Br. J. clin. Pharmac., (1984), **18**, 951–954

The first pass metabolism of nifedipine in man

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Oral administration of nifedipine (20 and 30 mg tablets) to six volunteers was associated with a bioavailability of 0.43 and the presence of its nitropyridine analogue in the plasma. This metabolite was present in only trace amounts in samples taken from the same volunteers following i.v. administration of nifedipine. The peak plasma concentrations and area under the plasma concentration-time curve suggest that the nitropyridine analogue is a major, first pass, metabolite of nifedipine.

Keywords nifedipine first pass metabolism pharmacokinetics

Introduction

Nifedipine (4-[2′-nitrophenyl]-2,6-dimethyl-1,4-dihydroipyridine-3,5-dicarboxylic acid dimethyl ester) is a dihydropyridine derivative used in the treatment of angina pectoris and hypertension. Similar amounts of radioactivity were detected in the urine after oral and i.v. doses of [^{14}C]-nifedipine (Horster *et al.*, 1972) demonstrating that the drug was well absorbed from the gastrointestinal tract. However, the oral bioavailability (based on measurement of the area under the plasma concentration–time curve (AUC) of the parent drug is only 0.45 (Foster *et al.*, 1983) which suggests that the drug undergoes extensive first pass metabolism in man.

Foster *et al.* (1983) detected an additional peak on g.l.c. analysis of plasma samples obtained after oral, but not i.v., dosing but did not identify this peak. However, the nitropyridine analogue of nifedipine (4-[2′-nitrophenyl]2,6-dimethylpyridine-3,5-dicarboxylic acid dimethyl ester) (B4759) has been detected in the plasma of patients receiving nifedipine using recently developed h.p.l.c. g.l.c. and capillary g.l.c. techniques (Dokladalova *et al.*, 1982; Raemsch & Sommer, 1983; Rosseel & Bogaert, 1983; Bach, 1983). This metabolite is formed also from nifedipine by a photochemical reaction under u.v. light (Pietta *et al.*, 1981), so that nifedipine assays must be performed either under subdued lighting or by using gold fluorescent light to minimise artefactual formation of compound B4759. In this study we have used h.p.l.c. to analyse nifedipine and its metabolite, B4759, in the plasma of volunteers receiving both an i.v. dose and two new oral formulations of nifedipine.

Methods

The formulations of nifedipine studied were supplied by Bayer UK Limited (100 μg/ml sterile solution; 20 mg and 30 mg biphasic release tablets). Seven healthy, non-smoking, male volunteers (24–41 years; 65–85 kg) were studied. All seven subjects received an i.v. dose of 3.5 mg given as an infusion over 4 min; five received both oral formulations and two received only one oral formulation. The subjects fasted for 12 h prior to and for 3 h after each dose. Drug administration and blood sampling (up to 6 h after i.v. and 30 h after oral dosing) were performed under subdued light. The samples were anticoagulated with lithium heparin and centrifuged immediately. Duplicate aliquots of plasma (1 ml) were pipetted into screw capped glass tubes (Brunswick) and any excess plasma was retained. The samples were frozen and

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stored at −20°C protected from light until analysis (within 2 weeks).

The plasma samples were mixed with internal standard (nitrendipine; 100 ng in 10 μl methanol) and extracted with toluene (5 ml) by shaking for 10 min in a laboratory shaker, the tubes being wrapped in foil to prevent photodegradation. The tubes were centrifuged and the toluene layer removed, evaporated to dryness at 65°C under oxygen free nitrogen and the residue kept in a light proof box until immediately prior to analysis. The later stages of the assay were carried out using a sodium lamp as the sole source of illumination. The residue was dissolved in the mobile phase used for chromatography (200 μl) which consisted of acetonitrile (43%) and aqueous 0.01 M ammonium phosphate buffer (pH 3.5; 57%). Separation of nifedipine (256 s), nitrendipine (531 s) and B4759 (238 s) was achieved using an Ultrasphere ODS 5 μm column (4.6 mm × 150 mm; Beckman), with a solvent flow of 2 ml/min. The compounds were detected using a Waters model 441 u.v. detector operating at 229 nm and set at 0.01A full scale deflection. After every fourth injection the solvent was adjusted to 70% acetonitrile for 10 min to prevent interference by slowly eluting plasma components. The concentration of nifedipine in the plasma was determined by measurement of the peak height ratio of nifedipine to nitrendipine, and comparison to known standards added to control plasma and analysed with each batch of samples.

