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ABSORPTION AND DISPOSITION OF A NEW LOW-DOSE COMBINATION FORMULATION OF HYDROCHLOROTHIAZIDE AND TRIAMTERENE*

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ABSTRACT

Two studies are reported that assess the bioequivalence of a new half-strength drug combination containing 25 mg hydrochlorothiazide and 37·5 mg triamterene compared to a full-strength formulation containing 50 mg hydrochlorothiazide and 75 mg triamterene. The first study (I) compared the absorption and disposition of the two drugs after administration of two tablets of the half-strength product as a single dose compared to a single dose of the full-strength product. The second study (II) assessed the bioavailability of the new product given as a single tablet on two occasions separated by an interval of 12 h compared to the full-strength product given as a single dose. Urine parameters in the first study indicated bioequivalence of the half-strength to the full product for both rate and extent of absorption. When given in divided doses, the half-strength product demonstrated bioequivalence to the full-strength product for extent of absorption. Additional data from the second study suggest that absorption of triamterene is greater when given in smaller divided doses and when given at night.

KEY WORDS Hydrochlorothiazide Triamterene Bioavailability

INTRODUCTION

In 1984 a new drug combination containing 50 mg of hydrochlorothiazide and 75 mg of triamterene (Maxzide®, Lederle Laboratories) was introduced for the treatment of mild to moderate hypertension. Absorption of the two drugs in the combination was shown to be equivalent to that of liquid formulations of each drug alone or both in combination.[1] Further interest in combinations of hydrochlorothiazide and triamterene has focused on lowering the dose of hydrochlorothiazide. The impetus for a lower dose of hydrochlorothiazide derived from reports suggesting that 25 mg of hydrochlorothiazide daily[2] or even lower doses[3,4] are effective in the treatment of hypertension. A clinical study performed under our direction has demonstrated that 37·5 mg triamterene

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with 25 mg of hydrochlorothiazide once daily will correct hypokalemia and maintain eukalemia. Based on these data, a new half-strength dose of the 1984 combination containing 25 mg hydrochlorothiazide and 37·5 mg triamterene is now available for once daily dosing (Maxzide-25, Lederle Laboratories).

In this report we document the bioavailability of the new half-strength formulation in comparison to both the full-strength formulation and to liquid preparations of the two drugs. When coupled with bioequivalence data for the full-strength formulation from earlier studies, the data document the consistent absorption of both formulations over several years of development and production. Additional data in this report suggest that absorption of triamterene may be increased when the drug is given in smaller divided doses and when given at night.

METHODS

Clinical study

Bioequivalence data from two clinical studies are presented. Both studies were conducted in the Drug Studies Unit at the University of California, San Francisco. The clinical protocols and consent forms were approved by the University of California, San Francisco, institutional review board. Twenty-four healthy males entered and completed each study. In the first study (Study I), subjects received the following three single treatments orally, randomized for sequence:

1. two half-strength tablets each containing 25 mg hydrochlorothiazide and 37·5 mg triamterene (Treatment A);
2. one full-strength tablet containing 50 mg hydrochlorothiazide and 75 mg triamterene (Treatment B);
3. a liquid dose containing 50 mg hydrochlorothiazide in solution and 75 mg triamterene in suspension (Treatment C).

Doses were given at approximately 8 am. In the second study (Study II), subjects received the following two treatments orally, randomized for sequence:

1. one full-strength tablet containing 50 mg hydrochlorothiazide and 75 mg triamterene at 6 am (Treatment D);
2. one half-strength tablet containing 25 mg hydrochlorothiazide and 37·5 mg triamterene at 6 am and again at 6 pm (Treatment E).

Morning doses were given after a 10 h fast. All doses were given with 240 ml of water. Urine was collected frequently (11 samples) in timed intervals for 72 h after each single dose treatment. For the two dose treatment (Treatment E, Study II), urine was collected for 84 h (17 samples). After measurement

of volume, aliquots of each collection were stored at −20° until analysis. Blood was also collected frequently after each treatment from an indwelling non-heparin-requiring catheter but was not assayed. Standard clinical study procedures regarding diet, fasting, avoidance of alcohol and caffeine-containing foods or fluids, exercise, and confinement were followed.

