Uropepsin Excretion and the Effect of Antacid Materials

By D. D. ABBOTT, J. W. E. HARRISSON, and R. C. BROGLE*

The effect of a series of antacid materials upon uropepsin output was evaluated in a group of 15 normal adults. The antacids, namely, sodium bicarbonate, calcium carbonate, magnesium hydroxide, hydrated magnesium aluminate-sulfate activated (HMAS), and bismuth subsalicylate, were administered on the comparable basis of acid consuming power (ACP). Urine specimens, both control and test, were evaluated for total proteolytic activity. Statistical analysis of the results showed all test materials, except calcium carbonate, to have elicited significant decreases ($P < 0.05$) in uropepsin excretion.

THE THERAPEUTIC usefulness of gastric antacids in the treatment of gastritis and peptic ulcer is a result of their capacity to both reduce the acidity and inactivate pepsin of gastric secretions (1). This latter action has been mainly attributed to a denaturation of pepsin at pH values of 4 or higher. This has been demonstrated for aluminum hydroxide, in animals, by Komarov and Komarov (2), Komarov and Kruegar (3), and Schiffrin and Komarov (4).

A previous investigation (5), in these laboratories, studied dihydroxyaluminum sodium carbonate (DASC), aluminum hydroxide, calcium carbonate, and sodium bicarbonate for antisecretory and antipeptic activity in histamine stimulated rabbits. Therein the aluminum containing antacids elicited greater antisecretory effects than did calcium carbonate and sodium bicarbonate. *In vivo* decreases in proteolytic activity for the various antacids were in relation to the degree of pH elevation. However, under *in vitro* conditions DASC was observed to decrease proteolytic activity to a greater degree than could be anticipated from pH changes alone.

The present study in humans was conducted in an effort to study further the antisecretory effect of antacids using uropepsin excretion as an indirect means of determination. Janowitz and Hollander (6) have estimated that the proteolytic activity of urine, attributed to uropepsin, approximates 1% of gastric peptic output. This relationship is dependent upon many variables but mainly the rate at which pepsinogen enters the general circulation from the chief cells of the gastric mucosa and its subsequent excretion, into the urine, through the glomerular apparatus. Although uropepsin as an index of gastric pepsin secretion is subject to many inconsistencies, the authors have attempted to employ this parameter in the evaluation of a series of antacid materials.

EXPERIMENTAL

Materials—Sodium bicarbonate; calcium carbonate; magnesium hydroxide (as milk of magnesia); hydrated magnesium aluminate-sulfate activated (HMAS); HMAS, 4.22% and bismuth subsalicylate 4.54% (liquid); bismuth subsalicylate.

Dosages—The dosages of the antacid test materials, given t.i.d., after meals, were based upon the acid consuming power (ACP) of the individual items. The ACP values and the individual doses for each of the antacid materials appear in Table I.

Procedure—A total of 15 subjects (13 males and 2 females) ranging in age from 20 to 55 years were utilized. None of the subjects claimed any past history of gastroenterological condition that would preclude their participation.

During the course of study a total of six 24-hr. control urine specimens were obtained from each subject at weekly intervals. Comparable urine specimens were obtained on the day following the collection of the control specimens, during which each subject took the assigned test material, three times a day after each meal. The subjects were assigned to each of the individual test materials in a random fashion.

TABLE I—ACP AND DOSAGE (t.i.d.) OF ANTACID MATERIALS

Material	ACP[a]	Dose[b]
Sodium bicarbonate	124/Gm.	1.303 Gm.
Calcium carbonate	222/Gm.	0.728 Gm.
Magnesium hydroxide (milk of magnesia)	26.6/ml.	6.08 ml.
Hydrated magnesium aluminate-sulfate activated (HMAS)	248.6/Gm.	0.65 Gm.
HMAS and bismuth subsalicylate, 2.3% (liquid)	17.6/ml.	9.2 ml.
Bismuth subsalicylate	0	0.210 Gm.[c]

[a] Milliters 0.1 *N* HCl neutralized. [b] Amount required to neutralize 161.6 ml. 0.1 *N* HCl. [c] Amount contained in HMAS–bismuth subsalicylate combination.

The total volume of each 24-hr. urine specimen was measured prior to the determination of uropepsin activity in accordance with the method of Grey *et al.* (7) as described by Green and Power (8). A unit of uropepsin activity is defined as that amount which during 30 min. of incubation at 37°, under the conditions of assay, releases 0.04 mg. of tyrosine-like substances from a hemoglobin substrate.

RESULTS

The total 24-hr. uropepsin excretion levels during drug administration and during the paired control periods are presented in Table II. Both the mean values and the ranges are given. The results for the individual subjects with each of the test materials are presented in Fig. 1.

The significance of the observed differences in uropepsin excretion between the individual pairs of control and test specimens for each subject on each test material was assessed using a one-sided *t* test.

