N-monodesmethyldiltiazem is the predominant metabolite of diltiazem in the plasma of young and elderly hypertensives

S. C. MONTAMAT & D. R. ABERNETHY

Section on Hypertension/Clinical Pharmacology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

- 1 Twelve young (ages 30–39 years) and twelve elderly (ages 65–83 years) hypertensives were administered diltiazem twice daily for 2 weeks at doses up to 240 mg day⁻¹.
- 2 Plasma was analysed for diltiazem, *N*-monodesmethyldiltiazem, and desacetyldiltiazem concentrations after a single 10 min intravenous infusion of 21.8 mg diltiazem HCl on day 1 and after the morning oral dose of 120 mg diltiazem base on day 14.
- 3 *N*-monodesmethyldiltiazem accumulated to higher plasma concentrations than desacetyldiltiazem at steady state on day 14 in both age groups.
- 4 Prolongation of plasma diltiazem half-life occurred after 2 weeks of oral diltiazem therapy in both age groups.
- 5 There were no significant differences between the young and elderly with regard to half-life, area under the curve, and the peak and trough plasma concentrations of diltiazem, *N*-monodesmethyldiltiazem, and desacetyldiltiazem; systemic clearance and volume of distribution of diltiazem were also similar in both groups.

Keywords diltiazem *N*-monodesmethyldiltiazem pharmacokinetics

Introduction

Diltiazem is a calcium entry blocker currently approved for the treatment of angina pectoris. It is also undergoing investigation for use as an antihypertensive and antiarrhythmic drug. Diltiazem is extensively metabolized by the liver with very little drug excreted unchanged in the urine (Sugihara *et al.*, 1984). Major pathways of biotransformation include *O*-deacetylation, *N*-demethylation, and *O*-demethylation. Desacetyldiltiazem had been considered to be the predominant metabolite in plasma after an oral dose of diltiazem (Morselli *et al.*, 1978; Rovei *et al.*, 1980; Piepho *et al.*, 1980; Smith *et al.*, 1982), but *N*-monodesmethyldiltiazem has been found to be the major unconjugated metabolite in urine (Sugihara *et al.*, 1984) (Figure 1). Studies in dogs have shown both metabolites to produce coronary vasodilation and blood pressure reduction. Des-

acetyldiltiazem is more potent with regard to these effects, but *N*-monodesmethyldiltiazem has a longer duration of action (Yabana *et al.*, 1985). Because diltiazem exhibits a 'first pass' effect, plasma concentrations of its metabolites are much lower after an intravenous dose. The pharmacokinetics of *N*-monodesmethyldiltiazem during chronic oral diltiazem therapy have not been described previously. Therefore, we have studied the disposition of diltiazem at steady state during oral dosing in groups of young and elderly hypertensive patients.

Methods

Subjects

Twelve young (ages 30–39 years) and 12 elderly (ages 65–83 years) hypertensive volunteers were

Figure 1 Structural formulae of diltiazem (DTZ), *N*-monodesmethyldiltiazem (M_A), and desacetyldiltiazem (M_1).

studied. Both groups comprised ten males and two females. The younger group included eight white and four black patients, whereas the older group were all white patients. There were no cigarette smokers, and all patients were within 20% of ideal body weight for their height and frame according to the 1983 Metropolitan Life Insurance tables. Patients were screened by history and physical examination, 12-lead electrocardiogram, chest radiograph, SMA-20 chemistry profile, complete blood count, and urinalysis. Patients received no medication for 2 weeks, and blood pressure was measured using a mercury sphygmomanometer every 3–7 days. Only patients with supine diastolic (Korotokoff phase V) blood pressures greater than 95 mm Hg were included in the study. Patients did not take any medications known to alter drug metabolism for the duration of the study.

Study design

On day 1, patients received a constant intravenous infusion of 21.8 mg of diltiazem hydrochloride (Marion Laboratories) over 10 min. Blood samples were drawn into Venoject collection tubes containing sodium heparin immediately after the infusion and at various times during the 14 h following drug infusion. The plasma from these samples was analysed for diltiazem concentration. On the following morning, the patients began a course of one 60 mg diltiazem tablet orally every 12 h. The dose was increased on day 8 to two 60 mg tablets every 12 h. On day 14, patients had blood samples drawn just prior to

the morning oral dose of 120 mg diltiazem (trough level), and several blood samples were drawn during the 18 h following this dose. The evening dose was omitted on day 14. Plasma from these samples was analysed for diltiazem, *N*-monodesmethyldiltiazem, and desacetyldiltiazem concentrations.

Plasma, drug, and metabolite analyses

Plasma samples from the intravenous infusion study were analysed for diltiazem concentration as described previously (Abernethy *et al.*, 1985). Plasma samples from the steady state were analysed for diltiazem, *N*-monodesmethyldiltiazem, and desacetyldiltiazem concentrations by a modification of this method (Montamat *et al.*, 1986).

