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*Report*

# Effects of Formulation and Food on the Absorption of Hydrochlorothiazide and Triamterene or Amiloride from Combination Diuretic Products

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The absorption of three combination formulations of hydrochlorothiazide and either triamterene or amiloride was studied over a 5-year period in seven separate investigations under varying conditions of food and fasting. The most widely prescribed combination, containing 25 mg of hydrochlorothiazide and 50 mg of triamterene, demonstrated impaired absorption in the fasting state that was partially corrected by the addition of a breakfast high in fat. The increase in the fat content of the food appeared to correlate directly with the amount of both drugs absorbed from this formulation. The second formulation studied, a new combination formulation of 50 mg of hydrochlorothiazide and 75 mg of triamterene, demonstrated acceptable absorption in the fasting state that was not altered by the concurrent administration of a high-fat breakfast. The absorption of the third formulation, a combination of 50 mg hydrochlorothiazide and 5 mg amiloride, was acceptable in the fasting state and demonstrated a slight reduction in the absorption of the amiloride component when administered concurrently with a high-fat meal. The clinical and biopharmaceutic implications of these observations are discussed.

KEY WORDS: hydrochlorothiazide; triamterene; Dyazide; Maxzide; amiloride; Moduretic; food–drug interactions; food-formulation interactions.

## INTRODUCTION

In the last 5 years, we conducted seven studies which quantified the absorption of three combination formulations containing hydrochlorothiazide and either triamterene or amiloride after fasting or following the administration of meals of varying composition. The three combination formulations were as follows: (I) a capsule formulation containing 25 mg hydrochlorothiazide and 50 mg triamterene (Dyazide, Smith Kline Corp.), (II) a tablet formulation containing 50 mg hydrochlorothiazide and 75 mg triamterene (Maxzide, Lederle Laboratories), and (III) a tablet formulation containing 50 mg hydrochlorothiazide and 5 mg amiloride (Moduretic, Merck, Sharp and Dohme). The results from two of these investigations were used to support premarketing regulatory requirements for II and have been published elsewhere (1,2). All seven studies were conducted under virtually identical experimental conditions, except for the fed- or fasting-state conditions, thus permitting cross-study comparisons. The data for all seven studies are summarized in this report.

## METHODS

*Clinical.* Male subjects were determined to be in good health prior to participation on the basis of interview, physical examination, complete blood count with differential, SMA-12, and urinalysis. Subjects were within 10% of normal weight for height and frame size (3). Consent forms and protocols for the studies were approved by the University of California, San Francisco, institutional review board. Unless a single treatment was given as occurred in one of the studies, all studies were conducted with a balanced treatment sequence and with subjects randomly assigned in equal numbers to each of the possible treatment sequences.

All treatments were given as a single oral dose separated by a 1-week washout period for those studies with more than one treatment. The sequence of events following each dose was similar and is described in detail for one dosing as follows. Subjects came to the clinic at 7:00 AM, after fasting from 10:00 PM the prior evening. At 7:00 AM, weight, temperature, pulse, and blood pressure were measured, and subjects drank 240 ml of water. A urine sample (blank) was collected between 7:00 and 8:00 AM. At 7:45 AM, subjects who were designated to receive a test meal ingested their food. At 8:00 AM, the dose of the formulation was administered. Blood samples were collected just prior to dosing (0 hr) and at frequent intervals to 48 hr. Blood was centrifuged within 1 hr of collection, and the plasma stored at −20°C. Urine was collected from −1 to 0, 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, 36 to 48, and 48 to

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72 hr after the dose. Urine volume and pH were recorded, and 60-ml aliquots were stored at −20°C. Subjects were confined for 24 hr after dosing and returned to the clinic for subsequent collections. Subjects were given 240 ml of water 2 hr after dosing; at 4 and 10 hr after dosing, they were given a standard lunch and dinner, respectively. No xanthine-containing foods or beverages were consumed from 12 hr before dosing until after the final sample collection for each treatment. At the conclusion of each study, subjects underwent a medical evaluation similar to the one performed on entry.

*Meals.* Three of the studies were designed to assess the effect of food on the absorption of the three diuretic combinations. In two of the studies, a standard high-fat, high-calorie breakfast (44 g fat, 724 kcal) recommended by the Food and Drug Administration (4) in the evaluation of drug absorption with food was ingested. Breakfasts containing between 15 and 45 g of fat were given in another study to investigate in detail the effect of a fat content on the absorption of I.

