Pharmacokinetics and Hypotensive Effect of Diltiazem in Rabbits: Comparison of Diltiazem with its Major Metabolites*

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Abstract

To assess the contribution of its metabolites to the antihypertensive effects of diltiazem, a previously established rabbit model has been used to compare the pharmacokinetics and haemodynamic effects of the drug with those of its major metabolites deacetyldiltiazem (M_1) and deacetyl-N-monodemethyldiltiazem (M_2).

Diltiazem, M_1 and M_2 were administered separately to each animal (n = 5 or 6 per study group) as a single 5 mg kg^{-1} intravenous dose. Blood samples, systolic and diastolic blood pressure (SBP and DBP) and heart rate were recorded for each rabbit up to 8 h, and urine samples were collected for 48 h post-dose. Plasma concentrations of diltiazem and its major metabolites were determined by HPLC. The results showed that systemic clearance (CL) and volume of distribution at steady state (Vd_{ss}) were smaller for diltiazem than for the metabolites. Diltiazem and the metabolites reduced both SBP and DBP, the effects of diltiazem being most potent. Their effects on heart rate were highly variable and not statistically different between treatment groups ($P > 0.05$).

These results indicate that diltiazem is a more potent hypotensive agent than M_1 or M_2, possibly because of the higher plasma concentrations secondary to the smaller CL and Vd_{ss} of diltiazem compared with the metabolites. The effects of the metabolites might, however, be more sustained.

Diltiazem is a calcium antagonist widely used in the treatment of angina and hypertension (Medical Letter 1993, 1994; Weir 1995). It is extensively metabolized in man by deacetylation, N-demethylation, O-demethylation and oxidative deamination, yielding a host of metabolites (Figure 1) some of which have potent pharmacological activity (Sugihara et al 1984; Sugawara et al 1988). It has been shown in dogs that the coronary vasodilating properties of deacetyldiltiazam (M_1), N-monodemethyldiltiazem (MA) and N-monodemethyldeacetyldiltiazem (M_2) were 50, 20 and 17%, respectively, that of diltiazem. The effect on reducing the mean blood pressure were similar for diltiazem and M_1, and the effects of M_2 and MA were approximately 30% that of diltiazem (Yabana et al 1985). When effects on platelet aggregation and uptake of adenosine by erythrocytes were com-

pared in-vitro some of the metabolites (e.g. M_1) were more potent than diltiazem (Kiyomoto et al 1983; Yeung et al 1991b).

Although species-variation of diltiazem metabolism has been demonstrated, the differences are mainly quantitative (Yeung et al 1990). The rabbit has previously been shown to be a valuable animal model for the study of the disposition of diltiazem (Yeung et al 1990, 1991c). It is also a very useful model for studying the cardiovascular and haemodynamic effects of pharmacological agents (Takeo et al 1988; Halbrugge et al 1993). Because of the potential of the metabolites as separate therapeutic entities, and their contribution to the effect of diltiazem in clinical drug therapy, the disposition and haemodynamic effects of diltiazem and its major metabolites M_1 and M_2 have been evaluated separately after single 5-mg kg^{-1} intravenous doses.