Plasma (1–2 ml) was extracted with 4 ml of 98:2 hexane/isoamyl alcohol twice, transferring the organic phase to a tube containing 0.01 M HCl. The drug and metabolites were then back extracted into the acid phase. Diphenhydramine hydrochloride was used as the internal standard. 20–90 μ l of the acid phase were injected into the liquid chromatographic system as described previously but using a mobile phase consisting of 0.06 M sodium acetate, acetonitrile, and methanol (60:35:5) containing 5 mM 1-heptanesulphonic acid at pH 6.30.

Pharmacokinetic calculations

Estimates of pharmacokinetic parameters were obtained from the intravenous data using non-linear regression analysis (Holford, 1982). The parameters were corrected for the time of infusion (Loo & Riegelman, 1970). Using the corrected intercepts and exponents, the area under the plasma drug concentration–time curve, systemic clearance, and volume of distribution using the area method were calculated. From the steady state, AUC over one dose interval was calculated for diltiazem, *N*-monodesmethyldiltiazem, and desacetyldiltiazem using the trapezoidal method. Metabolite AUC was calculated in the same manner for *N*-monodesmethyldiltiazem and desacetyldiltiazem. The elimination half-life at steady state ($t_{1/2,ss}$) was determined by linear regression analysis of the post-distribution log drug concentration versus time plot.

Statistical analysis

For each of the intravenous and steady state parameters, the young and elderly groups were compared using Student's unpaired *t*-test. Com-

parison of diltiazem half-life after the intravenous dose and oral steady state dose was made using Student's paired *t*-test. Differences in the sample means were considered significant at $P < 0.05$.

Results

Table 1 shows the pharmacokinetic parameters for diltiazem in the young and elderly hypertensive groups derived from the concentration-time curve after 21.8 mg of diltiazem hydrochloride was given intravenously over 10 min. Concentrations of *N*-monodesmethyldiltiazem and desacetyldiltiazem after single intravenous doses were below the limit of sensitivity of the analytical method. Values for total clearance (CL), volume of distribution (*V*), area under the curve (AUC), and elimination half-life ($t_{1/2}$) after single intravenous diltiazem doses were not significantly different between young and elderly patient groups.

The elimination half-lives of diltiazem and each of the two metabolites during steady state diltiazem administration are listed in Table 2. No statistically significant differences were observed between the young and elderly groups for the parent drug or metabolites. However, elimination half-lives tended to be prolonged in the elderly group, especially those of the two metabolites. Figure 2 shows plasma concentra-

Figure 2 Plasma concentrations of diltiazem (●), *N*-monodesmethyldiltiazem (■), and desacetyldiltiazem (▲) in representative subjects after 2 weeks chronic oral administration of diltiazem, 120 mg twice daily: (a) T.B., 35-years old, male; (b) F.W. 72-years old, male.

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d.) describing the disposition of diltiazem after intravenous administration

	Young (n = 12)	Elderly (n = 12)
AUC (ng ml ⁻¹ h)	497 $\pm$ 350	430 $\pm$ 220
CL (l h ⁻¹)	52.4 $\pm$ 27.4	53.5 $\pm$ 23.0
<i>V</i> (l)	271 $\pm$ 141	289 $\pm$ 126
$t_{1/2}$ (h)	3.69 $\pm$ 0.78	3.78 $\pm$ 0.67

Table 2 Pharmacokinetic parameters (mean $\pm$ s.d.) describing the kinetics of diltiazem, *N*-monodesmethyldiltiazem, and desacetyldiltiazem at steady state during chronic oral administration of diltiazem

		Young (n = 12)	Elderly (n = 12)
$t_{1/2}$ (h)	DTZ	5.20 $\pm$ 0.83	5.96 $\pm$ 1.84
	M _A	7.41 $\pm$ 1.12	10.37 $\pm$ 5.07
	M ₁	8.30 $\pm$ 1.97	10.92 $\pm$ 4.62
AUC (ng ml ⁻¹ h)	DTZ	1801 $\pm$ 705	2499 $\pm$ 1722
	M _A	834 $\pm$ 736	788 $\pm$ 336
	M ₁	382 $\pm$ 334	346 $\pm$ 213

DTZ, diltiazem; M_A, *N*-monodesmethyldiltiazem; M₁, desacetyldiltiazem.

tion-time curves of diltiazem and its metabolites in the young and elderly patient at steady state. There was a significant prolongation of the elimination half-life of diltiazem from day 1 to day 14 ($P < 0.001$) in both groups. Regarding AUC at steady state, there was no statistically significant difference for diltiazem between the two age groups. However, again the elderly tended to have an increased AUC. Also, no statistically significant difference was found between the two groups for the AUC values of *N*-monodesmethyl diltiazem and desacetyl diltiazem. Percentage diltiazem AUC over one dose interval was used to compare the amount of each metabolite appearing in plasma over time with respect to diltiazem. For the younger group, about 50% and 20% of diltiazem AUC was attained for *N*-monodesmethyl diltiazem and desacetyl diltiazem, respectively. For the elderly, percent diltiazem AUC was less, being 30% and 15% for the two metabolites, respectively, but these differences were not statistically significant.

