# On the Mechanisms Responsible for the Phosphaturia of Bicarbonate Administration

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ABSTRACT Experiments were carried out in normal dogs to characterize the mechanisms by which sodium bicarbonate administration results in increased excretion of phosphate. Infusion of sodium bicarbonate alone increased fractional phosphate excretion from 0.8 to 29.3%. During bicarbonate administration, ionized calcium fell and mean parathyroid hormone values increased from 59.6 to 230.4 μleq/ml. In the same group of dogs, administration of sodium bicarbonate plus calcium prevented the fall in ionized calcium, and parathyroid hormone levels remained unchanged. In these dogs fractional phosphate excretion increased from 2.4 to only 4.9%. Similar results were obtained in thyroparathyroidectomized dogs receiving sodium bicarbonate. In these dogs fractional excretion of phosphate increased from 0.6 to 4.5%. Under all three experimental conditions no differences were observed in sodium or bicarbonate excretion or in urinary or plasma pH. Administration of hydrochloric acid, after phosphaturia had been induced by the infusion of bicarbonate, resulted in a decrease in plasma bicarbonate and an acid urine; however, the phosphaturia persisted even in the presence of an acid urine pH. In five thyroparathyroidectomized dogs infused with parathyroid hormone throughout, administration of identical amounts of sodium as either NaCl or $NaHCO_3$ resulted in a similar degree of phosphaturia despite significant differences in urine pH. These experiments suggest that a rise in parathyroid hormone levels, resulting from a fall in ionized calcium, is the major mechanism by which bicarbonate administration produces phosphaturia. An increased natriuresis per nephron, as a consequence of extracellular fluid volume expansion, contributes to the phosphaturia. On the other hand, alkalinization of the urine does not play a significant role in the phosphaturia seen after bicarbonate administration.

## INTRODUCTION

The administration of sodium bicarbonate results in increased excretion of phosphorus in the urine in dogs and men despite a fall in serum phosphorus levels (1-4). In view of recent reports (5-7) concerning the effect of extracellular fluid (ECF)[1] volume expansion on the renal reabsorption of phosphate, it seems likely that the effect of infusing sodium bicarbonate on phosphorus excretion is partly due to expansion of ECF volume. The effect of sodium chloride administration on phosphorus excretion is also presumably mediated by ECF volume expansion (5-7). However, Puschett and Goldberg (4) found greater phosphaturia after the infusion of sodium bicarbonate than was observed after the infusion of an equivalent amount of sodium chloride. This suggests that bicarbonate ion per se has a phosphaturic effect.

Another explanation for the phosphaturia of bicarbonate administration relates to alkalinization of the tubular fluid (1, 3, 4). Alkalinization of proximal tubular fluid during bicarbonate infusion would favor a shift from $H_2PO_4^-$ to $HPO_4^=$, resulting in an increase in the concentration of the latter species (8). It has been suggested that the divalent ion, $HPO_4^=$, is less readily reabsorbed by the renal tubules than the monovalent form, $H_2PO_4^-$ (2-4). Therefore, alkalinization of the tubular fluid during bicarbonate administration may be responsible for the phosphaturic effect.

It is also possible that the systemic alkalosis that results from bicarbonate administration by decreasing the

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[1] *Abbreviations used in this paper:* ECF, extracellular fluid; GFR, glomerular filtration rate; PTH, parathyroid hormone; TPTX, thyroparathyroidectomy; TRP, tubular reabsorption of phosphate.

plasma concentration of ionized calcium might invoke increased parathyroid hormone (PTH) secretion, and in turn, decrease the tubular reabsorption of phosphate (TRP).

The present experiments were designed to reexamine the mechanisms by which bicarbonate administration produces phosphaturia. The results indicate that ECF volume expansion and alkalinization of the urine are not quantitatively the major mechanisms responsible for the phosphaturia of bicarbonate administration. Increased PTH levels, the consequence of hypocalcemia, seem to be the main mediator of the phosphaturia seen after bicarbonate infusion.

## METHODS

A total of 39 experiments were performed in 16 adult female mongrel dogs weighing between 12 and 25 kg. The studies were conducted in trained unanesthetized animals, fed a standard dog chow diet and allowed free access to water. Food was removed from the cages 16 h before the clearance studies.

On the day of the experiment, the animals were placed in slings and catheters were inserted into the jugular vein for the collection of blood samples, into the bladder for urine collection, and into a hind limb vein for the infusion of the different solutions. The dogs received 500 ml of tap water via gastric tube and 1 ml/kg body wt of a solution containing 5% creatinine in 2.5% dextrose in water as a prime. Thereafter, a sustaining solution of 5% creatinine in 2.5% dextrose in water was given at a rate of 2.5 ml/min. After 1 h of equilibration, three control clearance periods were obtained. After this, different experimental protocols were used and three additional periods were collected. The experimental maneuvers included:

*Administration of sodium bicarbonate alone.* In five normal dogs, after collection of three control clearance periods, the sustaining solution was changed to a 5% sodium bicarbonate solution containing creatinine, administered at a rate of 4 ml/min to deliver 2.38 meq of $NaHCO_3$/min. After 90 min of equilibration with this solution, three additional clearance periods were collected.

*Administration of sodium bicarbonate and calcium.* In the same group of five dogs, a prime of 90 mg of calcium as calcium gluceptate was given, followed by a sustaining infusion containing calcium in 2.5% dextrose in water, given at a rate of 3 ml/min and calculated to deliver 5 mg of Ca/kg of body wt/h. The amount of bicarbonate infused was the same as in the preceding group of experiments. The calcium and bicarbonate solutions were infused through two catheters placed in different hind limbs. The amount of calcium given was chosen to assure the maintenance of normal ionized calcium levels in these animals.

*Administration of sodium bicarbonate to thyroparathyroidectomized (TPTX) dogs.* In four dogs, studies were conducted after thyroparathyroidectomy. To evaluate the completeness of the surgical procedure, serum calcium levels were obtained before and at 24, 48, and 72 h after surgery. If the animal developed hypocalcemia and clinical manifestations of tetany, the parathyroidectomy was judged to be complete. Mean serum Ca levels were 9.75±0.25 mg/100 ml before surgery and 6.75±0.14 mg/100 ml 48 h after parathyroidectomy ($P < 0.001$). All animals were given a high calcium intake after surgery to maintain serum calcium from falling too markedly. The experimental protocol used in these parathyroidectomized dogs was identical to that described for the group receiving sodium bicarbonate alone.

