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Steady-State Pharmacokinetics of Diltiazem and Hydrochlorothiazide Administered Alone and in Combination

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ABSTRACT: Diltiazem and hydrochlorothiazide are widely used to treat cardiovascular disease, often in combination. The purpose of this investigation was to determine whether a drug–drug pharmacokinetic interaction exists between diltiazem and hydrochlorothiazide. In a randomized, crossover, open study, multiple doses of diltiazem (60 mg four times daily for 21 doses) and hydrochlorothiazide (25 mg twice daily for 11 doses) were administered alone and in combination on three separate occasions to 20 healthy male volunteers. Trough and serial blood samples were collected and plasma was assayed for diltiazem, hydrochlorothiazide, and diltiazem metabolites (desacetyldiltiazem and N-desmethyldiltiazem) using HPLC. Total urine was also collected and quantified for hydrochlorothiazide.

Coadministered hydrochlorothiazide did not significantly ($p > 0.05$) alter diltiazem (alone versus combination) steady-state maximum plasma concentration ($C_{ss_{max}}$; 145 versus 158 ng mL^{-1}, respectively), time to maximum plasma concentration (t_{max}; 3.0 versus 2.8 h, respectively); area under the plasma concentration–time curve (AUC_{ss}; 688 versus 771 ng·h mL^{-1}), oral clearance (Cl_{oral}; 96.2 versus 88.0 L h^{-1}), or elimination half-life ($t_{1/2}$; 5.2 versus 5.2 h). Similarly, administration of diltiazem did not significantly ($p > 0.05$) influence hydrochlorothiazide (alone versus combination) $C_{ss_{max}}$ (221 versus 288 ng mL^{-1}), t_{max} (1.8 versus 2.0 h), AUC_{ss} (1194 versus 1247 ng·h mL^{-1}), Cl_{oral} (22.4 versus 21.2 L h^{-1}); $t_{1/2}$ (9.8 versus 9.6 h), or renal Cl (15.5 versus 15.2 L h^{-1}). In conclusion, a clinically significant pharmacokinetic interaction between diltiazem and hydrochlorothiazide does not exist. © 1998 John Wiley & Sons, Ltd.

Key words: diltiazem; hydrochlorothiazide; drug interactions; absorption; excretion; pharmacokinetics

Introduction

Diltiazem hydrochloride is a calcium antagonist widely used in the treatment of hypertension and angina pectoris [1,2]. Diltiazem produces vascular smooth muscle relaxation and vasodilation by altering calcium ion flux into cells [3]. The vasodilating properties of diltiazem may be responsible for the antihypertensive response observed in patients with essential hypertension, in addition to the antianginal response seen in patients with stable angina and coronary artery spasm [4]. Hydrochlorothiazide is a thiazide diuretic that increases renal excretion of sodium, chloride, and water by interfering with the transport of sodium ions across distal renal tubules [5]. Hydrochlorothiazide is used in the treatment of hypertension and edematous states.

In patients with hypertension refractory to single-drug therapy, the addition of a second drug is recommended [6]. Since diltiazem and hydrochlorothiazide have complimentary blood pressure lowering effects, this is a logical combination in the stepwise approach for managing hypertension [6,7]. In order to maximize therapy with drug combinations, however, potential drug interactions must be identified. Therefore, the purpose of this present investigation was to evaluate whether the pharmacokinetics of diltiazem and hydrochlorothiazide are altered when these two drugs are coadministered.

Methods

Subjects

Twenty-five healthy, nonsmoking, male volunteers between the ages of 21 and 39 years (27.8 ± 5.7 years) and within 10% of the average weight for individuals of their build and age (171.11 ± 19.4 lbs) participated in this randomized, three-way complete crossover, open-label study. Based on prestudy medical history, laboratory evaluations, and physical examinations, study subjects were documented to be free of any significant organ abnormality or disease; without a history of mental illness

