Br. J. clin. Pharmac. (1991), **32**, 11–16 ADONIS 030652519100110N

Stereoselective pharmacokinetics of oral and intravenous nitrendipine in healthy male subjects

P. A SOONS & D. D. BREIMER
Center for Bio-Pharmaceutical Sciences, Division of Pharmacology, Leiden University, P.O. Box 9503, Leiden, The Netherlands

1 Stereoselectivity in the pharmacokinetics of nitrendipine was investigated by re-analysing plasma samples of a previously published study (Soons *et al.*, 1989).

2 Racemic nitrendipine was administered intravenously (40 $\mu g\ kg^{-1}$) and orally, both as plain tablet (20 mg) and in an osmotic pump device (40 mg Osmet®) to nine healthy male subjects. Nitrendipine enantiomers were measured with a stereoselective assay.

3 Upon oral administration (tablet) the bioavailability of (S)-(–)-nitrendipine (13.4% ± 5.6%) was 75% {50% – 98%} higher than that of (R)-nitrendipine (7.9% ± 4.0%) (mean ± s.d. {95% confidence interval}). Values of AUC and C_{max} for (S)-nitrendipine were 90% {55% – 121%} and 77% {51% – 100%} higher respectively, than those for (R)-nitrendipine. Similar results were obtained with the osmotic system.

4 The clearance of intravenously administered (S)-nitrendipine was slightly (7%) lower than that of (R)-nitrendipine, but elimination half-lives and volumes of distribution were similar.

5 The difference in disposition of nitrendipine enantiomers is most likely related to a difference in activity of the cytochrome P-450 system towards the enantiomers, giving rise to a two-fold difference in first-pass elimination.

6 Stereoselectivity in the first pass metabolism of nitrendipine exhibited little inter-subject variability and therefore is not a major factor in the wide variability in systemic availability of the more-potent (S)-enantiomer.

Keywords stereoselectivity nitrendipine pharmacokinetics

Introduction

Nitrendipine (Figure 1), a chiral dihydropyridine calcium entry blocker, is used as the racemate for the treatment of hypertension. The pharmacokinetics of the racemic drug have been studied in young healthy subjects (Krol *et al.*, 1987; Mikus *et al.*, 1987; Rämsch *et al.*, 1986; Soons *et al.*, 1989). In all studies a wide inter-individual variability in the pharmacokinetics of orally administered racemic nitrendipine was observed, comparable with the variability known to occur with other orally administered dihydropyridines (Soons *et al.*, 1991). Most of this variability can be attributed to variable presystemic elimination of the drug since it is much less following intravenous administration, and the absorption from the g.i. tract is almost complete (Krol *et al.*, 1987; Mikus *et al.*, 1987).

Since nitrendipine is a racemate, differences between its two enantiomers (Figure 1) are to be anticipated, both in their pharmacodynamic and pharmacokinetic properties (Drayer 1986; Jamali *et al.*, 1989; Vermeulen & Breimer, 1983). It has recently been shown that most of the calcium entry blocking potency in man *in vivo* resides in the (S)-(–)-enantiomer (Mikus *et al.*, 1989a; Mörike *et al.*, 1989). *In vitro* bindings studies and *ex vivo* pharmacodynamic experiments suggest an eight-fold difference in potency of the nitrendipine enantiomers (Eltze *et al.*, 1990).

Stereoselective disposition of stable-isotope-labelled nitrendipine (pseudo-racemate) has been shown to occur in healthy subjects (Mikus *et al.*, 1989a,b), with the more active (S)-enantiomer reaching higher plasma

Correspondence: Professor Dr D. D. Breimer, Division of Pharmacology, Center for Bio-Pharmaceutical Sciences, P.O. Box 9503, NL-2300 RA Leiden, The Netherlands

