Time Course and Dose Dependence of Antacid Effect on Urine pH

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Abstract □ Daily administration of a proprietary magnesium and aluminum hydroxides suspension, 15 ml four times a day, to normal adult volunteers resulted in a statistically significant increase in urine pH on the 1st day of treatment. The urine pH's on the 2nd and subsequent days of treatment were statistically significantly higher than on the 1st day. A 7.5-ml dose of the antacid suspension, taken four times a day, had only a small and not statistically significant effect on urine pH, while 30 ml four times a day increased urine pH by approximately the same magnitude as the 15-ml doses. The effect of the antacid on urine pH persisted for at least 1 day after discontinuation of dosing.

Keyphrases □ Antacid—magnesium and aluminum hydroxides suspension, effect on urine pH □ Magnesium and aluminum hydroxides suspension—effect on urine pH □ Aluminum and magnesium hydroxides suspension—effect on urine pH □ pH, urine—effect of magnesium and aluminum hydroxides suspension

Regular administration of certain antacids can increase urine pH sufficiently to have pronounced effects on the kinetics of elimination of some acidic and alkaline drugs (1). A widely used proprietary antacid product containing magnesium and aluminum hydroxides[1] was the most effective of the products tested in increasing urine pH. To extend the information obtained in the initial study (1), an investigation was undertaken to determine the time course and dose dependence of the effect of this antacid on urine pH.

EXPERIMENTAL

The study panel consisted of eight healthy males, 23–38 years of age, who by education and experience (graduate students in pharmaceutics) were capable of giving their informed consent to participate in this investigation. The subjects were under no dietary restrictions but took no drugs during the study. They were instructed to empty their bladders and to collect the urine from 8:00 am to 10:00 am, 10:00 am to 2:00 pm, and 2:00 pm to 4:00 pm. The urine pH was determined immediately after voiding. All measurements were carried out by the same individual on a pH meter[2], which was routinely standardized with buffer solutions of pH 4.0, 7.0, and 9.0.

To determine the time course of the antacid effect on urine pH, seven subjects collected urines on the 1st and 2nd days and took 15 ml of the antacid suspension at 8:00 am, 1:00 pm, 6:00 pm, and 11:00 pm from the 3rd to 8th day. Urine samples were collected until the 10th day, except on Days 6 and 7.

To determine the effect of antacid dose on urine pH, eight subjects took 0, 7.5, 15, or 30 ml of the antacid suspension at 8:00 am, 1:00 pm, 6:00 pm, and 11:00 pm on a Sunday and Monday according to a Latin-square experimental design. Urine samples were obtained on Mondays and Tuesdays, *i.e.*, the 2nd day of antacid administration and the day after antacid was discontinued.

The daily mean pH values reported in the tables were obtained by averaging as such the pH of the three urine samples obtained from every subject.

[1] Maalox, William H. Rorer, Inc., Fort Washington, Pa.
[2] Beckman Zeromatic II.

Table I—Time Course of Urine pH Change Caused by Administration of Magnesium and Aluminum Hydroxides Suspension in Healthy Adults

Day	Antacid[a]	Mean Urine pH ± *SD*[b]	Significance of Difference from Control pH (*p* Values)[c]
1	—	5.78 ± 0.42	—
2	—	5.83 ± 0.51	—
3	+	6.16 ± 0.40	<0.025
4	+	6.94 ± 0.41	<0.0025
5	+	6.46 ± 0.29	<0.0125
6	+	—[d]	—
7	+	—[d]	—
8	+	6.76 ± 0.28[e]	<0.0005
9	—	6.07 ± 0.41[f]	N.S.
10	—	5.80 ± 0.66[e]	N.S.

[a] Fifteen milliliters of Maalox Suspension at 8:00 am, 1:00 pm, 6:00 pm, and 11:00 pm. [b] Mean of seven subjects except where indicated. [c] Paired *t* test, compared to average pH on Days 1 and 2. [d] Not determined (Saturday and Sunday). [e] Mean of six subjects (one subject discontinued antacid on Day 6 due to a respiratory infection). [f] Mean of five subjects (a second subject was unable to collect urine samples on that day).

RESULTS AND DISCUSSION

The time course of urine pH change caused by administration of 15 ml of the antacid four times a day for 6 days is summarized in Table I. A small but statistically significant increase in urine pH was noted on the 1st day of antacid administration. There was no increase in urine pH with time on that day (mean pH 6.28 ± 0.62, 6.09 ± 0.54, 6.14 ± 0.64 for the first, second, and third collection periods, respectively). The previous study had shown that there are no significant differences in control urine pH for the three urine collection periods (1).

The mean urine pH on the 2nd, 3rd, and 6th days of antacid administration was almost 1 unit higher than during the control period and was also statistically significantly higher than during the 1st day of antacid administration. There was no systematic change

Table II—Relationship between Dose of Magnesium and Aluminum Hydroxides Suspension and Urine pH in Healthy Adults

Dose[a], ml	Day[b]	Mean Urine pH ± *SD*[c]	Significance of Difference from Control pH (*p* Values)[d]
0	2	5.73 ± 0.42	—
0	3	5.74 ± 0.38	—
7.5	2	6.08 ± 0.54	N.S.
0	3	6.14 ± 0.61	N.S.
15	2	6.56 ± 0.40	<0.0025
0	3	6.17 ± 0.45	<0.025
30	2	6.44 ± 0.57	<0.01
0	3	6.45 ± 0.34	<0.0025

[a] Volume of Maalox Suspension taken at 8:00 am, 1:00 pm, 6:00 pm, and 11:00 pm. [b] Antacid was taken on Days 1 and 2 except in the control experiment. [c] Mean of eight subjects. [d] Paired *t* test, compared to average pH of Days 2 and 3 of the control period.

in mean urine pH with time from the 2nd to the 6th day of antacid administration. The mean pH on the 1st day after discontinuation of the antacid was somewhat above the control value but not statistically significantly so. Urine pH was in the normal control range on the following day.

