasian volunteers.
2 The area under the plasma concentration-time curve (AUC) of nifedipine was three fold higher in South Asians (989 ± 166 ng ml^{-1} h) than in Caucasians (323 ± 116 ng ml^{-1} h).
3 The ratio of the AUC of nifedipine to that of the nitropyridine analogue, which is formed largely as a first pass metabolite, was significantly higher in South Asians (4.6 ± 1.9) than in Caucasians (2.3 ± 1.1) indicating a lower first pass metabolism in South Asians.
4 The terminal half-lives of nifedipine and the nitropyridine metabolite were significantly greater in South Asians than in Caucasians.
5 Consumption of a spicy curry diet for 3 days by Caucasians did not significantly affect the pharmacokinetics of a single oral dose of nifedipine.
6 The treatment of patients of South Asian origin with nifedipine should be initiated with lower doses than would be given to Caucasians.

Keywords nifedipine ethnic differences pharmacokinetics

Introduction

Nifedipine is a dihydropyridine calcium channel blocker that is used widely in the treatment of hypertension and angina. The drug undergoes extensive first pass metabolism resulting in an oral bioavailability of about 45% (Foster *et al.*, 1983; Waller *et al.*, 1984). Nifedipine shows a high plasma clearance which is primarily due to hepatic extraction and metabolism (Challenor *et al.*, 1987) with initial oxidation to the pyridine analogue followed by formation of acid metabolites which are excreted in urine (Horster *et al.*, 1972). High concentrations of the pyridine analogue are present in plasma after oral but not intravenous administration (Waller *et al.*, 1984).

Interest in the metabolism of nifedipine was intensified by the report by Kleinbloesem *et al.* (1984a) that almost 20% of a European population showed impaired metabolism of nifedipine following a single oral dose of 20 mg as capsules. The cytochrome P450 responsible for the oxidation of nifedipine (cytochrome P450IIIA3; Nebert *et al.*, 1987) has been purified from human liver (Guengerich *et al.*, 1986) and shown to oxidise several dihydropyridines as well as performing a limited number of other xenobiotic oxidations (Guengerich *et al.*, 1987). Subsequent studies in European populations have failed to detect polymorphic metabolism of nifedipine following 10 mg as capsules (Renwick *et al.*, 1988) or 20 mg as the slow release formulation (given together with sparteine and phenytoin) (Schellens *et al.*, 1988). In the latter paper the authors concluded that their earlier publication (Kleinbloesem *et al.*, 1984a) may have represented a false positive result due to the limited size of the population studied. Recently Hoyo-Vadillo *et al.*, (1989) reported that about one half of a Mexican population were poor metabolisers following a single oral dose of nifedipine using the criteria for a poor metaboliser defined by Kleinbloesem *et al.* (1984a).

During studies on the influence of dose on the pharmacokinetics of nifedipine (unpublished data) we observed a high area under the plasma concentration-time curve following oral administration of 20 mg as capsules to an individual from Bangladesh. The present paper investigates the influence of ethnic origin and spicy diets on the pharmacokinetics of nifedipine.

Methods

The influence of ethnic origin on the pharmacokinetics of nifedipine was studied in 27 adult Caucasians (26 males; average age 25 years (range 19–46); average body weight 74 kg (range 60–92)) and five South Asians (four

Correspondence: Dr A. G. Renwick, Clinical Pharmacology Group, University of Southampton, Medical and Biological Sciences Building, Bassett Crescent East, Southampton SO9 3TU

males; four from Bangladesh and one from India; average age 28 years (range 25–32); average body weight 66 kg (range 59–84)). The South Asians had retained their original dietary practices including abstention from alcohol in four of the subjects, whereas the Caucasians all consumed a typical Western diet.

The influence of diet was studied in six Caucasians (five males; average age 25 years (range 19–46); average body weight 69 kg (range 60–77)). These subjects were studied once while on their normal diet and on a second occasion following 3 days of intake of Indian meals consumed at midday and in the evening. The 'minimum spice content' for each meal was set as the 'medium' defined on the restaurant menu although in most cases the curries consumed were much spicier, e.g. Madras and Vindaloo.