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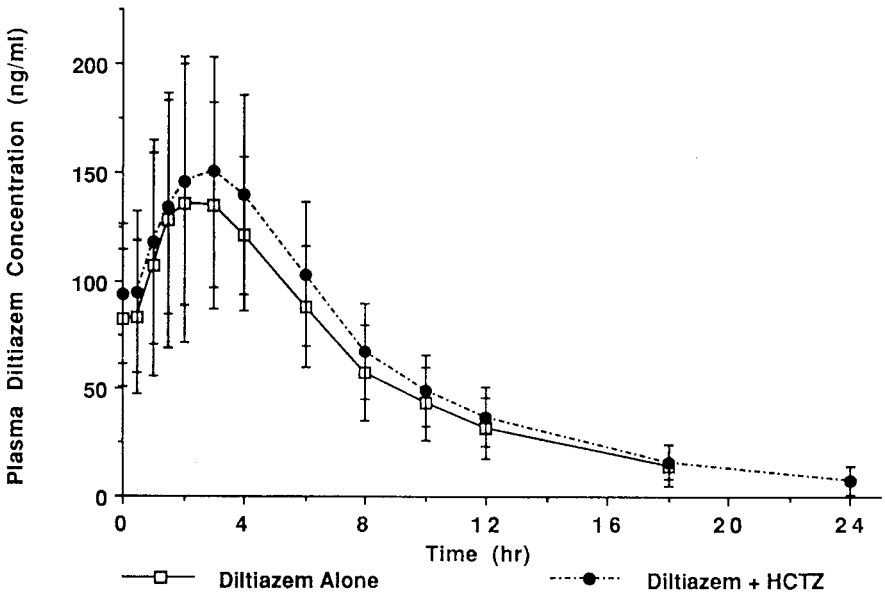

Figure 1. Diltiazem plasma concentration–time profiles for Treatments A (diltiazem alone) and C (diltiazem plus hydrochlorothiazide) ($N = 20$)

or a recent history of smoking, alcohol ingestion, or drug abuse; and to have not taken any prescription of nonprescription medication within 14 days prior to study entry. Prior to enrolment, all subjects signed written informed consent.

Study Procedures

Study subjects were admitted to and required to remain in the clinical facility (Harris Laboratories, Inc., Lincoln, NE) on three separate occasions for a period of 7 days each. In randomized order, subjects received each of the following treatments: Treatment A, one diltiazem HCl 60 mg tablet (Cardizem, Hoechst Marion Roussel; Lot No. R6013) every 6 h for 21 doses (5.5 days); Treatment B, one hydrochlorothiazide 25 mg tablet (Hydrodiuril, Merck Sharp & Dohme; Lot No. K2487) every 12 h for 11 doses (5.5 days); or Treatment C, coadministration of Treatments A and B. An 8 to 15 day washout period separated treatment periods. At prespecified times during the 7-day clinic stay, study subjects received nutritionally balanced meals and snacks containing no caffeine.

During each treatment period, blood (plasma) samples were collected just prior to the 07:00 h dose on Days 1, 5, and 6 for trough diltiazem plasma concentration determinations. Serial blood samples were obtained 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 h on Day 6 after the last dose of study drug for determination of steady-state diltiazem and diltiazem metabolite (desacetyldiltiazem and N-desmethyldiltiazem) pharmacokinetic parameters. Blood samples were centrifuged immediately and plasma was stored at -20°C until analysed. Urine samples were collected at the following intervals: before the 07:00 h dose on Day 1 and 0–4, 4–8, 8–12, 12–24, 24–36, and 38–48 h after the last dose of study drug on Day 6 of Treatments B and C. Aliquot urine samples were stored at -20°C until analysed.

Pharmacokinetic Analyses

Plasma diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem concentrations were determined by a specific high performance liquid chromatographic method (HPLC) with UV detection. The analytes and internal standard were isolated from plasma samples that had been buffered and subsequently extracted with an organic solvent. The organic solvent was then back extracted with dilute aqueous acid solution and an aliquot injected into the chromatograph. The chromatographic system consisted of a phenyl column and a mobile phase containing a mixture of acetonitrile, a buffer, and a competing amine. Quantitation was performed by interpolation from the line of best fit calculated by least squares regression of the ratio of the detector response of each of the respective analytes to the internal standard detector response versus known calibration standard concentrations that were extracted from plasma in a fashion identical to the known samples.