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Materials and Methods

Chemicals

Diltiazem and its metabolites were from Tanabe Seiyaku (Japan) via Hoechst Marion Roussel
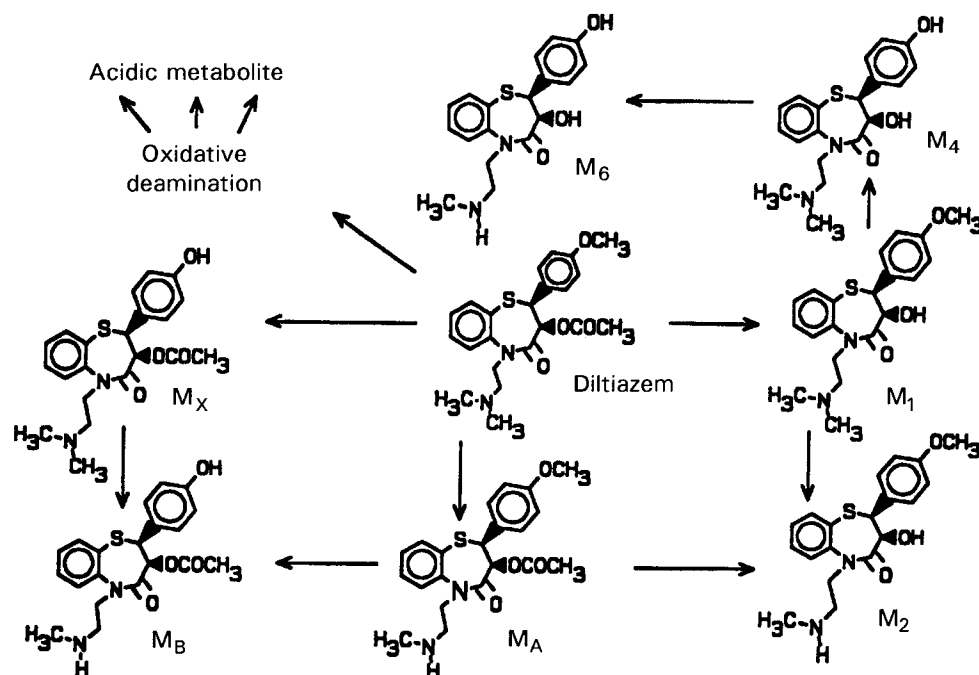
Figure 1. The metabolism of diltiazem.

Canada Research (Laval, QC, Canada). Racemic metabolites O-demethyldiltiazem (M_x) and N,O-didemethyldiltiazem (M_B) were from Dr P. S. Farmer of the College of Pharmacy, Dalhousie University, Halifax, NS, Canada (Li et al 1992). Solvents were HPLC grade (BDH, Halifax, NS, Canada) and other chemicals were reagent grade (Fisher Scientific, Ontario, Canada).

Study protocol

The study protocol was approved by the Dalhousie University Committee on Laboratory Animals. Female New Zealand white rabbits (Riemens Ranch, Ontario, Canada), 3·3–4·5 kg, were housed in steel metabolism cages for 1 week before the study, for acclimatization to the environment, and had free access to food (Co-Op, NB, Canada) and water, although each animal was fasted overnight before the experiment. The animals were divided into four groups (n = 5 or 6 in each). On the day of the experiment a 21G ¾-in needle butterfly catheter (E-Z set, Desert Medical, Becton Dickinson) attached to 2 cm × 0·030 in i.d. × 0·065 in o.d. silastic tubing (Dow Corning, Midland, MI) was placed in a central ear artery for blood sampling and recording of systolic and diastolic blood pressure (SBP and DBP) and heart rate. The animal was rested in a restraining cage (Nalgene, Fisher Scientific Canada) for 0·5 h before dosing. Each animal received 5 mg kg⁻¹ diltiazem, M_1 or M_2 intravenously (2–3 mL) via the other ear over

5 min, or the same volume of normal saline (control). Blood samples (1·0 mL) were collected from each animal via the catheter 0, 0·1, 0·15, 0·25, 0·5, 1·0, 2, 3, 4, 6, 7 and 8 h post-dose into heparinized microcentrifuge tubes; urine was collected for 48 h post-dose. Intra-arterial blood pressure and heart rate were recorded at each sampling time using a Sorenson pressure transducer (Abbott Laboratories, IL) coupled to a Tektronix monitor (Mondel 414) and recorder (Model 400, OR). The measurement was the average of a 10-s recording. The blood samples were immediately centrifuged (3000 rev min⁻¹ 4°C, 10 min) to separate plasma; this was stored at −20°C until analysis by HPLC (Yeung et al 1989, 1996). All samples (plasma and urine) were analysed within 3 months of collection to avoid possible deterioration (Caille et al 1989; McLean et al 1991; Yeung et al 1991a).