None of the subjects had received medication, except for paracetamol or ibuprofen, in the week preceding the study. The studies had been approved by the local Ethics Committee, and subjects gave their written, informed consent.

The protocol on the study days was the same on each occasion. Following an overnight fast each subject was given a single oral dose of 20 mg of nifedipine (two Adalat capsules) with 100 ml water. They remained semi-recumbent and continued to fast for a period of 4 h. Venous blood samples (10 ml) were withdrawn into heparinised tubes 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 plasma separated and stored at −20° C until analysis. A urine sample was collected prior to the dose and the complete urine output collected at 2 hourly intervals for 8 h and then from 8–12 and 12–24 h after the dose. Some of the subjects in each study group received soluble paracetamol (1 g) during the study period, for relief of headache.

The plasma samples were analysed for nifedipine and its nitropyridine metabolite by the reverse phase h.p.l.c. method described previously (Waller *et al.*, 1984). All procedures involving plasma samples were undertaken using precautions to prevent photo-decomposition as described previously (Waller *et al.*, 1984). The principal acid metabolite in urine was measured using a published modification (Renwick *et al.*, 1987) to the method described by 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 ± 3, 91 ± 3, 93 ± 4 and 90 ± 4% of the AUC to infinity for nifedipine in the Caucasian, South Asian, pre-curry and post-curry groups and 91 ± 5, 81 ± 10, 89 ± 3 and 84 ± 6% of the total AUC for the metabolite in these groups. 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). Statistical significance (taken as $P < 0.05$) was determined by Wilcoxon's rank sum test or signed rank test as appropriate.

Results

Higher plasma concentrations of nifedipine were detected in the South Asian volunteers at each time point after the dose (Figure 1). The differences up to 1.5 h were not statistically significant due to the wide interindividual variations in the time taken to reach the maximum plasma concentration (Table 1). The significantly higher concentrations of nifedipine from 1.5 h after the dose resulted in an approximately three fold greater AUC and terminal half-life in South Asians compared with Caucasians (Table 1). The AUC of nifedipine in each of the South Asians was higher than the maximum value detected in the Caucasians (Figure 2).

The plasma pharmacokinetics of the nitropyridine metabolite in South Asians showed a slightly, but not significantly lower maximum plasma concentration but a significantly greater AUC and terminal half-life compared with Caucasians. There was some overlap in the AUC of the metabolite between the two groups (Figure 2). The absence of an inverse relationship between the AUC of nifedipine and that of the nitropyridine metabolite meant that calculation of the drug metabolite ratio (Figure 3) did not enhance the separation of the South Asians and Caucasians, although the ratio was significantly higher in South Asians (Table 1).

The total amount of the principal acid metabolite excreted in urine within 24 h was similar in Caucasians and South Asians, although there was evidence of a slower elimination of this metabolite by South Asians (Table 1). The terminal half-life calculated for one of the