Using 1.0 mL of plasma, the calibration curves of diltiazem, desacetyldiltiazem, N-desmethyldiltiazem were linear over a concentration range of 3.12–400 ng mL^{-1}. The lower limits of quantitation using this method were 6.25 ng mL^{-1} for diltiazem, 3.12 ng mL^{-1} for desacetyldiltiazem, and 3.12 ng mL^{-1} for N-desmethyldiltiazem. Over the concentration range studied, the within-batch accuracy varied from 85.4 to 112.6%, 68.9 to 125.3%, and 81.7 to 121.2% for diltiazem, desacetyldiltiazem, and N-

Table 1. Mean (coefficient of variation, %) steady-state diltiazem pharmacokinetic parameters ($N = 20$)

Pharmacokinetic parameter	Diltiazem alone	Diltiazem plus HCTZ	% Pairwise difference	90% Confidence interval
C_{max} (ng mL^{-1})	144.6 (41)	157.9 (35)	2.2	−15.8, 24.2
t_{max} (h)	2.98 (28)	2.75 (28)	−2.7[a]	−21.7, 16.3
$AUC_{0-6\ h}$ (ng·h mL^{-1})	688.2 (37)	770.6 (34)	4.6	−11.5, 23.7
$t_{1/2}$ (h)	5.2 (22)	5.2 (22)	−2.1	−12.0, 7.8
Cl_{oral} (L h^{-1})	96.2 (30)	88.0 (39)	−4.1	−19.0, 10.9
C_{min} (ng mL^{-1})	79.2 (40)	89.6 (36)	5.8[a]	−16.4, 33.8

[a] Not entirely within −20%, +25% by 90% confidence interval test.

Table 2. Mean (coefficient of variation, %) steady-state desacetyldiltiazem and N-desmethyldiltiazem pharmacokinetic parameters ($N = 20$)

Pharmacokinetic parameter	Diltiazem alone	Diltiazem plus HCTZ	% Pairwise difference	90% Confidence interval
Desacetyldiltiazem				
C_{max} (ng mL^{-1})	14.2 (39)	15.7 (42)	0.3	−11.2, 13.3
$AUC_{0-6\ h}$ (ng·h mL^{-1})	75.1 (40)	84.1 (45)	−10.4[a]	−27.7, 10.9
C_{min} (ng mL^{-1})	10.8 (41)	12.6 (40)	11.3[a]	−11.7, 40.2
N-Desmethyldiltiazem				
C_{max} (ng mL^{-1})	45.7 (32)	48.3 (34)	−0.4	−10.0, 10.2
$AUC_{0-6\ h}$ (ng·h mL^{-1})	248.3 (31)	263.1 (33)	0.4	−9.5, 11.3
C_{min} (ng mL^{-1})	36.0 (36)	37.8 (34)	2.1	−11.4, 15.5
$t_{1/2}$ (h)	8.4 (16)	8.6 (17)	1.5	−10.7, 13.7

[a] Not entirely within −20%, +25% by 90% confidence interval test.

desmethyldiltiazem, respectively. Within-batch precision varied from 0.8 to 15.7%, 0.7 to 12.8%, and 0.8 to 14.3% for diltiazem, desacetyldiltiazem and N-desmethyldiltiazem, respectively. Among-batch accuracy varied over this range from 98.1 to 99.8%, 98.6 to 102.9%, and 97.9 to 100.3% for diltiazem, desacetyldiltiazem and N-desmethyldiltiazem, respectively. Among batch precision varied from 4.2 to 14.1%, 2.3 to 21.2% and 2.5 to 17.8% for diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem, respectively.

