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Report

The Effects of Urine pH Modification on the Pharmacokinetics and Pharmacodynamics of Phenylpropanolamine

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To determine whether uninary alkalinization had an effect on the plasma pharmacokinetics and pharmacodynamics of phenylpropanolamine, a double-blind crossover study was conducted in four healthy, normotensive male volunteers. The subjects received 25 mg immediate-release phenylpropanolamine and either placebo or sodium bicarbonate in a balanced randomized order. The bicarbonate treatment consisted of 6 g sodium bicarbonate 30 min prior to the phenylpropanolamine and then 3 g sodium bicarbonate every 4 hr for the next 16 hr. During the control treatment, phenylpropanolamine and a placebo for bicarbonate (lactose) were given on the same schedule. Blood and urine samples were collected over 24 hr and analyzed by HPLC. A supine blood pressure and pulse were obtained before each blood sample. The bicarbonate treatment significantly increased the urine pH throughout the study period and decreased phenylpropanolamine renal clearance by 33.5%. The apparent total-body clearance was also decreased by 31.5% and resulted in higher postabsorptive plasma phenylpropanolamine concentrations in each subject as compared to the control treatment. Both systolic and diastolic blood pressures changed significantly from baseline in both treatments. The bicarbonate treatment was accompanied by significantly higher diastolic blood pressures than in the control treatment, but there was no effect on systolic blood pressures. Generally, when the blood pressure–concentration pairs were plotted chronologically, clockwise hysteresis curves resulted. Heart rates did not change significantly from baseline values for either treatment. In this small group of normotensive healthy male volunteers, urinary alkalinization significantly depressed the renal clearance of phenylpropanolamine, producing higher postabsorptive phenylpropanolamine plasma concentrations and a small but significant increase in the diastolic blood pressure.

KEY WORDS: phenylpropanolamine; urinary pH modification; urine alkalinization; renal clearance; pharmacokinetics; pharmacodynamics.

INTRODUCTION

Phenylpropanolamine, a sympathomimetic amine, is available as a racemic mixture of *d,l*-norephedrine in over 80 nonprescription formulations for decongestion and appetite suppression (1). The usual and therapeutic doses of phenylpropanolamine (25 mg immediate-release or 75 mg sustained-release) have not significantly increased blood pressure (2–5). However, doses of 37.5 mg of immediate-release phenylpropanolamine have been associated with significant blood pressure changes (6). Concomitant administration of therapeutic doses of phenylpropanolamine with a drug that increased the phenylpropanolamine plasma concentrations might lead to enhanced blood pressure responses.

About 90% of an oral dose of *l*-norephedrine is excreted unchanged in the urine in 24 hr (7). The renal excretion rates of *l*-norephedrine and racemic phenylpropanolamine were significantly decreased by concomitant treatment with sodium bicarbonate (8,9), as expected for a weakly basic compound with a pK_a of 9.44. The effects of urinary alkalinization on phenylpropanolamine's renal clearance, plasma concentrations, and blood pressure responses have not previously been studied. The specific objectives of the present study were to determine the effect of urinary alkalinization with sodium bicarbonate on the renal clearance of phenylpropanolamine and to determine if a pH-induced change in drug clearance would alter the blood pressure or heart rate response to a therapeutic dose. Because the phenylpropanolamine and sodium bicarbonate were administered orally, a third objective was to assess whether the phenylpropanolamine absorption from the gastrointestinal tract was affected by bicarbonate.

MATERIALS AND METHODS

Subjects

The four male subjects, ages 24–26 years, underwent a physical examination and granted written informed consent prior to participation in the study. The subjects had normal

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supine blood pressures (≤140/90 mm Hg), less than a 10-mm Hg drop in systolic blood pressure after standing for 1 min, weights within 25% of ideal body weight (89.6 ± 4.3 kg, mean ± SD), and normal resting electrocardiograms. The subjects had no history of hypertension, diabetes, glaucoma, depression, or known hypersensitivity or idiosyncrasy to the sympathomimetic amines. Subjects were instructed to discontinue the use of any sympathomimetic amines 1 week prior to the study. The study was approved by the Investigational Review Committee of Hennepin County Medical Center.