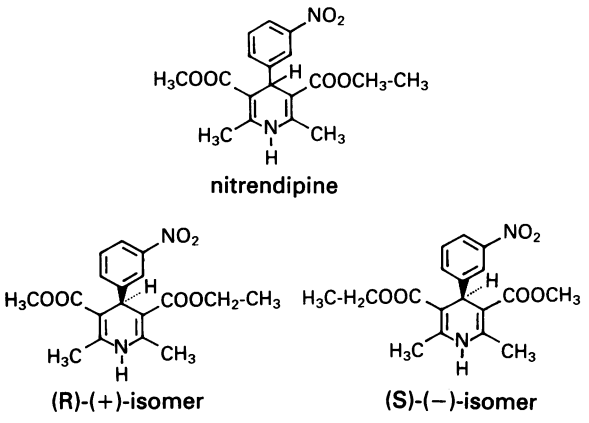

Figure 1 Structural formulas of nitrendipine and its enantiomers.

concentrations. We have recently developed an analytical method, based on chiral-column liquid chromatography with off-line detection using gas chromatography with electron capture detection, that allows stereoselective analysis of nitrendipine-enantiomers (and of various other dihydropyridine calcium entry blockers) when administered as the unlabelled racemate (Soons *et al.*, 1990a). Some preliminary results with nitrendipine, administered as unlabelled racemate, have been reported (Soons *et al.*, 1990b).

We have previously reported on the pharmacokinetics and oral absorption profile of racemic nitrendipine (Soons *et al.*, 1989). At the time of that study (1986) stereoselective analytical methodology was not available. Therefore, no distinction could be made between the (S)- and (R)-enantiomers, and hence some of the parameters reported (especially clearance and bioavailability) are hybrid parameters. Therefore, all available plasma samples from this previous study were reanalysed and we now report the stereoselective disposition of nitrendipine in young healthy male subjects after both oral and intravenous administration.

Methods

The present data were obtained by reanalysing plasma samples obtained in a previous study published in this Journal where a full description of subjects, experimental drugs, ethics approval and experimental protocol is given (Soons *et al.*, 1989).

In short, nine healthy male subjects (age 24 ± 3 years, weight 74 ± 6 kg, height 187 ± 6 cm, three smokers of cigarettes) were given racemic nitrendipine at 1 week intervals by intravenous infusion (40 $\mu g\ kg^{-1}$ in 4 min), orally as a tablet (20 mg) and as a 40 mg oral osmotic pump device (Osmet®, ALZA, Palo Alto, USA) with an essentially zero-order release rate of 2.6 ± 0.2 $mg\ h^{-1}$ for 13 h. Although blood samples were taken up to 48 h on all occasions, only plasma samples up to 12 h (intravenous and tablet) and 24 h (Osmet) after administration were available for reanalysis. The samples had been stored at −30 °C for 3.5 years excluding all light. Plasma concentrations of racemic nitrendipine and of its enantiomers were measured using capillary gas chromatography with electron capture detection (Soons & Breimer, 1988) and chiral-column liquid chromatography with off-line GC-ECD detection (Soons *et al.*, 1990a), respectively. Limits of reliable determination were at least 0.2 ng ml^{-1} for all compounds and the inter-assay coefficient of variation was <9% for racemic nitrendipine and <15% for the enantiomers. For the purpose of this study chiral inversion was investigated, but could not be detected in human plasma, spiked with pure enantiomers of nitrendipine and stored at −30 °C for 10 months or for 14 days at room temperature (20–22 °C). Furthermore, no chiral inversion of nilvadipine-enantiomers was observed in dogs *in vivo* (Tokuma *et al.*, 1987).

Upon i.v. administration, the terminal half-life ($t_{1/2}$) and distribution volume of the central compartment (V_1) were calculated from the coefficients and exponents of two- or three-exponential functions fitted to the data using weighted non-linear regression analysis (Siphar® release 3.0, Simed, Créteil, France). A likelihood ratio test was applied to discriminate between functions (Landaw & DiStefano, 1984). All other pharmacokinetic parameters (area under plasma concentration-time curve (AUC), systemic plasma clearance (CL), absolute systemic bioavailability (F), volume of distribution at steady state (V_{ss}), mean residence time (MRT) and mean absorption time (MAT) were calculated using standard non-compartmental techniques (Gibaldi & Perrier, 1982; Soons *et al.*, 1989). As an index of stereoselectivity in pharmacokinetics, the S-to-R-ratio of pharmacokinetic parameters was calculated for each subject. Differences in pharmacokinetic parameters between (S)- and (R)-nitrendipine and between tablet and Osmet were tested using paired t-tests after logarithmic transformation of the data. Product-moment correlation coefficients were calculated and tested against zero. Results are reported as mean ± s.d. (range) {95% confidence interval} unless stated otherwise.

