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PHARMACOKINETICS OF ORAL DILTIAZEM AND FIVE OF ITS METABOLITES IN PATIENTS WITH CHRONIC RENAL FAILURE

MAHA TAWASHI[1], JULIEN MARC-AURÈLE[2], DANIEL BICHET[2], JEAN SPÉNARD[3]*, LYNE LARIVIÈRE[3], DANIEL PLANTE[3] AND GILLES CAILLÉ[1],

[1]*Department of Pharmacology, Université de Montréal, C.P. 6128, Succ. A., Montréal, Canada H3C 3J7*
[2]*Hôpital Sacré-Coeur, 5400, boul. Gouin ouest, Montréal, Canada H4J 1C5*
[3]*Nordic Laboratories, P.O. Box 403, St-Martin Branch, Laval, Canada H7S 2A4*

ABSTRACT

The pharmacokinetics of oral diltiazem were studied in 10 patients with chronic renal failure not requiring dialysis and in five healthy volunteers after a single dose of 120 mg. We found that patients with chronic renal failure had lower amounts of unchanged diltiazem and of its main metabolite (MA) in urine and a trend to have slightly higher values of plasma concentration. Since the terminal elimination phase is not affected by chronic renal failure we conclude that this trend is probably the result of alterations in the volume of distribution of diltiazem in these patients.

KEY WORDS Diltiazem Pharmacokinetics Chronic renal failure

INTRODUCTION

Diltiazem hydrochloride is a calcium channel blocker effective in the treatment of angina pectoris,[1] hypertension,[2] and supraventricular arrhythmias.[3].

Patients suffering from cardiovascular diseases often demonstrate varying degrees of renal function impairment. At present, little is known about the pharmacokinetics of diltiazem and of its metabolites in patients with chronic renal failure (CRF). A previous trial[4] reported that the elimination half-life of diltiazem in patients with severe CRF following a 120 mg oral dose was identical to that reported in the literature for healthy volunteers. However, few pharmacokinetic studies have been done in healthy volunteers and they have often shown large variations in kinetic parameters.[5–8] Much of this variation may result from inter- and intra-individual variability in first-pass metabolism. In addition, the use of limited numbers of subjects or inadequate analytical methods may also have contributed to this variation.[9–11]

Moreover, at least five metabolites in urine have been identified to date (Figure 1).[12] In dogs, some of these metabolites have been shown to possess 20 to 50 per cent of the hypotensive and vasodilatory effect of the parent

* Addressee for correspondence.

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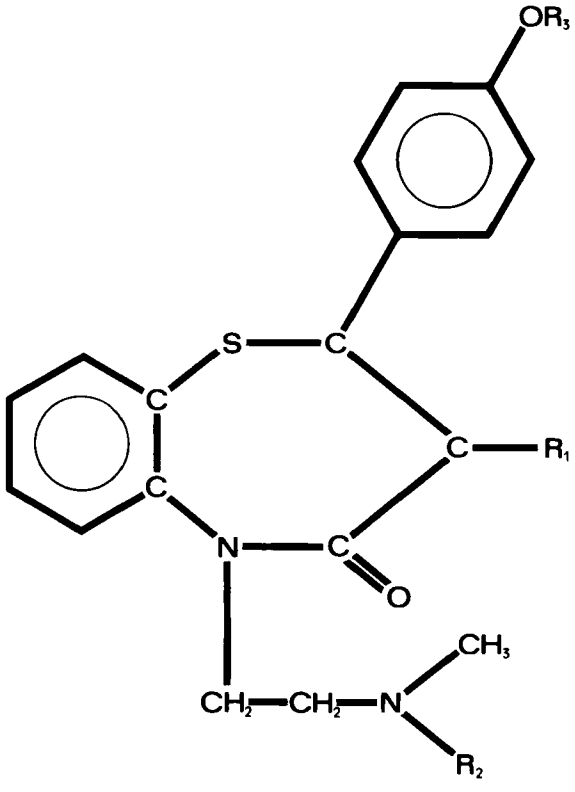

