Bioavailability of Hydrochlorothiazide from Tablets and Suspensions

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Abstract □ The bioavailability of hydrochlorothiazide was determined following single oral 25-, 50-, 100-, and 200-mg tablet and suspension doses in 12 healthy male volunteers. Plasma and urine levels of hydrochlorothiazide were determined by HPLC. Plasma levels of hydrochlorothiazide were satisfactorily described by a triexponential function. Mean peak plasma levels, C_{max} (127–135, 270–280, and 437–490 ng/mL from the 25-, 50-, and 100-mg doses, respectively) were dose proportional, as were areas under plasma profiles, $AUC_{0-\infty}$. Mean percentage recovery of unchanged hydrochlorothiazide in 48-h urine samples accounted for 50–59, 54–55, 60–63, and 54–57% of the 25-, 50-, 100-, and 200-mg doses, respectively. There were no significant differences among these values. Correlation coefficients between 48-h urinary recovery of hydrochlorothiazide and the plasma values (C_{max} and AUC_{0-36}) for the 25-, 50-, and 100-mg doses were 0.73 and 0.84. There were no differences in the net increases in electrolyte excretion among the treatments during the 0–12-h postdose period. The systematic availability of hydrochlorothiazide, unlike that of chlorothiazide, is dose proportional in the therapeutic range.

Keyphrases □ Hydrochlorothiazide—bioavailability from tablets and suspensions, pharmacokinetics □ Bioavailability—hydrochlorothiazide, tablets and suspensions, pharmacokinetics □ Pharmacokinetics—hydrochlorothiazide, bioavailability from tablets and suspensions

Despite their close molecular similarity, the diuretics chlorothiazide and hydrochlorothiazide appear to have different absorption characteristics after oral dosing. It has been reported that chlorothiazide absorption is incomplete and dose dependent, being more efficient with decreasing dosage (1–4). On the other hand, preliminary studies have suggested that hydrochlorothiazide absorption is dose proportional (5). Hydrochlorothiazide is also absorbed more efficiently than chlorothiazide, but is administered at lower doses (6). At a dose of 50 mg, the bioavailabilities of chlorothiazide and hydrochlorothiazide are similar (4).

The objective of this study was to explore the preliminary observation that hydrochlorothiazide absorption is dose proportional (5). The previous observation was based on 25–100-mg tablet doses to two individuals. In the present study, both tablet and suspension dosage forms were administered at a range of 25–200 mg to 12 individuals.

EXPERIMENTAL

Protocol—Twelve healthy male volunteers[1], 22–29 years of age (mean 24 years) and weighing 67–84 kg (mean 78 kg) participated in the study after passing a physical examination and giving informed consent. Each subject was instructed to refrain from taking any other medication for 2 weeks prior to and during the study and caffeine-containing beverages were restricted for 24 h prior to and during the study.

Subjects were divided into six groups of two, and the single oral 25-, 50-, and 100-mg oral tablet[2] and suspension doses of hydrochlorothiazide were administered as a 6 × 6 crossover design. Doses were administered 1 week apart. All doses were given at 8 a.m. after overnight fast; no food was permitted until 4-h postdose. Tablets were administered with 240 mL of water. Suspension doses were prepared by grinding the appropriate tablet to a fine powder in a beaker, adding 50 mL of water, and administering directly from the beaker. Quantitative dosing was ensured by repeated washes of the beaker with water to complete intake of 240 mL. Additional 240-mL water volumes were administered at 2, 4, 6, 8, and 12 h after each drug dose to ensure adequate urine output. Total urine output during the 12-h period prior to dosing and aliquots of urine collected during the 12-h postdose period were retained for electrolyte (K^+, Na^+, Cl^-) analysis.

Urine for drug analysis was collected quantitatively through 48 h postdose. Twenty-milliliter urine aliquots were stored at −20°C until assayed. Heparinized blood samples (~8 mL) were obtained from a forearm vein immediately before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 h postdose. Plasma was separated and stored at −20°C until assayed. Plasma and urine were assayed within 2 weeks of sampling.