Procedure

The subjects fasted for 12 hr overnight prior to the study and abstained from cigarettes and caffeine-containing products for 2 days prior to and during each study day. No food was ingested until 3 hr following phenylpropanolamine administration, but water intake was not controlled. All subjects received 25 mg immediate-release phenylpropanolamine (Super Odrinex, Fox Pharmacal Inc., Ft. Lauderdale, FL) on both treatment days. They also received capsules of either sodium bicarbonate or a bicarbonate placebo (lactose) according to a balanced, randomized, double-blind, crossover design. On each study day, 6 g of sodium bicarbonate or placebo was orally administered to a subject. One-half hour later the subject received the oral phenylpropanolamine dose. Three grams of sodium bicarbonate (or placebo) was then administered every 4 hr for 16 hr after the phenylpropanolamine dose. At least 4 days later, the subjects crossed over to the opposite treatment. In all cases, phenylpropanolamine was received between 8:00 and 9:00 AM.

An indwelling i.v. catheter was placed for obtaining venous blood samples (5 ml) predose and 0.25, 0.50, 0.75, 1, 1.25, 1.75, 3, 5, 7, 9, 11, 13, 18, and 24 hr after the phenylpropanolamine dose. Blood was collected into Vacutainers (Becton-Dickinson, Rutherford, NJ) containing EDTA and immediately centrifuged. The plasma was removed and stored at −20°C until assayed.

A blank urine sample was obtained from each subject prior to receiving bicarbonate (or placebo). After the phenylpropanolamine dose was ingested, the subjects' total urine output was collected over the following intervals postdose: 0–0.5, 0.5–1, 1–1.5, 1.5–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–14, 14–18, and 18–24 hr. The volume was measured and an aliquot of each sample was placed into a tube, tightly capped, and frozen at −20°C until assayed, at which time the urine pH was determined at room temperature.

Blood pressure was measured by auscultation with a mercury manometer. Supine blood pressures and pulses were taken every 5 min before the phenylpropanolamine dose until three consecutive blood pressures were within 6 mm Hg of each other. The baseline blood pressure and pulse were calculated as the mean of the last three measurements. After drug administration, the blood pressure and pulse were measured prior to each blood sample collection. The subject was supine for at least 10 min before each blood pressure measurement. All blood pressures for a given subject on both study days were obtained by the same person.

Drug Analysis

Plasma and urine were analyzed for racemic phenylpropanolamine by reversed-phase high-performance liquid chromatography with postcolumn fluorescent derivatization, as described in detail in a previous report (10). The between-day coefficient of variation for plasma concentrations was less than 10% over the entire range of concentrations. Recovery of phenylpropanolamine from the plasma was 94%, and the lower limit of quantitation was 4 ng/ml plasma. The between-day coefficient of variation for urine was less than 15% over the entire range of standards. The lower limit of quantitation in the urine assay was 0.25 μg/ml urine.

Pharmacokinetic Analysis

The area under the plasma concentration–time curve (AUC) was determined using the trapezoidal rule with the area from the last measured plasma concentration to infinity estimated as the last plasma concentration divided by the estimated terminal elimination rate constant (K). The terminal elimination rate constant was determined from fitting the plasma concentrations in the terminal portion of the plasma concentration–time profile with a monoexponential function by ELSFIT (11). The terminal elimination rate constant was determined for comparison purposes in a similar manner from the terminal slope of the urinary excretion rate vs the midpoint time of the urine collection interval. The apparent total body clearance (CL/F, where F represents the oral bioavailability) and the apparent volume of distribution at steady state (V_{ss}/F) were calculated by a noncompartmental approach (12) with the use of the program INDPARA (13). The renal clearance (Cl_R) was determined for each individual from linear regression of the slope of a plot of the urinary excretion rate vs the plasma concentration at the midpoint of the collection interval (12). The renal clearance for the entire group as a function of treatment was also determined by plotting the excretion rates vs the midpoint concentrations for all of the individuals. The maximum plasma concentration (C_{max}) and the time at which the C_{max} was reached (t_{max}) were determined by observation of the plasma concentration–time data.