Plasma and urine hydrochlorothiazide concentrations were also determined by a specific HPLC method with UV detection. Hydrochlorothiazide and an internal standard were isolated from plasma samples that had been buffered and subsequently extracted with an organic solvent. The organic solvent was then evaporated and reconstituted with mobile phase and an aliquot injected into the chromatograph. The chromatographic system consisted of an ODS column and a mobile phase containing a mixture of acetonitrile and phosphate buffer. Quantitation was performed in the same manner described above for diltiazem and its metabolites. Using 1.0 mL of plasma, the calibration curves for hydrochlorothiazide were linear over the concentration range of 5.0–200 ng mL^{-1}. Over the concentration range studied, the within-batch accuracy as indicated by the recovery of spiked samples varied from 93.8 to 110.8% while the within-batch precision varied from 1.9 to 22.3%. Among-batch accuracy varied over this range from 101 to 105% while among-batch precision varied from 2.9 to 15.8%. Using 0.5 mL of urine, the calibration curves for hydrochlorothiazide were linear over the concentration range of 5.0–40 μg mL^{-1}. Over the concentration range studied, the within-batch accuracy varied from 97.8 to 112% while the within-batch precision varied from 0.7 to 4.1%. Among-batch accuracy varied over this range from 98.6 to 104% while among-batch precision varied from 1.4 to 5.8%.

Pharmacokinetic parameters were determined using model-independent techniques. Maximum plasma concentrations at steady-state (C_{max}), time to reach maximum plasma concentration (t_{max}), and minimum plasma concentration at steady-state (C_{min}) were determined for diltiazem, desacetyldiltiazem, N-desmethyldiltiazem, and hydrochlorothiazide using visual inspection of the plasma concentration–time profiles. Area under the concentration–time curves at steady-state for each dosing interval ($AUC_{0-6\ h}$ for diltiazem, desacetyldiltiazem, and N-desmethyldiltiazem; $AUC_{0-12\ h}$ for hydrochlorothiazide) were calculated by the trapezoidal rule. Oral steady-state clearances (Cl_{oral}) for diltiazem and hydrochlorothiazide were determined by dividing the dose by the $AUC_{0-6\ h}$ and $AUC_{0-12\ h}$ respectively. Urine hydrochlorothiazide concentration and urine volume data were used to calculate urinary excretion rate and cumulative mass excreted in urine (A_e). Renal clearance (Cl_r) was determined as the ratio of cumulative mass of hydrochlorothiazide excreted over the dosing interval at steady-state (0–12 h) divided by AUC_{ss} for hydrochlorothiazide.

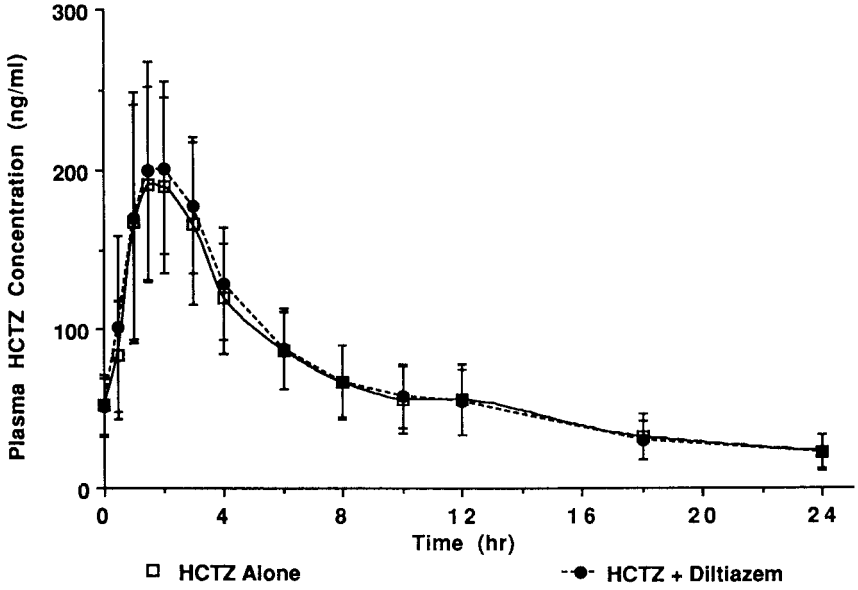

Figure 2. Hydrochlorothiazide plasma concentration–time profiles for Treatments B (hydrochlorothiazide alone) and C (diltiazem plus hydrochlorothiazide) ($N = 20$)