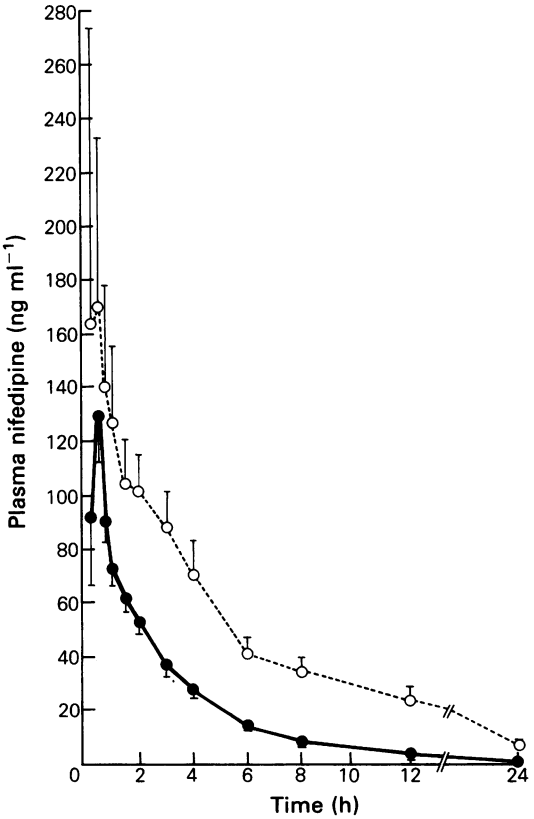

Figure 1 Plasma concentration-time curves of nifedipine following the administration of 20 mg as capsules to Caucasian (●) and South Asian (○) volunteers. The data are the means with standard errors indicated by vertical bar lines. The differences were statistically significant at 1.5 h ($P < 0.05$) and at all subsequent times ($P < 0.01$) by Wilcoxon's rank sum test.

Table 1 Ethnic differences in the pharmacokinetics of nifedipine following a single oral dose of 20 mg as capsules

	Caucasians	*South Asians*
Nifedipine		
C_{max} (ng ml^{-1})	172 ± 107 (32–460)	250 ± 189 (84–551)
t_{max} (h)	0.8 ± 0.8 (0.25–3.0)	1.2 ± 1.1 (0.25–3.0)
AUC (ng ml^{-1} h)	323 ± 116 (165–567)	989 ± 166 (766–1221)***
Half-life (h)	2.8 ± 1.1 (1.2–5.6)	8.3 ± 1.4 (6.1–9.8)***
Nitropyridine metabolite		
C_{max} (ng ml^{-1})	68 ± 33 (11–126)	48 ± 40 (17–110)
t_{max} (h)	1.0 ± 1.0 (0.25–4.0)	1.3 ± 1.2 (0.25–3.0)
AUC (ng ml^{-1} h)	154 ± 56 (56–279)	233 ± 55 (157–310)*
Half-life (h)	3.4 ± 1.7 (0.9–7.6)	10.2 ± 3.0 (7.2–14.9)***
Ratio $\frac{\text{AUC nifedipine}}{\text{AUC metabolite}}$	2.3 ± 1.1 (1.1–6.5)	4.6 ± 1.9 (3.0–7.8)**
Urinary excretion of acid metabolite		
0–8 h (% dose)	46.5 ± 13.6 (26.6–75.1)	36.3 ± 3.7 (30.5–40.5)
8–24 h (% dose)	9.5 ± 8.4 (0–37.4)	22.7 ± 9.4 (7.3–32.0)*
0–24 h (% dose)	51.6 ± 15.6 (29.6–97.6)	47.3 ± 6.2 (39.7–52.8)
Half-life (h)	2.6 ± 1.3 (0.9–7.6)	5.4 ± 2.4 (1.4–7.7)*

The results are the mean ± s.d. with the range in parentheses for 27 Caucasians and five South Asians.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, by Wilcoxon's rank sum test.

South Asians (1.4 h) was considerably shorter than the values for the other four subjects (5.8–7.7 h) and was inconsistent with the plasma elimination of the precursors, i.e. nifedipine and the nitropyridine metabolite, in this individual. Only one Caucasian had a terminal half-life of the acid metabolite greater than 4.1 h.

There was no indication that the consumption of a spicy diet by Caucasians was associated with higher plasma concentrations of nifedipine or of its nitropyridine metabolite as was found in the South Asian volunteers. The AUC of nifedipine was slightly lower in six Caucasians following 3 days of consumption of a spicy curry