Analytical procedures

Urine samples were assayed for hydrochlorothiazide, triamterene, and hydroxytriamterene sulfate (the major metabolite of triamterene) using high-performance liquid chromatography[5–7]. The lower limit of detection of each assay was 250 ng ml^{-1} for hydrochlorothiazide, 10 ng ml^{-1} for triamterene, and 10 ng ml^{-1} for hydroxytriamterene sulfate. Inter- and intraday coefficients of variation for calibrators and control samples over the concentration range of each assay were 10 per cent or less. Blank samples obtained prior to dosing revealed no interfering peaks for assayed compounds or their internal standards.

Data analysis

Pharmacokinetic variables calculated from urine data for hydrochlorothiazide, triamterene, and hydroxytriamterene sulfate consisted of total amount of drug or metabolite excreted in urine (mg), the peak rate of excretion (mg h^{-1}), and the time of this peak rate (h). Total triamterene in urine (mg) was calculated as the sum of triamterene and hydroxytriamterene sulfate amounts expressed in triamterene equivalents, i.e., the amount of triamterene plus the amount of hydroxytriamterene sulfate multiplied by 0·725. Urine amount of drug or metabolite was expressed as per cent dose in some analyses, again with hydroxytriamterene sulfate expressed in triamterene equivalents. Triamterene/hydroxytriamterene sulfate ratios were calculated as the total amount of triamterene divided by the total amount of hydroxytriamterene sulfate excreted in a collection period.

Some comparisons were performed in Study II using Treatment E urine amount data between 0 and 12 h and 12 and 24 h. In this instance, the 12–24 h data were adjusted to subtract an estimate of the amount of drug or metabolite from the first (6 am) dose of Treatment E excreted after administration of the second dose 12 h later at 6 pm. This estimate was calculated by fitting a line to the excretion rate versus time curve between 4 and 12 h and using the slope of this line (k) to estimate the area under the curve from 12 h to infinity (excretion rate at 12 h divided by k).

A statistically significant difference between treatments was identified with analysis of variance. Intra-treatment comparisons were performed using the paired t-test. A post-hoc test (Tukey) identified the location of statistically significant differences in the three treatment study (Study I).

Table 1. Study I peak urine excretion rate, time of peak rate, and total amount of drug or metabolite in urine after: (1) two tablets of 25 mg hydrochlorothiazide and 37·5 mg triamterene (treatment A); (2) one tablet of 50 mg hydrochlorothiazide and 75 mg triamterene (treatment B); and (3) liquid doses of 50 mg hydrochlorothiazide and 75 mg triamterene (treatment C) in 24 healthy subjects (mean ± SD)

Variable	Treatment A	Treatment B	Treatment C	p	Post-hoc*
Hydrochlorothiazide					
Peak excretion rate ($mg\ h^{-1}$)	6·15 ± 2·15	6·08 ± 1·78	6·21 ± 1·58	NS	—
Time of peak rate (h^{-1})	2·15 ± 0·78	2·37 ± 0·97	1·67 ± 0·72	0·0252	$\overline{\overline{BAC}}$
$Amount_{0-72\,h}$ (mg)	29·6 ± 5·38	30·1 ± 5·61	29·1 ± 4·84	NS	—
Per cent dose	59·2 ± 10·8	60·2 ± 11.2	58·2 ± 9·68		
Triamterene					
Peak excretion rate ($mg\ h^{-1}$)	2·76 ± 1·22	2·94 ± 1·20	2·77 ± 0·77	NS	—
Time of peak rate (hr)	1·20 ± 0·56	1·20 ± 0·56	0·98 ± 0·59	NS	—
$Amount_{0-72\,h}$ (mg)	8·75 ± 3·11	9·31 ± 2·74	8·27 ± 2·38	NS	—
Per cent dose	11·7 ± 4·15	12·4 ± 3·65	11·0 ± 3·17		
Hydroxytriamterene sulfate					
Peak excretion rate ($mg\ h^{-1}$)	10·9 ± 4·14	12·1 ± 4·54	11·3 ± 3·15	NS	—
Time of peak rate (h)	1·54 ± 0·47	1·72 ± 0·80	1·41 ± 0·60	NS	—
$Amount_{0-72\,h}$ (mg)	51·3 ± 9·77	55·2 ± 10·4	48·8 ± 6·42	0·0214	$\overline{\overline{BAC}}$
Per cent dose	49·6 ± 9·44	53·4 ± 10·0	47·2 ± 6·21		
Total triamterene					
$Amount_{0-72\,h}$ (mg)	45·9 ± 8·76	49·4 ± 7·58	43·6 ± 4·71	0·0181	$\overline{\overline{BAC}}$
Per cent dose	61·2 ± 11·7	65·9 ± 10·1	58·1 ± 6·28		