Diltiazem:	$R_1 = OCCH_3$ (O)	$R_2 = CH_3$	$R_3 = CH_3$
DAD :	$R_1 = OH$	$R_2 = CH_3$	$R_3 = CH_3$
MA :	$R_1 = OCCH_3$ (O)	$R_2 = H$	$R_3 = CH_3$
M_2 :	$R_1 = OH$	$R_2 = H$	$R_3 = CH_3$
M_4 :	$R_1 = OH$	$R_2 = CH_3$	$R_3 = H$
M_6 :	$R_1 = OH$	$R_2 = H$	$R_3 = H$

Figure 1. Chemical structure of diltiazem and five of its metabolites

drug.[13] Considering the importance which they may have to the overall effect of the drug, an analytical method was developed, allowing the determination of plasma and urine levels of diltiazem and five of its metabolites.

The primary objective of the current study was to compare the kinetics of single dose diltiazem and its metabolites, following single dose of the drug, in patients with CRF and in volunteers with normal renal function.

METHODS

Ten patients (six men, four women) with CRF with a mean weight (± standard error) of 61·2 (4·62) kg and a mean age of 45·1 (4·40) years and five participants (four men, one woman) with normal renal function with a mean weight of 70·8 (3·8) kg and a mean age of 28·4 (1·97) years were included in the study after giving written informed consent.

CRF patients were not on any form of dialysis. Their glomerular filtration rate was reduced by at least 50 per cent as shown by a renal creatinine clearance lower than 1 mL s^{-1}. Their BUN and serum creatinine were higher than 14·3 mmol L^{-1} and 227·0 μmol L^{-1}, respectively. Except for abnormalities explained by their CRF condition all patients had blood and urine analysis results free of clinically significant abnormalities. Electrocardiograms and physical examinations were also normal. Healthy volunteers underwent successfully the same tests.

Healthy volunteers and patients were excluded from participation if they had at least one of the following conditions: any AV block, childbearing potential, cardiovascular disease other than hypertension, diabetes mellitus, impaired liver function, or severe renal failure (BUN > 35·7 mmol L^{-1} or serum creatinine > 1180 μmol L^{-1}).

All participants refrained from drinking alcohol for 48 h preceding and following drug administration. Use of enzyme activity modifiers was also prohibited from 1 month before the trial up to the end of it. CRF patients were allowed to take their usual medication but healthy volunteers were not allowed to take any drugs. Patients' medication is presented in Table 1.

Following an overnight fast of 8 h subjects ate a light standardized breakfast 1 h before receiving two 60 mg tablets of diltiazem. Standardized meals were served 4 and 9 h later. Blood samples were collected by forearm venipunctures into heparinized tubes prior to and at 0·5, 1, 1·5, 2, 3, 4, 5, 6, 8, 9, 12, 24, and 48 h after drug administration. Blood samples were centrifuged immediately after collection and the plasma was transferred into air-tight tubes and frozen until assayed. Total urine was collected for four periods (0–6, 6–12, 12–24, and 24–48 h) following diltiazem administration. Urine volume was measured after each collection period and a sample was frozen in an air-tight tube until assayed.

All samples were assayed by HPLC using a detector at 237 nm. A C-18 column was used with an acetonitrile–0·005 M phosphase buffer (72:28) at pH 3. Plasma (1–2 mL) was extracted at pH 7·5 with 5 mL of methyl-tert-butyl ether. The organic phase was transferred to a tube containing 300 mL of 0·05 N H_2SO_4 for a back-