In a separate study, the same 12 subjects received single oral 200-mg doses of hydrochlorothiazide (2 × 100-mg tablets) under the same conditions as those described above. Urine was collected through 48 h to determine hydrochlorothiazide excretion. Plasma drug levels and electrolyte excretion were not determined in this study.

Analytical Procedures—Concentrations of hydrochlorothiazide in plasma and urine were determined by HPLC, as described previously (7). Assay response was linear for hydrochlorothiazide concentrations of 10–750 ng/mL in plasma and 1–100 μg/mL in urine, with correlation coefficients of 0.999 and 0.996, respectively. The coefficient of variation in assay response was <10%. Concentrations of K^+, Na^+, and Cl^- ions in urine were determined by direct potentiometry[3].

Data Analysis—Individual plasma hydrochlorothiazide concentration profiles following the 25-, 50-, and 100-mg doses were fitted to a triexponential function of the form:

$$C = xe^{-\alpha t} + ye^{-\beta t} + ze^{-\gamma t} \qquad \text{(Eq. 1)}$$

where C is the concentration of drug in plasma at any time t and other values are constants. Initial parameter estimates were obtained graphically. Improved estimates, with statistical analyses were obtained by nonlinear regression using the NREG computer program (8). Plasma and urine data were examined by ANOVA for crossover design. When significant treatment effects were observed, differences between specific dosages were examined by means of Tukey's test (9).

RESULTS

Mean plasma hydrochlorothiazide levels from the six treatments are given in Table I, the data are summarized in Fig. 1. Plasma pharmacokinetic values are given in Table II.

Absorption was rapid from all dosages, and peak drug levels in plasma occurred uniformly at ~2 h. Suspension doses tended to produce somewhat higher drug levels than the equivalent tablet doses at early sampling times and, with the 50- and 100-mg doses, somewhat lower values at later times. However, differences between the two dosage forms were significant ($p < 0.05$) only at 0.5 h. When plasma drug levels from all dosages were normalized for dose size, there were no significant treatment effects at sampling times after 0.5 h. The mean peak drug levels, C_{max}, were dose proportional: 127–134 ng/mL for the 25-mg doses, 270–280 ng/mL for the 50-mg doses, and 437–490 ng/mL for the 100-mg doses. Increasing the tablet dose from 25 to 100 mg resulted in a 3.4-fold increase in the

[1] Technical staff and graduate students.

[2] Hydrodiuril 25 mg (lot E0251), 50 mg (lot E0254), and 100 mg (lot E0509 tablets; Merck Sharp and Dohme, West Point, Pa.

[3] Technicon C800 System; Technicon Instruments Corp., Tarrytown, N.Y.

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Table I—Plasma Hydrochlorothiazide Levels Following Single Oral Doses to 12 Healthy Male Volunteers

Dosage, mg		Plasma Hydrochlorothiazide, ng/mL										
		0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	12 h	24 h	36 h
Tablet												
25	Mean	22.8	71.6	97.9	107	115	92.6	54.2	39.3	23.3	9.0	4.6
	SD	21.9	32.4	39.1	36	29	21.1	11.6	9.5	11.9	6.3	5.2
50	Mean	49.5	184	232	251	212	178	113	80.7	44.3	19.7	8.7
	SD	38.6	125	92	102	57	28	16	13.5	10.5	7.7	4.6
100	Mean	115	284	354	368	401	353	206	142	84.3	32.2	12.5
	SD	113	150	148	138	90	99	60	35	16.2	10.4	5.4
Suspension												
25	Mean	41.7	103	122	123	118	96.5	51.4	37.5	20.3	10.6	7.4
	SD	29.4	52	45	44	35	26.9	15.4	9.4	7.3	5.5	6.0
50	Mean	105	213	257	227	208	173	103	67.0	42.1	17.0	8.1
	SD	51	79	84	67	50	34	21	18.4	11.0	7.6	7.1
100	Mean	125	341	451	460	401	344	197	139	68.5	28.4	12.0
	SD	12	151	124	117	113	94	57	32	22.9	10.4	9.0

Table II—Pharmacokinetic Parameter Values for Hydrochlorothiazide [a]