* Means under the same line are not significantly different.

RESULTS

Results of the three treatment bioequivalence Study I are presented in Table 1. The hydrochlorothiazide solution formulation (Treatment C) produced an earlier peak rate in comparison to the full-strength tablet formulation (Treatment B). The full-strength combination produced significantly more urine hydroxytriamterene sulfate and in consequence total triamterene compared to the liquid dose of triamterene. No other statistically significant differences were noted between the three treatments in Study I.

Results of the two treatment bioequivalence Study II are presented in Table 2. For variables assessing rate of absorption (peak rate and time of peak rate), the half-strength formulation (Treatment E) given at 12 h intervals as expected demonstrated significantly lower peak rates and longer times of peak rate for all assayed species in comparison to administration of the full-strength formulation on a single occasion. For variables assessing extent of absorption (amount of drug or metabolite in urine), hydroxytriamterene and total triamterene were

Table 2. Study 2 urine peak excretion rate, time of peak rate, and total amount of drug or metabolite after: (1) one tablet of 50 mg hydrochlorothiazide and 75 mg triamterene at 6.00 am (Treatment D); and (2) one tablet of 25 mg hydrochlorothiazide and 37·5 mg triamterene at 6.00 am and 6.00 pm (Treatment E) in 24 healthy subjects (mean ± SD)

Variable	Treatment D	Treatment E	p
Hydrochlorothiazide			
Peak excretion rate (mg h^{-1})	6·79 ± 1·50	3·55 ± 0·67	0·0001
Time of peak rate (h)	1·88 ± 0·49	10·4 ± 5·93	0·0001
$Amount_{0-72h}$ (mg)	29·6 ± 4·30	29·0 ± 3·24	NS
Per cent dose	59·1 ± 8·60	58·0 ± 6·48	
Triamterene			
Peak excretion rate (mg h^{-1})	2·56 ± 0·81	1·41 ± 0·44	0·0001
Time of peak rate (h)	1·21 ± 0·55	5·46 ± 6·38	0·0042
$Amount_{0-72h}$ (mg)	7·63 ± 2·78	8·17 ± 2·18	NS
Per cent dose	10·2 ± 3·71	10·9 ± 2·91	
Hydroxytriamterene sulfate			
Peak excretion rate (mg h^{-1})	14·3 ± 4·56	8·88 ± 1·76	0·0001
Time of peak rate (h)	1·63 ± 0·45	9·46 ± 6·32	0·0001
$Amount_{0-72h}$ (mg)	47·1 ± 9·72	53·3 ± 8·90	0·0075
Per cent dose	45·6 ± 9·39	51·5 ± 8·60	
Total triamterene			
$Amount_{0-72h}$ (mg)	41·8 ± 7·97	46·8 ± 6·33	0·0076
Per cent dose	55·7 ± 10·6	62·4 ± 8·44	

approximately 10 per cent greater when the two drugs were given in the half-strength formulation every 12 h in comparison to the full-strength combination given as a single dose. Figure 1 presents Study II mean urine excretion rate data for the three assayed species.