Table 1. Drugs used by the patients

Patient number	Drug	Dosage
1	Fenfluramine	20 mg hs
	Brompheniramine 4 mg +	1 co hs
	Phenyleprhine 5 mg +	
	Phenylpropanolamine 5 mg	
2	$NaHCO_3$	500 mg qid
	KCl	750 mg qid
	Hydroxyzine	25 mg hs
	$CaCO_3$	3750 mg die
	Aluminium hydroxide	1282 mg tid
	Calcitriol	0·25 μg bid
3	Captopril	25 mg bid
	Nifedipine	10 mg qid
	Oxazepam	30 mg hs
4	Captopril	25 mg tid
	Furosemide	160 mg tid
	Metoprolol	50 mg tid
	Nifedipine	10 mg tid
	Calcitriol	0·25 μg die
	$CaCO_3$	420 mg tid
5	Minoxidil	10 mg bid
	Digoxin	0·125 mg die 5 days/week
	Furosemide	160 mg die
	Isosorbide dinitrate	30 mg qid
	KCl	600 mg tid
	Oxazepam	15 mg hs
6	Hydralazine	25 mg AM + hs
	Metoprolol	200 mg hs
	Indapamide	2·5 mg die
	Allopurinol	200 mg q 2 days
	Norgestrel + ethinylestradiol	die 21 days/28
7	Metoprolol	200 mg die
8	Prazosine	1 mg tid
	Metoprolol	100 mg bid
	Metoclopramide	10 mg bid
	Oxazepam	30 mg hs
	$CaCO_3$	2500 mg bid
9	Sulfamethoxazole +	100 mg +
	Trimethoprime	20 mg hs
10	Captopril	25 mg q 8 h
	Metoprolol	10 mg die

extraction of diltiazem and its metabolites. Extraction of unconjugated diltiazem and metabolites from urine was achieved at pH 8·4 using a boric acid–KCl buffer and 6 mL of methyl-tert-butyl ether containing 11 per cent 2-propanol. A back-extraction step into 150 mL of 0·05 M H_2SO_4 was also necessary to obtain a clear chromatogram. Loxapine (500 ng) was used as the internal standard.

A minimum sensitivity of 2·5 ng mL^{-1} for diltiazem, MA, DAD, M_2, M_6,

M_4 in plasma and of 25 ng mL^{-1} for all substances in urine were obtained. Recoveries of 93 per cent, 90·7 per cent, 67·8 per cent, 67·3 per cent, 76·7 per cent and 88·3 per cent from urine were obtained for diltiazem, DAD, MA, M_2, M_4, and M_6, respectively. Correlation coefficients (r^2) of diltiazem and metabolites were greater than 0·96 and day-to-day coefficients of variation were less than or equal to 12 per cent for diltiazem and 17 per cent for its metabolites both in plasma and urine.

The pharmacokinetic parameters were evaluated by using non-linear least squares regression softwares (JANA and NONLIN). Terminal elimination half-life ($t_{½el}$), absorption half-life ($t_{½ab}$), and distribution half-life ($t_{½di}$) were calculated by the formulae $t_{½el} = \ln 2/\beta$, $t_{½ab} = \ln 2/k_a$ and $t_{½di} = \ln 2/\alpha$, respectively. The cumulative areas under the concentration vs time curves (AUC) were calculated by the trapezoidal rule from time 0 to 48 h and extrapolated to infinity by adding the ratio of the last measurable C_p/β.

The results for CRF patients were compared to those of healthy volunteers by two-tailed t-tests for parallel groups after verifying homogeneity of variance by Cochran's test. In the cases where it did not occur, the degrees of freedom were approximated by the Welch's test.

The critical level of significance was set at 0·05.

RESULTS

The mean observed diltiazem plasma concentrations in healthy volunteers and in patients are presented in Figure 2. There is a trend for a slightly higher concentration in patients than in healthy volunteers. The mean pharmacokinetic parameters are presented in Table 2 which shows statistically significant differences between healthy volunteers and patients with CRF only for total clearance.