Data concerning haemodynamic and adverse effects, as well as pharmacokinetic data for the primary pyridine metabolite, have been reported previously (Soons *et al.*, 1989), and will not be discussed in this paper.

Results

After oral administration, plasma concentrations of (S)-nitrendipine were about twice those of the (R)-enantiomer, whereas after intravenous administration the difference was much smaller (Tables 1, 2 and 3).

After oral nitrendipine, highly significant differences in AUC, C_{max} and F were observed between the enantiomers, both with the tablet and with the Osmet (Tables 2 and 3). On average the AUC of (S)-nitrendipine was almost twice that of the (R)-enantiomer, and the bioavailability of (S)-nitrendipine was 75% {50% – 98%} and 82% {62% – 101%} higher than that of the (R)-enantiomer for the tablet and Osmet formulation respectively. No differences in MAT between enantiomers were observed, and the times of maximum plasma concentration (t_{max}) of both enantiomers were identical in all subjects. The S/R-ratios of AUC, C_{max} and F, were

Table 1 Pharmacokinetic parameters* of racemic nitrendipine and its (S)- and (R)-enantiomers after intravenous administration (40 μg kg^{-1} over 4 min) of the racemate.

	rac-nitrendipine	*(S)-enantiomer*	*(R)-enantiomer*	*S/R-ratio*	P†
CL (l min^{-1})	1.56 ± 0.25 (1.35 – 1.86)	1.51 ± 0.25 (1.22 – 1.80)	1.62 ± 0.25 (1.26 – 1.91)	0.93 {0.88 – 0.99}	0.024
V_1 (l kg^{-1})	1.49 ± 0.81 (0.59 – 3.03)	1.56 ± 0.82 (0.55 – 3.17)	1.49 ± 0.88 (0.60 – 2.91)	1.10 {0.93 – 1.26}	0.27
V_{ss} (l kg^{-1})	3.79 ± 1.32 (1.55 – 6.06)	3.94 ± 1.46 (1.58 – 6.41)	3.71 ± 1.27 (1.49 – 6.06)	1.06 {0.99 – 1.12}	0.097
$t_{1/2}$ (h)	4.0 ± 1.6 (1.3 – 6.1)	4.3 ± 1.9 (1.4 – 7.1)	4.0 ± 1.4 (1.3 – 5.9)	1.07 {0.98 – 1.15}	0.12
MRT (h)	3.0 ± 1.1 (1.4 – 1.1)	3.2 ± 1.3 (1.5 – 6.1)	2.8 ± 1.0 (1.4 – 5.0)	1.14 {1.07 – 1.20}	0.001

* (mean ± s.d. (range) {95% CI}) † (S)-enantiomer *vs* (R)-enantiomer

Table 2 Pharmacokinetic parameters* of racemic nitrendipine and its (S)- and (R)-enantiomers after oral administration (20 mg tablet) of the racemate.

	rac-nitrendipine	*(S)-enantiomer*	*(R)-enantiomer*	*S/R-ratio*	P†
AUC (ng ml^{-1} h)	21.4 ± 13.8 (10.7 – 54.1)	15.5 ± 8.5 (6.3 – 31.3)	8.5 ± 5.7 (4.5 – 22.8)	1.90 {1.55 – 2.21}	0.001
C_{max} (ng ml^{-1})	7.53 ± 6.89 (3.14 – 24.8)	4.67 ± 3.95 (2.14 – 14.3)	2.91 ± 3.09 (1.00 – 10.9)	1.77 {1.51 – 2.00}	0.001
F (%)	10.7 ± 4.7 (5.2 – 19.9)	13.4 ± 5.6 (6.0 – 23.3)	7.9 ± 4.0 (4.3 – 17.3)	1.75 {1.50 – 1.98}	0.001
$t_{1/2}$ (h)	3.3 ± 1.3 (2.0 – 6.0)	3.3 ± 1.3 (2.0 – 6.1)	3.2 ± 1.3 (1.9 – 5.8)	1.04 {0.96 – 1.11}	0.34
AUMC/AUC (h)	5.1 ± 1.1 (4.0 – 7.7)	5.2 ± 1.2 (4.0 – 7.9)	5.0 ± 1.1 (4.0 – 7.4)	1.05 {1.02 – 1.08}	0.009
MAT (h)	2.1 ± 1.3 (0.4 – 4.9)	2.0 ± 1.5 (0.0 – 4.9)	2.1 ± 1.3 (0.5 – 4.9)	0.80 {0.44 – 1.28}	0.25