Table 3 lists mean peak and trough plasma diltiazem and metabolite concentrations at steady state. There were no statistically significant differences between the groups, but the elderly group had higher diltiazem concentrations.

Discussion

N-monodesmethyl diltiazem accumulates to a greater degree than desacetyl diltiazem during chronic oral dosing of diltiazem, and in one patient it achieved higher plasma concentrations than those of the parent drug. The elderly patients tended to accumulate diltiazem to higher steady state concentrations after chronic dosing. However, none of the pharmacokinetic parameters were statistically different from those of the young patients. Much of the variability of plasma concentrations may be due to differences in hepatic blood flow between individuals, causing

great differences in rate of presentation to the liver of this extracted drug. Comparison of the two sample populations could have detected a 10% difference with a power of greater than or equal to 82%.

Single-dose pharmacokinetic parameters obtained after the intravenous administration of diltiazem were not significantly different between the two groups of patients. Graphic analysis was consistent with a two compartment model, from which pharmacokinetic parameters were derived. The clearance of diltiazem is due predominantly to hepatic metabolism with only 4% of parent drug excreted unchanged in the urine after an oral dose (Sugihara *et al.*, 1984). Two major routes of diltiazem biotransformation in humans are reported to be *O*-deacetylation and *N*-desmethylation. Concerning oxidative *N*-desmethylation, a biotransformation mediated by the hepatic cytochrome P-450 mixed function oxidase system, some data support a decrease in the activity of the mixed function oxidase system with ageing. However, drug deacetylation pathways have not been evaluated in such detail (Schmucker, 1985). The elderly also show decreases in hepatic blood flow which may affect disposition of high clearance drugs such as diltiazem (Bender, 1965). Because of the small number of patients in each group in this study, no statistically significant differences in kinetics between the young and elderly could be demonstrated.

After 2 weeks of diltiazem therapy, the elimination half-life of diltiazem was prolonged significantly in both groups. Assuming no change in distribution during chronic dosing, diltiazem clearance may be decreased during chronic drug administration when compared to single dose clearance. This may be due to inhibition of diltiazem biotransformation by accumulated metabolites or diltiazem itself, or the result of acute or chronic alteration in hepatic blood flow. Another possibility is that a deep compartment

Table 3 Plasma peak and trough concentrations (mean $\pm$ s.d.) of diltiazem, *N*-monodesmethyl diltiazem, and desacetyl diltiazem at steady state during chronic oral administration of diltiazem

		Young (n = 12)	Elderly (n = 12)
Peak plasma concentration (ng ml ⁻¹)	DTZ	254 $\pm$ 93	353 $\pm$ 306
	M _A	87 $\pm$ 68	74 $\pm$ 26
	M ₁	34 $\pm$ 24	31 $\pm$ 15
Trough plasma concentrations (ng ml ⁻¹)	DTZ	66 $\pm$ 27	78 $\pm$ 49
	M _A	31 $\pm$ 26	30 $\pm$ 15
	M ₁	18 $\pm$ 17	16 $\pm$ 12

DTZ, diltiazem; M_A, *N*-monodemethyl diltiazem; M₁, desacetyl diltiazem.

is revealed after steady state is achieved. Diltiazem has been shown to inhibit hepatic drug oxidation *in vivo* in humans when administered in therapeutic doses (Carrum *et al.*, 1986). Therefore, such drug or metabolite inhibition of parent drug biotransformation may account for the prolongation in half-life during chronic administration. However, alterations in hepatic blood flow and diltiazem hepatic extraction after oral administration cannot be ruled out. Verapamil, another calcium antagonist with vasodilating properties similar to diltiazem, has been shown to increase hepatic blood flow (measured by indocyanine green clearance) after acute administration to humans, with return of hepatic blood flow to baseline values during continued administration (Meredith *et al.*, 1985). Therefore, the variance between acute intravenous and chronic oral administration could conceivably be due to an acute increase in diltiazem clearance during acute intravenous administration.

In conclusion, *N*-monodesmethyldiltiazem is the predominant metabolite in plasma after chronic oral diltiazem therapy, with desacetyldiltiazem accumulating to a lesser extent. There were no significant differences in the disposition of diltiazem or the appearance of *N*-monodesmethyldiltiazem between young and elderly hypertensive patients at steady state. When describing the concentration-effect relationships of diltiazem, it may be necessary to allow for concentrations of *N*-monodesmethyldiltiazem, a major active metabolite.

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