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# PHARMACOKINETICS OF INTRAVENOUS DILTIAZEM AND FIVE OF ITS METABOLITES IN PATIENTS WITH CHRONIC RENAL FAILURE AND IN HEALTHY VOLUNTEERS

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## ABSTRACT

The pharmacokinetics of diltiazem were studied in seven patients with chronic renal failure (CRF) not requiring dialysis and in three healthy volunteers after a rapid i.v. infusion of 20 mg. Mean plasma concentrations at the end of infusion were 3·15 times higher in patients with CRF than in healthy volunteers. From 0·5 to 12 h post-infusion, the difference remained between 25 per cent and 73 per cent. Mean $AUC_{0-\infty}$ was statistically greater in patients than in volunteers while mean $V$ area, $CL_{tot}$, and $CL_{ren}$ were statistically lower. The $t_{½\alpha}$ and $t_{½\beta}$ values were not significantly ($p > 0·05$) different between patients and volunteers. Renal excretion was statistically more important in volunteers (6·6 per cent of the dose) than in patients (1·2 per cent of the dose). We therefore conclude that CRF does not influence $t_{½\beta}$ of diltiazem but it interferes with the extent and possibly the rate of its extravascular distribution. That could result in transient high plasma concentrations after rapid i.v. infusion.

KEY WORDS Diltiazem Intravenous Pharmacokinetics Patients Healthy volunteers

## INTRODUCTION

Recently we have compared the pharmacokinetic profile of a single oral dose of diltiazem in 10 patients with chronic renal failure (CRF) to the profile in five healthy volunteers.[1] Statistically significant differences were found in renal elimination but not in terminal elimination half-life. These results confirmed previous findings by Pozet *et al.*[2]

On the other hand, diltiazem mean plasma concentrations in patients with CRF were almost always (11 out of 12 sampling times) higher than in healthy volunteers by 22 per cent to 68 per cent. An alteration in the extravascular distribution process was proposed to explain this observation.

Until now few studies have been published on the pharmacokinetics of intra-

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venous diltiazem.[3,4] None of these has reported the renal excretion of diltiazem and of five of its metabolites and none has dealt with the administration of diltiazem to patients with CRF. The purpose of the present study was to assess the pharmacokinetics of intravenous diltiazem in patients with CRF.

## METHODS

Seven patients with CRF (four men, three women) and three healthy volunteers (two men, one woman) who had participated in the oral phase[1] agreed in writing to be included in this study. CRF patients had a mean age (SE) of 45·6 (4·6) years and a mean weight of 64·3 (5·5) kg. Healthy volunteers were 27·3 (2·9) years old and weighed 69·8 (6·0) kg.

CRF patients were not on any form of dialysis and had blood urea nitrogen and serum creatinine values higher than 14·3 mmol/L and 227 μmol/L, respectively. Their renal creatinine clearance was lower than 1 ml $s^{-1}$. Except for those 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 successfully underwent the same tests.

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

On the morning of the experiment the participants ate a light standardized breakfast 1 h before receiving 20 mg of diltiazem by intravenous infusion over 5 min. Blood samples were collected by forearm venipunctures into heparinized tubes prior to and at 5 and 30 min, and 1, 1·5, 2, 3, 4, 5, 6, 8, 9, 12, 24, and 48 h after the beginning of infusion. Total urine was collected for four periods (0–6, 6–12, 12–24, and 24–48 h) following diltiazem administration. Blood samples were centrifuged immediately after collection and the plasma was transferred into air-tight tubes and frozen until assayed. Urine volume was measured after each collection period and a sample was frozen in an air-tight tube until assayed by a previously described HPLC with UV detector method[1] for diltiazem, deacetyldiltiazem, deacetyl-N-desmethyldiltiazem, deacetyl-O-desmethyldiltiazem, deacetyl-N,O-desmethyldiltiazem, and N-monodesmethyldiltiazem.

