The metabolism and pharmacokinetics of nicardipine hydrochloride in man

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- 1 Studies have been carried out to investigate the disposition of nicardipine hydrochloride following intravenous and oral administration to male volunteers.
- 2 Following oral administration of a radiolabelled dose, nicardipine was shown to be rapidly and extensively metabolised and to be rapidly eliminated from plasma.
- 3 After intravenous infusion of nicardipine at 5 mg⁻¹ for 3 h, plasma levels declined biexponentially, and clearance values were of the same order as hepatic blood flow.
- 4 With repeated oral administration, 20 mg three times daily for 28 days, plasma levels rose over the first 3 days of administration and then declined to some extent. Possible reasons for this decline are discussed.
- 5 Steady-state plasma levels and bioavailability show a nonlinear relationship with doses over the range 10–40 mg three times daily.
- 6 Food consumption has been shown to reduce the bioavailability of nicardipine when the food is taken before or at the same time as nicardipine administration.

Keywords man metabolism nicardipine pharmacokinetics

Introduction

Nicardipine is a member of the class of dihydropyridine derivatives that have been shown to inhibit the intracellular migration of calcium ions. At present the drug is being evaluated in the therapy of hypertension, angina, and other cardiovascular indications.

The metabolism and pharmacokinetics of orally and intravenously administered nicardipine have been studied in animals. Following oral administration, nicardipine was rapidly absorbed, extensively metabolised, and rapidly eliminated (Higuchi *et al.*, 1977, 1980; Higuchi & Shiobara, 1980). Comparison with the intravenous findings showed that nicardipine was well absorbed but subject to extensive presystemic elimination. Nicardipine was metabolised predominantly in the liver (Higuchi & Shiobara, 1980) and the rate-limiting factor was blood supply to the liver.

The present studies were a continuation of those previously described (Graham *et al.*, 1984), which were carried out to investigate the

metabolism of nicardipine in man and to study the pharmacokinetics of nicardipine following oral and intravenous administration.

Methods

Subjects

The subjects were healthy, male volunteers from whom informed consent had been obtained before admission to the study. Further details of the individual studies are given in the Results Section.

Drug

Nicardipine was supplied by Syntex Research Scotland as the hydrochloride salt in capsules containing 20 and 30 mg or as an intravenous solution (1 mg ml⁻¹). Nicardipine labelled with

Figure 1 Structure of nicardipine and its pyridine analogue metabolite (M₅). The position of ¹⁴C in radiolabelled batches is shown (*).

¹⁴C in position 4 of the dihydropyridine ring (Figure 1) and supplies of nicardipine and metabolites for use as chromatographic standards were provided by Syntex Research, Palo Alto.

Analysis of nicardipine

Plasma levels of nicardipine were determined by gas chromatography (g.c.) (Higuchi *et al.*, 1975) and high-performance liquid chromatography (h.p.l.c.) (Wu *et al.*, 1984). Using g.c., nicardipine was quantified following oxidation to a pyridine analogue metabolite (M₅). It is thought that the ratio of the plasma levels of this metabolite (Figure 1) to those of nicardipine remain approximately constant and that qualitative aspects of results obtained by this method are not affected. The second, more recent method allows simultaneous specific quantitation of both nicardipine and M₅.

Isolation and characterisation of metabolites

Metabolites were isolated from urine by a combination of column chromatography, preparative h.p.l.c. and thin-layer chromatography (t.l.c.). Column chromatography utilized Amberlite XAD-2 resin whilst h.p.l.c. involved linear gradient elution chromatography using stainless steel columns (15 cm × 10 mm i.d.) packed with ODS-hypersil and a solvent system of aqueous KH₂PO₄:acetonitrile. Radioactive components in the eluate were detected using an in-line radioactivity monitor.

Thin-layer chromatography was carried out on silica gel 60 F₂₅₄ t.l.c. plates, 20 cm × 20 cm × 0.25 mm with 2.5 cm pre-concentration band using a solvent system of ethyl acetate:acetic acid:water (80:20:20:10 by volume). Radioactive components were located by autoradiography.

Analysis of purified metabolites was carried

out by direct insertion mass spectrometry or by combined gas chromatography-mass spectrometry on a VG16F mass spectrometer linked to a Pye 204 gas chromatograph via a single-stage jet separator.

Calculation of pharmacokinetic parameters

Areas under the plasma level-time curve (AUC) were calculated by the trapezoidal rule extrapolated to infinity for single-dose studies. Total plasma clearance was calculated from the following equation:

$$CL = \frac{\text{dose}}{AUC},$$

which gives a model independent estimate of clearance.