The results of the experiments to determine the relationship between the dose of the antacid and urine pH are summarized in Table II. Urine pH was determined on the 2nd day of treatment in view of the results obtained in the first part of this investigation. A dose of 7.5 ml four times a day had only a small and not statistically significant effect on urine pH *on the average*.

However, it was noted previously that the magnitude of the antacid effect on urine pH is inversely proportional to the urine pH during the control period (1). The same tendency was apparent in this study; some individuals with low control pH values showed an increase of more than 0.5 pH unit with the 7.5-ml dosing regimen. The 15-ml dosing regimen increased urine pH by more than 0.8 unit on the average, a highly statistically significant difference from the control value. No further increase was observed when the dose of the antacid was raised to 30 ml. Urine pH on the 1st day after discontinuation of the 15- and 30-ml doses was significantly above the control value; this residual effect was particularly pronounced after the 30-ml dose.

The results of this study show that a pharmacokinetically significant increase in urine pH is produced within 24 hr of administration of regular therapeutic doses of a widely used antacid and that this effect persists for about 24 hr after the antacid has been discontinued. The residual effect on urine pH is probably due to the retention of antacid in the GI tract for some time. It is not known if the lack of difference between the effect of the 15- and 30-ml dosage regimens on urine pH is paralleled by a similar lack of dose–response relationship with respect to antacid efficacy.

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ACKNOWLEDGMENTS AND ADDRESSES

Received December 23, 1974, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214*

Accepted for publication March 19, 1975.

Supported in part by Grant GM 20852 from the National Institute of General Medical Sciences, National Institutes of Health.

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GLC Determination of Underivatized Carbamazepine in Whole Blood

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Abstract □ This report describes a rapid GLC assay for carbamazepine in blood. Carbamazepine is chromatographed directly using phenyl methyl silicone gum as the stationary phase. The calibration curve is linear up to 50 μg/ml, with a lower limit of sensitivity of 1 μg/ml. Other anticonvulsants may be measured simultaneously, and the procedure works equally well with plasma or blood.

Keyphrases □ Carbamazepine—GLC analysis, whole blood □ Anticonvulsants—GLC analysis of carbamazepine in whole blood □ GLC—analysis, carbamazepine in whole blood

Carbamazepine is used for the relief of pain from trigeminal neuralgia (1) and in the treatment of epilepsy (2–4). Frequently, patients with complicated seizure disorders are given several other anticonvulsants (*e.g.*, phenytoin, primidone, and phenobarbital) as well as carbamazepine (the usual case in this hospital).

Methods of analysis for carbamazepine that rely on spectrophotometry (5) are complicated by interfering absorbances when mixtures of drugs are analyzed. For such mixtures, GLC is usually the preferred method, and several GLC methods for measuring carbamazepine in serum or plasma recently were reported (6–13). Because of various drawbacks (*e.g.*, tedious extraction requirements, necessity of derivative formation, and inability to use whole blood), none of these methods is considered suitable.

This paper describes a GLC method for the assay for carbamazepine levels in whole blood. This method is simple and rapid and does not require derivative formation. Furthermore, other anticonvulsants can be measured simultaneously.

EXPERIMENTAL

Reagents—Reagent grade chloroform, methanol, and acetic acid were used without further purification. Authentic iminostilbene was obtained commercially[1].

Standards—A stock solution equivalent to 1.0 mg/ml of heptabarbituric acid was prepared by dissolving exactly 108.4 g of dry heptabarbital sodium[2] in 0.9% saline, which had been made alkaline with 5.0 ml of 0.45 *N* sodium hydroxide. The final volume of the solution was adjusted to 100 ml with 0.9% saline. A 20.0-μg/ml working internal standard was prepared by diluting 10.0 ml of the stock solution to 500 ml with 0.9% saline. The 16.3-μg/ml carbamazepine blood standard was prepared by dissolving 4.80 mg of carbamazepine[2] in 10.0 ml of anhydrous methanol and then diluting a 0.34-ml aliquot of this solution with 100 ml of expired blood bank blood. Blood standards of other concentrations were prepared from the carbamazepine stock solution as needed.

Apparatus—The GLC analyses were performed on a gas chromatograph[3] equipped with dual flame-ionization detectors. The chromatograph was fitted with 1.83-m (6-ft) long, U-shaped, glass columns (4.0 mm i.d.) packed with 1.5% phenyl methyl silicone gum (OV-17) on Gas Chrom G HP[4] (80–100 mesh). For the combined analysis of primidone and carbamazepine, a column packed with 1.5% OV-225 on Gas Chrom G HP[4] (80–100 mesh) also was used. The columns were conditioned before use by heating at 290° (260° for OV-225) for 24 hr with 5-ml/min carrier gas flow.

[1] Aldrich Chemical Co., Milwaukee, Wis.
[2] Ciba Pharmaceutical Co., Summit, N.J.
[3] Varian model 2100.
[4] Applied Science, State College, Pa.