*Administration of sodium bicarbonate or sodium chloride to normal dogs.* Five dogs were used to study the effects of comparable degrees of volume expansion with either sodium bicarbonate or sodium chloride on phosphorus excretion. In these studies, after 90 min of equilibration with a solution of creatinine and dextrose (see above), two 10-min, control clearance periods were obtained. Immediately after termination of the second period, the dextrose solution was changed to another one containing either sodium bicarbonate or sodium chloride and comparable amounts of creatinine. The solutions were given at the rate of 4 ml/min to deliver 2.38 meq of sodium in each group. Clearance periods were collected at 20-min intervals immediately after the initiation of the infusion of sodium bicarbonate or sodium chloride. The sodium bicarbonate or the sodium chloride infusion studies were performed in the same five animals at a week interval.

*Administration of sodium bicarbonate or sodium chloride to TPTX dogs infused with PTH.* Five TPTX dogs infused with PTH were used to study the effects of comparable degrees of volume expansion with either sodium bicarbonate or sodium chloride on phosphorus excretion. In these experiments, after 90 min of equilibration with a solution of creatinine and dextrose, two control clearance periods were obtained. Thereafter 100 μg of highly purified PTH (Wilson Laboratories, Chicago, Ill.) was given i.v. as a bolus, followed by a solution delivering 1 μg of PTH/min. After 40 min two additional clearance periods were obtained. Thereafter, while the infusion of PTH was continued, the solution was changed to one containing either sodium bicarbonate or sodium chloride given at the same rate as above. Clearance periods were collected at 30-min intervals immediately after the infusion of sodium bicarbonate or sodium chloride. The sodium bicarbonate or the sodium chloride infusion studies were performed in the same five animals at a week interval.

*Administration of hydrochloric acid during continuous sodium chloride administration in dogs that had previously received sodium bicarbonate.* Five dogs were used to study the effects of changes in urinary pH on urinary phosphate excretion. After collecting three experimental clearance periods by the same methodology as with sodium bicarbonate alone, the solution of sodium bicarbonate was changed for another solution containing sodium chloride and creatinine and the same amount of sodium was infused per minute as was being given during the administration of sodium bicarbonate. At the same time, a priming dose of 5 meq of hydrochloric acid/kg of body weight was given, followed by a sustaining infusion that contained 0.2 meq of hydrochloric acid/ml given at a rate of 4 ml/min. After the urine became acid (which usually required 60–90 min), three additional clearance periods were again obtained.

Blood samples were collected in the middle of each clearance period for the determination of serum electrolytes, phosphorus, total calcium, magnesium, and creatinine. Samples for PTH were obtained during the control and experimental periods. Anaerobic samples were collected for the determination of ionized calcium and blood pH. All urine samples were collected under mineral oil for creatinine, electrolytes, phosphate, pH, and cyclic AMP determinations.

*Analytical procedures.* Glomerular filtration rate (GFR) was measured by the exogenous creatinine clearance; phosphate clearance was measured concurrently. Creatinine in urine and plasma was determined according to the method of Bonsnes and Taussky (9), phosphate by the method of

Gomori (10). Calcium and magnesium were measured with an atomic absorption spectrophotometer (IL Model 153, Instrumentation Laboratory, Inc., Lexington, Mass.). Ionized calcium was measured anaerobically with a flow-through electrode (Orion Research Inc., Cambridge, Mass.) (11), and urinary and plasma sodium were measured by an Instrumentation Laboratory flame photometer (Model 143). The pH and $P_{CO_2}$ determinations were made immediately after the collection of blood and urine with an Instrumentation Laboratory microgas analyzer (Model 123). Bicarbonate concentrations in urine were calculated with the Henderson-Hasselbach equation. The $pK$ of the equation was calculated with the formula $pK' = 6.33 - 0.5 \times \sqrt{B}$ where $B$ represents the total cation concentration, estimated in the urine as the sum of Na and K concentrations. The solubility value used was 0.0309. PTH was measured with an antiserum against bovine PTH produced in the chicken. This antibody has been shown to cross-react quite well with dog PTH (12). The sensitivity of the antibody and the methodology for the measurement of PTH levels has been described in detail elsewhere (12). Cyclic AMP in the urine was measured by a modification of the method of Gilman (13), as described previously (14). Standard formulae were used for the calculation of creatinine clearances and fractional excretions of sodium and phosphate. Statistics were calculated with Student's $t$ test for paired data.

## RESULTS

Table I summarizes the effects of sodium bicarbonate administration on urinary phosphate excretion and other parameters of renal function in five dogs. GFR increased from a mean value of 60.6 to 72.5 ml/min after bicarbonate administration. Serum phosphate increased from 3.4 to 3.8 mg/100 ml, total serum calcium fell from 10.1 to 9 mg/100 ml, and ionized calcium decreased from 4.53 to 3.45 mg/100 ml. Mean serum pH rose from 7.41 to 7.60. Urinary phosphate excretion increased from 17.8±4.7 to 784.1±136.3 μg/min and fractional phosphate excretion rose from 0.8 to 29.3% Bicarbonate excretion, fractional sodium excretion, and urinary pH rose significantly after the administration of sodium bicarbonate. Mean PTH values increased from 59.6±4.79 to 230.4±13.04 μleq/ml.