Data analysis

Pharmacokinetic parameters were calculated by means of a computer-assisted non-linear curve-fitting program using a two-compartment model after bolus intravenous injection (Rstrip, MicroMath Scientific Software, Salt Lake City, UT). The area under the plasma-concentration–time curve (AUC) from time 0 to the last sampling time and the area under the first moment curve (AUMC) were calculated by the trapezoidal method (Rstrip). Systemic clearance (CL) was calculated from the equation CL = D/AUC, where D was the intra-

venous dose. Mean residence time (MRT) was calculated from the ratio AUMC/AUC (Gibaldi & Perrier 1982). The volume of distribution at steady-state (Vd_{ss}) was equal to CL × MRT (Gibaldi & Perrier 1982). Renal clearance (CL_r) was calculated from the equation $CL_r = A_e/AUC$, where A_e was the amount of unchanged drug excreted in the urine over 48 h and AUC was the corresponding area (Fleishaker et al 1989; Yeung et al 1991c).

Relationships between plasma concentrations of diltiazem, M_1 or M_2 and haemodynamic effects (SBP, DBP, mean blood pressure (MBP) and heart rate) were evaluated by the inhibitory sigmoidal E_{max} Model using non-linear regression (PCnonlin V. 3.0, SCI Software, Apex, NC). Because blood pressure (both SBP and DBP) decreased both in drug-treated rabbits and the controls during the experiment, the haemodynamic data obtained from the control animals were subtracted from those obtained from the treated rabbits before use for modelling of the effects of the drugs (i.e. % change = [% change in drug-treated rabbits]− [mean % change in control rabbits], where % change = [individual time data]/[data obtained before injection] × 100). Plasma concentration and haemodynamic variables were fitted for each animal using the equation $E = E_0 - (E_{max} \times C_p^n/EC50_n + C_p^n)$; where E_0 was the effect before injection, E_{max} was the maximum effect (both expressed as percentage of the control result), EC50 was the concentration having 50% the maximum effect, C_p was the plasma concentration of the injected compound and n was a theoretical measure of the sigmoid nature of the curve (Hill factor) (Holford & Sheiner 1981; Gabrielsson & Weiner 1994). The effects of the drugs were evaluated by analysis of variance followed by the Dunnett test for difference between haemodynamic data before and after drug administration; differences were considered significant for $P < 0.05$. The haemodynamic effects of each compound at each sampling time were evaluated by analysis of variance followed by the Tukey test for differences between results from the control and from the study agents; differences were considered significant for $P < 0.05$ (Systat, Evanston, IL).

Results

After a single intravenous administration, plasma concentrations of diltiazem, M_1 and M_2 declined biexponentially with apparent terminal half-lives, $t_{\frac{1}{2}}$, of 4.5 ± 3.8, 2.1 ± 0.5 and 2.8 ± 0.7 h, respectively ($P > 0.05$) (Figure 2 and Table 1). The CL and Vd_{ss} of diltiazem were 24 ± 14 mL min^{-1} kg^{-1} and 1.9 ± 1.2 L kg^{-1}, respectively. The CL and Vd_{ss}
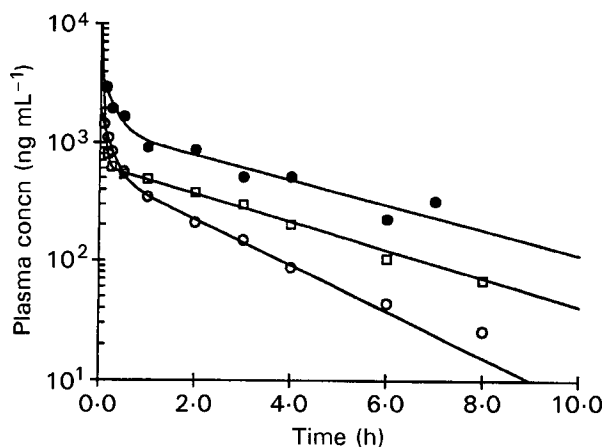
Figure 2. Mean plasma concentration–time profiles of diltiazem (●), deacetyldiltiazem (○) and N-monodemethyldiltiazem (□) in rabbits after a single 5-mg kg^{-1} intravenous dose. The solid line represents concentrations predicted by the model using mean data.