Table 2. Mean pharmacokinetic parameters (±SE) of diltiazem

	Healthy volunteers	CRF patients	p
$t_{½el}$	3·2 h (0·13)	3·7 h (0·76)	0·6580
$t_{½di}$	1·7 h (0·5)	2·5 h (0·41)	0·2841
$t_{½ab}$	0·9 h (0·2)	1·5 h (0·13)	0·0511
C_{max}	174·7 ng mL^{-1} (29·9)	220·5 ng mL^{-1} (22·3)	0·2488
t_{max}	4·6 h (0·40)	4·9 h (0·10)	0·4436
AUC	2134 ng mL^{-1} h (335)	2782 ng mL^{-1} h (206)	0·1045
$V_{d\,area}/F$	138·5 L (6·2)	78·8 L (20·0)	>0·05
Cl_{tot}	30·5 L h^{-1} (2·6)	12·9 L h^{-1} (1·5)	0·0014

The mean amount of diltiazem excreted unchanged in urine at each sampling time is presented in Table 3 which shows statistically significant differences for intervals 0–6 h and 6–12 h and also for overall amount. As for diltiazem,

Table 3. Mean amount of diltiazem excreted unchanged in urine (±SE)

Sampling time	Healthy volunteers	CRF patients	*p*
0–6 h	1226·8 (210) μg	324·3 (106) μg	0·0015
6–12 h	791·6 (119) μg	393·5 (46) μg	0·0035
12–24 h	937·4 (446) μg	261·4 (43) μg	>0·05
24–48 h	116·1 (39) μg	102·7 (26) μg	>0·05
Cumulative (0–48 h)	3071·9 (609) μg	1081·9 (167) μg	<0·05

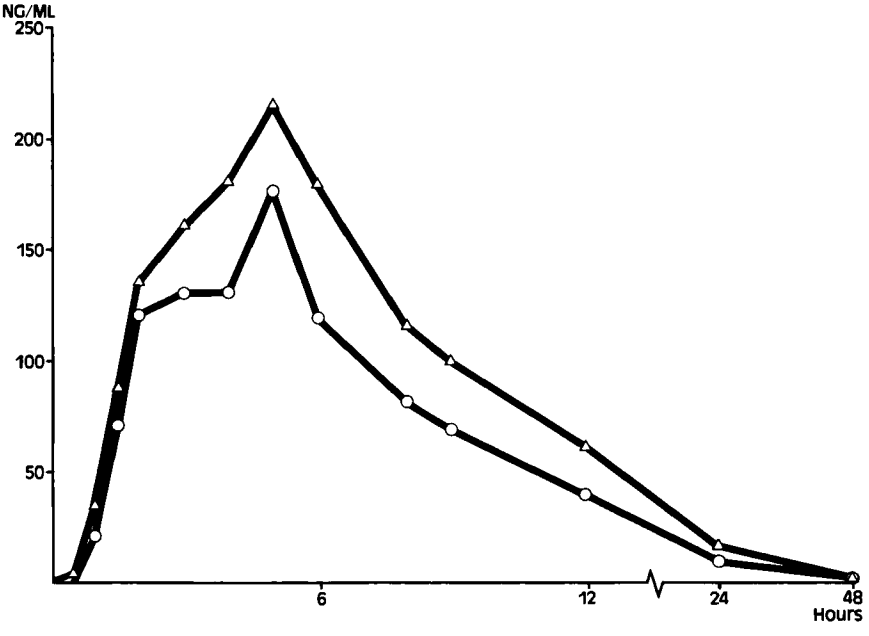

Figure 2. Mean plasma concentrations versus time of unchanged diltiazem in patients with chronic renal failure (△) and in healthy volunteers (○) following a dose of 120 mg of diltiazem

the mean observed MA plasma concentrations tended to be higher in patients with CRF than in healthy volunteers as shown in Figure 3. The corresponding areas under the curves from 0 to 48 h for MA were significantly higher for patients with CRF (768 ng mL^{-1} h ± 68) than for healthy volunteers (396 ng mL^{-1} h ± 34). Other metabolites (DAD, M_2, M_4, and M_6) did not give statistically significant differences in pharmacokinetics between patients and healthy volunteers except for $t_{½el}$ of M_4 as shown in Table 4.