To define the role of the increased PTH levels observed after bicarbonate administration in the phosphaturia, experiments were conducted in which calcium was administered simultaneously with bicarbonate in an effort to prevent any decrease in ionized calcium and consequently any increase in the release of PTH. The results of these experiments are summarized in Table II. Mean GFR rose from 61.4 to 68.3 ml/min and serum phosphate from 3.3 to 4.4 mg/100 ml. Total serum calcium increased from 9.9 to 11.4 mg/100 ml. However, ionized calcium values remained unchanged. Serum pH increased from 7.41 to 7.61, an increase similar to that observed in the dogs given sodium bicarbonate alone. The increases in the urinary excretion of bicarbonate and sodium were comparable to those observed in the group given sodium bicarbonate alone, and urine pH rose from a mean of 6.4 to 7.9. However, urinary phosphate excretion rose from 56±22 to 162.4±27.9 μg/min

TABLE I

*Effect of $NaHCO_3$ Administration on Urinary Phosphate Excretion*

| Dog | GFR | Serum P | Serum Ca | Ionized Ca | Serum pH | $U_{PO_4}V$ | $FE_{PO_4}$ | $U_{HCO_3}V$ | $FE_{Na}$ | Urine Ph | PTH |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *ml/min* | *mg/100 ml* | *mg/100 ml* | *mg/100 ml* | | *μg/min* | *%* | *μeq/min* | *%* | | *μleq/ml* |
| 1 Control | 42.4 | 3.4 | 10.4 | 4.44 | 7.41 | 10.9 | 0.8 | 7.3 | 0.1 | 6.6 | 73.0 |
| Exp. | 49.9 | 3.2 | 9.4 | 3.41 | 7.58 | 547.2 | 34.3 | 974.5 | 11.1 | 7.95 | 234.0 |
| 2 Control | 62.8 | 4.2 | 10.1 | 4.76 | 7.41 | 27.4 | 1.3 | 6.8 | 0.1 | 6.6 | 61.5 |
| Exp. | 71.8 | 5.0 | 8.8 | 3.38 | 7.61 | 1,017.8 | 28.5 | 1,666.0 | 17.8 | 8.0 | 184.5 |
| 3 Control | 70.1 | 3.1 | 9.9 | 4.21 | 7.43 | 31.1 | 1.4 | 7.2 | 0.3 | 6.15 | 55.0 |
| Exp. | 76.3 | 4.0 | 9.2 | 3.65 | 7.60 | 1,189.8 | 39.5 | 999.3 | 12.3 | 8.0 | 248.0 |
| 4 Control | 67.9 | 3.4 | 10.2 | 4.91 | 7.40 | 10.1 | 0.4 | 3.1 | 0.1 | 6.45 | 44.5 |
| Exp. | 93.6 | 4.0 | 8.8 | 3.44 | 7.62 | 670.7 | 19.5 | 1,357.0 | 15.9 | 7.97 | 224.5 |
| 5 Control | 59.9 | 2.9 | 10.0 | 4.45 | 7.40 | 9.6 | 0.5 | 2.1 | 0.1 | 6.3 | 64.5 |
| Exp. | 71.0 | 2.9 | 9.0 | 3.44 | 7.61 | 495.1 | 24.8 | 787.0 | 11.3 | 7.95 | 261.0 |
| Control | | | | | | | | | | | |
| Mean | 60.6 | 3.4 | 10.1 | 4.53 | 7.41 | 17.8 | 0.8 | 5.3 | 0.14 | 6.41 | 59.6 |
| ±SEM | 2.68 | 0.12 | 0.05 | 0.07 | 0.00 | 4.70 | 0.10 | 0.82 | 0.02 | 0.05 | 4.79 |
| Experimental | | | | | | | | | | | |
| Mean | 72.5 | 3.8 | 9.0 | 3.45 | 7.60 | 784.1 | 29.3 | 1,169.0 | 13.7 | 7.96 | 230.4 |
| ±SEM | 3.77 | 0.20 | 0.06 | 0.03 | 0.00 | 136.3 | 1.94 | 97.03 | 0.77 | 0.01 | 13.04 |
| $2P$ | 0.02 | 0.1 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

$U_{PO_4}V$, excretion rate of phosphate; $FE_{PO_4}$, fractional excretion of phosphate; $U_{HCO_3}V$, excretion rate of bicarbonate; $FE_{Na}$, fractional excretion of sodium. The $2P$ values apply to the control vs. experimental mean values for each parameter.

TABLE II

*Effects of $NaHCO_3$ and Calcium Administration on Urinary Phosphate Excretion*

| Dog | GFR | Serum P | Serum Ca | Ionized Ca | Serum pH | $U_{PO_4}V$ | $FE_{PO_4}$ | $U_{HCO_3}V$ | $FE_{Na}$ | Urine pH | PTH |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *ml/min* | *mg/100 ml* | *mg/100 ml* | *mg/100 ml* | | *μg/min* | % | *μeq/min* | % | | *μleq/ml* |
| 1 Control | 46.0 | 2.5 | 10.0 | 3.92 | 7.42 | 9.6 | 0.8 | 3.7 | 0.2 | 6.35 | 76.5 |
| Exp. | 49.3 | 3.9 | 11.8 | 3.93 | 7.64 | 74.1 | 3.6 | 1,003.0 | 15.9 | 7.95 | 80.0 |
| 2 Control | 64.6 | 3.4 | 9.2 | 3.91 | 7.39 | 48.7 | 2.2 | 7.0 | 0.1 | 6.75 | 59.5 |
| Exp. | 70.8 | 4.6 | 10.2 | 3.92 | 7.58 | 213.3 | 5.9 | 1,219.0 | 12.9 | 8.0 | 56.0 |
| 3 Control | 70.7 | 3.7 | 10.6 | 4.89 | 7.41 | 105.7 | 4.2 | 3.9 | 0.1 | 6.25 | 47.0 |
| Exp. | 75.8 | 4.5 | 12.9 | 4.90 | 7.60 | 119.9 | 3.5 | 1,120.0 | 14.3 | 7.87 | 50.0 |
| 4 Control | 64.9 | 3.8 | 10.0 | 3.88 | 7.41 | 7.9 | 0.3 | 4.5 | 0.1 | 6.5 | 48.0 |
| Exp. | 73.4 | 5.2 | 10.5 | 3.83 | 7.62 | 193.5 | 5.0 | 1,174.0 | 15.7 | 8.0 | 47.3 |
| 5 Control | 61.0 | 3.4 | 9.8 | 4.29 | 7.41 | 108.1 | 4.3 | 5.0 | 0.1 | 6.25 | 76.0 |
| Exp. | 71.9 | 4.0 | 11.4 | 4.28 | 7.61 | 211.4 | 6.9 | 923.0 | 12.0 | 7.9 | 75.0 |
| Control | | | | | | | | | | | |
| Mean | 61.4 | 3.3 | 9.9 | 4.17 | 7.41 | 56.0 | 2.4 | 4.8 | 0.13 | 6.4 | 61.4 |
| ±SEM | 2.27 | 0.12 | 0.12 | 0.13 | 0.00 | 22.0 | 0.46 | 0.50 | 0.02 | 0.07 | 6.45 |
| Experimental | | | | | | | | | | | |
| Mean | 68.3 | 4.4 | 11.4 | 4.17 | 7.61 | 162.4 | 4.9 | 1,088.0 | 14.2 | 7.9 | 61.7 |
| ±SEM | 2.59 | 0.12 | 0.26 | 0.11 | 0.00 | 27.9 | 0.38 | 38.07 | 0.43 | 0.02 | 6.67 |
| *2P* | 0.05 | <0.001 | <0.001 | NS | <0.001 | 0.05 | 0.001 | <0.001 | <0.001 | <0.001 | NS |

