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Technical Note

The Effect of Urinary pH Modification on the Disposition of Phenylpropanolamine[1]

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INTRODUCTION

Phenylpropanolamine (PPA)[4] is a sympathomimetic amine which is widely available in the United States as an over-the-counter decongestant and as an anorexigenic agent (1). Despite its availability in over 100 over-the-counter formulations (1), relatively little work has been done to study the possible pharmacokinetic and pharmacodynamic interactions between PPA and other prescription and nonprescription drugs.

PPA is a weak base with a pK_a of 9.44. After a single oral dose of 25 mg in an aqueous solution as the hydrochloride, approximately 90% was excreted unchanged in the urine in 24 hr (2). In three subjects receiving a single dose of an oral solution, the excretion rate of PPA appeared to be depressed when the urine was alkaline, presumably because under these conditions, tubular reabsorption of the unionized compound was favored (3). Because the renal excretion of PPA is pH dependent, any concomitant medication which increases the urinary pH could delay the excretion of PPA and prolong any adverse effects associated with the drug. For example, PPA has been shown to increase significantly the supine systolic blood pressure in normotensive subjects after a single oral dose of 37.5 mg (4).

Previous studies on urinary pH modification and PPA pharmacokinetics lacked a sufficient number of subjects to allow a rigorous statistical comparison of excretion rates under the various conditions. In addition, no control studies were carried out to determine the excretion patterns in the case of uncontrolled urinary pH (3). The present study determined the effect of the concomitant administration of formulated PPA and two commonly used over-the-counter medications, sodium bicarbonate and ascorbic acid (5,6).

MATERIALS AND METHODS

This study received approval from the University of Minnesota Committee on the Use of Human Subjects in Research. Six normal healthy volunteers (four males, two females) ages 22–30 were randomized to one of three treatments each week for 3 weeks: the control, bicarbonate, or ascorbic acid treatment. In the control treatment, each subject ingested a single oral dose of 37.5 mg of PPA (Dietac, Menley & James Laboratories, Philadelphia, Pa.), followed by a series of urine collections over 24 hr. In the bicarbonate treatment, each subject ingested sixteen 648-mg tablets (approximately 10 g) of sodium bicarbonate (Eli Lilly and Co., Indianapolis, Ind.) orally; 0.5 hr later the subject took 37.5 mg of PPA orally followed by a series of urine collections over 24 hr. In the ascorbic acid treatment, each subject took fourteen 500-mg tablets (7 g) of ascorbic acid (Rugby Laboratories Inc., Rockville Centre, N.Y.) orally; 0.5 hr later the subject took 37.5 mg of PPA, followed by a series of urine collections over 24 hr.

On the day of the assay, the urine collections were thawed, and the pH was measured. Two milliliters of each urine sample was placed in a centrifuge tube to which 40 μl of amphetamine sulfate (1 mg/ml) was added as an internal standard. The sample was vortexed and centrifuged at 800*g* for 15 min. The sample was then placed in an injection vial for injection by the WISP Model 710B auto-sampler (Waters Associates, Milford, Mass.). The high-performance liquid chromatographic (HPLC) assay was adapted from that of Dye *et al.* (7) and involved postcolumn derivatization with *o*-phthalaldehyde and fluorescence detection.

Excretion rates of PPA were plotted vs the midpoint of the urine collection interval. The excretion rates, the cumulative amount of PPA, and the urinary hydrogen ion concentrations (8) in each time interval were compared between treatments using ANOVA with Scheffé's test for multiple comparisons (9).

In order to test the dissolution characteristics of the dosage form over the widest pH range possible, dissolution studies were carried out over 30 min with the dosage forms at several pH values with the use of U.S.P. dissolution apparatus I. Five hundred milliliters of U.S.P. simulated gastric fluid without pepsin was prepared giving a pH of 1.6 (10).

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[1] This work was presented in preliminary form at the 39th Meeting of the American Pharmaceutical Association Academy of Pharmaceutical Sciences [*Abstracts* 15(2):138 (1985)].

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[4] Abbreviations used: PPA, phenylpropanolamine; HPLC, high-performance liquid chromatography; ANOVA, analysis of variance.

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The medium was then used as such, or adjusted to a pH of 7.5 or 10.0 with 0.1 *N* NaOH, and warmed to 37°C. The dissolution samples were filtered and injected directly onto the HPLC.

Six replicate dissolution experiments were run at 120 rpm at each pH. The dissolution data are reported as percentages of the labeled dose dissolved. The percentages of the dose dissolved in a given time in the media at various pH's were compared by ANOVA.

