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Urinary Excretion of Methenamine and Formaldehyde: Evaluation of 10 Methenamine Products in Humans

RAMACHANDER GOLLAMUDI, ARTHUR B. STRAUGHN, and MARVIN C. MEYER ˣ

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Abstract □ The urinary excretion of both methenamine and formaldehyde was measured for 48 hr after the oral administration of 10 different methenamine products to 10 human subjects in a crossover study. The following dosage forms were evaluated: a tablet of methenamine base, a methenamine hippurate tablet, and eight products containing methenamine mandelate, including six enteric-coated tablets, a suspension, and a granule dosage form. The nonenteric-coated dosage forms were absorbed more rapidly, based on maximum excretion rates that occurred within 3 hr after dosing. The enteric-coated tablets, which were designed not to release methenamine until reaching the intestinal tract, exhibited maximum excretion rates that did not occur until 7–17 hr after dosing. There were no significant differences ($p > 0.05$) among products in terms of total excretion of free formaldehyde in the urine. However, large differences ($p < 0.05$) were noted among products for urinary recovery of total methenamine, with the amount of administered dose recovered ranging from 16 to 83%.

Keyphrases □ Methenamine—evaluation of 10 products, urinary excretion of formaldehyde □ Bioavailability—methenamine in 10 products, humans □ Urinary tract antibacterials—evaluation of 10 methenamine products, excretion of formaldehyde □ Antibacterials, urinary tract—evaluation of 10 methenamine products, excretion of formaldehyde

Methenamine (hexamethylenetetramine) is a urinary tract antibacterial agent. It is absorbed from the intestinal tract, circulates unchanged in blood, and is excreted in the urine. Under acidic conditions in the urine, it undergoes hydrolysis to formaldehyde. Approximately 10–30% of the drug also is believed to be converted to formaldehyde in the acidic environment of the stomach (1). Enteric-coated preparations are designed to withstand such premature hydrolysis by releasing drug only in the intestine. With such dosage forms, drug absorption may be delayed due to slow gastric emptying or may be incomplete due to failure of the product to release methenamine in the intestine.

A crossover study was undertaken to evaluate the relative bioavailability of 10 methenamine products. The urinary excretion of both methenamine and formaldehyde was determined in 10 human volunteers who received all 10 dosage forms.

EXPERIMENTAL

Methenamine Products—The 10 methenamine products evaluated are summarized in Table I. Products 1–3 were included as reference products for comparison with the hippurate tablet and the six enteric-coated tablets. All products were supplied by the U.S. Food and Drug Administration, except Products 1 and 2, which were purchased from a local pharmacy.

Table I—Methenamine Products Tested

Product[a]	Dosage Form	Administered Dose	Calculated Methenamine Content, g
1	Methenamine tablets (0.5 g)	1 tablet	0.500
2	Methenamine mandelate suspension (50 mg/ml)	20 ml	0.480
3	Methenamine mandelate granules (0.5 g/package)	2 packages	0.480
4	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
5	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
6	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
7	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
8	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
9	Methenamine mandelate tablets (0.5 g)[b]	2 tablets	0.480
10	Methenamine hippurate tablets (1.0 g)	1 tablet	0.439

[a] Manufacturer (lot number): 1, Eli Lilly (9SW09A); 2, Warner/Chilcott (8425105A); 3, Warner/Chilcott (9607055-B); 4, Warner/Chilcott (6479016A); 5, J.W.S. Delavau Co. (unknown); 6, Tablicaps (31931); 7, Standard Pharmacal (41870); 8, Vangard Laboratories (420924); 9, Heather Drug Co. (510059); and 10, Riker Laboratories (57729). [b] Enteric coated.

Study Protocol—Ten male volunteers[1], average age 26 years (range of 23–30 years), average weight 81 kg (range of 63.5–95.3 kg), and average height 179.9 cm (range of 170.1–190.5 cm) underwent a hematological and blood chemistry[2] analysis and a urinalysis to ensure inclusion of only healthy subjects. One subject was dropped after the 3rd week because of illness that was not related to the study. He was replaced by Subject 6, who received all 10 products in the order originally assigned to the dropped subject.