of M_1 were considerably larger than those of diltiazem ($P < 0.05$). The Vd_{ss}, but not the CL, of M_2 was also larger than that of diltiazem ($P < 0.05$) (Table 1). There was, however, no significant difference between the CL_r of diltiazem and those of its metabolites (diltiazem 1.2 ± 1.8 compared with M_1 0.81 ± 0.63 or M_2 0.57 ± 0.23 mL min^{-1} kg^{-1}, $P > 0.05$). After a single intravenous dose of diltiazem M_1 was the only metabolite which reached concentrations high enough to enable adequate pharmacokinetic characterization; M_2 was the only metabolite which could be adequately characterized after a single intravenous dose of M_1. No identifiable basic metabolite could be quantified in the plasma of the animals after the intravenous dose of M_2.

Diltiazem and the metabolites M_1 and M_2 significantly reduced SBP and DBP, although they differed in their in-vivo potencies and duration. Their effects on heart rate were highly variable and not statistically different between treatment groups ($P > 0.05$). When given intravenously as a 5 mg kg^{-1} bolus injection diltiazem reduced DBP significantly for the first hour ($P < 0.05$) with maximum effect in the first 15 min. The hypotensive effects of M_1 and M_2 were significant only for the first 30 min and the first 10 min, respectively (Figure 3). Diltiazem and M_2, but not M_1, also reduced SBP, although the effects were of much shorter duration (< 30 min). The hypotensive effect of diltiazem was greater than those of M_1 or M_2, particularly in the first 30 min ($P < 0.05$).

Use of the haemodynamic data after subtraction of the results from the control animals gave E_{max} and EC50 values for the hypotensive effect on DBP of $42 \pm 25\%$ and 1600 ± 1700 ng mL^{-1},

Table 1. Pharmacokinetic parameters of diltiazem, deacetyldiltiazem and deacetyl-N-monodemethyldiltiazem in rabbits after single intravenous injections ($5\ mg\ kg^{-1}$).

Parameters	Diltiazem	Deacetyldiltiazem	Deacetyl-N-mono-demethyldiltiazem	$P < 0.05$
Apparent $t_{\frac{1}{2}}$ (h)	4.5 ± 3.8	2.1 ± 0.5	2.8 ± 0.7	–
MRT (h)	1.5 ± 0.5	1.7 ± 1.0	4.0 ± 0.6	M_2 compared with M_1; M_2 compared with diltiazem
AUC ($ng\ h\ mL^{-1}$)	4800 ± 3100	1300 ± 210	2000 ± 290	Diltiazem compared with M_1
CL ($mL\ min^{-1}\ kg^{-1}$)	24 ± 14	60 ± 10	38 ± 5	Diltiazem compared with M_1; M_1 compared with M_2
CL_r ($mL\ min^{-1}\ kg^{-1}$)	1.2 ± 1.8	0.81 ± 0.63	0.57 ± 0.23	–
CL_{nr} ($mL\ min^{-1}\ kg^{-1}$)	23 ± 15	59 ± 12	37 ± 5	Diltiazem compared with M_1; M_1 compared with M_2
Vd_{ss} ($L\ kg^{-1}$)	1.9 ± 1.2	5.9 ± 3.3	9.0 ± 2.0	Diltiazem compared with M_1 and with M_2

Values are means $\pm$ s.d. $t_{\frac{1}{2}}$ = half-life; MRT = mean residence time; AUC = area under the plasma concentration–time curve; CL = clearance; CL_r = renal clearance; CL_{nr} = non-renal clearance; Vd_{ss} = volume of distribution at steady-state.