*Drug Assay.* Urine samples were assayed for hydrochlorothiazide, triamterene, hydroxytriamterene sulfate (a major metabolite of triamterene), and amiloride, using specific high-performance liquid chromatographic (HPLC) methods (5–7). These assays have a lower limit of detection of 250 ng/ml hydrochlorothiazide, 10 ng/ml triamterene and hydroxytriamterene sulfate, and 100 ng/ml amiloride. Intraday and interday coefficients of variation for calibrators and control samples over the concentration range of each assay were 10% or less. Blank samples obtained prior to dosing revealed no interfering peaks for assayed compounds or their internal standards. In all cases, concentrations in the 48- to 72-hr urine samples approximated or were below assay detection limits. Although collected, blood samples were not assayed in all studies to reduce costs. All comparisons are thus based on the urine recovery of unchanged drug or, in the case of triamterene, of unchanged drug and primary metabolite.

*Data Analysis.* Assessment of absorption of hydrochlorothiazide, triamterene, and amiloride was based on the recovery of unchanged drug in the urine expressed as the percentage administered dose. The metabolite of triamterene, hydroxytriamterene sulfate, was also quantified. Triamterene and hydroxytriamterene sulfate amounts were summed to give an expression of total triamterene in urine 0–72 hr postdosing after adjustment of hydroxytriamterene sulfate data for molecular weight difference from triamterene (multiplication by 0.725). Repeat-measures analysis of variance was used to test for statistically significant treatment, period (intrasubject), or sequence (intersubject) effects. For multiple-treatment studies, a post-hoc test (Duncan's) was used to identify the location of statistically significant differences.

## RESULTS

Information about the seven investigations is presented in Table I. The first two studies were pilot investigations, either comparing the bioequivalence of two capsules of I to a nonmarketed test formulation of triamterene and hydrochlorothiazide (Study 1) or assessing the absorption characteristics of two capsules of I alone (Study 2). The third and fourth studies evaluated the bioequivalence of II relative ei-

**Table I.** Summary of Seven Studies Assessing the Absorption of Hydrochlorothiazide and Triamterene or Amiloride from Three Diuretic Combinations (I, II, III)[a]

| Study | Date of performance | *N* | Age (years) | Weight (kg) | Treatments | |
|---|---|---|---|---|---|---|
| | | | | | Number | Description |
| 1 | 1981 | 6 | 23–40 | 58–84 | 2 | Two capsules I, fasting<br>Nonmarketed test formulation, fasting |
| 2 | 1982 | 6 | 23–40 | 60–77 | 1 | Two capsules I, fasting |
| 3 (1) | 1982 | 24 | | | 4 | One tablet II, fasting<br>Triamterene suspension, fasting<br>Hydrochlorothiazide solution, fasting<br>Hydrochlodrothiazide solution/ Triameterene suspension, fasting |
| 4 (2) | 1983 | 24 | 19–36 | 56–85 | 3 | One tablet II, fasting<br>Two capsules I, fasting<br>One tablet IV, fasting |
| 5 | 1984 | 12 | 21–45 | 56–85 | 2 | Two capsules I, fasting<br>Two capsules I, with food[b] |
| 6 | 1984 | 20 | 21–28 | 60–82 | 4 | One tablet II, fasting<br>One tablet II, with food[b]<br>One tablet III, fasting<br>One tablet III, with food[b] |
| 7 | 1985 | 16 | 23–40 | 66–86 | 4 | Two capsules I, fasting<br>Two capsules I, 15 g fat meal<br>Two capsules I, 30 g fat meal<br>Two capsules I, 45 g fat meal |

[a] (I) Dyazide (25 mg hydrochlorothiazide/50 mg triamterene), Smith Kline Corp.; (II) Maxzide (50 mg hydrochlorothiazide/75 mg triamterene), Lederle Laboratories; (III) Moduretic (50 mg hydrochlorothiazide/5 mg amiloride), Merck, Sharp and Dohme; (IV) Hydrodiuril (50 mg hydrochlorothiazide), Merck, Sharp and Dohme.