* (mean ± s.d. (range) {95% CI}) † (S)-enantiomer *vs* (R)-enantiomer

Table 3 Pharmacokinetic parameters* of racemic nitrendipine and its (S)- and (R)-enantiomers after oral administration (40 mg Osmet) of the racemate.

	rac-nitrendipine	*(S)-enantiomer*	*(R)-enantiomer*	*S/R-ratio*	P†
AUC (ng ml^{-1} h)	38.4 ± 12.6 (20.9 – 56.2)	25.6 ± 9.2 (12.4 – 40.2)	12.9 ± 3.8 (8.5 – 20.0)	1.97 {1.66 – 2.26}	0.001
C_{max} (ng ml^{-1})	3.33 ± 1.70 (1.30 – 6.58)	2.22 ± 1.26 (0.77 – 4.85)	1.10 ± 0.43 (0.53 – 1.75)	1.94 {1.58 – 2.26}	0.001
F (%)	8.7 ± 1.9 (5.0 – 11.0)	11.1 ± 2.6 (6.0 – 14.7)	6.1 ± 1.2 (4.1 – 7.6)	1.82 {1.62 – 2.01}	0.001
$t_{1/2}$ (h)	6.8 ± 4.8 (4.0 – 19.2)	5.7 ± 1.8 (4.0 – 9.3)	5.5 ± 1.4 (3.9 – 7.6)	1.03 {0.91 – 1.31}	0.30
AUMC/AUC (h)	10.7 ± 1.5 (9.2 – 14.1)	10.8 ± 1.5 (9.1 – 14.2)	10.5 ± 1.4 (9.4 – 14.0)	1.03 {0.99 – 1.07}	0.13
MAT (h)	7.7 ± 1.0 (6.4 – 9.3)	7.6 ± 1.1 (6.1 – 9.4)	7.7 ± 0.9 (6.4 – 9.0)	0.99 {0.91 – 1.06}	0.66

* (mean ± s.d. (range) {95% CI}) † (S)-enantiomer *vs* (R)-enantiomer

the same for the tablet and the osmotic system (all $P > 0.10$).

After intravenous administration, a small but significant difference in clearance of the two enantiomers was observed: the CL of (S)-nitrendipine was 7% {1%–12%} lower than that of (R)-nitrendipine. Distribution volumes (V_1 and V_{ss}) of the enantiomers were not significantly different and neither were the elimination half-lives, both after oral and intravenous administration.

The average S/R-ratio of plasma concentrations after i.v infusion and the Osmet are shown in Figure 2. After i.v. nitrendipine, a small but clear deviation from unity developed between 1.5 and 4 h after administration. Subsequently, the mean ratio remained essentially constant at a level of 1.2 – 1.3. With the Osmet the mean ratio remained constant at a level of 1.7 – 1.9. However, inter-individual variability was much larger for the Osmet compared with i.v. administration.

The shape of the input profiles of nitrendipine-enantiomers into the body, as obtained by numerical deconvolution and normalized for systemic availability, were similar to those reported previously for the racemate (Soons *et al.*, 1989). The profiles for the two enantiomers were almost super-imposable, and statistical analysis revealed identical results to the racemate.