The data in Table 3 summarize the data for the urine per cent dose of hydrochlorothiazide, triamterene, hydroxytriamterene sulfate, and total triamterene excreted in the first (0–12 h) and second (12–24 h) 12 h collection period in Study II. In these comparisons, Treatment E data for the second 12 h period are reduced by estimates of the amount of drug or metabolite excreted in this period from the first dose given 12 h earlier (see Methods). Comparing the full-strength to the half-strength combination in the first 12 h of collection, the data indicate only a statistically significant increase in the urine amount of hydrochlorothiazide after dosing with the full-strength combination. Trends in the data for hydroxytriamterene sulfate and total triamterene for this period suggested that the smaller drug dose of triamterene in the half-strength formulation was better absorbed in comparison to the larger dose of the full-strength formulation. Comparing the urine elimination of the full-strength formulation in the first 12 h (6 am to 6 pm) to the half-strength combination in the second 12 h (6 pm to 6 am) of collection, the half-strength formulation produced statistically significant increments in the urinary excretion of triamterene and

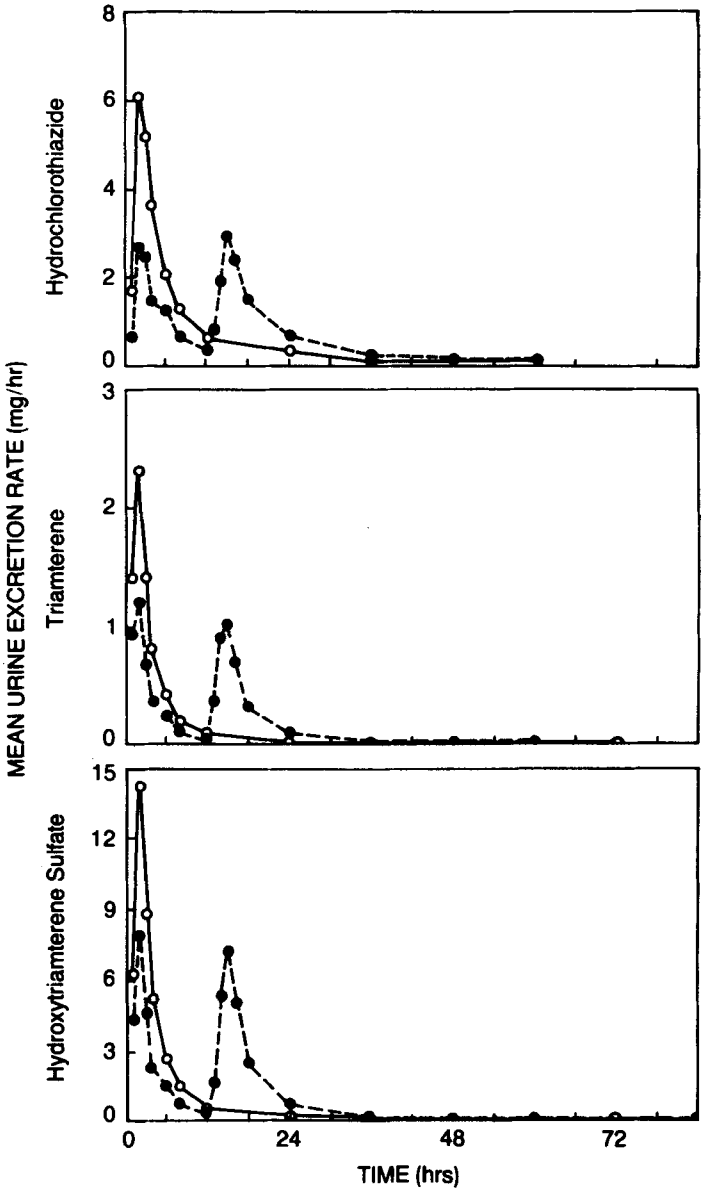

Figure 1. Mean urine excretion rate versus midpoint of the collection interval for hydrochlorothiazide, triamterene and hydroxytriamterene sulfate after a single dose of 50 mg hydrochlorothiazide and 75 mg triamterene given at 6 am compared to 25 mg hydrochlorothiazide and 37·5 mg triamterene given at 6 am and 6 pm (Study II)