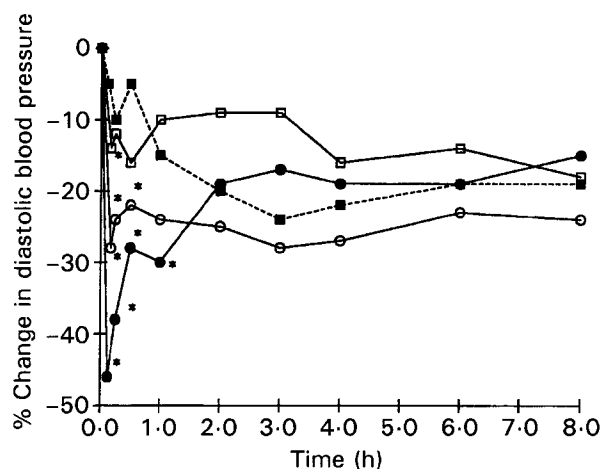

Figure 3. Percentage change in mean diastolic blood pressure in rabbits after a single 5-mg kg^{-1} intravenous dose of diltiazem, deacetyldiltiazem or N-monodemethyldiltiazem: ●, diltiazem; ○, deacetyldiltiazem; □, N-monodemethyldiltiazem; ■, control. *$P < 0.05$, compared with the control result.

respectively, for diltiazem; $20 \pm 8.3\%$ and 420 ± 160 ng mL^{-1} for M_1; and $15 \pm 20\%$ and 430 ± 120 ng mL^{-1} for M_2 (Table 2 and Figure 4). These differences were not statistically significant ($P > 0.05$). A plot of the percentage changes in DBP against plasma concentrations of diltiazem, M_1 or M_2 for the pooled data is shown in Figure 4.

Discussion

As reported previously for diltiazem, the pharmacokinetics and haemodynamic data were highly variable (Yeung et al 1991c; Tsui et al 1998). Owing to the large variability and the small number of animals used in the study, for many observations apparent differences were not statistically significant. Although it is very tempting to be able to assess metabolite effects when only parent drugs

are given, the methodology requires many assumptions. The plasma concentrations of the metabolites after injection of the parent compounds (diltiazem, M_1 or M_2) were measurable only in scattered samples (except M_1 after administration of diltiazem), and the somewhat limited number of samples obtained from each animal ($n = 11$ total) precluded meaningful assessment of their individual haemodynamic effect. It would be very difficult to delineate the effects of the parent drugs from the metabolites under these conditions. Further, the model would require further validation. It is for these reasons that the current manuscript focuses on describing the concentration–effect relationships of the parent compounds without taking into account the contribution from the metabolites, albeit that it is very small under these conditions. The disposition kinetics of diltiazem in rabbits after the intravenous dose were similar to those reported previously (Yeung et al 1991c) and could be described adequately by a two-compartment model with terminal (β) $t_{\frac{1}{2}}$ of 4.5 ± 3.8 h, CL 24 ± 14 mL min^{-1} kg^{-1} and Vd_{ss} 1.9 ± 1.2 L kg^{-1} (Table 1). Diltiazem is predominantly metabolized before excretion (95%). Whereas several basic metabolites, e.g. M_1, M_2, M_A, M_4, M_6, M_x and M_B, were measurable after the intravenous dose of diltiazem (Yeung et al 1991c), only M_1 reached plasma concentrations high enough for adequate characterization by pharmacokinetic analysis (unpublished results). Compared with diltiazem the same dose (5 mg kg^{-1}) of metabolites M_1 and M_2 resulted in much lower plasma concentrations although only the difference between diltiazem and M_1 was statistically significant (Table 1). The administered metabolites were cleared more effectively from plasma, but at the same time were also distributed more extensively into tissues (Table 1).

Table 2. Haemodynamic effects of diltiazem, deacetyldiltiazem and deacetyl-N-monodemethyldiltiazem in rabbits after a single intravenous 5-mg kg^{-1} injection.