Discussion

An almost two-fold difference in plasma concentrations and AUC between the enantiomers of nitrendipine was observed after oral administration, with the more potent (S)-(–)-enantiomer having the highest systemic availability. The differences in the pharmacokinetics of the enantiomers after i.v. administration were much smaller, with no differences in elimination half-lives. This was to be expected because of flow-limited clearance and similar volumes of distribution of the enantiomers. Several other dihydropyridine calcium entry blockers have been shown to exhibit stereoselectivity in their pharmacokinetics after oral administration to man. For felodipine (Soons *et al.*, 1990a,b) also the (S)-(–)-enantiomer has the highest AUC,

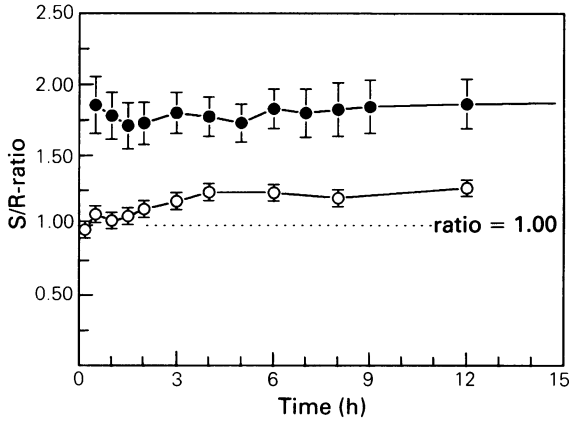

Figure 2 Plasma concentration ratio (S over R) for nitrendipine after intravenous (40 μg kg^{-1}) administration (○) and after oral administration of 40 mg Osmet (●). (mean ± s.e. mean, all points $n = 9$).

whereas for nilvadipine (Tokuma *et al.*, 1987) and nisoldipine (Frost *et al.*, 1990) the (+)-enantiomer reaches the highest concentrations. For all these dihydropyridines studied in man it is the more potent enantiomer that has the higher AUC after oral administration.

The marked difference in AUC between enantiomers upon oral administration could theoretically be accounted for partially by differences in the extent of absorption from the intestinal lumen. However, since the absorption of the racemate is at least 80–90% (Krol *et al.*, 1987; Mikus *et al.*, 1987), a difference of only 25–50% could cause such a difference in absorption. In general, absorption from the g.i. tract of lipophilic drugs such as nitrendipine involves mainly passive diffusion which does not discriminate between enantiomers; carrier-mediated absorption of dihydropyridines has not been described. Furthermore, the S/R-ratio of AUCs after i.v. infusion correlated with those following the tablet ($r^2 = 0.60$, $P = 0.014$) and the Osmet ($r^2 = 0.70$, $P = 0.005$). Thus, most of the stereoselectivity after oral administration can be explained by a phenomenon which also applies to systemic elimination, thereby excluding stereoselective absorption.

The most likely cause of the observed difference in pharmacokinetic behaviour is a difference in intrinsic clearance of the two enantiomers. At present it cannot be discerned whether this is caused by differences in protein binding or by differences in intrinsic clearance of the unbound drug. Preliminary data on the plasma protein binding of nitrendipine enantiomers in human plasma suggest only a minor difference ((S)-nitrendipine 98.4 ± 0.5% and (R)-nitrendipine 98.7 ± 0.6%) (Soons, unpublished observations) which is supported by the almost identical V_{ss} of both enantiomers. Biotransformation plays the predominant role in the elimination of nitrendipine, and this takes place almost exclusively by oxidative metabolism (Krol *et al.*, 1987; Rämsch *et al.*, 1986), presumably mediated by cytochrome P-450 IIIA4 or closely related isoenzymes (Guengerich, 1989; Guengerich & Böcker, 1988; Guengerich *et al.*, 1986). *In vitro* experiments with human and rat liver microsomes and purified cytochrome P-450 isoenzymes have shown a two-fold difference in V_{max}/K_m for the (unbound) enantiomers of nilvadipine (Niwa *et al.*, 1988), of niguldipine (Simon *et al.*, 1988) and of the dihydropyridine calcium entry promoter Bay k 8644 (Guengerich & Böcker, 1988). Stereoselective disposition of nilvadipine in man could not be accounted for by stereoselective protein binding (Niwa *et al.*, 1988). Further research is required to confirm that the stereoselectivity in the pharmacokinetics of nitrendipine is caused by a difference in the activity of (specific) cytochrome P-450 isoenzymes.