Parameter	Tablet			Suspension		
	25 mg	50 mg	100 mg	25 mg	50 mg	100 mg
C_{max}, ng/mL[b]	127 ± 34	280 ± 108	437 ± 105	134 ± 44	270 ± 76	490 ± 130
t_{max}, h[c]	2.4 ± 0.9	2.1 ± 1.0	2.3 ± 1.0	2.4 ± 0.9	1.8 ± 0.7	1.8 ± 0.3
$AUC_{0\text{-}36}$, ng·h/mL[d]	978 ± 237	1968 ± 390	3554 ± 779	1038 ± 282	1910 ± 344	3493 ± 735
CL_R, mL/min[e]	257 ± 83	222 ± 36	232 ± 52	232 ± 78	233 ± 83	256 ± 89

[a] Mean ± 1 *SD*; $n = 12$. [b] Maximum concentration of hydrochlorothiazide in plasma. [c] Time of C_{max}. [d] Area under hydrochlorothiazide concentration curve in plasma from 0 to 36 h, calculated by the trapezoidal rule. [e] Renal clearance of hydrochlorothiazide, calculated from $Au_{36}/AUC_{0\text{-}36}$ where Au_{36} is the 0–36-h urinary recovery. This parameter could not be calculated for the 200-mg dose.

Table III—Values of Rate Constants Obtained by Fitting Individual Plasma Hydrochlorothiazide Profiles to Eq. 1

Parameter	Tablet			Suspension		
	25 mg	50 mg	100 mg	25 mg	50 mg	100 mg
α, h^{-1}	0.40 ± 0.35	0.32 ± 0.28	0.32 ± 0.12	0.30 ± 0.07	0.29 ± 0.05	0.26 ± 0.05
β, h^{-1}	0.085 ± 0.084	0.082 ± 0.084	0.10 ± 0.11	0.060 ± 0.060	0.067 ± 0.031	0.081 ± 0.062
γ, h^{-1}	0.90 ± 0.30	0.99 ± 0.34	0.85 ± 0.77	0.94 ± 0.28	1.26 ± 0.63	0.98 ± 0.27
$t_{1/2\beta}$, h	8.2 ± 8.4	8.4 ± 5.4	12.1 ± 8.9	10.9 ± 9.6	10.4 ± 5.6	8.5 ± 6.4
r^2	0.97 ± 0.03	0.96 ± 0.03	0.97 ± 0.02	0.97 ± 0.01	0.98 ± 0.02	0.97 ± 0.02

[a] Mean ± *SD*; $n = 12$. [b] Half-life of the slowest rate constant β, calculated from $t_{1/2\beta} = \ln 2/\beta$. [c] Coefficient of determination, $r^2 = (\Sigma_{obs}^2 - \Sigma_{dev}^2)/\Sigma_{dev}^2$.

mean value of C_{max} and a 3.8-fold increase in the mean area under the drug plasma curve for 0 to 36 h, $AUC_{0\text{-}36}$. Increasing the suspension dose from 25 to 100 mg resulted in a 3.7-fold increase in C_{max} and a 3.5-fold increase in $AUC_{0\text{-}36}$.

Plasma levels from all dosages exhibited the familiar triphasic characteristic (3, 6, 7). After peak concentrations had been reached, drug levels declined rapidly through 12 h and then at a slower rate. In some subjects there was evidence of curvature in the logarithmic drug level *versus* time profiles throughout the postabsorptive period.