Each subject received one methenamine product at intervals of at least 1 week, except for Subject 6 who received doses at 4-day intervals to permit completion of the study at the same time as the other nine subjects. The administration sequence was based on a crossover matrix designed to minimize any residual or cumulative effects of the preceding dose (2).

Each methenamine product was given along with 200 ml of water after an overnight fast. Subsequent water intake was unrestricted but was

[1] Staff and students of the University of Tennessee Center for the Health Sciences. Written informed consent was obtained.
[2] SMA 12/60.

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Table II—Mean Free Formaldehyde Urine Concentration [a] (Micrograms per Milliliter) at Various Sampling Times

Product	Urine Collection Time, hr								
	1	2	4	6	8	12	24	36	48
1	19.9	22.5	35.0	32.7	39.5	39.7	23.4	9.96	9.84
	(116)	(124)	(112)	(83.4)	(75.1)	(82.6)	(72.2)	(54.7)	(116)
2	12.7	25.6	25.6	34.4	34.5	39.7	25.8	9.40	3.18
	(133)	(110)	(110)	(106)	(109)	(99.9)	(140)	(112)	(140)
3	28.2	21.3	11.6	23.3	25.3	55.8	21.7	28.5	4.54
	(81.8)	(104)	(112)	(104)	(107)	(163)	(72.7)	(273)	(116)
4	3.48	1.06	9.55	23.9	37.4	28.6	37.3	6.29	4.97
	(157)	(216)	(114)	(103)	(99.4)	(59.8)	(44.5)	(103)	(117)
5	8.82	7.31	1.80	10.3	10.7	42.7	18.5	28.5	11.5
	(267)	(186)	(115)	(228)	(140)	(180)	(199)	(160)	(118)
6	6.42	5.28	16.0	40.6	44.3	42.4	32.9	10.6	8.16
	(180)	(104)	(67.3)	(78.7)	(124)	(109)	(73.1)	(72.6)	(47.9)
7	1.90	1.46	3.06	19.5	19.9	34.2	26.8	21.8	7.10
	(119)	(181)	(138)	(112)	(111)	(93.4)	(112)	(204)	(110)
8	1.91	2.22	13.8	38.5	38.9	27.3	42.4	16.3	5.92
	(134)	(115)	(76.6)	(112)	(90.6)	(64.2)	(85.2)	(59.9)	(137)
9	2.91	3.17	16.4	40.4	23.2	29.1	36.9	6.59	6.40
	(156)	(158)	(94.6)	(145)	(71.4)	(116)	(78.4)	(121)	(96.5)
10	17.3	26.3	23.7	16.6	36.7	44.2	12.2	8.67	7.37
	(113)	(113)	(136)	(150)	(126)	(77.9)	(92.9)	(94.3)	(62.3)

[a] Mean values of 10 subjects with percent relative standard deviation in parentheses. See Table I for product number identification.

maintained at a sufficient level to provide for adequate urine output. No food was permitted until 4 hr after drug administration.

Urine samples were obtained at 0, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hr. The subjects were instructed to provide complete urine collections at each voiding. Immediately upon voiding, the urine volume and pH[3] were measured. A urine aliquot was diluted 15 times with water and stored at −18° until analysis, which was performed within 7 days. Samples voided at other times were collected similarly and stored. At the time of analysis, samples voided between sampling times were combined with the sample obtained at the next required sampling time. The samples were pooled using aliquot volumes proportional to the individual volumes of voided urine.

Urine Analysis—Urine formaldehyde and methenamine concentrations were determined in duplicate using a spectrophotometric method (3).

Statistical Analysis—Urine free formaldehyde concentrations, as well as free formaldehyde and total methenamine excretion rates and the cumulative amount and percent excreted, were subjected to an analysis of variance to determine the level of significance for differences among products, subjects, and weeks. The data were analyzed using a logarithmic transformation because of significant nonadditivity in the untransformed data. Where significant differences were found ($p < 0.05$), the Newman–Keuls *a posteriori* test was applied to identify where these differences occurred.