Although the bioavailability of racemic nitrendipine and of its enantiomers, comparing tablet and Osmet, were not significantly different (all $P > 0.15$), there was only a modest relationship between these parameters for the two oral formulations (all $r^2 < 0.5$, $P > 0.03$). However, high correlations between the tablet and the Osmet were found for the S/R-ratios of AUC ($r^2 = 0.93$, $P < 0.001$), C_{max} ($r^2 = 0.65$; $P = 0.009$) and F ($r^2 = 0.88$, $P < 0.001$). This slight intra-individual variability in

stereoselectivity is unlikely to contribute substantially to the intra-subject variability in the AUC of the enantiomers. Furthermore, the well-known inter-subject variability in the pharmacokinetics of oral nitrendipine seems to be independent of stereochemical factors as indicated by the poor correlation between the S/R-ratio of AUCs and AUC of the racemate (for all formulations $r^2 < 0.2, P > 0.2$). The AUC (i.v. and p.o.) and bioavailability (p.o.) of the more-active (S)-enantiomer were highly correlated with the AUC of the racemate after intravenous ($r^2 \geq 0.88$, $P < 0.001$) and oral administration (tablet and Osmet both $r^2 \geq 0.96$, $P < 0.001$). Apparently, plasma concentrations, AUC and F of the more potent (S)-enantiomer can be predicted on the basis of a knowledge of these parameters for the racemic drug, at least in this (homogenous) group of young healthy subjects.

Generally the pharmacokinetic parameters of the racemate deviated more (V_{ss}, $t_{1/2}$, MRT, MAT) or less (CL, F, V_1, AUC) from the previously published values. This can be explained by the fact that only samples up to 12 h were used for the present evaluation. The half-life of drugs exhibiting multiexponential disposition kinetics is dependent on the sampling period (Soons *et al.*, 1989) and influences the extrapolation to infinity of AUC and AUMC and parameters derived therefrom. The presently reported $t_{1/2}$ (4–7 h) is not the terminal $t_{1/2}$ since a value of 12–14 h was observed with a 48 h sampling period (Soons *et al.*, 1989).

The mean blood/plasma concentration ratios of (S)-nitrendipine, (R)-nitrendipine and the racemate are 1.57, 1.31 and 1.46, respectively (Soons, unpublished observations). Using these values, a blood clearance of both enantiomers and of the racemate of 2.1–2.4 l min^{-1} was calculated which exceeds the expected splanchnic blood flow in these subjects (1.6–1.7 l min^{-1}) by about 20–40% (Richardson & Withrington, 1981), indicating substantial extra-hepatic elimination of intravenous nitrendipine. Dihydropyridine-oxidising cytochrome P-450 IIIA-isozymes have been detected in several human tissues besides the liver, in particular in intestinal and lung preparations (Guengerich, 1989; de Waziers *et al.*, 1990). Intestinal (e.g. gut wall) elimination, however, is unlikely to contribute to the apparently erratically high systemic clearance since intestinal perfusion is almost completely in series with hepatic perfusion (Richardson & Withrington, 1981). Possibly a small (*circa* 10%) extraction across the lungs contributes significantly to the systemic clearance of i.v. administered nitrendipine because the lungs are located presytemically relative to the venous sampling site ('first-pass' effect) and because the total lung blood flow is very high (*circa* 6 l min^{-1}).

The present pharmacokinetic parameters are not necessarily identical to the parameters of the separate enantiomers, because they were administered together and therefore may have influenced each other's kinetics. A pharmacokinetic interaction between nitrendipine enantiomers was observed when administering pure, labelled enantiomers and the labelled pseudo-racemate (Mikus *et al.*, 1989a,b). The AUC of oral (R)-nitrendipine was almost doubled by simultaneous oral administration of (S)-nitrendipine. In addition to inhibition at the enzyme level (Mikus *et al.*, 1989b), a pharmacodynamic effect may also account for the observed interaction. Several dihydropyridines have been shown to increase liver blood flow, which appears to be a temporary effect during the oral absorption phase (Soons *et al.*, 1991; van Harten *et al.*, 1989). Only (S)-nitrendipine will increase liver blood flow, thereby decreasing presystemic elimination of (R)-nitrendipine upon simultaneous administration. When (R)-nitrendipine is administered alone, it will be subject to higher presystemic elimination because splanchnic blood flow remains at its baseline value. In both situations, the elimination of (R)-nitrendipine during systemic recirculation will be similar since liver blood flow will have returned to its (low) baseline value after the absorption phase is over.