[b] High-fat, high-calorie FDA breakfast (4).

ther to liquid preparations of hydrocholorothiazide and triamterene (Study 3) or to two capsules of I and one 50-mg tablet of hydrochlorothiazide (Study 4). Results of these studies have been reported in detail elsewhere (1,2). Studies 5 and 7 assessed the absorption of two capsules of I either with the standard breakfast recommended by the Food and Drug Administration (Study 5) or with breakfasts of varying fat content (Study 7). Study 7 was initiated when the results of Study 5 indicated a marked effect of a high-fat, high-calorie breakfast on the absorption of I. Study 6 assessed the influence of the standard breakfast recommended by the Food and Drug Administration on the absorption of II and III.

The estimated composition of the breakfasts used in Studies 5, 6, and 7 appears in Table II. The total kilocalories and protein composition of the breakfasts for Study 7 were relatively constant, while fat was increased from 15 to 45 g.

Table III presents the percentage dose of hydrochlorothiazide, triamterene, hydroxytriamterene sulfate, and (for Study 6) amiloride excreted in the urine in 72 hr after dosing with the formulations under the conditions noted in Table I. The data in Table III document the low and variable absorption of hydrochlorothiazide from I in comparison to both II and III after an overnight fast. Between the studies, the range of mean percentage hydrochlorothiazide dose absorbed from I in the fasting state varied between approximately 30 and 47%, while II and III demonstrated absorption of hydrochlorothiazide in the range of approximately 56 to 59%, comparable to that absorbed from the single-entity formulation of hydrochlorothiazide (61%) (Table III). In the fasting state, the absorption of triamterene from I was consistently less (21 to 26% of the dose administered for total triamterene) than from II (54 to 60%). Approximately 43% of the amiloride was recovered unchanged in the urine from III when dosed in the fasting state (Study 6).

Studies 5 and 6 present information about the absorption of I, II, and III following ingestion of the standard high-fat, high-calorie breakfast recommended by the Food and Drug Administration. The data in Study 6 show no apparent effect of this breakfast on the absorption of hydrochlorothiazide or triamterene from II or hydrochlorothiazide from III. Ingestion of this breakfast reduced amiloride absorption from III by approximately 25% (43 to 33%), a change that was statistically significant. The data in Study 5 document a marked effect of the "FDA" breakfast on the absorption of both components of I, increasing them to levels that were comparable to those for II in either the fasting or the fed state. Based on this finding, the seventh study in this series was performed. In this study, the effect of breakfasts of varying fat content on the absorption of I was assessed. The results of this study document that increments in the fat content of a breakfast resulted in almost proportional increments in the absorption of hydrochlorothiazide and triamterene from I. The marked variability in the absorption of hydrochlorothiazide and triamterene from I in comparison to II with different meals and in the fasting state is documented in the range of means from the different studies.

Table II. Fat, Protein, Carbohydrate, and Kilocalorie Content of Food Served in Studies 5, 6, and 7

| | | Study 7 | | |
|---|---|---|---|---|
| | Studies 5 and 6[a] | Low fat[b] | Medium fat[c] | High fat[d] |
| Fat | 44 | 15 | 30 | 45 |
| Protein | 28 | 10 | 10 | 10 |
| Carbohydrate | 54 | 110 | 77 | 71 |
| Kilocalories | 724 | 615 | 618 | 729 |

[a] Two scrambled eggs, two strips bacon, one slice toast with butter, 4 oz hash brown potatoes, and one glass whole milk (FDA breakfast).

[b] One egg (poached without fat), two slices toast, 2 tsp margarine, 4 Tbsp jelly, and 1 Cup apple juice.

[c] One-half cup Half & Half, 1 oz corn flakes, two slices toast, 4 tsp margarine, 1 Tbsp jelly, and 0.5 C orange juice.

[d] Three-fourths cup light cream, 1 oz corn flakes, one and one-half slices toast, 2 tsp margarine, and 0.5 C apple juice.