The height of the nifedipine peak approximated to 2 mm/ng and the duplicate analyses were within 5% of the mean value at concentrations greater than 15 ng/ml and ± 1 ng for concentrations less than 15 ng/ml. Predose plasma samples contained only traces of interfering material equivalent to 0.4 ng/ml (0–1.6 ng/ml).

B4759 was quantitated by comparison of its peak height with that of nifedipine. Analysis of plasma samples which had been spiked with equal amounts of B4759 and nifedipine gave peak height ratios of 0.853. The concentration of B4759 in individual samples was calculated as

$$\frac{\text{peak height of B4759 in sample}}{\text{peak height of nifedipine in sample}} \times \frac{\text{conc. of nifedipine measured}}{0.853}.$$

Pre-dose plasma samples frequently contained a small peak which interfered with that of B4759 such that low concentrations (3 ng/ml) could not be determined reliably. The duplicate values of B4759 in the plasma samples collected

Table 1 Pharmacokinetic parameters of nifedipine and its nitropyridine analogue (B4759)

	Nifedipine			*B4759*		
	Intravenous (3.5 mg)	*Oral (20 mg)*	*Oral (30 mg)*	*Intravenous (3.5 mg)*	*Oral (20 mg)*	*Oral (30 mg)*
Maximum plasma concentration (ng/ml)	205 ± 31	64 ± 31	75 ± 30	3 ± 2‡	38 ± 9	40 ± 12
Time of maximum concentration (h)	0†	1.8 ± 1.1	2.1 ± 1.5	0.3 ± 0.1‡	1.8 ± 1.1	1.8 ± 1.4
[1]Terminal half-life (h)	1.9 ± 0.4	5.4 ± 2.6**	6.6 ± 2.4*	—	2.2 ± 0.8	3.4 ± 1.1
AUC (ng ml^{-1} h)	123 ± 29	298 ± 137	502 ± 241	4 ± 4‡	145 ± 62	203 ± 52
Bioavailability (*F*)	—	0.43 ± 0.10	0.43 ± 0.14	—	—	—
Metabolite ratio	0.03 ± 0.03	0.54 ± 0.14***	0.46 ± 0.19***	—	—	—

The results are the mean ± s.d. for six (oral) or seven (intravenous) subjects.
† – The intravenous dose was given over a period of 4 min and a blood sample taken at the end of the infusion.
‡ – Approximate results since peak heights were less than twice background.
[1] – Calculated by least squares regression analysis.
AUC – Area under the plasma concentration time curve, calculated by the trapezoidal rule with extrapolation to infinite time.
F – Calculated as $\frac{\text{AUC oral}}{\text{AUC i.v.}} \times \frac{\text{dose i.v.}}{\text{dose oral}}$

Metabolite ratio $\frac{\text{AUC B4759}}{\text{AUC Nifedipine}}$

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared with intravenous administration by Student's *t*-test for paired data.

after oral doses were in nearly all cases within 5% of the mean value.

Results

Comparison of the AUC of nifedipine after oral and intravenous doses gave a bioavailability for the tablets of 0.43. The terminal half-lives after the oral doses were greater than after i.v. administration suggesting that the formulation showed absorption rate limited elimination.