In conclusion, stereoselective disposition of nitrendipine occurs in healthy subjects with the more active (S)-enantiomer reaching almost two-fold higher plasma concentrations than the (R)-enantiomer on oral administration.

The skilful technical assistance of Margret C. M. Roosemalen is gratefully acknowledged. Part of the data have been presented at the XIth International Congress of Pharmacology of IUPHAR, Amsterdam, 1–6 July 1990.

References

de Waziers, I., Cugnenc P., Yang, C. S., Leroux, J-P. & Beaune, P. H. (1990). Cytochrome P-450 isoenzymes, epoxide hydrolase and glutathione transferases in rat and human hepatic and extrahepatic tissues. *J. Pharmac. exp. Ther.*, **253**, 387–394.

Drayer, D. E. (1986). Pharmacodynamic and pharmacokinetic differences between drug enantiomers in humans: an overview. *Clin. Pharmac. Ther.*, **40**, 125–133.

Eltze, M., Boer, R., Sanders, K. H., Boss, H., Ulrich, W. R. & Flockerzi, D. (1990). Stereoselective inhibition of thromboxane-induced coronary vasoconstriction by 1,4-dihydropyridine calcium channel antagonists. *Chirality*, **2**, 233–240.

Frost, N., Ahr, G., Weber, H. & Kuhlmann, J. (1990). Nisoldipine enantiomers — Assessment of pharmacokinetics by stable isotope technique. In *Dose-Response Relationship of Drugs,* eds. Kuhlmann, J. & Wingender, W., pp. 87–92. Munich: W. Zuckschwerdt Verlag.

Gibaldi, M. & Perrier, R. (1982). *Pharmacokinetics,* second edition. New York: Marcel Dekker.

Guengerich, F. P. (1989). Characterization of human microsomal cytochrome P-450 enzymes. *Ann. Rev. Pharmac. Toxicol.*, **29**, 241–264.

Guengerich, F. P. & Böcker, R. H. (1988). Cytochrome P-450-catalyzed dehydrogenation of 1,4-dihydropyridines. *J. biol. Chem.*, **263**, 8168–8175.

Guengerich, F. P., Martin, M. V., Beaune, P. H., Kremers, P., Wolff, T. & Waxman, D. J. (1986). Characterization of

rat and human liver microsomal cytochrome P-450 involved in nifedipine oxidation, a prototype for genetic polymorphism in oxidative drug metabolism. *J. biol. Chem.*, **261**, 5051–5060.

Jamali, F., Mehvar, R. & Pasutto, F. M. (1989). Enantioselective aspects of drug action and disposition: therapeutic pitfalls. *J. pharm. Sci.*, **78**, 695–715.

Krol, G. J., Lettieri, J. T., Yeh, S. C., Burkholder, D. E. & Birkett, J. P. (1987). Disposition and pharmacokinetics of ^{14}C-nitrendipine in healthy volunteers. *J. cardiovasc. Pharmac.*, **9** (suppl. 4),. S122–S128.

Landaw, E. M. & DiStefano, J. J. (1984). Multiexponential, multicompartmental, and noncomparmental modelling. II. Data analysis and statistical considerations. *Am. J. Physiol.*, **246**., R665–R677.

Mikus, G., Fischer, C., Heuer, B., Langen, C. & Eichelbaum, M. (1987). Application of stable isotope methodology to study the pharmacokinetics, bioavailability and metabolism of nitrendipine after i.v. and p.o. administration. *Br. J. clin. Pharmac.*, **24**, 561–569.