For definition of abbreviations see Table I.

and fractional phosphate excretion increased from 2.4 to only 4.9%, as compared to an increase to 29.3% in the group that did not receive calcium. In the dogs receiving calcium, no change in PTH levels was observed after bicarbonate administration. Mean values for PTH were 61.4±6.45 μleq/ml during control periods and 61.7± 6.67 μleq/ml after the administration of sodium bicarbonate and calcium.

Table III summarizes the effects of bicarbonate administration to parathyroidectomized dogs. Dogs subjected to parathyroidectomy were studied 72 h after the surgical procedure. In this group of dogs GFR increased

TABLE III

*Effect of $NaHCO_3$ Administration on Urinary Phosphate Excretion in TPTX Dogs*

| Dog | GFR | Serum P | Serum Ca | Ionized Ca | Serum pH | $U_{PO_4}V$ | $FE_{PO_4}$ | $U_{HCO_3}V$ | $FE_{Na}$ | Urine pH |
|---|---|---|---|---|---|---|---|---|---|---|
| | *ml/min* | *mg/100 ml* | *mg/100 ml* | *mg/100 ml* | | *μg/min* | % | *μeq/min* | % | |
| 1 Control | 62.7 | 4.1 | 7.7 | 3.79 | 7.39 | 13.1 | 0.5 | 6.2 | 0.1 | 6.4 |
| Exp. | 63.5 | 3.8 | 7.1 | 3.03 | 7.60 | 5.7 | 0.3 | 1,097.0 | 13.0 | 8.0 |
| 2 Control | 77.8 | 3.3 | 7.4 | 3.24 | 7.44 | 16.8 | 0.7 | 9.6 | 0.4 | 6.4 |
| Exp. | 82.6 | 4.2 | 6.4 | 2.87 | 7.62 | 88.7 | 2.6 | 1,518.0 | 12.3 | 8.0 |
| 3 Control | 80.8 | 4.4 | 7.9 | 4.01 | 7.41 | 36.7 | 0.7 | 9.0 | 0.1 | 6.5 |
| Exp. | 93.1 | 5.3 | 7.1 | 2.96 | 7.67 | 377.3 | 7.6 | 1,553.0 | 11.6 | 8.15 |
| 4 Control | 78.1 | 3.8 | 7.3 | 2.85 | 7.35 | 11.8 | 0.4 | 6.7 | 0.1 | 6.7 |
| Exp. | 92.5 | 4.5 | 6.0 | 2.19 | 7.58 | 264.5 | 6.3 | 1,080.0 | 12.0 | 7.95 |
| Control | | | | | | | | | | |
| Mean | 74.8 | 3.9 | 7.5 | 3.47 | 7.41 | 19.6 | 0.6 | 7.8 | 0.17 | 6.5 |
| ±SEM | 2.23 | 0.14 | 0.11 | 0.12 | 0.01 | 5.8 | 0.09 | 0.87 | 0.03 | 0.06 |
| Experimental | | | | | | | | | | |
| Mean | 84.7 | 4.5 | 6.7 | 2.76 | 7.62 | 184.1 | 4.5 | 1,339.0 | 12.1 | 8.0 |
| ±SEM | 3.52 | 0.18 | 0.10 | 0.04 | 0.01 | 84.0 | 0.91 | 92.47 | 0.19 | 0.03 |
| *2P* | 0.025 | 0.01 | <0.001 | <0.001 | <0.001 | 0.05 | 0.001 | <0.001 | <0.001 | <0.001 |

For definition of abbreviations, see Table I.

from a mean of 74.8 to 84.7 ml/min after bicarbonate administration. There was an increase in plasma phosphate and a significant decrease in both total and ionized calcium after bicarbonate administration. Blood pH rose from a mean of 7.41 to 7.62. Urinary excretion of phosphate rose from 19.6±5.8 μg/min to 184.1±84.0 μg/min and fractional excretion of phosphate increased from 0.6% to 4.5% after bicarbonate administration. The increase in bicarbonate excretion and fractional sodium excretion in these animals was comparable to that seen in normal dogs given sodium bicarbonate. Urine pH increased from a mean of 6.5 to 8.0 after the administration of sodium bicarbonate.

Fig. 1 depicts the mean values for fractional phosphate and sodium excretion before and after bicarbonate administration in three groups of dogs. Despite comparable natriuresis, the phosphaturia was markedly blunted in normal dogs receiving sodium bicarbonate and calcium and in parathyroidectomized dogs.

The relationship between fractional phosphate excretion and PTH levels in plasma is presented in Fig. 2. In normal dogs bicarbonate administration resulted in a marked rise in PTH levels and fractional phosphate excretion. In normal dogs receiving calcium and bicarbonate PTH levels did not change and phosphaturia was markedly decreased. In the parathyroidectomized dogs, the phosphaturia observed after bicarbonate administration was small and PTH levels were undetectable.

The effects of similar degrees of ECF volume expansion produced by the administration of sodium bicarbonate or sodium chloride on phosphate excretion were studied in five normal dogs. The results of these ex-

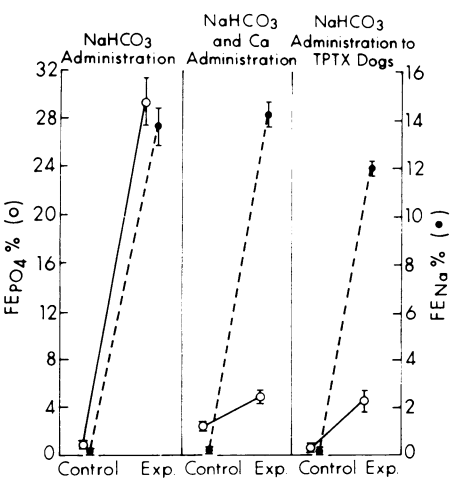


FIGURE 1 Fractional phosphate (solid lines) and sodium (broken lines) excretion before and after the administration of bicarbonate or bicarbonate plus calcium to normal dogs, or the administration of bicarbonate to TPTX dogs. Each point is the mean of results obtained in either four or five dogs.