RESULTS AND DISCUSSION

Free Formaldehyde Concentrations—The mean urine free formaldehyde concentrations at each sampling are presented in Table II. The maximum mean formaldehyde concentrations ranged from 34.2 (Product 7) to 55.8 (Product 3) μg/ml at 12 hr. Although this difference was not significant ($p > 0.05$), significant differences ($p < 0.05$) were evident at 1, 2, 4, and 24 hr. The Newman–Keuls *a posteriori* test indicated the enteric-coated formulations (Products 4–9) generally resulted in lower formaldehyde concentrations than the other products during the first 4 hr. This finding is consistent with the fact that an enteric-coated dosage form must reach the intestinal tract before drug can be released. Maximum mean free formaldehyde concentrations were attained between 6 and 12 hr with all products, except Product 8, which had a maximum mean concentration at 24 hr.

The minimum inhibitory concentration for formaldehyde in urine was reported to range from 13 (4) to 18 μg/ml (5). Mean free formaldehyde levels in this range were attained within 1–2 hr from the nonenteric-coated Products 1–3 and 10; the enteric-coated products required 4–12 hr to provide free formaldehyde concentrations in this range.

The therapeutic efficacy of a methenamine product is thought to be related to the formaldehyde concentration in the urine. Formaldehyde formation is governed mainly by the rate and extent of intestinal absorption and renal excretion of methenamine and by the volume and pH of the urine. The mean free formaldehyde concentrations exhibited high relative standard deviations, partially because fluid intake and urine pH were not controlled in these subjects. In general, the urine pH ranged from 5.5 to 6.8, and the fluctuations within and among individuals obscured any correlations between urine pH and the formaldehyde concentrations obtained with the different products.

The mean cumulative 48-hr excretion of formaldehyde from each dosage form, expressed as methenamine equivalents, ranged from 26.8 (Product 10) to 37.7 (Product 6) mg. This 29% difference among products was not significant ($p > 0.05$). Since the total amount of methenamine administered was not identical in all 10 products, the cumulative amount of formaldehyde excreted at each sampling also was calculated as a percent of the total methenamine dose. The cumulative percent of formaldehyde excreted at 48 hr (Fig. 1) ranged from 5.5 (Product 2) to 8.7% (Product 8), but this 37% difference among products also was not significant ($p > 0.05$).

Cumulative Excretion of Total Methenamine—Although the measurement of free formaldehyde provided useful information, the large variations in these levels precluded a meaningful evaluation of dosage form bioavailability. Thus, the excretion of total methenamine equiva-

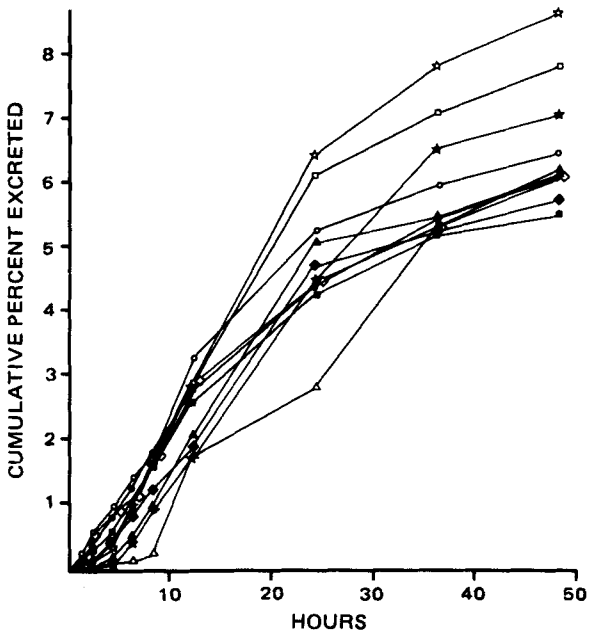

Figure 1—*Cumulative excretion of free formaldehyde, calculated as methenamine and expressed as a percent of the total methenamine dose. Each data point represents the mean of 10 subjects. Key: ●, Product 1; ■, Product 2; ○, Product 3; ▲, Product 4; △, Product 5; □, Product 6; ☆, Product 7; ★, Product 8; ◆, Product 9; and ◇, Product 10.*

[3] Hydrion test paper, pH range 5.5–8.0, Micro-Essential Laboratory, Brooklyn, N.Y.