Treatment	Systolic blood pressure				
	Before drug administration (mm Hg)	E_{max} (% change from control)	E_0 (% change from control)	EC50 (ng mL^{-1})	Hill factor
Diltiazem	96 ± 8·9	37 ± 27	0·0 ± 10	1700 ± 1700	14 ± 7·4
Deacetyldiltiazem	98 ± 4·6	20 ± 18	2·7 ± 3·4	620 ± 310	4·5 ± 5·0
Deacetyl-N-monodemethyldiltiazem	90 ± 6·4	15 ± 7	9·0 ± 4·0	450 ± 46	10 ± 0·001
Control	96 ± 12	NA*	NA	NA	NA

	Diastolic blood pressure				
	Before drug administration (mm Hg)	E_{max} (% change from control)	E_0 (% change from control)	EC50 (ng mL^{-1})	Hill factor
Diltiazem	75 ± 9·5	42 ± 25	1·0 ± 9·0	1600 ± 1700	11 ± 7·8
Deacetyldiltiazem	74 ± 6·7	20 ± 8·3	0·5 ± 9·0	420 ± 160	7·9 ± 3·7
Deacetyl-N-monodemethyldiltiazem	63 ± 4·4*	15 ± 20	9·0 ± 5·4	430 ± 120	7·2 ± 3·9
Control	78 ± 7·2	NA	NA	NA	NA

Values are means ± s.d. NA = not available. *$P < 0.05$, compared with control result.

Consequently, their plasma concentrations were much lower than that of diltiazem, whereas the terminal t½ values were similar for all three compounds (diltiazem 4·5 ± 3·8; M_1 2·1 ± 0·5; M_2 2·8 ± 0·7 h; $P > 0.05$). Like diltiazem, M_1 and M_2 were also predominantly metabolized before excretion (1% and 2%, respectively). Thus the larger CL observed for the metabolites is attributed mainly to a non-renal or metabolic mechanism. Compared with diltiazem, however, very few basic metabolites were measurable after injection of M_1 or M_2, suggesting that M_1 and M_2 could be metabolized more by phase-II conjugation, and by other routes of metabolism not taken into account in this study (e.g. oxidative deamination).

The haemodynamic variables (blood pressure and heart rate) reported in this study were comparable with those reported in other studies of conscious rabbits when data were collected via the carotid artery (Halbrugge et al 1993), indicating that the experimental design was adequate. The lower DBP in the group receiving M_2, compared with the others, before the study (Table 2) should not interfere with data interpretation because they were normalized before analysis. It is clear that diltiazem and the two major metabolites M_1 and M_2 had significant hypotensive activity. The effects were greatest for diltiazem such that the E_{max} for hypotension was approximately 40% for diltiazem compared with ca 20% for M_1 or M_2, although the effects attributed to diltiazem could be shared by its metabolites (Table 2 and Figure 4). It is also interesting to note that the mean E_0 values after M_2

for lowering both SBP and DBP were higher than those after diltiazem or M_1, although the differences were not statistically significant (Table 2). This was attributed mainly to the smaller percentage reduction in blood pressure after M_2 compared with the control 1 h after injection (Figure 3). It is not clear whether or not the haemodynamic effect of M_2 is inherently different from those of diltiazem and M_1 or is related to the group of animals, for which the DBP before the experiment was significantly lower (Table 2). Previous studies using the anaesthetized dog as an animal model have also shown that diltiazem was more potent than its metabolites M_1 and M_2 in dilating the coronary artery and reducing mean blood pressure, although no pharmacokinetic measurements were made in those studies (Yabana et al 1985). Although it is still not certain whether or not the more potent hypotensive effect of diltiazem compared with its metabolites after their separate injection can be attributed to greater plasma concentrations rather than to inherently different pharmacological properties, pharmaco-kinetics are clearly important in the in-vivo activity of these agents. Further studies should be performed with increased doses of the metabolites to determine if the model-derived E_{max} and EC50 are increased.