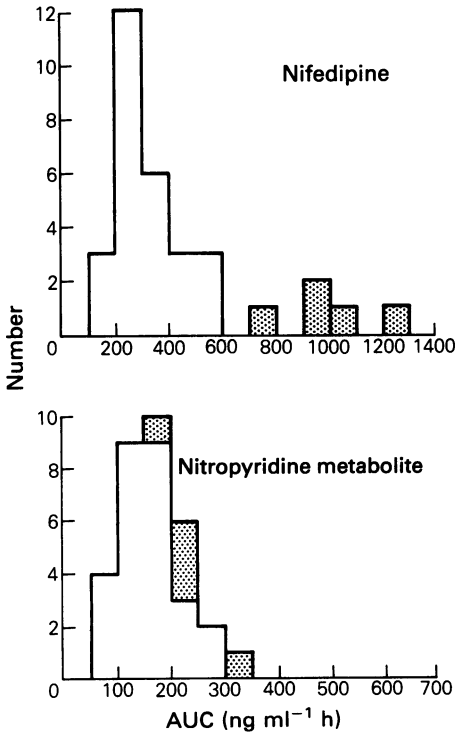

Figure 2 Area under the plasma concentration-time curve for nifedipine and its nitropyridine metabolite in 27 Caucasians (plain) and five South Asians (hatched blocks).

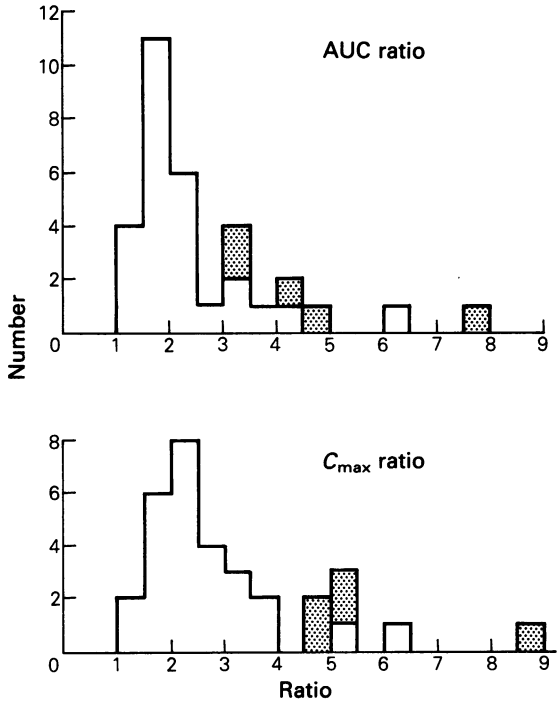

Figure 3 Ratio of the amount of nifedipine in plasma to the amount of the nitropyridine metabolite calculated using the AUC or the observed C_{max}.

Table 2 The influence of a spicy diet on the pharmacokinetics of nifedipine as a single oral dose of 20 mg as capsules

	Western diet	*Spicy diet*
Nifedipine		
C_{max} (ng ml^{-1})	125 ± 67 (59–218)	119 ± 48 (43–172)
t_{max} (h)	0.8 ± 0.6 (0.5–2.0)	0.8 ± 1.1 (0.25–3.0)
AUC (ng ml^{-1} h)	317 ± 93 (217–439)	283 ± 82 (201–405)
Half-life (h)	3.3 ± 0.8 (2.2–4.7)	4.2 ± 0.9 (3.0–5.6)
Nitropyridine metabolite		
C_{max} (ng ml^{-1})	59 ± 39 (24–116)	58 ± 34 (15–101)
t_{max} (h)	1.3 ± 1.4 (0.5–4.0)	0.8 ± 1.1 (0.25–3.0)
AUC (ng ml^{-1} h)	169 ± 45 (111–242)	162 ± 22 (125–187)
Half-life (h)	4.1 ± 0.8 (2.6–4.7)	5.1 ± 1.0 (3.9–6.8)
Ratio $\frac{\text{AUC nifedipine}}{\text{AUC metabolite}}$	1.9 ± 0.6 (1.4–3.0)	1.8 ± 0.5 (1.2–2.5)

The results are the mean ± s.d. with the range in parentheses for six Caucasians on their normal diet and after 3 days of spicy Indian food.

diet but neither this nor any of the other differences detected was statistically significant (Table 2).