## DISCUSSION

In the fasting state, the absorption of hydrochlorothiazide and triamterene from I is markedly impaired, ranging on average from 30 to 46% of the administered hydrochlorothiazide dose and consistently less than 25% of the administered triamterene dose. In contrast, liquid formulations of these drugs alone or in combination after an overnight fast generally result in the urinary recovery of about 60% of each administered dose (1). Following the administration of I with a standard high-fat, high-calorie meal, the absorption of both drugs increased to levels seen with liquid preparations of hydrochlorothiazide and triamterene. In a subsequent study (Study 7), the percentage dose of hydrochlorothiazide and triamterene absorbed from I is directly related to the fat content of the meal injested just prior to dosing (Table III). Increasing the fat content of the breakfast also appeared to reduce the variation in the absorption of both hydrochlorothiazide and triamterene from I. This is apparent in the reduction in the coefficient of variation of the data obtained after meals in Studies 5 and 7 in comparison to the fasting state. Food did not affect the absorption of either of the two drugs in Formulation II. For III, the standard high-fat, high-calorie "FDA" breakfast produced no apparent change in the absorption of the hydrochlorothiazide component but caused a moderate reduction (25%) in the absorption of amiloride.

The influence of food on drug absorption has been the subject of numerous reports in recent years. Data from these studies have identified at last two ways that food can effect drug absorption. One is by a direct effect on the drug absorption that can occur irrespective of the formulation in which it is given. The second way is an effect of food on release from a formulation that is not demonstrable when the drug is given as a solution or suspension. In both instances, food can initiate physiologic changes in the gastrointestinal tract that can influence the absorption of a drug or drug release from a formulation. Food is known to produce changes in stomach emptying time, gastric motility, and gastrointestinal secretion of acid, bile, and various proteolytic enzymes (8). Food can also affect drug absorption by changing the gastrointestinal pH and altering drug dispersion and dissolution (9).

Most of the investigations that assess the effect of food

Table III. Absorption of Hydrochlorothiazide, Triamterene, and Amiloride from Three Diuretic Combination Formulations

| Study | Formulation[a] | Condition | Percentage administered dose in urine, 0–72 hr | | | | | Treatment | Statistical significance[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Hydrochlorothiazide | Triamterene | Hydroxy-triamterene sulfate | Total triamterene | Amiloride | | Hydrochlorothiazide | Triamterene | Hydroxy-Triamterene sulfate | Total triamterene | Amiloride |
| 1[c] | I | Fasting | 38.2 ± 11.2 | 6.7 ± 0.9 | 16.8 ± 3.4 | 23.5 ± 4.1 | — | — | | | | | |
| 2 | I | Fasting | 30.8 ± 9.4 | 4.6 ± 1.8 | 20.9 ± 9.1 | 25.5 ± 10.6 | — | — | | | | | |
| 3 (1)[c] | II | Fasting | 59.4 ± 12.8 | 8.9 ± 3.6 | 47.1 ± 9.6 | 56.0 ± 11.4 | — | — | | | | | |
| 4 (2) | II | Fasting | 56.2 ± 9.4 | 11.5 ± 3.9 | 48.3 ± 10.7 | 59.7 ± 12.8 | | 1 | $\overline{1\,3\,2}$ | $\overline{1\,2}$ | $\overline{1\,2}$ | $\overline{1\,2}$ | |
| | I | Fasting | 32.8 ± 8.8 | 4.0 ± 1.9 | 19.2 ± 5.3 | 23.3 ± 6.9 | — | 2 | | | | | |
| | IV | Fasting | 61.4 ± 9.4 | — | — | — | — | 3 | | | | | |
| 5 | I | Fasting | 46.5 ± 16.7 | 4.5 ± 1.8 | 19.2 ± 7.2 | 23.6 ± 8.5 | — | 1 | $\overline{1\,2}$ | $\overline{1\,2}$ | $\overline{1\,2}$ | $\overline{1\,2}$ | |
| | I | Food (FDA) | 64.6 ± 7.3 | 11.3 ± 2.8 | 44.6 ± 7.9 | 55.9 ± 9.3 | — | 2 | | | | | |
| 6 | II | Fasting | 58.6 ± 8.1 | 9.6 ± 4.4 | 44.8 ± 7.7 | 54.4 ± 10.5 | — | 1 | $\overline{1\,2\,3\,4}$ | $\overline{1\,2}$ | $\overline{1\,2}$ | $\overline{1\,2}$ | $\overline{3\,4}$ |
| | II | Food (FDA) | 61.0 ± 8.5 | 11.7 ± 4.5 | 47.8 ± 7.3 | 59.4 ± 9.1 | | 2 | | | | | |
| | III | Fasting | 59.1 ± 9.8 | — | — | — | 43.3 ± 8.7 | 3 | | | | | |
| | III | Food (FDA) | 61.8 ± 7.8 | — | — | — | 33.0 ± 9.7 | 4 | | | | | |
| 7 | I | Fasting | 46.8 ± 16.1 | 3.9 ± 1.5 | 17.4 ± 5.9 | 21.2 ± 7.0 | — | 1 | $\overline{1\,2\,3\,4}$ | $\overline{1\,2\,3\,4}$ | $\overline{1\,2\,3\,4}$ | $\overline{1\,2\,3\,4}$ | |
| | I | Food (15 g fat) | 47.2 ± 14.0 | 5.7 ± 5.4 | 22.4 ± 6.8 | 28.1 ± 9.9 | — | 2 | | | | | |
| | I | Food (30 g fat) | 49.0 ± 11.3 | 6.1 ± 3.1 | 28.0 ± 0.5 | 34.0 ± 10.7 | | 3 | | | | | |
| | I | Food (45 g fat) | 56.2 ± 12.4 | 8.8 ± 6.3 | 34.2 ± 11.2 | 43.0 ± 12.4 | — | 4 | | | | | |