The relative importance of each metabolite, determined by the ratio of AUC_{0-48} metabolite/AUC_{0-48} diltiazem, was in healthy volunteers: MA (26 per cent),

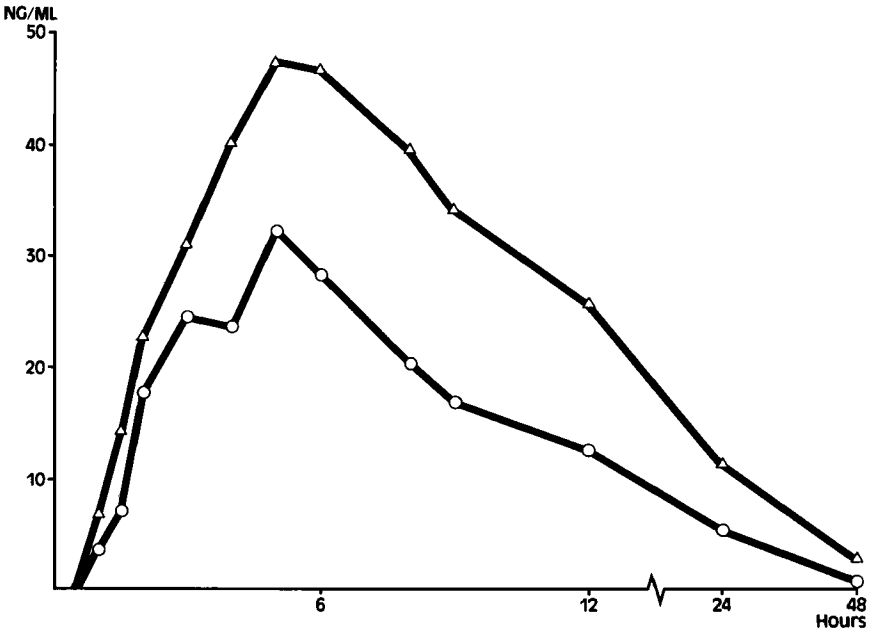

Figure 3. Mean plasma concentrations versus time of unchanged N-desmethyldiltiazem in patients with chronic renal failure (△) and in healthy volunteers (○) following a dose of 120 mg of diltiazem

Table 4. Mean elimination half-life of metabolites (±SE)

Metabolite	Healthy volunteers	CRF patients	*p*
MA	13·8 h (0·4)	12·0 h (0·4)	NS
DAD	5·3 h (0·4)	8·9 h (0·6)	NS
M_2	6·7 h (0·7)	15·4 h (1·4)	NS
M_4	5·3 h (0·2)	12·6 h (0·7)	<0·05
M_6	6·6 h (0·8)	12·8 h (1·2)	NS

M_2 (24 per cent), M_6 (20 per cent), M_4 (13 per cent), and DAD (12 per cent). The order was the same in patients who presented: MA (39 per cent), M_2 (28 per cent), M_6 (21 per cent), M_4 (13 per cent) and DAD (11 per cent).

The urinary excretion of the unconjugated metabolites MA, DAD, M_2, and M_4 were reduced by 63 per cent, 36 per cent, 33 per cent, and 65 per cent, respectively in patients as shown in Table 5 while M_6 was increased by 98 per cent. Only changes in MA and M_4 were statistically significant.