In order to determine whether the bicarbonate treatment had any effect on the absorption of phenylpropanolamine from the gastrointestinal tract, ELSFIT was also used to fit the plasma concentrations to a one-compartment model with either first- or zero-order absorption, assuming a bioavailability of 100%. The best-fit model was determined by comparing the values for the modified negative log likelihood (using the Leonard criterion) between the two models, as well as examining the residual and standardized residual plots.

Plasma concentrations, urinary excretion rates, urine H^+ concentrations (14), pH, supine blood pressures (systolic and diastolic), and pulses were analyzed by repeated-measures ANOVA, evaluating for differences in the variables due to time after the dose, treatment, and the interaction between time and treatment (15). Statistical comparisons of pharmacokinetic parameters were carried out with ANOVA, with the main effects being subject, treatment, and treatment order (15). A P value <0.05 was considered significant. For each analysis, the model was checked for normality and constant variance. A paired t test was carried out on the baseline blood pressures and heart rates between the

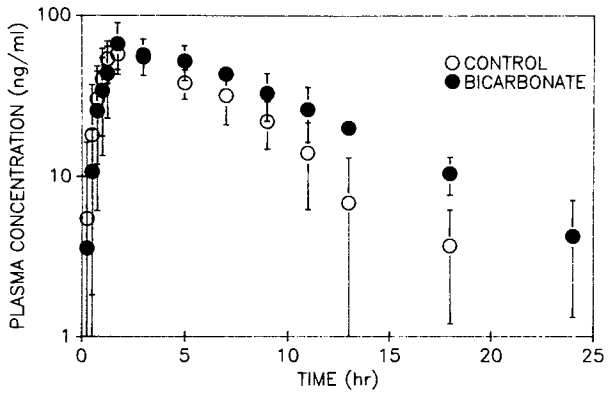


Fig. 1. Mean plasma concentrations of phenylpropanolamine during the control and bicarbonate treatments. The postabsorptive plasma concentrations were significantly higher in the bicarbonate treatment (repeated-measures ANOVA).

control and bicarbonate treatments. The combined excretion rate vs midpoint concentration data for all four subjects in each treatment was analyzed by regression analysis, and a small-sample *t* test was used to determine whether the slopes of the regression lines for the two treatments (and thus the renal clearances) were different (16). Regression analysis was also carried out to determine whether renal clearance was a function of urine flow or pH.

RESULTS

The mean plasma concentrations of phenylpropanolamine for the control and bicarbonate treatment days are depicted in Fig. 1. The mean postabsorption concentrations were significantly higher in the bicarbonate treatment than in the control treatment. In the control treatment, phenylpropanolamine was not detected in the plasma at 24 hr postdose, in contrast to the detectable levels in the bicarbonate group. No difference existed in the C_{max} or t_{max} values between treatments (Table I).

A one-compartment model with zero-order absorption best described the plasma concentration–time profile of phenylpropanolamine with and without bicarbonate treatment in seven of the eight cases. For one subject, the concentration–time profile during bicarbonate treatment was best fit with a first-order absorption model. This subject's control and bicarbonate treatment data were therefore eliminated from further analysis of oral absorption. The zero-order absorption rate constants (k_o) did not differ between the control and the bicarbonate treatments (Table II).

Table I. Noncompartmental Pharmacokinetic Parameters of Phenylpropranolamine after Control and Bicarbonate Treatment[a]

	Control	Bicarbonate
C_{max} (ng/ml)	68.9 ± 8.99	75.0 ± 15.7
t_{max} (hr)	2.27 ± 0.87	2.89 ± 1.54
CL/*F* (ml/min/kg)	10.0 ± 1.08	6.90 ± 0.52*
V_{ss}/F (L/kg)	4.06 ± 0.47	3.92 ± 0.22
K (hr^{-1})	0.173 ± 0.018	0.129 ± 0.008*
Elimination half-life (hr)	4.03 ± 0.41	5.39 ± 0.34*
Cl_R (ml/min/kg)	7.16 ± 0.89	4.76 ± 1.40
AUC (ng-hr/ml)	466 ± 50.2	678 ± 52.8*
% recovery in 24 hr	79.1 ± 4.6	79.4 ± 8.0

[a] Numbers listed as means ± SD (n = 4).
* Significantly different from control as determined by ANOVA.