Following intravenous infusion, data were fitted to an equation of the form described by Gibaldi & Perrier (1975):

$$C = \frac{R_0(k_{21} - \alpha)(e^{-\alpha T} - 1)}{V_c \alpha(\alpha - \beta)} e^{-\alpha t} + \frac{R_0(\beta - k_{21})(e^{-\beta T} - 1)}{V_c \beta(\alpha - \beta)} e^{-\beta t}$$

where

- C Plasma concentration (ng ml⁻¹),
- R_0 Infusion rate (mg h⁻¹),
- k_{21} Apparent first-order mass rate constant associated with movement of the drug from the peripheral to the central compartment (h⁻¹),
- V_c Volume of the central compartment (l),
- α, β Hybrid rate constants (h⁻¹),
- t Time following start of infusion (h),
- T Duration of infusion (h).

The bioavailability of nicardipine was calculated as follows:

$$\text{bioavailability (\%)} = \frac{AUC \text{ p.o.} \times \text{dose i.v.}}{AUC \text{ i.v.} \times \text{dose p.o.}} \times 100.$$

Figure 2 Proposed metabolic pathway for nicardipine hydrochloride in man. Pyridine forms of metabolites are not shown. The metabolite in parenthesis has not been isolated in man.

Determination of radioactivity in excreta

Radioactivity in urine was determined by directly adding an aliquot to scintillation fluid followed by scintillation counting. Faecal samples were homogenised in water by agitation. Aliquots of the homogenate were then combusted in a sample oxidiser (Packard), and the radiolabelled CO_2 was collected and quantified by scintillation counting.

Results

Metabolism

The metabolism of nicardipine was studied following administration of a single dose of radiolabelled nicardipine (30 mg; 40 μCi) as a solution to four healthy, male volunteers. Plasma, urine, and faeces were collected up to 168 h post dose. Following rapid absorption, compound-related radioactivity was rapidly eliminated. In total, 60% of excreted ^{14}C was recovered in the urine.

Investigation of the metabolites in urine showed that there were two main classes of metabolites: those where the dihydropyridine ring was intact and those where oxidation had occurred resulting in the pyridine analogue metabolite (Figure 1). Several metabolites were identified where sequential metabolism of the *N*-benzyl side chain had occurred.

The probable metabolic pathway of nicardipine is shown in Figure 2. It is likely that pyridine analogues of each of the metabolites exist, but not all have been isolated and characterized. Similarly, only the pyridine form of the metabolite shown in parenthesis has been isolated and characterized. The extent of oxidation that occurs *in vivo* has not been fully documented. It has been shown that during the isolation procedures, under the influence of light, nicardipine may be oxidised to its pyridine form to a small extent. Other metabolites may oxidise to a greater or lesser extent, thus making it impossible to estimate *in vivo* oxidation. The major metabolites in urine are the glucuronide conjugates of the alcohol metabolites.

Table 1 Pharmacokinetic parameters derived following infusion of nicardipine hydrochloride at 5 mg h⁻¹ for 3 h

Subject	CL (ml min ⁻¹ kg ⁻¹)	α (h ⁻¹)	β (h ⁻¹)	V _c (l)	t _{1/2} α (h min)	t _{1/2} β (h min)
1	7.01	2.41	0.146	20.6	0:17	4:44
2	7.50	6.40	0.245	14.6	0:06	2:49
3	13.0	2.12	0.149	31.2	0:19	4:39
4	7.15	3.78	0.389	18.1	0:11	1:46
5	6.48	2.39	0.071	18.5	0:17	9:45
Mean	8.23	3.42	0.200	20.6	0:14	4:45
s.d.	2.69	1.79	0.122	6.31	0:15	3:04

Figure 3 Plasma profile in a male volunteer during and after infusion of nicardipine hydrochloride at 5 mg h⁻¹ for 3 h. Reproduced with permission from the *Postgraduate Medical Journal*. **Figure 4** Plasma profile in a male volunteer after administration of a single oral dose of 30 mg nicardipine hydrochloride. Reproduced with permission from the *Postgraduate Medical Journal*.

Pharmacokinetics after intravenous infusion

The pharmacokinetics of nicardipine following intravenous infusion were studied at a dose of 5 mg h⁻¹ for 3 h, a rate predicted from a bolus administration pilot study to give steady state values of approximately 100 ng ml⁻¹.

Plasma concentrations were fitted to a two-compartment model using the non-linear regression programme ELSFIT, and the parameters derived are given in Table 1. A typical profile showing bi-exponential decline following cessation of infusion is shown in Figure 3. For comparison, Figure 4 shows a plasma profile following a single oral dose of 30 mg.