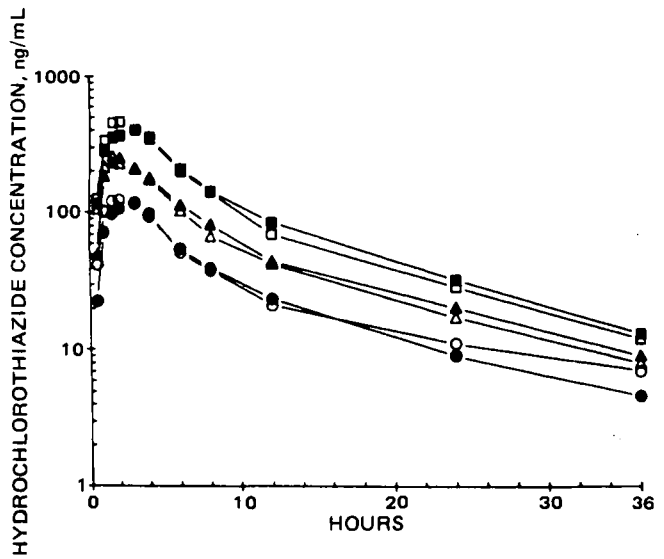

Figure 1—*Mean plasma levels of hydrochlorothiazide following single 25- (●), 50- (▲), and 100-mg (■) tablet and 25- (○), 50- (△), and 100-mg (□) suspension doses (n = 12).*

Analysis of individual drug curves in terms of Eq. 1 yielded the numerical values for the first-order rate constants α, β, and γ shown in Table III. The value of each constant was similar for all treatments, and no significant treatment effects were detected by ANOVA. The uniformly high coefficients of determination (r^2) show that individual drug profiles are satisfactorily described by a triexponential function. The mean half-life of the slowest rate constant β, which represents the terminal drug elimination half-life in plasma, ranged from 8.2 to 12.1 h; this is consistent with previously reported values (6, 7).

The mean cumulative recovery of hydrochlorothiazide in urine at 6, 24, and 48 h is summarized in Fig. 2. Recovery was markedly consistent between dose levels at each collection interval. The mean percentage urinary recoveries from the 25-, 50-, 100-, and 200-mg tablet doses were 62.9, 54.5, 50.3, and 54.0%, respectively. From equivalent suspension doses, the percentage recovery was 60.2, 54.1, 59.0, and 57.3%. There were no significant dosage or formulation effects in the percentage recovery at any collection time. The mean renal clearance of chlorothiazide (Table II), 222–257 ng/mL, was similar from all treatments for which this parameter could be calculated and is in close agreement with values reported earlier (6, 7).

The mean net increases in electrolyte excretion during the 0–12-h post-dose period following the 25-, 50-, and 100-mg doses, compared with the 12–0-h predose period are summarized in Table IV. There was considerable individual variation in these values. The mean net increases were 93–140 mmol for Na^+, 15.2–23.0 mmol for K^+, and 132–176 mmol for Cl^-. The increases were independent of dose size and formulation. Similar observations to these have been made with chlorothiazide administered over a 125–500-mg dosage range (2).

DISCUSSION

Previous studies have shown that the absorption efficiency of orally administered chlorothiazide is dose dependent over a dosage range of

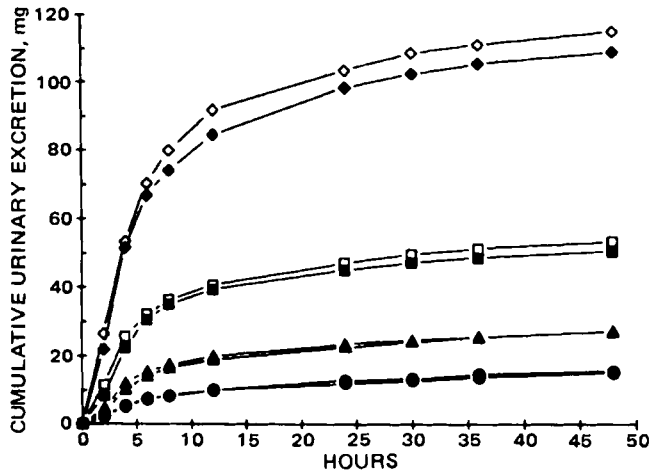

Figure 2—*Mean cumulative urinary recovery of hydrochlorothiazide following 25- (●), 50- (▲), 100- (■), and 200-mg (◆) tablet and 25- (○), 50- (△), 100- (□), and 200-mg (◇) suspension doses (n = 12).*

50–500 mg, the efficiency decreasing with increasing dose (1–4). The results of this study confirm the previous suggestion that the absorption efficiency of oral hydrochlorothiazide, unlike that of chlorothiazide, is independent of dose size (5).