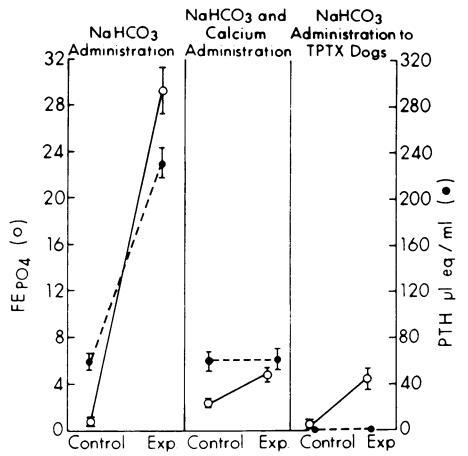


FIGURE 2 Comparison of fractional phosphate excretion (solid lines) and plasma PTH levels (broken lines) in normal dogs receiving bicarbonate, or calcium plus bicarbonate, and in TPTX dogs receiving bicarbonate. In the TPTX dog PTH levels were undetectable.

periments are summarized in Figs. 3 and 4. The administration of sodium bicarbonate resulted in a significant decrease in ionized calcium after 20-40 min and a marked increase in the levels of cyclic AMP in the urine was observed 40 min after the start of the infusion. The rise in excretion of cyclic AMP in the urine persisted for the remainder of the study. Phosphate excretion increased markedly at 60 min and rose progressively over the next 90 min. The increase in cyclic AMP excretion clearly preceded the increase in phosphate excretion. The results obtained with the administration of comparable amounts of sodium chloride were somewhat different (Fig. 4). The fall in ionized calcium was significantly smaller ($P < 0.01$) than that observed with the administration of sodium bicarbonate and there was a decrease rather than an increase in the urinary excretion of cyclic AMP. The increase in phosphate excretion was delayed and the magnitude of the rise at any time interval was smaller than that observed after the administration of comparable amounts of sodium bicarbonate. Significant differences ($P < 0.01$) in phosphate excretion after saline and bicarbonate administration were observed at 60, 80, 100, and 150 min. No significant change in the levels of endogenous PTH was observed with saline administration during the course of these experiments. On the other hand, with sodium bicarbonate administration there was a progressive increase in PTH levels. Comparable degrees of natriuresis were observed with sodium bicarbonate or sodium chloride administration. Values for fractional sodium excretion were 0.1-0.2% in the control periods and rose to 10.5 and 10.9% with sodium bicarbonate and to 10.1 and 12.1% with sodium chloride after 100 and 150 min of infusion, re-

spectively. The results of these experiments indicate that the administration of sodium bicarbonate produces a greater phosphaturia than the infusion of sodium chloride, despite comparable natriuresis and presumably similar degrees of ECF volume expansion.

To delineate the role of urine pH in the phosphaturia of bicarbonate administration, experiments were carried out in which PTH levels and ECF volume expansion were comparable, but urine pH differed. The results of administering identical amounts of sodium as sodium bicarbonate or sodium chloride to TPTX dogs infused with PTH throughout the experiment are presented in Table IV. Plasma phosphate levels and fractional excretion of sodium and phosphate were comparable when dogs were expanded with sodium bicarbonate or sodium chloride. Urine pH, on the other hand, was greater by about 1 pH unit in the dogs receiving bicarbonate. These results suggest that urinary alkalinization does not play a major role in the phosphaturia of sodium bicarbonate administration.

To further evaluate the effects of changes in urinary pH per se on phosphate excretion, experiments were conducted in which the solution being infused was changed to sodium chloride after an initial period of bicarbonate administration. The amount of sodium delivered was the same. Simultaneously, hydrochloric acid was administered so as to decrease blood pH and urinary pH. Table V shows the effects of bicarbonate administration and subsequent sodium chloride and hydrochloric acid administration on urinary phosphate excretion in five dogs. Mean GFR values increased from 65.8 to 74.8 ml/min after bicarbonate administration and to 79.3 after sodium chloride and hydrochloric acid. Plasma phosphate did not change significantly and plasma calcium decreased during continuous sodium administration. Ionized calcium decreased from a mean of 4.6 to 3.6 mg/100 ml after bicarbonate and values increased again to 5 mg/100 ml after sodium chloride and hydrochloric acid administration. Serum pH increased from 7.44 to 7.63 after bicarbonate and decreased to 7.34 after sodium chloride and hydrochloric acid administration. Urinary bicarbonate increased from 7.6 to 1,181 μeq/min and decreased to 26.9 μeq/min after sodium chloride and hydrochloric acid. Fractional excretion of sodium rose from 0.2 to 15.2% after bicarbonate and 12.5% after sodium chloride and hydrochloric acid. Urine pH increased from 6.30 to 7.90 after bicarbonate and decreased again to 6.60 after sodium chloride and hydrochloric acid. PTH levels, which had risen from a mean control value of 59.6 μleq/ml to 257 μleq/ml after bicarbonate, decreased to 105 μleq/ml during sodium chloride and hydrochloric acid. However, this latter value was significantly different ($P < 0.01$) from the mean PTH value of 59.6 obtained during the control periods. Despite a marked decrease in urine pH from 7.9 to 6.60, urinary phosphate excretion, which had risen from 39.1 to 982.9 μg/min during bicarbonate administration, remained high at 760.8 μg/min during sodium chloride and hydrochloric

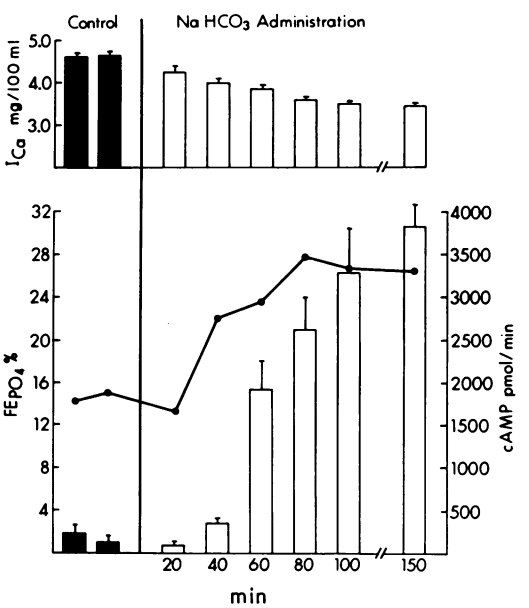


FIGURE 3 Effects of sodium bicarbonate administration on ionized calcium ($I_{Ca}$), fractional phosphate excretion ($FE_{PO_4}$), and cyclic AMP excretion (●——●) in five normal dogs. Two control clearance periods were obtained before the administration of $NaHCO_3$ was begun.