The pharmacokinetic parameters were evaluated by using non-linear least squares regression softwares (JANA and NONLIN). All $C_p$ vs time curves were analysed using the two-compartment open model. This decision was based on a better correlation between $C_p$ observed and $C_p$ estimated using this model over the one-compartment open model and on the obvious two phases in decline

Table 1. Drugs used by the patients

| Patient number | Drug | Dosage |
|---|---|---|
| 1 | Fenfluramine | 20 mg hs |
| | Brompheniramine 4 mg + | 1 co hs |
| | Phenylephrine 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 |

in the ln $C_p$ vs time curves. Terminal elimination half-life ($t_{½\beta}$) and distribution half-life ($t_{½\alpha}$) were calculated by the formulae $t_{½\beta} = \ln 2/\beta$ and $t_{½\alpha} = \ln 2/\alpha$, respectively. The cumulative areas under the concentration vs time curves from 0 to 48 h ($AUC_{0-48}$) were calculated by the trapezoidal rule and extrapolated to infinity ($AUC_{0-\infty}$) by adding the ratio of the last measurable $C_p/\beta$.

The results for patients with CRF 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 Welch's test. Statistical significance was set at 0·05.

## RESULTS

Mean plasma concentrations vs time curves are presented in Figures 1 and 2 for times 5 min to 1 h and 30 min to 24 h, respectively. Variation, expressed as SE/mean, ranged from 6·5 per cent to 26·4 per cent for CRF patients and from 5·6 per cent to 26·3 per cent for healthy volunteers. For the sake of clarity, means at 48 h are not included in Figure 2; they are 0 ng mL$^{-1}$ for healthy volunteers and 0·7 ng mL$^{-1}$ for patients with CRF. The mean for patients is higher than for healthy volunteers at all sampling times and this difference is statistically significant at 5 and 30 min post-dose. The corresponding mean pharmacokinetic parameters are presented in Table 2. Differences in $AUC_{0-\infty}$, $V_{area}$, $Cl_{tot}$, and $Cl_{ren}$ were found to be statistically significant. Mean amount of unchanged diltiazem recovered in urine is presented in Table 3. There is a significant difference between the two groups for the cumulative 48-h excretion and for the period between 0 and 6 h post-dose. Urinary excretion accounted for elimination of 1·2 per cent of the dose in patients and 6·6 per cent in healthy volunteers.

Plasma concentrations of metabolites were all very low. Except for deacetyldiltiazem that presented mean concentrations of 49·4 ng mL$^{-1}$ and 23·1 ng mL$^{-1}$ at 5 and 30 min and post-dose, respectively, for patients with CRF and 17·3 ng mL$^{-1}$ at 5 min post-dose for healthy volunteers all other observations for all metabolites were lower than 5·4 ng mL$^{-1}$. Cumulative excretion of metabolites is presented in Table 4 and showed large differences in favour of healthy volunteers; however, statistical significance is reached only for N-monodesmethyldiltiazem.

## DISCUSSION

The present trial confirms previous observations[1,2] that the CRF condition does not modify the $t_{½\beta}$ of diltiazem. This is most likely the result of the remote importance of the kidney in the elimination of unchanged diltiazem (1·2 per cent to 6·6 per cent in this study). However, the conclusion that dose adjustment is not necessary in CRF patients must be questioned.

Actually this trial shows, as did a previous one,[1] that patients with CRF almost always have higher plasma concentrations than healthy volunteers despite similar $t_{½\beta}$ values. A smaller volume of distribution in CRF patients may well explain the differences in plasma concentrations and in clearances observed here. As was previously reported, this smaller volume of distribution could be the result of an increase in plasma $\alpha$-glycoproteins[5] to which diltiazem is highly bound.[6] Such an increase in protein binding may explain the constant difference in $C_p$ after 0·5 h where patients have $C_p$ higher by 25 per cent to 70 per cent.