A peak corresponding to the nitropyridine analogue (B4759) was detected by h.p.l.c. in the plasma of all subjects following each oral dose (Table 1). The plasma concentration-time curve (Figure 1) resembled closely that of the parent drug. Negligible amounts of B4759 were present in the plasma following intravenous administration and the levels given (Table 1) represented only about twice the amount apparently in blank plasma due to an interfering peak. Since the analysis of oral and intravenous samples were interspersed during a period of 2 months the presence of high concentrations of the nitropyridine analogue in oral samples cannot be an analytical artefact. In addition, no B4759 was detected in standard plasma spiked with nifedipine. The route of administration difference could have originated in the presence of B4759 as a contaminant of the oral formulations. However no B4759 was detected when samples of each tablet formulation were crushed, suspended with the buffer used in the mobile phase (6 ml) for 1 h, diluted with acetonitrile (4 ml) and analysed by h.p.l.c.

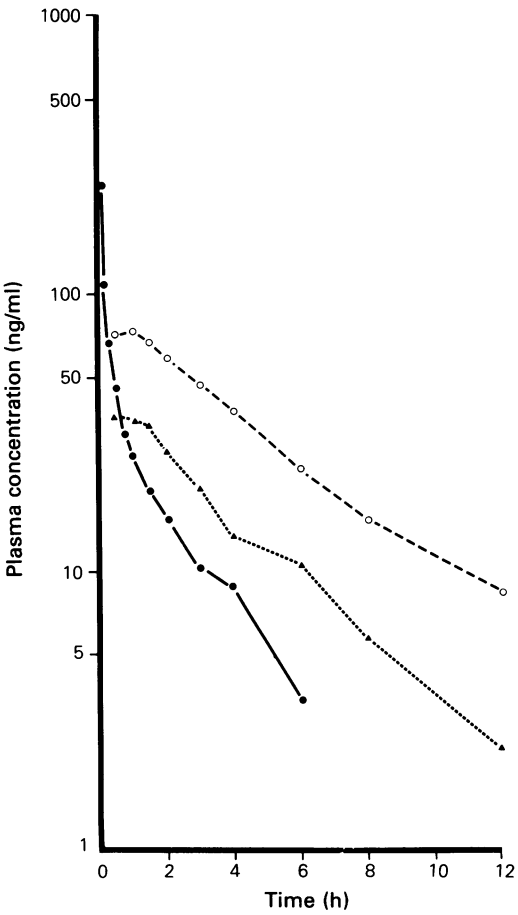

Figure 1 The concentration of nifedipine (○, ●) and its nitropyridine analogue (▲) in plasma following oral (○, 30 mg) and intravenous (●, 3.5 mg) administration of nifedipine to a normal subject. The concentrations of the nitropyridine following intravenous administration were too low to allow accurate measurement (see text for details).

Discussion

The terminal half-life (1.9 h) and plasma clearance (495 ± 108 ml/min) after intravenous administration (3.5 mg) were similar to the values reported by Foster *et al.* (1983) for a dose of 1 mg. The high plasma clearance but negligible renal elimination of the parent drug (Raemsch & Sommer, 1983) suggest that nifedipine would undergo extensive first-pass metabolism after oral administration. The bioavailabilities of the 20 mg and 30 mg biphasic release tablets (0.43) are consistent with this possibility and similar to the value (0.45) reported for the capsule formulation by Foster *et al.* (1983). Foster *et al.* (1983) used an assay method which is capable of differentiating between nifedipine and its nitropyridine analogue but did not positively identify the latter. However, the detection of high concentrations of this compound in plasma after oral, but not intravenous dosing, suggests that it is formed as a result of metabolism at the first pass, possibly by the gastrointestinal tract. This conclusion is supported by the much higher ratios of the AUC of the metabolite to the AUC of the parent compound after oral administration. Furthermore the plasma concentrations and AUC values suggest that the compound is a major circulating metabolite following oral doses. Higher apparent oral bioavailabilities (0.56–0.77) have been reported in some studies (Raemsch & Sommer, 1983). However, this paper gave both specific and non-specific assay methods for nifedipine, and it seems likely that in some studies B4759 present in plasma contributed to the values obtained for nifedipine. Clearly, assay specificity is an essential require-

ment of all future studies on the pharmacokinetics of nifedipine.

We are grateful to Bayer UK Limited, Newbury, Berkshire for the different formulations and for financial support.

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(Received May 24, 1984, accepted July 20, 1984)