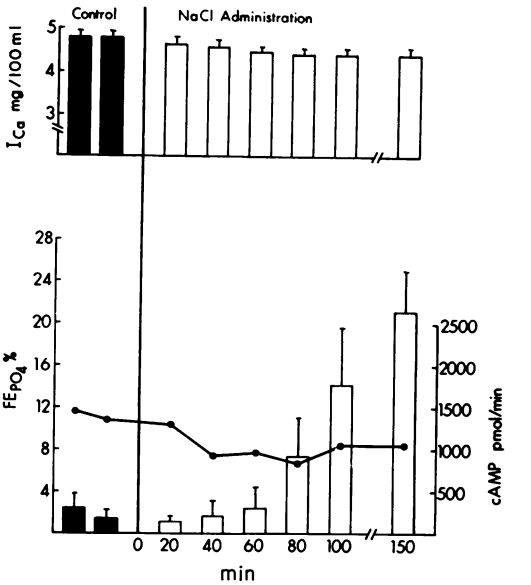


FIGURE 4 Effects of sodium chloride administration on ionized calcium ($I_{Ca}$), fractional phosphate excretion ($FE_{PO_4}$), and cyclic AMP excretion (●——●). The dogs were the same used in the studies reported in Fig. 3.

TABLE IV

*Effect of Infusing Equivalent Amounts of Sodium as NaCl or $NaHCO_3$ on Sodium and Phosphate Excretion in TPTX Dogs Given PTH*

| | GFR | | $P_{PO_4}$ | | $FE_{Na}$ | | $FE_{PO_4}$ | | Urine pH | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NaCl | $NaHCO_3$ | NaCl | $NaHCO_3$ | NaCl | $NaHCO_3$ | NaCl | $NaHCO_3$ | NaCl | $NaHCO_3$ |
| | *ml/min* | | *mg/100 ml* | | % | | % | | | |
| Control | 52.2 ±6.8 | 53.8 ±7.1 | 4.4 ±0.24 | 3.94 ±0.34 | 0.23 ±0.01 | 0.09 ±0.03 | 5.32 ±2.80 | 4.32 ±2.40 | 6.32 ±0.34 | 6.32 ±0.10 |
| PTH Infusion | 60.7 ±9.4 | 64.7 ±10.5 | 3.22 ±0.36 | 3.08 ±0.33 | 0.58 ±0.20 | 0.40 ±0.11 | 34.8 ±6.6 | 25.0 ±7.3 | 6.82 ±0.39 | 6.73 ±0.19 |
| PTH infusion continued. Start NaCl or $NaHCO_3$ infusion at 4 ml/min (2.38 meq of sodium delivered/min). | | | | | | | | | | |
| Time | | | | | | | | | | |
| 0–30 min | 67.0 ±8.7 | 67.1 ±12.8 | 2.86 ±0.25 | 2.76 ±0.26 | 1.88 ±0.41 | 3.81 ±1.00 | 37.1 ±5.9 | 29.0 ±8.5 | 6.87 ±0.21 | 7.05 ±0.26 |
| 30–60 min | 75.8 ±9.6 | 64.2 ±8.3 | 2.78 ±0.24 | 2.65 ±0.22 | 5.61 ±0.60 | 8.45 ±0.99 | 41.3 ±7.6 | 35.3 ±8.4 | — | — |
| 60–90 min | 78.4 ±8.4 | 62.3 ±6.8 | 2.88 ±0.24 | 2.98 ±0.26 | 9.39 ±2.38 | 13.3 ±0.51 | 50.0 ±5.5 | 42.7 ±8.3 | 6.90 ±0.13 | 7.92 ±0.18 |
| 90–120 min | 76.0 ±7.5 | 60.3 ±5.6 | 2.90 ±0.21 | 3.07 ±0.28 | 12.9 ±2.8 | 15.5 ±0.9 | 57.2 ±4.2 | 44.2 ±9.6 | — | — |
| 120–150 min | 77.8 ±4.8 | 60.4 ±4.8 | 3.06 ±0.29 | 3.04 ±0.31 | 14.4 ±3.0 | 18.5 ±1.9 | 57.8 ±4.4 | 55.0 ±5.5 | 6.88 ±0.09 | 7.93 ±0.09 |

The results represent the mean values and SEM for five dogs. The control values are the mean of two clearance periods. The PTH infusion values are the mean of two clearance periods obtained after 40 min of equilibration with PTH (see Methods). After the start of the NaCl or $NaHCO_3$ infusion, clearance periods were collected at 30-min intervals without an equilibration period.

acid administration. Fractional excretion of phosphate rose from 1.9 to 36.5% after bicarbonate and remained at 28.1% during sodium chloride and hydrochloric acid. These data strongly suggest that changes in urinary pH did not markedly alter the excretion of phosphate in these dogs.