However, this increase in binding by itself is unlikely to be responsible for

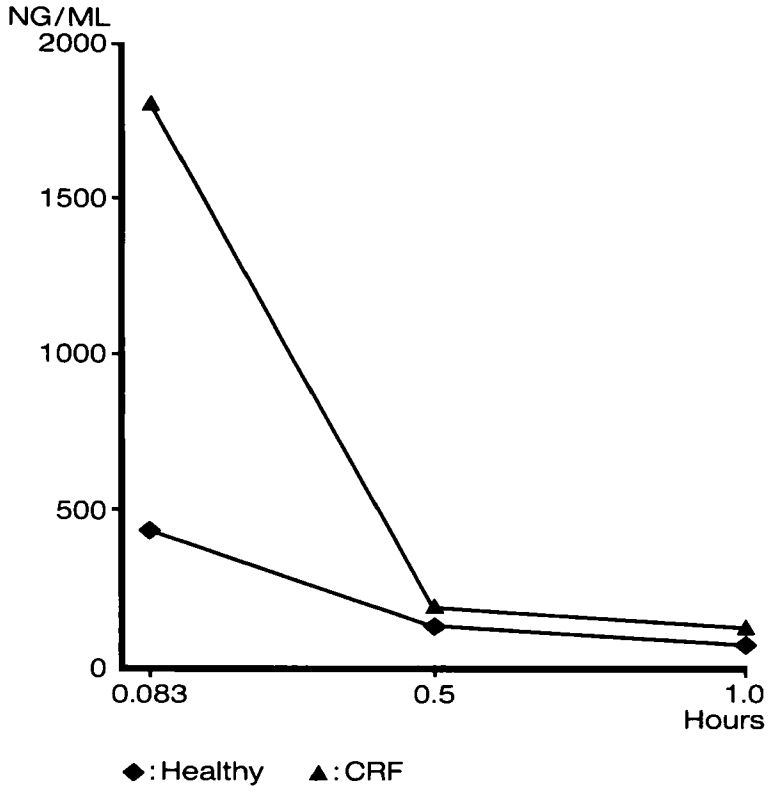


Figure 1. Mean plasma concentrations of diltiazem vs time from 5 min after the beginning of a rapid i.v. infusion to 1 h

the 315 per cent difference in $C_p$ seen at 5 min. This suggests that another mechanism may be present to produce this shift from 25–70 per cent to 315 per cent.

It is therefore suspected that the initial rate of distribution to extravascular tissues is slower in CRF patients. This, in addition to increased protein binding, may explain the tremendous difference seen at 5 min. Such an alteration in the rate of distribution by waste product has already been described for digoxin.[7]

Surprisingly, in this study there were no significant differences between CRF patients and healthy volunteers for $t_{½\alpha}$. This could be due to insufficient samples during the distribution phase, which seems to be mostly completed by 0·5 h, to the small sample size, or both. Despite these limitations there is a statistically significant difference in $C_p$ at 5 min and, from Figure 1, there is visual difference in the shape of the $\alpha$ phase, suggesting that there is indeed a different process even if this trial did not find significant difference in $t_{½\alpha}$ because it concentrated on $t_{½\beta}$.