Pharmacokinetics after repeated oral administration

The changes in the pharmacokinetics of nicardipine after repeated oral administration were investigated in two separate studies. In total,

eight volunteers received nicardipine (20 mg three times daily) for up to 28 days. Plasma samples for analysis of nicardipine levels were obtained on days 1, 2, 3, 7, 14, and 28 of the studies. Mean values of AUC for each study day are shown in Figure 5.

Oral administration at 10, 20, 30, and 40 mg

Six healthy males received sequentially 10, 20, 30, and 40 mg nicardipine every 8 h for at least 3 days. On the fourth day, plasma samples were taken at each dose level to allow investigation of dose-related changes in pharmacokinetics. The 30 mg dose was administered for 6 days. Concomitantly with the morning dose on day 4, an intravenous bolus dose of nicardipine labelled with ¹⁴C was administered as a tracer (0.89 mg, 32 μ Ci) to allow quantitation of the oral bioavailability. Making the assumption that elimination kinetics are linear, the bioavailability at other dose levels was calculated. Figure 6

Figure 5 Mean area under the plasma level-time curve (AUC) in volunteers following administration of nicardipine hydrochloride, at 20 mg three times daily for up to 28 days (bars show s.d.). Reproduced with permission from the *Postgraduate Medical Journal*.

Figure 7 Relationships between bioavailability and dose in normal male volunteers. (Bars show s.d.). Reproduced with permission from the *Postgraduate Medical Journal*.

Figure 6 Plasma profiles at steady state in male volunteer receiving 10 (▲), 20 (□), 30 (◇), and 40 mg (○) every 8 h for 3 days. Reproduced with permission from the *Postgraduate Medical Journal*.

Figure 8 Mean plasma profiles in volunteers who received nicardipine (20 mg) 1 h before (▲) or 1 h after (□) a standard meal. Reproduced with permission from the *Postgraduate Medical Journal*.

shows plasma levels at each dose in one volunteer, while the relationship between bioavailability and dose is shown in Figure 7.

Effect of food on bioavailability

The effect of food on the bioavailability of nicardipine was investigated in a blind cross-over study where healthy, male volunteers received nicardipine 20 mg 1 h before, during or 1 h after a standard meal. In each of the three study phases, volunteers received nicardipine 20 mg three times daily for 3 days prior to the study. Mean plasma profiles following nicardipine administration before and after the standard meal are shown in Figure 8.

Discussion

The studies presented in this paper show that the metabolism of nicardipine in man is rapid and extensive, as had been predicted by the animal studies. It is likely that the liver is the major eliminating organ, and it is clear that, although no nicardipine is excreted unchanged in the urine, the kidney plays a role in the excretion of a large proportion of any administered dose. The major products, at least in urine, are conjugates of the alcohol metabolites.

Investigation of the bioavailability of an oral dose shows that there is a dose dependency. The moderately low bioavailability is the result of presystemic elimination, not of poor absorption.

It is likely that the dose-dependent bioavailability is due to increasing saturation of the presystemic elimination processes. From the studies carried out so far, there has been no indication of dose dependency in elimination kinetics.

The terminal elimination rates appear to differ following different oral doses, and the elimination rate following the intravenous infusion is of the same order as that seen with the low oral doses. The simplest explanation of this is that the analytical method is not adequately sensitive to detect and quantitate late elimination phases where the dose is low or the duration of dosing is short.

The changes seen in AUC on repeated oral administration of nicardipine show an initial increase, which is probably related to saturation and to equilibration of presystemic elimination processes. However, the subsequent decrease is less easily explained, and its exact mechanism remains to be elucidated. It has been shown that nicardipine does not alter the indices of hepatic-drug-metabolising enzyme status (Dow & Graham, 1984), so it is unlikely that nicardipine

is inducing its own metabolism. By altering blood flow patterns through a pharmacological action, nicardipine may alter either its clearance (which is blood-flow limited) or its bioavailability (by changing blood flow during the absorption phase).

The presence of food in the gastrointestinal tract during the absorption phase of nicardipine appears to reduce its bioavailability and to delay the achievement of peak plasma levels of nicardipine. A reduction in the rate of absorption may decrease portal blood concentrations. As a result, the fraction of the dose eliminated during the first-pass will increase because of the nonlinear nature of the absorption kinetics of nicardipine.

Thus in conclusion, in common with other dihydropyridine compounds, nicardipine has been found to be rapidly and extensively metabolised, with both its metabolism and pharmacokinetics under hepatic control. Saturable presystemic elimination processes result in nonlinear kinetics and explain the effects of food on nicardipine bioavailability.

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