RESULTS AND DISCUSSION

The purpose of this study was to determine the effects of two commonly used over-the-counter urinary pH modifiers on the excretion of PPA. In order to rule out any interaction in the gastrointestinal tract that could be pH dependent, dissolution studies were run on the dosage form at various pH values, but there was no significant difference in the rate or extent of dissolution. Therefore, the difference in excretion rates cannot be attributed to an interaction at the level of the absorption of PPA but, rather, to an interaction at the excretory level.

Figure 1 illustrates that treatment with a single oral dose of 10 g sodium bicarbonate significantly increased the urinary pH over both the ascorbic acid-pretreatment group and the control group for up to 10 hr after the administration of PPA. This increase in urinary pH was accompanied by a depression of the excretion rate of PPA, which remained depressed until 10 hr postdose, when the urinary pH was no longer significantly elevated. For example, at 1.75 hr, the mean excretion rate in the bicarbonate group was 1452.6 μg/hr, vs 4488.9 μg/hr in the control group, a 68% decrease in the excretion rate. The alkaline urinary pH favored the nonionized form of PPA and therefore more extensive reabsorption of PPA occurred than in the control group. When the pH was no longer alkaline, the portion of the PPA dose that was previously reabsorbed could then be excreted, leading to a higher excretion rate than in the control case. The excretion rate in the bicarbonate group was significantly increased from 11 to 16 hr after the dose of PPA in comparison with the other two groups. At 13 hr after the PPA dose, the mean excretion rate in the bicarbonate group was 120% higher than in the control group (1405.6 vs 636.7 μg/hr). Similarly, at 16 hr after the dose, the mean excretion rate was 146% higher in the bicarbonate group than in the control group (795.0 vs 323.7 μg/hr). Figure 2 illustrates the excretion rate plots for a representative subject receiving the three different treatments.

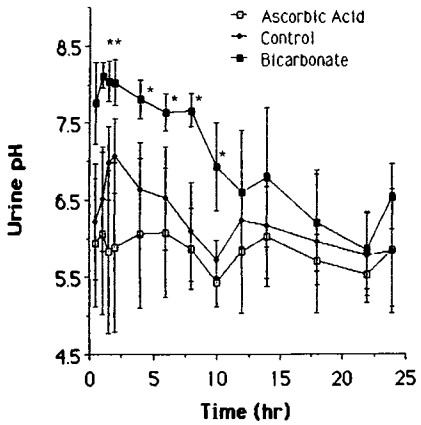

Fig. 1. Urine pH (means ± SD) over 24 hr as a function of pretreatment regimen (N = 6). (*) Significant difference ($P < 0.05$) between groups as determined by ANOVA on the H^+ ion concentration in each urine sample.

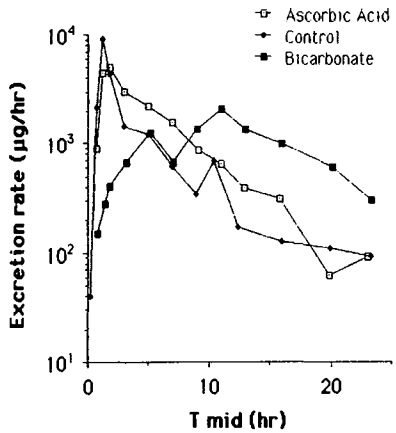

Fig. 2. Urinary excretion rates of PPA over 24 hr as a function of pretreatment regimen in a representative subject.

For up to 4 hr postdose, the cumulative urinary excretion was significantly lower in the bicarbonate group than in the control group (6.36 ± 3.28 vs 13.62 ± 5.81 mg). However, after 4 hr there was no significant difference in the cumulative excretion between the three groups. In 24 hr, approximately 80% of the dose was recovered in the urine.

In contrast with the results in the bicarbonate group, the urinary pH was not significantly changed when ascorbic acid was administered prior to PPA. The urinary pH in the control group did vary throughout the day, a result that has been reported by other authors (11). It should be noted that although Fig. 1 plots urinary pH vs time for ease of comparison, the statistical analysis was carried out on the urinary H^+ concentrations, as suggested by Ayres *et al.* (8).

Because bicarbonate is widely available in over-the-counter formulations, the possibility of comedication with PPA exists. The present study indicates a profound disturbance of the normal excretion patterns of PPA by a single large dose of bicarbonate. Since the hypertensive effects associated with PPA may be linked to the blood level it achieves, a delay in the excretion of PPA could be of pharmacodynamic consequence.

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