Discussion

The three fold greater AUC of nifedipine in South Asians than in Caucasians probably arose from both an increased bioavailability and decreased plasma clearance. The bioavailability of nifedipine in Caucasians is about 0.45 and therefore an increase in bioavailability alone would not be sufficient to account for the magnitude of the difference in the AUC. The significantly longer terminal half-life in the South Asians is consistent with a lower systemic clearance; although a greater apparent volume of distribution cannot be ruled out. Similar, but less extensive differences in nifedipine pharmacokinetics have been reported in elderly Caucasians (> 73 years), although there was a far less pronounced effect on half-life (Robertson *et al.*, 1988).

The nitropyridine metabolite is detected in plasma to a far greater extent after oral than after intravenous dosing (Waller *et al.*, 1984) and therefore it represents a first pass metabolite. The nitropyridine analogue is reported to be the primary metabolite of the single pathway of nifedipine metabolism which itself undergoes biotransformation to the acidic urinary metabolites. Thus the AUC for the nitropyridine metabolite would depend on both the amount which is formed in and released from the liver, mostly during absorption, and the plasma clearance of the metabolite. The higher AUC of the metabolite in South Asians compared with Caucasians is probably due to lower clearance rather than increased formation. The longer terminal half-life of the metabolite in South Asians is consistent with this.

The poor metabolisers of nifedipine identified in a Caucasian population by Kleinbloesem *et al.* (1984a) showed both a high AUC for nifedipine (500–800 ng ml^{-1} h) and a low urinary excretion of the principal acid metabolite (< 25% of the dose in 8 h). The very high AUC in the South Asian subjects was not associated with a low excretion of the acid metabolite (30.5–40.5% of the dose in 8 h) although there was evidence of slower excretion compared with Caucasians.

It has been suggested by Schmid *et al.*, (1986) that calculation of the ratio of the AUC of nifedipine to that of its first pass nitropyridine metabolite would enhance the separation and identification of any poor metabolisers in a Caucasian population. However, the results in Figures 2 and 3 demonstrate clearly that the lower metabolising ability of South Asians was not associated with a low AUC of the primary metabolite and that calculation of the metabolite ratio based on AUC or even maximum plasma concentration (Figure 3) did not enhance the separation of the two groups.

All of the South Asian volunteers complained of marked palpitations which were not reported by the Caucasians, indicating that there may have been ethnic differences in pharmacodynamic response. However, cardiovascular parameters were not measured in this pharmacokinetic study and this observation requires proper validation. In this context it is interesting to note that ethnic differences between South Asians and Caucasians in their response to β-adrenoceptor blockers have been reported recently by Rahman & Bennett (1990).

The biological basis for the higher AUC and longer half-life in South Asians could be either i) a genetically determined difference in cytochrome P450IIIA3, arising from a difference in enzyme affinity or a decreased amount of enzyme expression, ii) increased plasma protein binding or iii) the presence of a component of spicy diets which inhibits cytochrome P450IIIA3. Nifedipine is highly bound to plasma proteins (Otto & Lesko, 1986) and therefore an increase in albumin and or α_1-acid glycoprotein concentrations in South Asians could give higher plasma concentrations. However, nifedipine is a high clearance drug and therefore an increased plasma protein binding would give a lower apparent volume of distribution and a shorter half-life. The longer half-life detected indicates a decrease in metabolism not an increase in protein binding.

The possibility of an inhibitory dietary component, which would be consistent with the high AUCs of nifedipine in Mexicans (Hoyo-Vadillo *et al.*, 1989), was in-