Table II. Pharmacokinetic Parameters of Phenylpropranolamine Determined for a One-Compartment Model Incorporating Zero-Order Absorption After Control and Bicarbonate Treatment[a]

	Control	Bicarbonate
k_o (mg/hr)	16.1 ± 6.97	16.6 ± 5.65
K (hr^{-1})	0.191 ± 0.044	0.127 ± 0.034*

[a] Numbers listed as mean ± SD (n = 3).
* Significantly different from control as determined by the Student's paired *t* test.

Although it has previously been suggested that H^+ concentrations rather than pH values should be used for statistical comparisons (14), in the present study an increasing variance with increasing H^+ concentration was detected by plotting the residuals vs the predicted values of H^+ concentration. With the use of the log transformation (i.e., pH), a constant variance was observed. The pH was therefore considered to be the appropriate variable for statistical analysis. Urine pH changed significantly over the 24-hr study period in both treatments. The pH changes probably reflected the diurnal oscillation that has been reported previously (9,17). Significantly higher urine pH values were maintained with sodium bicarbonate treatment than with the control treatment for the 24-hr study period (Fig. 2).

In the bicarbonate treatment the higher urine pH was accompanied by a statistically significant decrease of 31.5% in the apparent total-body clearance (Table I). Because the apparent volume of distribution did not change, the decreased clearance was responsible for a 33.7% increase in the elimination half-life. The renal clearance also appeared to decrease by 33.5% in the bicarbonate treatment but was not statistically significant in the ANOVA. However, when the excretion rates were plotted vs the plasma concentrations at the midpoint of the collection interval for all of the subjects during the control and bicarbonate treatments, the slopes of the regression lines (and thus the renal clearances) were significantly different (Fig. 3). The renal clearance es-

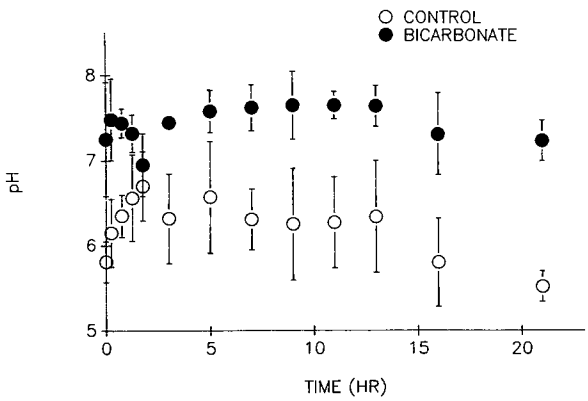


Fig. 2. Mean urine pH values during the control and bicarbonate treatments. The urine pH changed significantly as a function of both time and treatment (repeated-measures ANOVA).

Table III. Pharmacodynamics of Phenylpropanolamine in Subjects Receiving Control (C) and Bicarbonate (B) Treatments[a]

Subject No.	Baseline blood pressure (mm Hg)		Baseline heart rate (beats/min)		Maximum blood pressure (mm Hg)		Time to max. pressure (hr)	
	C	B	C	B	C	B	C	B
1	117/73	118/72	58	53	126/80	128/80	1/1	1.25/1.25
2	117/71	113/69	61	60	124/78	124/78	1/0.5	11/1
3	116/56	120/79	48	45	126/62	128/84	1/0.75	1/0.5
4	122/71	125/80	76	72	124/81	128/80	24/1	0.75/0.5

[a] No statistical difference in baseline blood pressure or heart rate was observed as a function of treatment (paired Student's t test).

timates by the two methods were similar. The mean of the individual renal clearance estimates was 7.16 ± 0.89 ml/min/kg (mean ± SD) in the control treatment and was 7.26 ml/min/kg in the group data. Similarly, the renal clearance estimates from the individual and group data in the bicarbonate treatment were 4.76 ± 1.40 and 4.51 ml/min/kg, respectively. Figure 4 shows the relationship between renal clearance and urine flow for the control and bicarbonate treatment. There appeared to be little dependence of renal clearance on urine flow for either treatment (r^2 = 0.0061 for control and r^2 = 0.0027 for bicarbonate), and the slope of neither regression line was significantly different from zero. The renal clearance was also plotted as a function of measured urine pH. Data from both treatments were combined to construct Fig. 5. Although significant scatter existed in the data (r^2 = 0.1707), the slope of the line was significantly different from zero, indicating a negative association between renal clearance and urine pH.