Table III—Product Ranking for Total Methenamine Excreted [a]

Parameter	Product Ranking (Lowest to Highest) [b]									
Cumulative percent of total methenamine excreted at:										
1 hr	7	5	4	8	6	9	2	10	1	3
2 hr	7	5	4	6	8	9	2	3	10	1
4 hr	5	7	4	8	6	9	2	3	1	10
6 hr	5	7	4	8	6	9	2	3	1	10
8 hr	5	7	4	8	6	9	2	3	10	1
12 hr	5	7	4	8	6	9	3	2	1	10
24 hr	5	7	4	8	6	3	2	9	1	10
36 hr	5	7	4	8	3	6	2	9	10	1
48 hr	5	7	4	8	3	6	2	9	10	1
Maximum excretion rate, mg/hr	5	7	4	8	6	9	2	3	10	1
Maximum excretion rate, % dose/hr	5	7	4	8	6	9	2	3	1	10
Time of maximum excretion rate, hr	1	3	10	2	9	8	6	4	7	5

[a] All data were subjected to a ln $(X + 0.1)$ transformation because of a significant nonadditivity in the untransformed data. [b] Products ranked on the basis of the Newman–Keuls *a posteriori* test. Products underlined by a common line did not differ significantly ($p > 0.05$). See Table I for product number identification.

Table IV—Mean [a] Maximum Excretion Rates and Time of Maximum Excretion Rate for Total Methenamine

Product	Maximum Rate of Total Methenamine, mg/hr	Maximum Rate of Total Methenamine, % of dose/hr	Time of Maximum Rate of Total Methenamine, hr
1	57.6 (18.8)	11.5 (18.8)	1.59 (32.0)
2	43.7 (22.3)	9.12 (22.3)	2.90 (62.1)
3	43.4 (30.5)	9.89 (30.5)	1.90 (46.1)
4	28.9 (35.7)	6.05 (35.7)	8.00 (20.8)
5	4.78 (151.1)	1.00 (150.9)	17.1 (72.6)
6	32.6 (31.2)	6.81 (31.2)	7.40 (25.6)
7	13.4 (20.8)	2.81 (20.7)	12.6 (50.5)
8	31.1 (29.0)	6.50 (29.0)	7.22 (26.6)
9	37.8 (15.7)	7.89 (15.7)	6.81 (15.1)
10	51.3 (13.8)	11.7 (13.7)	2.30 (41.3)

[a] Mean values of 10 subjects with percent relative standard deviation in parentheses. See Table I for product number identification.

lents also was determined. The sum of the amount of methenamine excreted as free formaldehyde and as free methenamine was expressed as milligrams of total methenamine. Statistical analysis of the mean cumulative amounts of total methenamine excreted at various sampling times showed highly significant differences ($p < 0.001$) among products at all sampling times.

One hour after administration of Products 1, 3, and 10, the mean cumulative amount of total methenamine excreted was 42.2, 39.8, and 31.1 mg, respectively. These recoveries were significantly higher than those for the other products. The 17.4 mg excreted at 1 hr with Product 2 was significantly higher than the amount for the enteric-coated tablets. The lowest levels at 1 hr were found with Product 5 (0.1 mg). At 2 and 4 hr, the excretion of total methenamine was significantly higher ($p < 0.05$) for the nonenteric-coated products than for the other dosage forms. Among the enteric-coated preparations, Products 5 and 7 gave the lowest total methenamine recoveries. At subsequent collections, Product 5 resulted in cumulative total methenamine levels that were significantly lower than those for all other products. Product 7 gave significantly higher cumulative total methenamine levels than Product 5 at 4, 6, 8, and 12 hr, but the levels with this product were lower than those attained with any other product.