In contrast with the significant hypotensive effect, the effects of these agents on heart rate were highly variable and consequently not statistically significant ($P > 0.05$). Diltiazem has been shown to reduce both blood pressure and heart rate in rats when administered as a single 20-mg kg^{-1} bolus
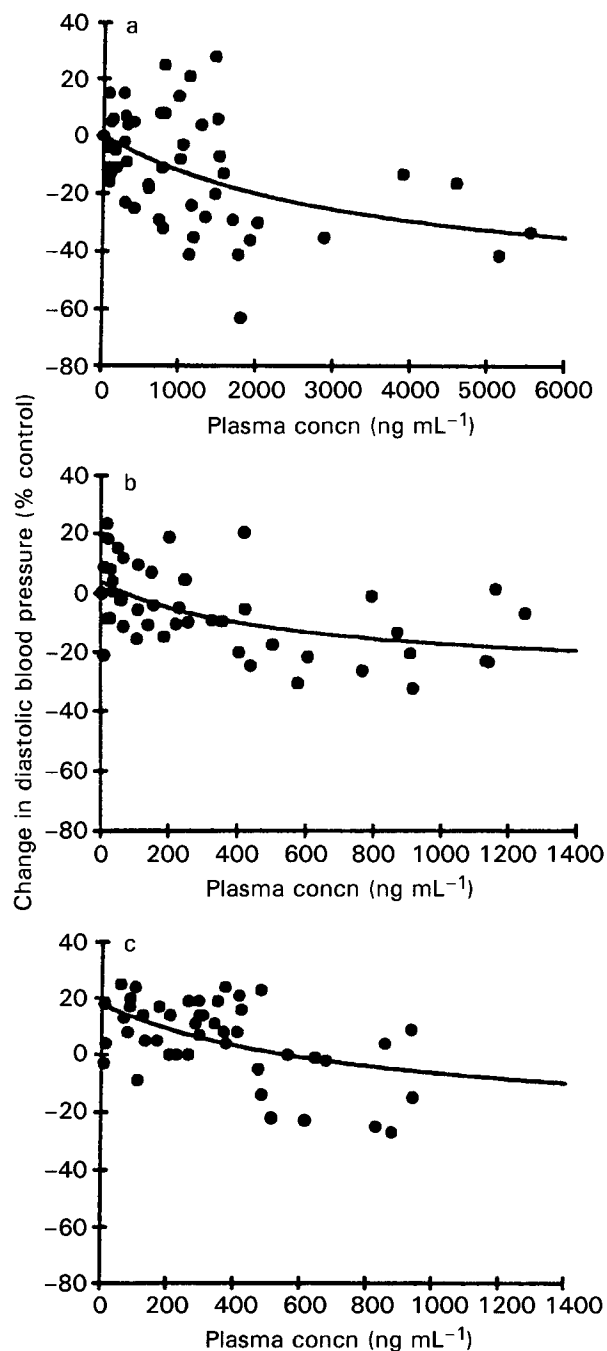
Figure 4. Concentration–effect relationships for diastolic blood pressure after single 5-mg kg^{-1} intravenous doses of diltiazem (a), deacetyldiltiazem (b) or N-monodemethyldiltiazem (c). The solid lines represent percentage changes predicted by the model using pooled data.

injection (Tsui et al 1998). These differences could be attributed to the much higher (approximately 2-fold) plasma concentrations in the rats, and possible inherent species differences in the haemodynamic response to diltiazem. The lack of a significant reflex tachycardia as a consequence of reducing the blood pressure shown in the current study could be

an attractive feature of diltiazem and its metabolites M_1 and M_2. Other calcium antagonists, particularly short-acting ones such as nifedipine, induce reflex tachycardia in man and in animal models (Eliot et al 1997; Epstein 1997). This mechanism is believed to be a crucial factor responsible for some of the serious adverse cardiac events of the calcium antagonists (Epstein 1997; White 1997). Previous studies have shown that diltiazem and its basic metabolites have widely different inhibitory effects on the uptake of adenosine in-vitro, and that diltiazem inhibits the oxidative metabolism of adenosine in normal volunteers and patients with effort angina, although the long-term effects have not been established (Yeung et al 1991b, 1997). Future studies should be performed to explore the neuro-hormone effects of diltiazem and its metabolites.

In summary, the results of this study have shown that diltiazem, and its metabolites M_1 and M_2 reduce blood pressure without having a significant effect on heart rate. The in-vivo hypotensive effect of diltiazem is more potent than those of M_1 or M_2, probably because of its higher plasma concentration secondary to its smaller CL and Vd_{ss}.

Acknowledgement

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