Received April 14, 1967, from LaWall and Harrisson Research Laboratories, Inc., Philadelphia, PA 19103
Accepted for publication July 27, 1967.
Presented to the Pharmacology and Biochemistry Section, A.PH.A. Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.
* Warner-Lambert Research Institute, Morris Plains, NJ 07950

TABLE II—UROPEPSIN EXCRETION
(TOTAL UNITS/24 hr.)
$N = 15$

Material	Test Values Range	Test Values Mean	"Paired" Control Values Range	"Paired" Control Values Mean
Sodium bicarbonate	470–3770	1696	91–4590	2385
Calcium carbonate	122–4460	2034	175–3305	1775
Magnesium hydroxide	128–3086	1637	550–3950	2209
HMAS	240–4340	1467	494–4240	2225
HMAS and bismuth subsalicylate	225–3558	1609	0–6265	2449
Bismuth subsalicylate	0–3474	1309	238–4430	2057

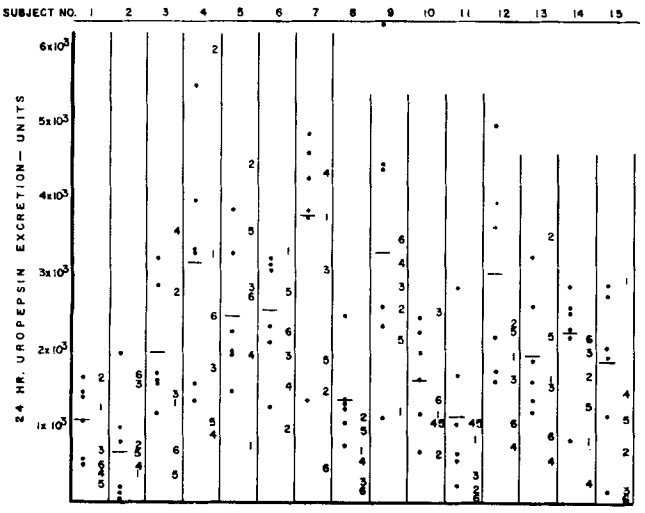

Fig. 1—Uropepsin excretion (units/24 hr.) test and control data. Key: 1, sodium bicarbonate; 2, calcium carbonate; 3, magnesium hydroxide; 4, HMAS; 5, HMAS and bismuth subsalicylate; 6, bismuth subsalicylate; ●, individual control values; —, mean values.

When the results were so evaluated, all test materials, except calcium carbonate, elicited significant decreases ($P < 0.05$) in uropepsin excretion.

An evaluation of the data showed a significant correlation ($P < 0.001$) within treatment groups between the magnitude of the control uropepsin level and the decrease in level upon treatment with the test materials. Higher control levels tended to be associated with greater decreases. Therefore, using an analysis of covariance, the decreases were adjusted for the differences in control levels. Based on Duncan's new multiple range test and owing to the large residual variances, none of the differences among the adjusted mean decreases for the various test treatments are statistically significant.

DISCUSSION

Of major consequence to the over-all evaluation of the uropepsin results obtained in this study is the extremely large variation in the 24-hr. excretion values by the individual subjects under the control conditions. The majority of subjects showed a variation in control uropepsin values of approximately two to fivefold. The over-all range of the control uropepsin values was 0–6265. These findings are in keeping with normal range by Corazzo and Myerson (9).

Notwithstanding the wide variations observed in the normal control values, both within and among the test subjects, there were statistically significant decreases in uropepsin excretion associated with the administration of all the test materials, except calcium carbonate. The basic reason for this occurrence remains to be elucidated. The decrease could result from inhibition of over-all gastric secretion, selective inhibition of pepsinogen formation, change in the partition of pepsinogen between gastric secretion and plasma, or a decrease in the excretion of pepsinogen by the glomerular apparatus. The results of earlier studies in animals (5) tend to support the initial possibility.

It is apparent from these findings that the usefulness of uropepsin excretion as a parameter in the evaluation of antacids is limited. This limitation is accentuated by the large variations noted in uropepsin excretion both within and among the test subjects.

SUMMARY

The effect of six antacid materials upon uropepsin excretion was evaluated in 15 test subjects. The effect was assessed by comparing total uropepsin excretion during a 24-hr. control period with that excreted in the next 24-hr. period during which a test material was taken three times a day after meals. The doses of the antacid were comparable, based upon their acid consuming power. All test materials evaluated, except calcium carbonate, resulted in decreases in uropepsin excretion that were significant at $P < 0.05$. The rationale of this effect upon uropepsin excretion requires further study of the many factors influencing uropepsin excretion.

REFERENCES

(1) Modell, W., "Drugs of Choice," C. V. Mosby Co. St. Louis, Mo., 1960, p. 357.
(2) Komarov, S. A., and Komarov, O., *Am. J. Digest. Diseases*, **7**, 177(1940).
(3) Komarov, S. A., and Kruegar, L., *ibid.*, **7**, 170(1940).
(4) Schiffrin, M. J., and Komarov, S. A., *ibid.*, **8**, 215 (1941).
(5) Packman, E. W., Abbott, D. D., Trabin, B., and Harrisson, J. W. E., *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 46 (1959).
(6) Janowitz, H. D., and Hollander, F., *Gastroenterology*, **17**, 591(1951).
(7) Grey, S. J., Ramsey, C. G., and Reifenstein, R. W., *New Engl. J. Med.*, **25**, 835(1954).
(8) Green, P. A., and Power, M. H., *Staff Meetings Mayo Clinic*, **32**, 6(1957).
(9) Corazzo, L. J., and Myerson, R. M., *J. Am. Med. Assoc.*, **165**, 146(1957).