The original objectives of this study were (*a*) to examine the absorption efficiency of hydrochlorothiazide from tablets and suspension doses within the normal therapeutic range of 25- 100 mg, (*b*) to compare urinary excretion and plasma levels, and (*c*) to evaluate the effect of dose size on electrolyte excretion. Mean plasma levels of hydrochlorothiazide were independent of formulation and proportional to dose size, and mean urinary recovery accounted for 50–60% of all dosages.

To determine whether hydrochlorothiazide absorption continued to be dose proportional at dose levels similar to those of chlorothiazide, and also in view of the good agreement between urinary excretion of hydrochlorothiazide and plasma levels, an additional dose of 200 mg was administered to the same subjects and absorption efficiency was assessed from urinary recovery alone. The percent urinary recovery of hydrochlorothiazide from this dose was the same as from the lower doses. The absorption efficiency of oral hydrochlorothiazide is thus independent of dose size over an eight-fold dosage range, which extends into the therapeutic dosage range for chlorothiazide.

These data show that hydrochlorothiazide and chlorothiazide exhibit different absorption characteristics. Whereas chlorothiazide exhibits a marked saturation or "absorption window" effect, hydrochlorothiazide absorption is constant over a wide dosage range. The absorption efficiency of chlorothiazide approaches that of hydrochlorothiazide only at the 50-mg dose level (4).

The reason for the different absorption behavior of the two thiazides is uncertain. The small differences in their molecular structure and physical and chemical characteristics should not cause differences in their absorption if both drugs are absorbed by passive mechanisms.

A possible explanation for their different behavior is that hydrochlorothiazide is efficiently absorbed by a passive process, while chlorothiazide absorption is controlled by an active, saturable component, together with a passive component which is less efficient than that of hydrochlorothiazide. Alternatively, chlorothiazide availability may be influenced by an "absorption window" to a far greater extent than that of hydrochlorothiazide.

Table IV—Net Increase in Electrolyte Excretion in Urine During the 12-h Interval Following All Hydrochlorothiazide Administrations

Dosage, mg	Increase in Electrolyte Excretion, mmol		
	Na^+	K^+	Cl^-
Tablet			
25	102 ± 64	20.2 ± 17.9	136 ± 71
50	93 ± 62	23.0 ± 12.5	132 ± 66
100	109 ± 76	15.2 ± 20.3	142 ± 85
Suspension			
25	103 ± 57	15.3 ± 21.3	137 ± 61
50	125 ± 58	20.7 ± 19.3	160 ± 67
100	140 ± 95	20.4 ± 16.6	176 ± 106

[a] Mean ± *SD*.

Whereas other studies in this laboratory and elsewhere have reported poor correlations between plasma levels and urinary excretion of hydrochlorothiazide (6, 10, 11), good agreement was obtained between these parameters over the dosage range used in this study. Typically, linear regressions of 48-h urinary recovery against AUC_{0-36} and C_{max} values for the combined 25-, 50-, and 100-mg tablet and suspension dosages yielded quite high correlation coefficients of 0.84 and 0.73, respectively. Thus, both plasma level and urinary data may be suitable for determining hydrochlorothiazide bioavailability, but the relative ease of obtaining urine data makes this the method of choice.

The electrolyte excretion data indicate that regardless of the absorption efficiency of hydrochlorothiazide, the maximum pharmacological effect occurs at low doses. There were no increases in net electrolyte excretion as doses were increased from 25 to 100 mg. These results are similar to those reported elsewhere (12, 13). Whether the plateau in pharmacological effect is due to maximal response at lower doses or to an inhibition effect at higher doses (13) cannot be ascertained from our data. Whatever the reason for the plateau effect it is evident that the therapeutic effectiveness of both chlorothiazide and hydrochlorothiazide may be limited at high doses, but for different reasons.

The mechanism causing biphasic elimination of hydrochlorothiazide is uncertain; the prolonged α phase of decline, extending to 12 h postdose, is probably too long to explain in terms of tissue uptake or redistribution according to usual two-compartment model concepts (14). A factor common to studies in which this phenomenon has been reported is water loading during the initial 12 h postdose in order to ensure adequate urine output (4, 5). This may influence hydrochlorothiazide elimination by a variety of mechanisms, including decreased reabsorption of drug from the bladder (15).

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