Statistical Analyses

Differences in plasma drug concentrations and pharmacokinetic parameters (with the exception of t_{max}) for each subject were tested for normality using the Shapiro–Wilk test, as computed by PROC UNIVARIATE in SAS, for both the original and log-transformed data. The appropriate transformation was selected based on the results of the test. Analysis of variance was performed on the data with terms for group, subject within group, treatment, carryover, period, group-by-treatment, and group-by-period effects. Since t_{max} is a discrete variable, these values from all treatments and from all subjects were ranked and analysed with the analysis of variance model described above to obtain p-values. Adjusted means and confidence intervals were obtained from the original data. Statistical significance was defined as $p \leq 0.05$. Ninety percent confidence intervals were computed for the difference between treatments. Treatment differences and confidence intervals were converted to percent differences from the treatment comparison. If a confidence interval fell entirely within -20, $+25\%$, statistical equivalence was concluded. In turn, if a confidence interval fell entirely outside the limit, statistical inequivalence was concluded. If the 90% confidence interval limits were only partially within -20, $+25\%$, but zero was included in the limits, treatment differences were considered not to be significantly different.

Results

Twenty-one of the 25 subjects who entered the study completed all three treatment periods. One volunteer withdrew because of personal reasons and three subjects were discontinued due to treatment-related adverse effects: urticaria during Treatment C; premature ventricular contractions during Treatment B; and persistent vomiting, hypertension, tachycardia, and CNS irritability during Treatment B. Before discharge from the study, full recovery from the adverse experience was documented for all three subjects. An additional subject who completed all three drug treatments, but was subsequently found to be a protocol violator, was excluded from all pharmacokinetic analyses. Therefore, this report describes the results obtained in 20 volunteers.

The diltiazem plasma–concentration profiles following Treatments A and C are depicted in Figure 1 and mean steady-state diltiazem pharmacokinetic parameters are listed in Table 1. Coadministration of hydrochlorothiazide did not significantly alter the absorption or disposition of diltiazem. At steady-state, there were no significant differences ($p > 0.05$) in diltiazem C_{max}, C_{min}, t_{max}, $AUC_{0-6\,h}$, $t_{1/2}$, or Cl_{oral} after Treatments A (diltiazem alone) and Treatment C (diltiazem plus hydrochlorothiazide). The pairwise differences were less than 6% for all diltiazem pharmacokinetic parameters. Although the 90% confidence interval for pairwise differences in C_{max}, t_{max}, and C_{min} were only partially contained within -20, $+25\%$ window, zero was included in the intervals demonstrating that treatment differences were not statistically significant. Similarly, as summarized in Table 2, coadministration of hydrochlorothiazide did not alter the disposition of the two principal diltiazem metabolites, desacetyldiltiazem and N-desmethyldiltiazem. Percent pairwise differences were less than 3% for the N-desmethyl metabolite and less than 12% for desacetyldiltiazem. Although the 90% confidence

Table 3. Mean (coefficient of variation, %) steady-state hydrochlorothiazide pharmacokinetic parameters ($N = 15$)[a]

Pharmacokinetic parameter	HCTZ alone	HCTZ plus diltiazem	% Pairwise difference	90% Confidence interval
C_{max} (ng mL^{-1})	221.8 (29)	228.3 (22)	14.0[b]	−12.6, 40.6
t_{max} (h)	1.77 (41)	2.03 (38)	−2.1[b]	−38.0, 33.9
AUC_{0-12h} (ng·h mL^{-1})	1193.9 (26)	1247.2 (26)	3.8	−12.2, 19.8
$t_{1/2}$ (h)	9.74 (17)	9.58 (16)	−1.4	−17.0, 14.1
Cl_{oral} (L h^{-1})	22.4 (27)	21.2 (23)	−11.2[b]	−27.4, 5.0
C_{min} (ng mL^{-1})	50.7 (29)	48.8 (35)	−2.5[b]	−23.7, 18.8
Cl_r	14.4 (38)	15.5 (35)	7.8[b]	−20.9, 18.8

[a] Data from five subjects with interferences present in plasma were not included.
[b] Not entirely within −20%, +25% by 90% confidence interval test.

interval limits were only partially within −20, +25% for desacetyldiltiazem C_{min} and $AUC_{0-6\ h}$, none of the treatment differences for desacetyldiltiazem or N-desmethyldiltiazem were statistically significant.