Mikus, G., Mast, V., Ratge, D., Wisser, H. & Eichelbaum, M. (1989a). Pharmacokinetics, hemodynamic and biochemical effects of the nitrendipine enantiomers. *Eur. J. clin. Pharmac.*, **36** (suppl.), A179.

Mikus, G., Mast, V. & Eichelbaum, M. (1989b). First-pass-metabolismus, bioverfügbarkeit und pharmacokinetik der nitrendipin-enantiomere. *Klin. Wochenschr.*, **67** (suppl. 16), 121–122.

Mörike, K., Mast, V., Mikus, G., Ratge, D., Wisser, H. & Eichelbaum, M. (1989). Hämodynamische und biochemische wirkungen der nitrendipin-enantiomere. *Klin. Wochenschr.*, **67** (suppl. 16), 120–121.

Niwa, T., Tokuma, Y., Nakagawa, K., Noguchi, H., Yamazoe, Y. & Kato, R. (1988). Stereoselective oxidation and plasma protein binding of nilvadipine, a new dihydropyridine calcium antagonist, in man. *Res. Comm. chem. Path. Pharmac.*, **60**, 161–172.

Rämsch, K.-D., Graefe, K.-H., Scherling, D., Sommer, J. & Ziegler, R. (1986). Pharmacokinetics and metabolism of calcium-blocking agents nifedipine, nitrendipine and nimodipine. *Am. J. Nephrol.*, **6**(suppl. 1), 73–80.

Richardson, P. D. I. & Withrington, P. G. (1981). Liver blood flow: I Intrinsic and nervous control of liver blood flow. *Gastroenterol.*, **81**, 159–173.

Simon, W. A., Mayer, A. & Zech, K. (1988). Stereospecific and species dependent biotransformation of the Ca^{++}-antagonist niguldipine in vitro. Presented at the *11th European Workshop on Drug Metabolism*, 11–16 September 1988, Konstanz, FRG.

Soons, P. A. & Breimer, D. D. (1988). Gas chromatographic analysis of nitrendipine and its pyridine metabolite in human plasma. *J. Chromatogr.*, **428**, 362–368.

Soons, P. A., de Boer, A. G., van Brummelen, P. & Breimer, D. D. (1989). Oral absorption profile of nitrendipine in healthy subjects: a kinetic and dynamic study. *Br. J. clin. Pharmac.*, **27**, 179–189.

Soons, P. A., Mulders, T. M. T., Uchida, E., Cohen, A. F. & Breimer, D. D. (1990b). Stereoselective kinetics of felodipine and nitrendipine in man. *Clin. Pharmac. Ther.*, **47**, 158.

Soons, P. A., Roosemalen, M. C. M. & Breimer, D. D. (1990a). Enantioselective determination of felodipine and other chiral dihydropyridine calcium entry blockers in human plasma. *J. Chromatogr.*, **528**, 343–356.

Soons, P. A. Schellens, J. H. M. & Breimer, D. D. (1991). Variability in pharmacokinetics and metabolism of nifedipine and other dihydropyridine calcium entry blockers. In *Genetic Factors Influencing the Metabolism of Foreign Compounds*, ed. Kalow, W. Oxford: Pergamon Press (in press).

Tokuma, Y., Fujiwara, T. & and Noguchi, H. (1987). Plasma levels of (+)- and (−)-nilvadipine after oral dosing with racemic (±)-nilvadipine in man. *Res. Comm. chem. Path. Pharmac.*, **57**, 229–237.

van Harten, J., Burggraaf, J., Danhof, M., van Brummelen, P. & Breimer, D. D. (1989). The contribution of nisoldipine-induced changes in liver blood flow to its pharmacokinetics after oral administration. *Br. J. clin Pharmac.*, **27**, 581–586.

Vermeulen, N. P. E. & Breimer, D. D. (1983). Stereoselectivity in drug and xenobiotic metabolism. In *Stereochemistry and Biological Activity of Drugs*, eds. Ariëns, E. J., Soudijn, W. & Timmermans, P. B. M. W. M., pp. 33–53. Oxford: Blackwell Scientific Publications.

(Received 5 October 1990, accepted 14 January 1991)