vestigated by studying the pharmacokinetics of nifedipine in Caucasians on a normal western diet and following 3 days of consumption of a spicy curry diet. There was no evidence of any trend towards an increased AUC of nifedipine following the curry diet (Table 2) or other changes consistent with the ethnic differences shown in Table 1. Although this study is of low power, the AUC of nifedipine following the curry diet was actually lower than following the normal diet and this difference approached statistical significance by 2-way analysis of variance; therefore even if many more subjects had been studied a highly statistically significant increase in AUC is very unlikely to have been detected. A further possible criticism of this study concerns the duration of dietary modification. If an inhibitory spice component had a half-life greater than 1 day, then steady-state would not have been approached in the Caucasians, and this could have resulted in the failure to detect an increase in the AUC. Thus if the postulated inhibitory component had a half-life of 10 days, the Caucasians would have reached less than 20% of the steady state concentration that would be present in the South Asians, all of whom had retained their original dietary practices. Nevertheless the absence of any suggestion of an increase in the AUC of nifedipine indicates that the consumption of a spicy diet is unlikely to be the source of the ethnic differences detected. An alternative explanation of the data is that the Western diet contains an inducer of cytochrome P450IIIA3, a possibility that cannot be excluded from the data presented in this paper.

In conclusion, these observations indicate that individuals of South Asian origin show a lower ability to metabolise nifedipine than Caucasians. This difference would result in higher plasma concentrations following chronic administration and therefore lower doses of nifedipine should be given to South Asians to obtain therapeutic benefits without excessive side effects.

We are grateful to the Association of Commonwealth Universities and Bayer, UK for financial support, and the Association of Commonwealth Universities for a scholarship for C. H. Ahsan.

References

Challenor, V. F., Waller, D. G., Renwick, A. G., Gruchy, B. S. & George, C. F. (1987). The transhepatic extraction of nifedipine. *Br. J. clin. Pharmac.*, **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. Pharmac.*, **2**, 161–170.

Gibaldi, M. & Perrier, D. (1982). In *Pharmacokinetics*, pp. 56–59. New York: Marcel Dekker.

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.

Hoyo-Vadillo, C., Castaneda-Hernandez, G., Herrera, J. E., Vidal-Garate, J., Moreno-Ramos, A., Chavez, F. & Hong, E. (1989). Pharmacokinetics of nifedipine slow release tablet in Mexican subjects: further evidence for an oxidation polymorphism. *J. clin. Pharmac.*, **29**, 816–820.

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. Pharmac.*, **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.

Nebert, D. W., Adesnik, M., Coon, M. J., Estabrook, R. W., Gonzalez, F. J., Guengerich, F. P., Gungsalus, I. C., Johnson, E. F., Kemper, B., Levin, W., Phillips, J. R., Sato, R. & Waterman, M. R. (1987). The P-450 gene superfamily: recommended nomenclature. *DNA*, **6**, 1–11.

Otto, J. & Lesko, L. J. (1986). Protein binding of nifedipine. *J. Pharm. Pharmac.*, **38**, 399–400.

Rahman, M. A. & Bennett, T. (1990). The effects of propranolol or atenolol on the cardiovascular responses to central hypovolaemia in Europeans and Bengalees. *Br. J. clin. Pharmac.*, **29**, 69–77.

Renwick, A. G., Le Vie, J., Challenor, V. F., Waller, D. G., Gruchy, B. & George, C. F. (1987). Factors affecting the pharmacokinetics of nifedipine. *Eur. J. clin. Pharmac.*, **32**, 351–355.

Renwick, A. G., Robertson, D. R. C., Macklin, B., Challenor, V., Waller, D. G. & George, C. F. (1988). The pharmacokinetics of oral nifedipine—a population study. *Br. J. clin. Pharmac.*, **25**, 701–708.

Robertson, D. R. C., Waller, D. G., Renwick, A. G. & George, C. F. (1988). Age related changes in the pharmacokinetics and pharmacodynamics of nifedipine. *Br. J. clin. Pharmac.*, **25**, 297–305.

Schellens, J. H. M., Soons, P. A. & Breimer, D. D. (1988). Lack of bimodality in nifedipine plasma kinetics in a large population of healthy subjects. *Biochem. Pharmac.*, **37**, 2507–2510.

Schmid, B., Penny, H., Feher, M., Sever, P. & Idle, J. (1986). Impaired metabolic dehydrogenation of nifedipine. *Acta Pharmac. Tox.*, **59**, Suppl. 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 23 July 1990, accepted 14 November 1990)