The hydrochlorothiazide plasma concentration–time profiles following Treatments B and C are depicted in Figure 2, mean steady-state hydrochlorothiazide pharmacokinetic parameters are listed in Table 3, and urinary hydrochlorothiazide excretion data are presented in Figure 3 and Table 4. Due to significant interferences present in the plasma obtained from five volunteers, plasma hydrochlorothiazide concentration–time data were obtained in 15 subjects. Coadministration of diltiazem did not alter the absorption or elimination of hydrochlorothiazide. Plasma steady-state C_{max}, C_{min}, t_{max}, $AUC_{0-12\ h}$, $t_{1/2}$, and Cl_{oral}, cumulative mass excreted, and Cl_r of hydrochlorothiazide were similar following Treatments B (hydrochlorothiazide alone) and C (hydrochlorothiazide plus diltiazem). Percent pairwise differences in plasma hydrochlorothiazide pharmacokinetic parameters were less than 15%. In addition, zero was included in the confidence interval limits. Similarly, the percent pairwise differences in hydrochlorothiazide excreted over the dosing interval (0–12 h), as well as over the 48-h collection period following the last hydrochlorothiazide dose, where less than 2% with zero included in the confidence interval limits.

Discussion

Drugs with complementary mechanisms of action are frequently used as combination therapy in patients with cardiovascular disorders. Indeed, the addition of diltiazem to hydrochlorothiazide therapy has proved to be a safe and effective approach for the management of refractory hypertension [8–12]. In order to maximize combination therapy, however, a thorough understanding about how one drug influences the pharmacodynamic and pharmacokinetic properties of the coadministered drug is needed. In a pharmacodynamic investigation in rats, diltiazem was found to significantly enhance the effect of hydrochlorothiazide on urinary sodium excretion without altering urine volume [13]. To the best of our knowledge, this is the first investigation to determine whether a pharmacokinetic interaction exists between hydrochlorothiazide and a calcium antagonist. No changes in the disposition of either diltiazem or hydrochlorothiazide were found with coadministration compared to each drug administered alone.

Hydrochlorothiazide has been identified as a drug with potential bioavailability problems [14]. Absorption of hydrochlorothiazide is generally assumed to obey first order kinetics [15,16], but a zero order process may better characterize the absorption of hydrochlorothiazide from ingested tablets [17]. A number of factors that alter hydrochlorothiazide absorption have been identified, including drugs (e.g. cholestyramine), food, and disease states (e.g. congestive heart failure) [15]. Based on cumulative urinary excretion studies, the oral bioavailability of hydrochlorothiazide is approximately 70% [15]. Hydrochlorothiazide is excreted almost entirely as unchanged drug in the urine [15]. Renal clearance is about 300 mL min^{-1} [16,18], which indicates that both glomerular filtration and active renal tubular secretion are involved. A wide variation in elimination half-life, from 2 to 15 h, has been reported for hydrochlorothiazide. The main reason for the large variation in $t_{1/2}$ is that hydrochlorothiazide's elimination is biphasic; thus, a positive correlation exists between half-life and the length of sampling time—the longer the sampling period, the longer the terminal half-life. The best estimate of hydrochlorothiazide $t_{1/2}$ is 9–10 h [15,19]. All of these published pharmacokinetic values for hydrochlorothiazide are consistent with the values we found when hydrochlorothiazide was administered alone and in combination with diltiazem.

Diltiazem undergoes extensive first-pass metabolism after oral ingestion, with an absolute bioavailability of 40% [20–22]. Only 1–3% of an oral dose of diltiazem is excreted unchanged in the urine, while 35% of the dose is recovered as metabolites in the urine [20–22]. The two primary metabolites, desacetyldiltiazem and N-desmethyldiltiazem, represent 10 and 45%, respec-