Table 3. Study 2 urine per cent dose of drug or metabolite: (1) one tablet of 50 mg hydrochlorothiazide and 75 mg triamterene at 6.00 am (Treatment D) and (2) one tablet of 25 mg hydrochlorothiazide and 37·5 mg triamterene at 6.00 am and 6.00 pm (Treatment E) in 24 healthy subjects (mean ± SD)

Percent dose	Treatment D (0–12 h)	Treatment E (0–12 h)	Treatment E (12–24 h)	p		
				D_{0-12} VS E_{0-12}	D_{0-12} VS E_{12-24}	E_{0-12} VS E_{12-24}
HCTZ	49·6 ± 7·80	46·0 ± 7·91	46·1 ± 11·0	0·0239	NS	NS
Triamterene	9·92 ± 3·36	10·4 ± 3·41	11·3 ± 2·90	NS	0·0194	NS
Hydroxytriamterene sulfate	42·5 ± 14·1	46·4 ± 9·54	54·2 ± 12·9	NS (0·0637)	0·0009	0·0062
Total triamterene	52·4 ± 10·3	56·8 ± 10·5	65·5 ± 13·3	NS (0·0643)	0·0008	0·0118
Ratio*	0·18 ± 0·08	0·17 ± 0·08	0·16 ± 0·06	NS	NS	0·0497

* Triamterene amount/hydroxytriamterene sulfate amount.

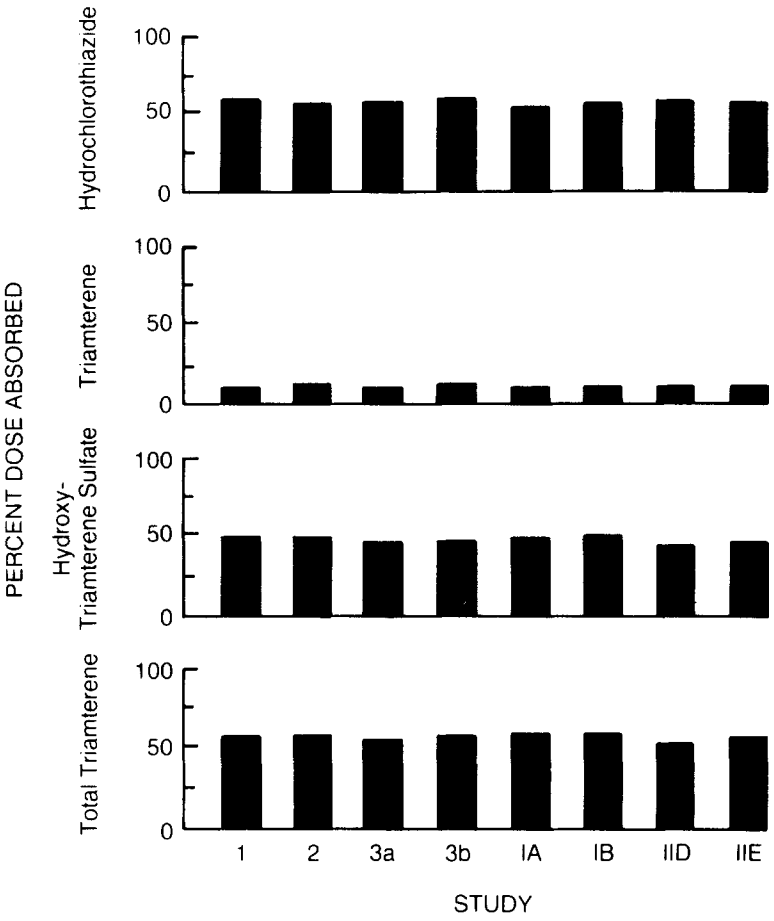

Figure 2. Per cent dose of hydrochlorothiazide, triamterene, and hydroxytriamterene sulfate excreted in urine after administration of a full (Maxzide®) or half-strength (Maxzide-25®) tablet of hydrochlorothiazide and triamterene in five different bioequivalence studies. Studies I and II are presented in this report. See text for description of Studies 1–3

hydroxytriamterene sulfate. Less extensive but similar increments occurred for the half-strength combination between the first and second 12 h collection periods. Ratios of triamterene to hydroxytriamterene sulfate for the two treatments in Study II in the two periods of collection are also noted in Table 3. The data for this variable indicate only a minor and statistically borderline difference ($p = 0{\cdot}0497$) for the half-strength combination between the first and second 12 h collection periods.