The baseline blood pressures and heart rates between the control and the bicarbonate treatments were not statistically different (paired t test, Table III). Analysis of the supine blood pressures by repeated-measures ANOVA indicated that both systolic and diastolic blood pressures changed significantly with time after the dose of phenylpropanolamine (Fig. 6). In addition, the diastolic blood pressure was significantly affected by the bicarbonate treatment. The heart rate was not affected either as a function of time after dose or by treatment (data not shown). None of the subjects reported any adverse effects.

In order to determine the relationship between plasma concentration and blood pressure effect, the blood pressures were plotted against plasma concentration in chronological order. In three of four cases in the control treatment and in all cases in the bicarbonate treatment a clockwise hysteresis

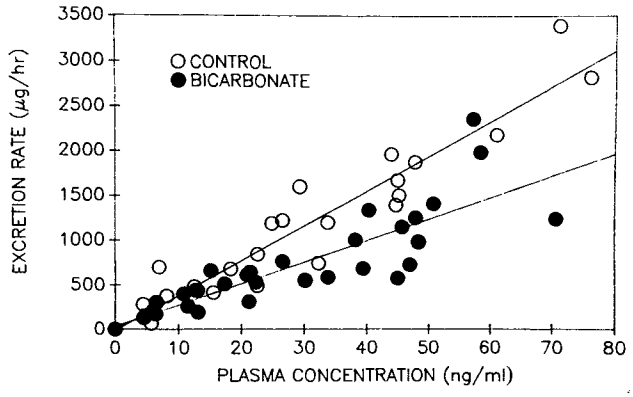


Fig. 3. Renal clearance of phenylpropanolamine for all individuals during the control and bicarbonate treatment. Renal clearance was calculated for each treatment from the slope of the regression line of the urinary excretion rates plotted vs plasma concentration at the midpoint of the urine collection interval. The renal clearance in the control treatment was found to be significantly higher than that of the bicarbonate treatment by a small-sample t test comparing the slopes of the regression lines.

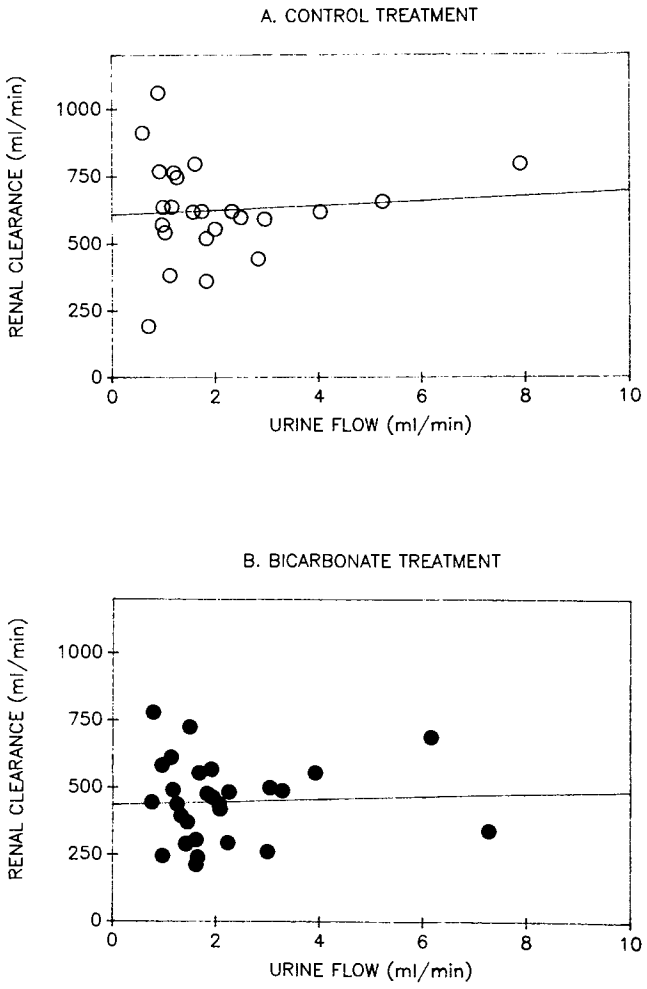


Fig. 4. (A) Plot of the renal clearance as a function of urine flow in the control treatment. The slope of the regression line was not significantly different from zero. (B) Plot of the renal clearance as a function of urine flow in the bicarbonate treatment. The slope of the regression line was not significantly different from zero.