Table 5. Mean (±SE) overall excretion of unconjugated metabolites in urine

Metabolites	Healthy volunteers	CRF patients	*p*
MA	3029·3 μg (350)	1121·9 μg (154)	0·0002
DAD	334·8 μg (96)	213·0 μg (45)	0·2246
M_2	457·1 μg (99)	306·5 μg (96)	0·3553
M_4	1827·4 μg (385)	637·0 μg (172)	0·0075
M_6	32·5 μg (22)	64·3 μg (56)	NS

DISCUSSION

In a previous report,[4] diltiazem was found to have a mean elimination half-life of 3·38 h in nine patients with severe renal failure. However in that study there was no control group and evaluation of kinetic parameters, other than elimination half-life of diltiazem, was not performed.

In the present study, patients with CRF showed higher maximum plasma concentrations and larger areas under the curve of diltiazem. Even though these differences did not reach a statistically significant level, their importance (+25·6 per cent and +26·7 per cent, respectively) must be questioned. A small sample size and a large standard deviation may well be responsible for the lack of statistical significance. This finding is supported by the fact that patients had mean plasma concentrations of diltiazem at 11 out of 12 sampling times (0 and 48 h not included) higher than healthy volunteers did. The difference in mean age between the two groups can hardly be responsible for the difference based on a previous study that showed that people 65 to 83 years old did not present significant differences in pharmacokinetics of diltiazem from people 30 to 39 years old.[14]

In Table 2 the difference in V_d area/F seems larger than the difference in AUC. This may be explained by a difference in F. Actually 10 of these CRF patients and three of these healthy volunteers were later given an i.v. bolus of diltiazem. The mean Fs observed were 0·53 for CRF patients and 0·77 for healthy volunteers. This further reinforces the view that a different disposition mechanism operates in CRF since such patients show higher plasma concentrations than volunteers despite a lower mean F value.

Chronic renal failure usually interferes with drug absorption because of higher gastric pH due to ammonia buffering or secondary to bowel edema.[15] A higher maximum concentration would have necessitated faster absorption of diltiazem which is unlikely to happen here if one considers that increase in gastric pH would favour diltiazem degradation and bowel edema would disfavour absorption. The difference is therefore unlikely to be caused by the absorption process.

Renal excretion of unchanged diltiazem and its unconjugated metabolites MA and M_6 was significantly reduced in patients with CRF. Only 0·8 per cent of the dose was excreted unchanged in patients as compared to 2·6

per cent in those with normal renal function. The difference in diltiazem renal excretion is small, and therefore is not likely to explain higher plasma concentrations and areas under the curve in patients. The kidney indeed represents only a minor route of elimination for this drug.[12] Furthermore, the elimination half-life of diltiazem and MA were unchanged with CRF.

Since neither absorption nor elimination of diltiazem may have contributed significantly to higher levels of plasma concentrations of diltiazem in patients with CRF, changes in the distribution of the drug remain one likely possibility. Diltiazem is a liposoluble drug which is vastly and rapidly distributed to body tissues[5-8]. Almost 85 per cent of diltiazem is bound to plasma proteins, the majority of which are α-glycoproteins.[16] A reduction in the volume of distribution and/or in the rate of distribution of diltiazem may account for most of the kinetic changes observed in patients with impaired renal function. CRF has been asociated with an increase in plasma α-glycoproteins as have several other diseased states.[17] Moreover, a decrease in the uptake of a drug by tissues due to alterations in receptor configuration or displacement by accumulated waste products has been shown for digoxin when given to patients with CRF.[18] The same mechanism may also occur for diltiazem, but its characterization is more difficult with this oral formulation where elimination and distribution overlap. This could explain why $t_{½di}$ are not statistically different even if distribution could be affected. The final outcome of impaired distribution would be a greater amount of diltiazem in plasma and a reduction in its systemic clearance as seen here.

These results confirm that CRF does not alter diltiazem elimination half-life, as was previously reported,[4] but the constant observation of higher plasma concentration values in patients with CRF suggests that the distribution process may be altered. Consequently further studies using chronic administration of diltiazem in patients with CRF are required before the pharmacokinetics of this drug in this condition is completely defined and further studies using an i.v. formulation are needed to carefully investigate tissue distribution of diltiazem in patients with CRF.

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