The data in Figure 2 indicate the mean per cent dose of hydrochlorothiazide, triamterene and hydroxytriamterene sulfate excreted in urine after administration of the full- and half-strength formulations of the hydrochlorothiazide/

triamterene drug combination to healthy males in different clinical studies. Data for treatments other than these two formulations in these studies are not shown. Studies 1 and 2 compared, respectively, the full-strength formulation to liquid preparations of the two components of the combination[2] or to other marketed products of hydrochlorothiazide alone or with triamterene.[8] Study 3 assessed the influence of food (a) versus fasting, (b) on the absorption of the full-strength combination.[9] The remaining data are from Studies I (Treatments A and B only) and II in this report.

DISCUSSION

In 1984 a new drug combination containing 50 mg of hydrochlorothiazide and 75 mg of triamterene (Maxzide®, Lederle Laboratories) became available for the treatment of hypertension. Clinical studies of the combination demonstrated the efficacy of this dose of triamterene in correcting the hypokalemia associated with daily administration of 50 mg of hydrochlorothiazide,[10] and clinical safety studies documented that patients taking another combination formulation of triamterene and hydrochlorothiazide (Dyazide®, Smith Kline Corporation), containing 25 mg of hydrochlorothiazide and 50 mg of triamterene could be safely transferred to the new formulation.[11] Bioavailability studies in support of the new combination documented excellent absorption in comparison to a standard hydrochlorothiazide formulation (HydroDiuril®, Merck Sharp and Dohme) and to liquid preparations of hydrochlorothiazide and triamterene alone or in combination.[2,8] Additional pharmacokinetic studies documented excellent absorption of the new formulation in the fed and fasted states.[9] These data are in contrast to those for the original formulation of hydrochlorothiazide and triamterene (Dyazide®), which demonstrates poor absorption in the fasting state that is variably affected by meals of differing fat content.[8,9] The absorption of hydrochlorothiazide in these prior studies and in the studies summarized in this report was determined by measurement of unchanged drug in urine. Because triamterene is rapidly metabolized following absorption to its primary (and active) metabolite, hydroxytriamterene sulfate, assessment of the absorption of triamterene was determined by measurement of this metabolite and to a lesser extent by measurement of unchanged triamterene.

The two studies in this report document the bioequivalence of a new half-strength formulation of the combination of hydrochlorothiazide and triamterene compared to the full-strength combination introduced in 1984. When given as two tablets in a single dose, the new half-strength formulation is bioequivalent to the full-strength combination for both rate and extent of absorption (Study I, Table 1). When given as one tablet every 12 h, the new half-strength combination is bioequivalent for extent of absorption to the full-strength combination (Study II, Table 2).

Additional data presented in Tables 2 and 3 suggest a disparity in the absorption of triamterene between the half-strength combination given at 12 h intervals and the full-strength combination given as a single dose (Study II). Hydroxytriamterene sulfate per cent dose excreted in urine was increased when the combination was given in divided doses every 12 h versus in a larger single dose (Table 2). The triamterene per cent dose excreted in urine was also increased, although this difference did not achieve statistical significance. Several hypotheses can account for this observation:

1. a smaller dose allows for better dispersion and dissolution of a relatively insoluble drug such as triamterene within the gastrointestinal tract;
2. higher concentrations of hydroxytriamterene after administration of a larger single dose are associated with saturation of one or more active elimination processes;
3. absorption of triamterene may differ between day and night.