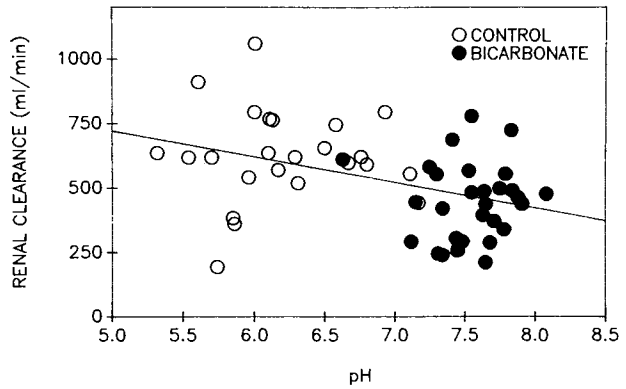


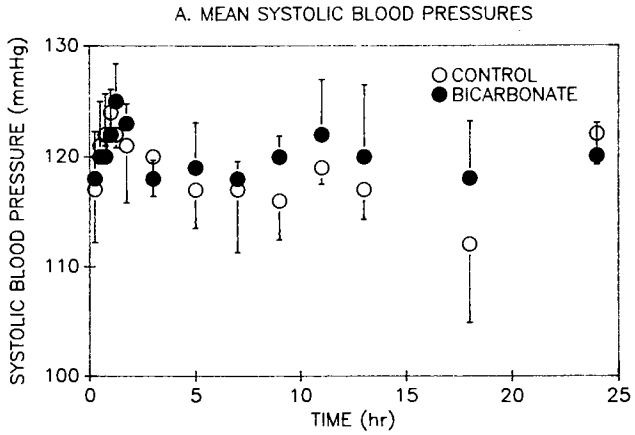
Fig. 5. Plot of the renal clearance as a function of urine pH. The slope of the regression line was significantly different from zero, indicating a significant relationship between renal clearance and urine pH.

loop was observed for the diastolic blood pressures. A similar pattern was observed for the systolic blood pressure plots in two of four cases in each treatment. Figure 7 shows the systolic and diastolic blood pressure concentration–effect plots for the control and bicarbonate treatment in one of the subjects, with the arrows indicating the progression of time.

DISCUSSION

The pharmacokinetic parameters of racemic phenylpropanolamine in the control treatment were similar to those recently reported following either 0.44 mg/kg intravenous phenylpropanolamine (10) or oral administration of 50 mg phenylpropanolamine in an aqueous solution (18). To determine if bicarbonate treatment affected the absorption of oral phenylpropanolamine, the plasma concentration–time data were fit with a one-compartment model with either first- or zero-order absorption. A zero-order absorption model better described the data, as has been shown by others (18). Since the bicarbonate had no effect on the zero-order absorption rate constant or the volume of distribution, changes in the pharmacokinetics of phenylpropanolamine were strictly a function of changes in elimination processes.

In the present study, the renal clearance of phenylpropanolamine (7.16 ± 0.89 ml/min/kg) approached the value of renal plasma flow, indicating substantial net renal tubular secretion. The concept that alkalinization of the urine may depress the urinary excretion rate of phenylpropanolamine and other weak bases by increasing the percentage of the unionized form, leading to increased reabsorption, has been well documented (8,17). However, until recently (19,20) the lack of a sensitive assay for phenylpropanolamine in plasma precluded the direct investigation of the effects of urinary alkalinization on the plasma pharmacokinetics, renal clearance, and pharmacodynamics of phenylpropanolamine. The increased urine pH associated with bicarbonate treatment caused a significant decrease in the renal clearance of phenylpropanolamine. This was indicated both by the decreased slope of the excretion rate vs midpoint plasma concentration plot (Fig. 3) and in the plot of renal clearance vs urine pH (Fig. 5). The decreased renal clearance led to higher phenylpropanolamine plasma concentrations in the postabsorptive phase of the pharmacokinetic profile in the bicarbonate treatment. In contrast to what was suggested by an earlier report (8), there appeared to be little dependence of renal clearance on urine flow. However, water intake was not controlled and a wider range of urine flow might have led to a significant relationship.