[a] As in Table I, footnote *a*.

[b] Means under the same line are not significantly different.

[c] Data presented only for Formulation I (Study 1) and Formulation II (Study 3).

on drug absorption have addressed direct drug/food, and not formulation/food, interactions. In a recent review, Welling (10) noted that drug/food interaction studies have been performed for over 100 drugs, and most of these indicated some type of interaction. In this review, approximately 35 of the over 100 investigations indicated reduced absorption of the test drug with food, 28 noted a delay in drug absorption with food, 25 reported increased drug absorption with food, and 23 reported no change in drug absorption with food. Because our data disclosed no specific influence of food on the absorption of hydrochlorothiazide or triamterene from II, we believe that our data in general demonstrate a food/formulation interaction, as opposed to a food/drug interaction.

Various studies have evaluated the effect of food on the release of a drug from a specific formulation. Several of these have assessed the effect of various meals on the absorption of controlled-release theophylline formulations. When theophylline is given as an immediate-release formulation, food has no apparent influence on drug absorption. Early studies also suggested no significant effect of food on the absorption of controlled release theophylline preparations (12–14). More recently, Karim has documented either an increase in the absorption of theophylline from two sustained-release formulations with a high-fat, high-calorie breakfast or, in the case of a third formulation, a reduction in the absorption of the drug (15,16). Further studies have documented that the effect of food on one of the controlled-release theophylline formulations can be mitigated if the product is ingested with a breakfast containing less than 10 g of fat or if an hour is allowed to elapse between the time of dosing and the ingestion of food (17). The effect of food on the absorption of hydrochlorothiazide and triamterene from Formulation I is apparently similar to that for the two theophylline controlled-release products discussed by Karim. With increasing fat content of a meal, the absorption of both drugs in I is enhanced.

Our data do not identify why breakfasts with a high fat content increase the absorption of the drugs in Formulation I. Very high-fat-content meals might delay gastric emptying and increase gut transit time, thus permitting more time for disintegration and dispersion of the ingredients in Formulation I. Triamterene is a high-first-pass drug that is rapidly converted to hydroxytriamterene sulfate after oral administration. Despite this high-first-pass metabolism, we do not believe that the food is affecting the hepatic extraction of triamterene as has been proposed for other high-first-pass drugs (18–20) because of the apparent lack of influence of food on the absorption of triamterene from Formulation II.

We have no specific dosing recommendations to advance on the basis of the results of our study. Normalization of the absorption of Formulation I might occur in clinical practice if the formulation is ingested with an extremely high-fat, high-calorie breakfast. Following breakfasts with usual (i.e., lower) fat contents, the absorption of this formulation is as impaired as in the fasting state. Ingestion of the extremely high-fat breakfast (45 g fat) utilized for experimental purposes in this study is not recommended, particularly for individuals with cardiovascular disease requiring thiazide diuretics. Given the day-to-day variability in food intake, it is likely that the absorption of the two drugs from Formulation I in different patients is likely to be highly variable. Even within a single patient, absorption may vary from day to day unless breakfasts of uniform fat content are ingested daily. The absorption of the individual components of II and III is more predictable and less dependent on food content.

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