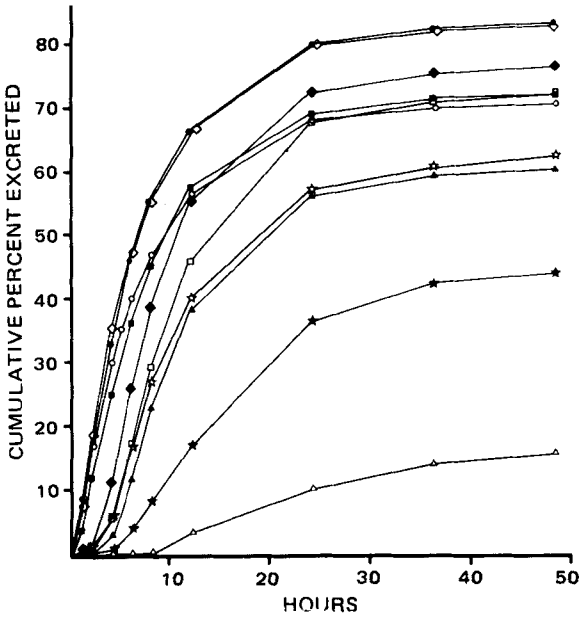

Figure 2—*Cumulative excretion of total methenamine, expressed as a percent of the administered dose. Each data point represents the mean of 10 subjects. Key:* ●, *Product 1;* ■, *Product 2;* ○, *Product 3;* ▲, *Product 4;* △, *Product 5;* □, *Product 6;* ☆, *Product 7;* ★, *Product 8;* ◆, *Product 9; and* ◇, *Product 10.*

The mean cumulative excretion of total methenamine, expressed as percent of administered dose at various collection times, is illustrated in Fig. 2. The results of the statistical evaluation are summarized in Table III. The percent of total methenamine excreted at 1 hr ranged from 0.03% for Products 5 and 7 to 8.4% for Product 1. At this sampling time, Products 1, 3, and 10 gave significantly higher total methenamine recoveries than did the other products. The 2-hr total methenamine values ranged from 0.06% for Product 7 to 18.6% for Product 1, with the values for Products 1, 3, and 10 being significantly higher than those for the other products.

The lowest cumulative total methenamine percentages at subsequent sampling times were with Product 5. Although the total methenamine excretion after Product 7 was significantly higher than after Product 5, it was lower than the values obtained with the other products at 4, 6, 8, 12, and 24 hr. The lowest cumulative percentage of total methenamine excreted at 48 hr was with Products 5 (16.2%) and 7 (44.2%). The total recoveries of all other products exceeded 60% at 48 hr.

Excretion Rate of Total Methenamine—The mean maximum excretion rates and times of the maximum excretion rate for total methenamine are summarized in Table IV. Statistically significant differences are indicated in Table III. The maximum excretion rate of total methenamine ranged from 4.8 mg/hr with Product 5 to 57.6 mg/hr with Product 1. The rates observed with Product 1 were significantly higher than those found with Products 4, 5, and 7. Product 5 exhibited significantly lower excretion rates compared to all others. The maximum excretion rate for Product 7 was higher than for Product 5 but was significantly lower than the rates for all other products.

In terms of percent of administered dose, the maximum excretion rate was highest for Product 10 (11.7%/hr) and lowest for Product 5 (1.0%/hr). The latter value was significantly lower than that observed after Product 7 (2.8%/hr). The times of the maximum excretion rate (T_{max}) were 1.6, 1.9, 2.3, and 2.9 hr for the nonenteric-coated Products 1, 3, 10, and 2, respectively. These times were significantly lower than those found for the other products. Products 5 and 7 yielded significantly longer T_{max} values of 17.1 and 12.6 hr, respectively.

Subject and Week Effects—Each urinary excretion parameter also was statistically analyzed to determine the significance of differences observed among subjects and administration sequences (weeks). Since Subject 6 began the study several weeks after the other nine subjects and took the medication at 4-day intervals, the analysis of weekly differences actually related to differences that could have arisen because a dose was the first, second, third, *etc.*, dose administered.