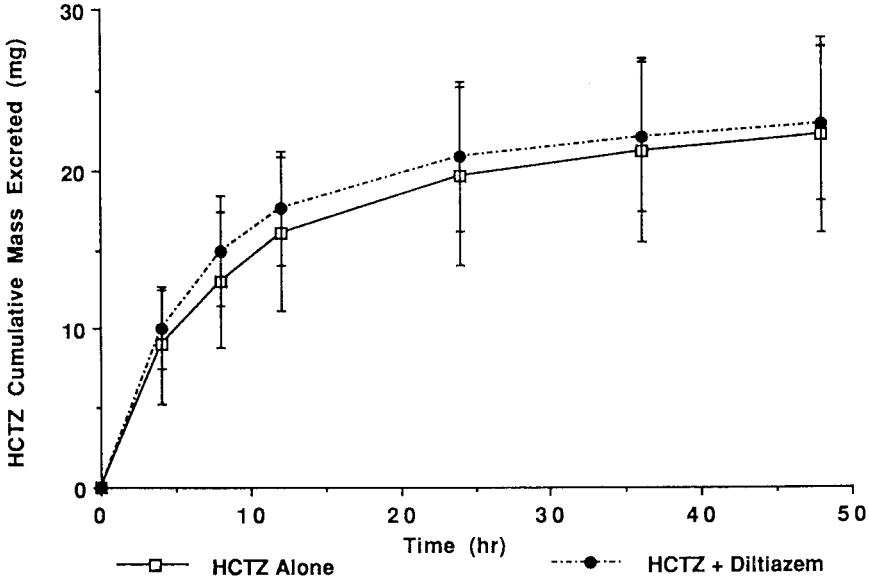

Figure 3. Cumulative mass excretion of hydrochlorothiazide for Treatment B (hydrochlorothiazide alone) and C (diltiazem plus hydrochlorothiazide) ($N = 20$)

Table 4. Mean (coefficient of variation, %) cumulative mass excreted for hydrochlorothiazide ($N = 20$)

Collection interval (h)	HCTZ alone (mg h^{-1})	HCTZ plus diltiazem (mg h^{-1})	% Pairwise difference	90% Confidence interval
0–4	9.0 (41)	10.0 (25)	−9.6[a]	−43.2, 24.0
0–8	13.1 (32)	15.0 (23)	5.0[a]	−23.9, 34.0
0–12	16.1 (30)	17.6 (20)	1.6[a]	−23.3, 26.5
0–24	19.6 (28)	20.9 (22)	0.5[a]	−26.0, 27.1
0–36	21.2 (27)	22.1 (21)	−0.7[a]	−25.4, 24.0
0–48	22.2 (27)	22.9 (21)	−1.1[a]	−25.6, 23.5

[a] Not entirely within −20%, +25% by 90% confidence interval test.

tively, of the parent drug concentration in plasma [20,21,23]. Based on preclinical data, desacetyldiltiazem is 25–50% as potent a coronary vasodilator as diltiazem, and the N-desmethyldiltiazem metabolite is about 20% as potent [24,25]. The $t_{1/2}$ of orally administered diltiazem averages about 4 h (range: 2–11 h) in healthy volunteers [21,22]. Again, these published values for diltiazem pharmacokinetic parameters are consistent with the values found in our study, including the large coefficients of variation for C_{max}, C_{min}, and $t_{1/2}$.

Based on the established pharmacokinetic properties of diltiazem and hydrochlorothiazide, a pharmacokinetic interaction between these drugs was not anticipated. However, it is conceivable that the haemodynamic effects of diltiazem might possibly influence the rate of absorption, distribution, or elimination of hydrochlorothiazide by changing splanchnic blood flow and perfusion of various extravascular tissues, including the kidneys—through which hydrochlorothiazide is almost exclusively eliminated from the body. On the other hand, it is also plausible that hydrochlorothiazide might increase the plasma concentration of diltiazem or its metabolites acutely through a reduction in plasma volume associated with its diuretic effect. Based on our findings, these potential sources for an interaction between diltiazem and hydrochlorothiazide do not exist.

In summary, the absorption and excretion characteristics of diltiazem and hydrochlorothiazide were not altered by the coadministration of the other drug. This finding is consistent with their different modes of elimination—diltiazem is primarily excreted via metabolism and hydrochlorothiazide by renal routes. Therefore, dosage adjustments are not required due to changes in disposition of either drug when the two are used in combination to treat cardiovascular diseases.

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