TABLE V

*Effects of $NaHCO_3$ and NaCl Plus HCl Administration on Urinary Phosphate Excretion*

| | GFR | Serum P | Serum Ca | Serum $I_{Ca}$ | Serum pH | $U_{PO_4}V$ | $FE_{PO_4}$ | $U_{HCO_3}V$ | $FE_{Na}$ | Urine pH | PTH |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *ml/min* | *mg/100 ml* | *mg/100 ml* | *mg/100 ml* | | *μg/min* | % | *μeq/min* | % | | *μleq/ml* |
| 500 ml of tap water p.o. Creatinine prime: 1 ml/kg body wt (50 mg/kg). Start sustaining infusion of a solution of creatinine in 2.5% dextrose in water at 2.5 ml/min. | | | | | | | | | | | |
| Control | | | | | | | | | | | |
| Mean | 65.8 | 3.3 | 9.9 | 4.6 | 7.44 | 39.1 | 1.9 | 7.6 | 0.2 | 6.30 | 59.6 |
| ±SEM | 3.1 | 0.06 | 0.04 | 0.08 | 0.06 | 10.6 | 0.51 | 1.34 | 0.006 | 0.02 | 4.7 |
| Change sustaining infusion to a solution of creatinine in 5% $NaHCO_3$ (595 meq/liter) at 4 ml/min. | | | | | | | | | | | |
| $NaHCO_3$ | | | | | | | | | | | |
| Mean | 74.8 | 3.7 | 9.1 | 3.6 | 7.63 | 982.9 | 36.5 | 1181.0 | 15.2 | 7.90 | 257.6 |
| ±SEM | 4.4 | 0.16 | 0.08 | 0.08 | 0.01 | 60.1 | 1.24 | 59.4 | 0.80 | 0.01 | 21.1 |
| Change sustaining infusion to a solution of creatinine in NaCl (595 meq/liter) at 4 ml/min plus HCl 0.2 meq/ml. HCl prime: 5 meq/kg body wt. | | | | | | | | | | | |
| NaCl plus HCl | | | | | | | | | | | |
| Mean | 79.3 | 3.4 | 8.6 | 5.0 | 7.34 | 760.8 | 28.1 | 26.9 | 12.5 | 6.60 | 105.0* |
| ±SEM | 8.5 | 0.14 | 0.13 | 0.06 | 0.01 | 74.4 | 1.59 | 4.82 | 0.41 | 0.04 | 17.7 |
| 2*P* | NS | NS | 0.01 | <0.001 | <0.001 | 0.025 | <0.001 | <0.001 | 0.01 | <0.001 | 0.001 |

For definition of abbreviations, see Table I. $n = 5$. The 2 *P* compares the NaCl plus HCl means values with the $NaHCO_3$ mean values.
* Significantly different from mean control value ($P < 0.01$).

TABLE VI

*Effects of Different Experimental Maneuvers on Absolute Phosphate Reabsorption*

| | GFR | $FL_{PO_4}$ | $U_{PO_4}V$ | TRP | TRP/100 ml GFR |
|---|---|---|---|---|---|
| | *ml/min* | *μg/min* | *μg/min* | *μg/min* | *μg/min* |
| Normal dogs | | | | | |
| Control (Table I) | 60.6 | 2,060.4 | 17.8 | 2,042.6 | 3,387.1±218.4 |
| $HCO_3^-$ | 72.5 | 2,755.0 | 784.1 | 1,970.9 | 2,715.9 ± 299* |
| Control (Table V) | 65.8 | 2,171.4 | 39.1 | 2,132.3 | 3,240.5±211.4 |
| $HCO_3^-$ | 74.8 | 2,767.6 | 982.9 | 1,784.7 | 2,386.0±278.6* |
| HCl | 79.3 | 2,696.2 | 760.8 | 1,935.4 | 2,440.6±261.3 |
| Control (Table II) | 61.4 | 2,026.2 | 56.0 | 1,970.2 | 3,208.8±220.8 |
| $HCO_3^-$ + Ca | 68.3 | 3,005.2 | 162.4 | 2,842.8 | 4,162.2±225.6 |
| TPTX dogs | | | | | |
| Control (Table III) | 74.8 | 2,921.1 | 19.6 | 2,901.5 | 3,879.0±230.1 |
| $HCO_3^-$ | 84.7 | 3,811.5 | 184.1 | 3,627.4 | 4,282.6±233.2 |

$FL_{PO_4}$, filtered load of phosphate.

* Significantly different from control ($P < 0.01$).

Table VI summarizes the effects of the different experimental maneuvers on the tubular reabsorption of phosphate (TRP). Two groups of dogs were studied before and after bicarbonate administration. In both of these groups TRP decreased slightly. However, when TRP values were expressed per 100 ml of GFR, there was a significant decrease ($P < 0.01$) after bicarbonate administration in normal dogs. After hydrochloric acid administration, TRP did not return to control values and when expressed per 100 ml of GFR, the absolute values were similar to those observed during bicarbonate administration. On the other hand, in the group of normal dogs that received bicarbonate plus calcium or in the dogs that received bicarbonate after parathyroidectomy, there was an increase in absolute values for TRP. In addition, when the values were expressed per 100 ml of GFR, TRP rose from 3,208 to 4,162 μg/min for normal dogs given bicarbonate plus calcium and from 3,879 to 4,283 μg/min for parathyroidectomized dogs given bicarbonate alone. These results reflect the increase in filtered load of phosphate that occurred in all groups. However, in the animals in whom parathyroid hormone was absent or did not rise because of administration of calcium concomitantly with bicarbonate, most of the increment in filtered load of phosphate was reabsorbed. On the other hand, when bicarbonate administration resulted in an increase in PTH levels, most of the increment in filtered load of phosphate was excreted in the final urine.

## DISCUSSION

The present studies clearly demonstrate that infusion of sodium bicarbonate results in increased phosphate excretion in the urine. Bicarbonate administration resulted in a fall in both total and ionized calcium. The decrease in total serum calcium is probably due to increased ECF volume with dilution of existing calcium. The change in ionized calcium is probably the consequence of both dilution (15) and an increase in plasma pH that would tend to decrease ionized calcium in plasma (11). The decrease in ionized calcium triggers the release of PTH, and PTH levels increased almost fivefold after the administration of sodium bicarbonate (see Table I). Since PTH has been clearly shown to increase phosphate excretion, it is reasonable to postulate that part of the increased phosphaturia after bicarbonate administration was mediated by increased levels of PTH. In the experiments in which calcium was administered together with bicarbonate (see Table II), ionized calcium remained unchanged, PTH levels measured before and after sodium bicarbonate administration did not change at all, and the degree of phosphaturia decreased markedly. To further evaluate the contribution of PTH levels to the phosphaturia of bicarbonate administration, additional studies were conducted in parathyroidectomized dogs. In this group of animals administration of sodium bicarbonate in amounts identical to those given to normal dogs resulted again in only modest phosphaturia. These data suggest that a major component of the phosphaturia of bicarbonate administration is mediated by PTH, released as a consequence of a decrease in ionized calcium. Similar urine excretion rates for Na and bicarbonate were present when normal dogs were given sodium bicarbonate alone or sodium bicarbonate plus calcium or when parathyroidectomized dogs were given sodium bicarbonate. Similar changes in blood pH