The clinical significance of this phenomenon, if any, is still unknown. Since

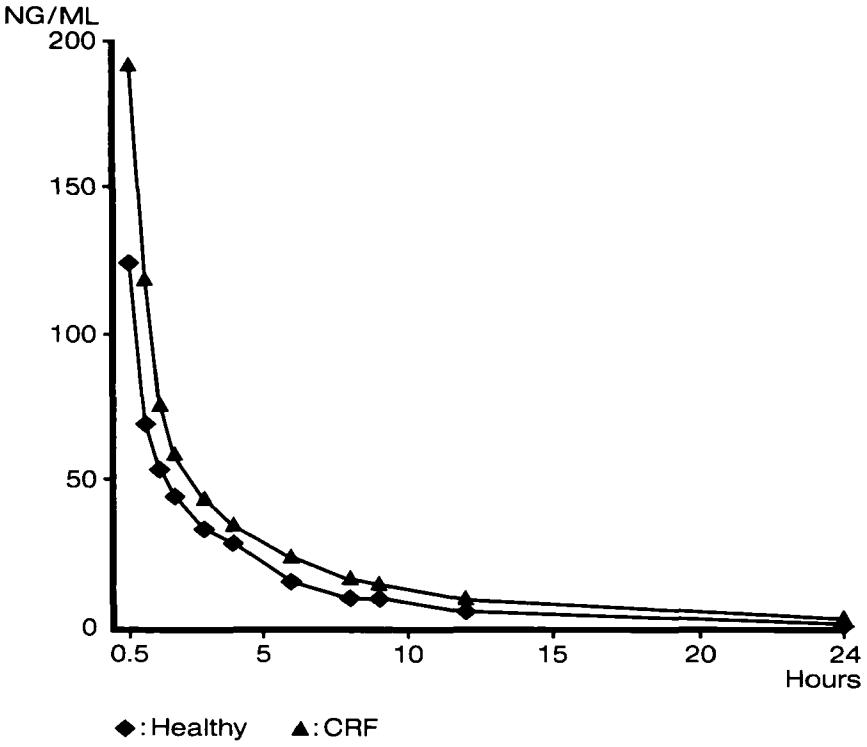


Figure 2. Mean plasma concentrations of diltiazem vs time from 1 h after the beginning of a rapid i.v. infusion to 24 h

Table 2. Means (±SE) of pharmacokinetic parameters

| Parameter | Healthy volunteers | CRF patients | *p* |
|---|---|---|---|
| $t_{½\alpha}$ (h) | 0·160 (0·045) | 0·200 (0·275) | NS |
| $t_{½\beta}$ (h) | 2·70 (0·41) | 2·24 (0·58) | NS |
| $AUC_{0-\infty}$ (ng ml$^{-1}$ h) | 408·0 (67·0) | 838·5 (177·3) | <0·01 |
| $V_{area}$ (l) | 196·2 (41·4) | 81·8 (31·0) | 0·003 |
| $Cl/_{tot}$ (l h$^{-1}$) | 50·4 (8·6) | 24·8 (4·8) | 0·001 |
| $Cl_{ren}$ (l h$^{-1}$) | 3·2 (0·1) | 0·32 (0·12) | <0·01 |

plasma is not the site of action of diltiazem it is not obvious that increased $C_p$ will result in increased response, on the contrary it may produce a decreased response by providing less drug in the peripheral tissues. This trial did not measure any pharmacodynamic response.

Intravenous diltiazem is used in the acute treatment of paroxysmal supraventricular tachycardia and of atrial fibrillation and flutter as single or multiple 2-min boli of 0·15 mg kg$^{-1}$ to 0·45 mg kg$^{-1}$.[8,9] When used as a 10–15 mg h$^{-1}$ con-

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

| Period | Healthy volunteers | CRF patients | $p$ |
|---|---|---|---|
| 0–6 h | 926·3 μg (109·0) | 164·8 μg (63·8) | <0·05 |
| 6–12 h | 245·6 μg (284·0) | 51·7 μg (32·9) | NS |
| 12–24 h | 104·7 μg (59·2) | 23·5 μg (13·0) | NS |
| 24–48 h | 43·8 μg (39·6) | 8·4 μg (8·3) | NS |
| Cumulative 0–48 | 1320·7 μg (483·7) | 248·4 μg (87·8) | <0·05 |

Table 4. Mean (±SE) cumulative amount of metabolites in urine between 0 and 48 h post-dose

| Metabolite | Healthy volunteers | CRF patients | $p$ |
|---|---|---|---|
| Deacetyl | 108·9 μg (96·2) | 34·2 μg (16·0) | NS |
| Deacetyl-N-desmethyl | 42·1 μg (15·3) | 41·3 μg (16·5) | NS |
| Deacetyl-o-desmethyl | 10·1 μg (12·8) | 1·2 μg (2·9) | NS |
| Deacetyl-N,o-desmethyl | 204·3 μg (103·8) | 69·8 μg (34·3) | NS |
| N-monodesmethyl | 499·5 μg (125·8) | 144·0 μg (49·3) | <0·05 |

tinuous infusion a 20 per cent heart rate reduction is predicted as a $C_p$ of approximately $70 \pm 64\,ng\,mL^{-1}$ (mean ± SD) and $EC_{50}$ is $99 \pm 51\,ng\,mL^{-1}$.[10] If an intravenous bolus is used in CRF patients, the $C_p$s will take longer to get back to this level and careful monitoring of PR interval is therefore needed for a longer period.

We therefore conclude that CRF does not significantly impair elimination of diltiazem but it does modify the extravascular distribution process. Since the clinical significance of this latter phenomenon has not been assessed, we suggest the need for care when using intravenous bolus doses of diltiazem in CRF patients and that vital signs and ECG be monitored for a longer period than usual.

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