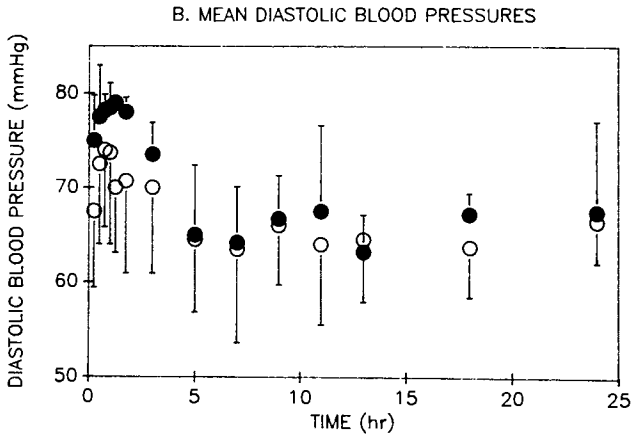


Fig. 6. (A) Mean systolic blood pressures plotted as a function of time after the phenylpropanolamine dose. Repeated-measures ANOVA indicated a significant change from baseline in the systolic blood pressure as a function of time. (B) Mean diastolic blood pressures plotted as a function of time after the phenylpropanolamine dose. Repeated-measures ANOVA indicated a significant change in the diastolic blood pressure as a function of time and of treatment.

In the control and the bicarbonate treatment small but statistically significant changes in systolic and diastolic blood pressures were observed with time after the dose of phenylpropanolamine. The blood pressures in both treatments appeared to increase rapidly after ingestion of the phenylpropanolamine dose. Because a placebo control treatment for phenylpropanolamine was not included, a diurnal variation in the blood pressure cannot be ruled out as the source for some of the observed change in blood pressure with time (2). The bicarbonate treatment was associated with a small but significant increase in diastolic blood pressure over that observed in the control treatment. The depression in renal clearance and subsequent increase in plasma phen-