Since there were no significant weekly differences, it may be concluded that the bioavailability of a particular dose of methenamine was not influenced by the previous administration of other dosage forms of the drug. Results of the analysis of the blank (zero time) urine samples also were monitored each week to determine if they showed any progressive increase, which would have occurred if the drug had been accumulating. No such trend was found in the blank readings. Furthermore, the statistical analysis did not indicate any significant differences among subjects in the excretion of either free formaldehyde or total methenamine.

CONCLUSIONS

Methenamine compressed tablets, methenamine mandelate granules, and methenamine hippurate tablets showed the highest methenamine urinary recovery and were considered bioequivalent. The suspension dosage form exhibited adequate bioavailability but was less well absorbed than the other dosage forms. In general, the enteric-coated products exhibited delayed urinary excretion of methenamine, but Products 4, 6, 8, and 9 did not differ significantly from the nonenteric-coated products in most measurements. Two enteric-coated products (Products 5 and 7) were significantly less bioavailable than all other products tested. None of the 10 products differed significantly ($p > 0.05$) in urinary formaldehyde concentrations. However, the large intersubject variability precluded an accurate assessment of dosage form bioavailability using only free formaldehyde determinations.

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Effect of Antacid on Bioavailability of Theophylline from Rapid and Timed-Release Drug Products

LEON SHARGEL ˣ, JUDY A. STEVENS, JOB E. FUCHS, and ANDREW B. C. YU *

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Abstract □ Magnesium aluminum hydroxide suspension (an antacid) was given concurrently with either theophylline anhydrous tablets or theophylline anhydrous timed-release capsules to 13 volunteers using a four-way crossover design. Serum theophylline was measured by reversed-phase high-pressure liquid chromatography. The serum level–time curves were individually fitted to an oral absorption one-compartment open model. The pharmacokinetic parameters (mean ± *SD*) K_A, K, AUC, and F/V for theophylline from the rapid release theophylline anhydrous tablets were 2.1 ± 1.3 hr^{-1}, 0.15 ± 0.06 hr^{-1}, 89.2 ± 30 μg hr/ml, and 0.0023 ± 0.002 kg/ml, respectively; from the anhydrous timed-release capsules, they were 0.27 ± 0.08 hr^{-1}, 0.20 ± 0.07 hr^{-1}, 79.0 ± 27 μg hr/ml, and 0.0030 ± 0.0007 kg/ml, respectively. The concurrent administration of 15 ml of antacid (magnesium aluminum hydroxide suspension) with the theophylline products did not significantly affect any of these pharmacokinetic parameters. The extent of theophylline bioavailability from all drug products was consistent and similar as shown by the F/V and AUC values.

Keyphrases □ Theophylline—effect of antacid on bioavailability, tablets and timed-release capsules □ Antacids—effects on theophylline bioavailability, tablets and timed-release capsules □ Pharmacokinetics—effect of antacid on theophylline, tablets and timed-release capsules □ Dosage forms—tablets and timed-release capsules, effect of antacid on theophylline bioavailability

Theophylline is used extensively in the treatment of various respiratory diseases (1–4). When taken in the recommended dosage, it relieves or prevents symptoms associated with asthma, bronchitis, and emphysema. The amount of relief produced is directly related to the serum drug concentration. Side effects (nausea, vomiting, headache, and restlessness) are usually associated with high blood theophylline levels (>20 μg/ml), although some individuals may experience side effects at lower levels (1–4).

Magnesium aluminum hydroxide suspension is a commonly used antacid for the symptomatic relief of hyperacidity, gastritis, and heartburn. However, antacids affect the bioavailability of various drugs (5–8). The object of this investigation was to determine the effect of concurrent antacid therapy on the rate and extent of theophylline absorption from theophylline anhydrous tablets and theophylline anhydrous timed-release capsules.

EXPERIMENTAL

Reagents and Chemicals—All reagents and chemicals including theophylline anhydrous[1], sodium acetate[1], 7-(β-hydroxypropyl)theophylline[1], β-hydroxyethyltheophylline[1], 8-chlorotheophylline[1], theo-

[1] Sigma Chemical Co., St. Louis, Mo.

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