To confirm or refute these hypotheses, we conducted the additional pharmacokinetic and statistical analyses summarized in Table 3. The data in this table indicate:

1. urine per cent dose excreted of triamterene and hydroxytriamterene sulfate over 12 h of collection appeared to be less after administration of the full-strength combination given at 6 am in comparison to the half-strength combination given at 6 am, even though these differences did not achieve statistical significance;
2. urine per cent dose excreted of triamterene and hydroxytriamterene sulfate was significantly less after administration of the full-strength combination at 6 am compared to administration of the second dose of the half-strength combination at 6 pm;
3. urine per cent dose of hydroxytriamterene sulfate was significantly less when the half-strength tablet was given at 6 am than when it was given at 6 pm, with trends in the data suggesting a comparable difference for triamterene.

Based on these observations, we conclude that administration of triamterene in divided doses, as assessed primarily by urine excretion of its hydroxytriamterene sulfate metabolite, facilitates its absorption, perhaps through better dispersion and dissolution of the lower dose tablet. This difference, however, is not apparent when one tablet of the full-strength combination and two tablets of the half-strength combination are given as single doses (Table 1). We also conclude that absorption of triamterene, again as assessed by urine excretion of its hydroxytriamterene sulfate metabolite, is facilitated at night (Treatment E 0–12 and 12–24 h data, Table 3). If saturation of one or more steps in the elimination of hydroxytriamterene occurred after absorption of the larger single dose, the ratio of triamterene to hydroxytriamterene sulfate should have differed between the two treatments in Study II. Because this did not occur

(Table 3), we do not consider saturable hydroxytriamterene sulfate elimination as a likely explanation for the different extents of absorption noted in Study II.

The data in Study I also suggest that administration of triamterene in a solid dose formulation rather than as a suspension improves drug absorption (Table 1). The data in Studies I and II do not indicate why changes in timing, size of dose, and formulation as a solid versus a suspension influence the absorption of triamterene, although perhaps all factors relate in some way to altered gastrointestinal dispersion and dissolution of this highly insoluble drug.

Several studies with the combinations of hydrochlorothiazide and triamterene (Maxzide and Maxzide 25) have documented their consistent absorption over several years of production and in various experimental settings. The data in Figure 2 summarizing these studies document not only the consistent absorption of these formulations, but also suggest that drug absorption of an adequately formulated product is remarkably consistent in a population of young healthy males.

REFERENCES

1. R. A. Upton, R. L. Williams, E. T. Lin, W. Liang-Gee, C. D. Blume and L. Z. Benet, *J. Pharmacokinet. Biopharm.*, **12**, 575 (1984).
2. R. L. Williams, N. C. Sambol and C. D. Blume, *Ann. Intern. Med.* (manuscript in preparation).
3. B. Beermann and M. Groschinsky-Grind, *Eur. J. Clin. Pharmacol.*, **13**, 195 (1978).
4. G. Berglund and O. Andersson, *Eur. J. Clin. Pharmacol.*, **10**, 177 (1976).
5. E. T. Lin, in *Clinical Liquid Chromatography*, P. M. Kabra and L. J. Marton (Eds), vol. I, CRC Press, Boca Raton, Florida, 115, 1984.
6. E. T. Lin, in *Clinical Liquid Chromatography*, P. M. Kabra and L. J. Marton (Eds), vol. I, CRC Press, Boca Raton, Florida, 123, 1984.
7. F. Sorgel, E. T. Lin, J. Hasegawa and L. Z. Benet, *J. Pharm. Sci.*, **73**, 831 (1984).
8. C. D. Blume, R. L. Williams, R. A. Upton, E. T. Lin and L. Z. Benet, *Am. J. Med.*, **77** (suppl. 5A), 59 (1984).
9. R. L. Williams, J. Mordenti, R. A. Upton, E. T. Lin, W. Liang-Gee, C. D. Blume and L. Z. Benet, *Pharm. Res.*, **4**, 348 (1987).
10. C. D. Blume and R. L. Williams, *Am. J. Med.*, **77** (suppl. 5A), 52 (1984).
11. R. L. Williams, T. Clark and C. D. Blume, *Am. J. Med.*, **77** (suppl. 5A), 62 (1984).