and urine pH were also observed, suggesting that changes in urine pH, bicarbonate excretion, or sodium excretion were not directly responsible for most of the phosphaturia observed after bicarbonate administration. It is evident, however, that a modest phosphaturia occurred even in the absence of parathyroid glands or in the presence of constant levels of PTH during bicarbonate and calcium administration. This phosphaturia probably resulted from decreased TRP as a consequence of ECF volume expansion (5-7, 16, 17) produced by the administration of sodium bicarbonate. When the effects of administering identical amounts of sodium as sodium bicarbonate or sodium chloride on phosphorus excretion were compared, a greater phosphaturia was observed after the administration of sodium bicarbonate. In addition, while there was a significant increase in the levels of immunoreactive PTH in plasma during bicarbonate administration over 150 min, there was a mild but not significant increase in the levels of PTH during sodium chloride administration. Similar results have been reported in sheep by Kaplan et al. (18). Sodium bicarbonate administration resulted in an increase in the levels of cyclic AMP in the urine. This increase preceeded the increase in phosphorus excretion. With sodium chloride, on the other hand, there was a decrease rather than an increase in cyclic AMP levels, and the rise in phosphaturia observed was delayed and smaller than that observed with sodium bicarbonate. The similar degree of natriuresis observed with the administration of sodium chloride or sodium bicarbonate suggests that the degree of ECF volume expansion was comparable in the two situations. The differences in phosphaturia, therefore, cannot be ascribed to differences in ECF volume expansion. It has been reported recently (19) that proximal phosphorus reabsorption is decreased to the same extent in normal and TPTX dogs during expansion of the ECF volume with sodium chloride. However, a significant phosphaturia occurred only when PTH was present. These data indicate that, even in the absence of PTH, proximal tubule phosphate reabsorption can be depressed by NaCl administration; however, increased reabsorption of phosphorus in distal segments prevents an increase in phosphaturia when PTH is absent or does not rise. With continuous ECF volume expansion and constant levels of PTH, the compensatory reabsorption of phosphorus in distal segments may be partially blocked and increased phosphaturia may result. This postulate is in agreement with recent observations suggesting that the increase in phosphorus excretion accompanying ECF volume expansion with sodium chloride is not dependent on an increase in serum PTH concentrations (20). In the present experiments bicarbonate alone, bicarbonate plus calcium, and bicarbonate administration to TPTX dogs may have resulted in similar decreases in phosphate reabsorption in the proximal tubule as those observed with sodium chloride administration. However, only when the levels of circulating PTH rose (as in normal dogs given sodium bicarbonate alone) was there a significant phosphaturia. Hence, most of the effects of PTH in mediating the phosphaturia of bicarbonate administration may occur in distal segments.

It is also possible that any changes induced by bicarbonate in the reabsorption of phosphate in the proximal tubule via a shift in the relative concentrations of $H_2PO_4^-$ and $HPO_4^=$ may not result in phosphaturia if the levels of PTH do not increase. Presumably, the three groups of dogs given sodium bicarbonate had similar changes in intratubular pH in the proximal tubule; however, only in those animals in which the levels of PTH rose was there a significant phosphaturia. Consequently, while alkalinization of the tubular fluid may be an important factor in controlling phosphorus reabsorption in the proximal tubule (8), it may not play an important role in the overall excretion of phosphate, and an increase in the levels of PTH is required for bicarbonate administration to produce marked phosphaturia.

Administration of sodium bicarbonate to TPTX dogs infused with exogenous PTH resulted in phosphaturia identical to that observed when the dogs received sodium chloride under identical conditions. However, the pH of the urine was consistently higher in the animals receiving sodium bicarbonate than in the dogs infused with sodium chloride, indicating that urine pH presumably does not play a major role in the phosphaturia of bicarbonate administration.

The results presented in Table V also suggest that the pH of the urine apparently is not a major factor in the phosphaturia of bicarbonate administration. In these experiments, after three control periods, sodium bicarbonate was administered and marked phosphaturia occurred. Thereafter sodium chloride and hydrochloric acid were given. This resulted in a marked decrease in urine pH and bicarbonate excretion. Despite the marked decrease in urine pH and in bicarbonate excretion after hydrochloric acid, the fractional excretion of phosphate, which had risen markedly after bicarbonate administration, did not fall appreciably. A previous report (3) demonstrated that administration of ammonium chloride by gastric tube to dogs receiving sodium bicarbonate resulted in a marked decrease in phosphaturia and that subsequent readministration of bicarbonate resulted again in increased phosphaturia. In the present experiments the infusion of sodium was continued during the administration of hydrochloric acid, and despite a marked change in urine pH, the phosphaturia persisted. This persistent phosphaturia probably can be attributed to the fact that PTH levels did not return to normal levels despite an

increase in ionized calcium. At the same time, fractional excretion of sodium remained at 12.5% during sodium chloride and hydrochloric acid administration. These results would tend to suggest that alkalinization of the urine per se is not the major mechanism by which sodium bicarbonate administration produces phosphaturia. While it is possible that intratubular pH plays a role in phosphate reabsorption, as recently suggested (8), the major mechanism by which sodium bicarbonate administration produces phosphaturia seems to be related to the release of PTH as a consequence of alterations in serum ionized calcium.

Administration of sodium bicarbonate and calcium to normal dogs or administration of sodium bicarbonate alone to parathyroidectomized animals also resulted in a significant phosphaturia, although the quantitative excretion of phosphate was not as great as that observed in normal animals receiving sodium bicarbonate alone. It is evident, therefore, that volume expansion per se, as a consequence of sodium bicarbonate administration, produces phosphaturia either by decreasing sodium and fluid reabsorption or through some other mechanism. ECF volume expansion also contributes to the phosphaturia observed after sodium bicarbonate administration.

In summary, the present studies suggest that a major component responsible for the phosphaturia of sodium bicarbonate administration relates to the release of endogenous PTH as a consequence of changes in serum ionized calcium. An increased natriuresis per nephron, as a consequence of ECF volume expansion, contributes to the phosphaturia. On the other hand, alkalinization of the urine does not seem to play a significant role in the phosphaturia of bicarbonate administration.

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