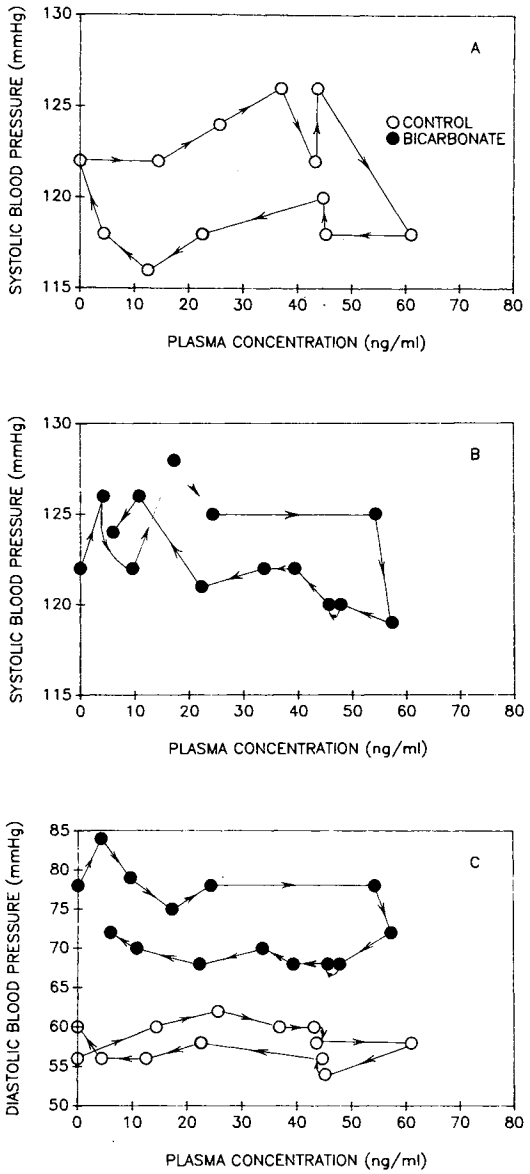


Fig. 7. Concentration–effect relationships for an individual. Arrows indicate the progression of time after the phenylpropanolamine dose. (A) Systolic blood pressure as a function of plasma concentration during the control treatment. (B) Systolic blood pressure as a function of plasma concentration during the bicarbonate treatment. (C) Diastolic blood pressure as a function of plasma concentration during the control and bicarbonate treatments.

ylpropanolamine concentrations caused by urinary alkalinization may have produced this increase in diastolic blood pressure. An alternative explanation could be that the sodium bicarbonate treatment itself was responsible for the increase in diastolic blood pressure.

Although sodium chloride and sodium bicarbonate may elevate blood pressure in salt-sensitive hypertensive patients, sodium bicarbonate does not appear to elicit a blood pressure effect in normotensive subjects. In two crossover studies, daily sodium chloride doses of 207 mEq (21) and 240 mEq (22) increased blood pressure in hypertensive patients, whereas 286 mEq of sodium bicarbonate (21) or 240 mEq of sodium citrate (the metabolite of which is bicarbonate) did not alter blood pressure (22). This blood pressure elevation may have been related to the increased plasma volume and urinary calcium excretion which was observed after sodium chloride but not after sodium citrate administration (22). However, Morgan *et al.* found that sodium bicarbonate (70 mEq daily) can increase blood pressure in salt-sensitive hypertensive patients. This increase was significantly less than after daily 70 mEq doses of sodium chloride [12/5 vs 19/14 mm Hg, respectively (23)]. In normotensive subjects, neither daily doses of less than 800 mEq sodium chloride (24,25) nor 286 mEq sodium bicarbonate (21) altered blood pressure. Therefore, the sodium bicarbonate (214 mEq) administered in the present study to normotensive subjects probably had no effect on blood pressure. The increased diastolic blood pressure in the sodium bicarbonate treatment must have been due to increased phenylpropanolamine concentrations secondary to decreased renal clearance.

Previous investigations with therapeutic doses of phenylpropanolamine have found few significant blood pressure changes (2–5). Only two studies evaluated the relationship between blood pressure response and phenylpropanolamine concentrations in serum or plasma. Saltzman *et al.* found insignificant blood pressure alterations and no correlation between concentration and response with 25-mg immediate-release or 75-mg sustained-release doses of phenylpropanolamine (3). In 10 normotensive subjects receiving 0.44 mg/kg phenylpropanolamine intravenously (10), most subjects displayed a linear increase in blood pressure with increasing serum concentration. Significant intersubject variability in blood pressure response was observed. Two of the subjects had the infusions discontinued early due to exaggerated blood pressure responses. Their peak phenylpropanolamine plasma concentrations were 67.3 and 107.8 ng/ml, which were within or slightly greater than the range of the C_{max} values observed in the present study in both treatments (57.4–95.3 ng/ml), indicating that the plasma concentrations achieved in the present study might have elicited clinically significant blood pressure elevations in sensitive individuals.

In almost all of the diastolic blood pressure vs plasma concentration plots, a clockwise hysteresis loop was observed. Half of the systolic blood pressure–concentration plots showed a similar pattern. A clockwise hysteresis loop suggests either the presence of an active metabolite or that the subjects became tolerant to the drug (26). Clockwise hysteresis has also been reported in two of the ten subjects receiving intravenous phenylpropanolamine (10). No evidence of an active metabolite has been reported, so the possibility exists that some subjects may become tolerant to the blood pressure effects of phenylpropanolamine after a single oral dose.

Concomitant treatment with bicarbonate significantly decreased the renal and total-body clearance of phenylpropanolamine and significantly increased the diastolic blood pressure. The blood pressure elevations were of little clinical significance in the nonobese normotensive subjects of the present study. Hypertensive responses are rare with therapeutic doses, but the present study does not rule out a more serious blood pressure response with urinary alkalinization in patients sensitive to phenylpropanolamine.

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