THE EFFECT OF CALCIUM CARBONATE, ALUMINUM PHOSPHATE, AND ALUMINUM HYDROXIDE ON MINERAL EXCRETION IN MAN [1]

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INTRODUCTION

In order to elucidate further the mechanism of the alkalosis observed during the alkali treatment of peptic ulcer, a detailed study of mineral excretion following the administration of relatively non-absorbable antacids seemed desirable. Hence, an investigation of the influence of calcium carbonate on mineral excretion in man was undertaken, and its action compared with the effects of aluminum hydroxide and aluminum phosphate, two non-absorbable compounds.

METHOD OF STUDY

Studies were carried out in 2 adult men and one female with peptic ulcer, in all of whom previous observations had indicated renal function to be satisfactory. A special metabolic ward and nursing staff were utilized. The patients were maintained on special ulcer diets (Tables I and II), without change, during the entire experiment. Chloride-free distilled water was used for drinking purposes. The daily fluid intake averaged approximately 3000 cc. The daily urinary output varied from 1200 to 3000 cc. There was no significant change in body weight during the entire experiment. The only medication permitted, aside from the substances studied, was the occasional administration of cascara to facilitate daily bowel activity,[2] and the use of mild sedatives for sleep. An interval of 4 to 6 days was allowed for adjustment to the diet, prior to the control observation. Mineral excretion was studied over periods of 4 days duration each. Ten grains of carmine were given at the onset of each period and repeated 96 hours later; the feces obtained between the carmine markers was collected for analysis. The 4-day collection was mixed thoroughly; accurately weighed 2.0 gram samples were taken for the various determinations. All analyses were done in duplicate or triplicate.

The chemical studies of the feces were carried out as follows:

The calcium content was determined by first boiling the sample with concentrated nitric acid and potassium permanganate. After cooling, the mixture was diluted with distilled water to 100 (or 200) cc. volume and adjusted to the proper pH (4.6 to 5.2), using Brom Cresol green as indicator. The procedure then followed was the same employed for blood serum (1). (Calculation: $\frac{\text{Titer}}{2} \times 10$ equals mgm. Ca per 1 gram feces.)

TABLE I

Composition of diet employed in case A. K.
(Daily values)

	Special diet	Standard values for sedentary adult female
Carbohydrates	198	
Protein	72	
Fat	104	
Calories	2016	
Chloride (mgm.)	2974	
Sodium (mgm.)	2029	
Potassium (mgm.)	3052	
Calcium (mgm.)	1159	800
Phosphate (mgm.)	1342	1320
Iron (mgm.)	10.5	12
Vitamin A (I.U.)	9570	5000
Thiamin (mgm.)	1.014	1.2
Riboflavin (mgm.)	2.51	1.8
Ascorbic Acid (mgm.)	78	70
Vitamin D (I.U.)	38	

TABLE II

Composition of diet employed in cases C. D. and W. G.
(Daily values)

	Special diet	Standard values 70 kgm. adult male
Carbohydrate	266	
Protein	58	
Fat	163	
Calories	2763	
Chloride (mgm.)	3047	
Sodium (mgm.)	2014	
Calcium (mgm.)	1140	800
Phosphate (mgm.)	1300	1320
Iron (mgm.)	7	12
Vitamin A (I.U.)	6200	5000
Thiamin (mgm.)	1.0	1.5
Riboflavin (mgm.)	1.2 to 2.4	2.2
Ascorbic acid (mgm.)	5 to 30	75
Vitamin D (I.U.)	160 to 385	

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[2] There was no instance of diarrhea.

For determining the chloride content, 5.0 cc. of a 0.1 N solution of silver nitrate were added to 2.0 gram samples of feces and the mixtures allowed to stand for several hours. Digestion then was carried out as with the calcium analysis. The mixtures were cooled, 5 per cent ferric alum added as indicator, and then titrated with a 0.1 N solution of potassium thiocyanate. (Calculation: $\frac{5 - \text{titer} \times 3.5}{2}$ equals mgm. chloride ion in 1.0 gram feces.)

The phosphate in the feces was determined in Case C. D. by wet ashing of the samples with nitric and sulphuric acids and, when necessary, superoxal. The mixtures then were cooled, adjusted to known volume with distilled water, and the phosphate content measured by the Fiske-Subbarow method (2) as adapted for the Evelyn photoelectric colorimeter. In Cases A. K. and W. G., the samples of feces were ashed in a muffle furnace and the analyses then carried out as above.

In Case A. K., the sodium content of the feces was measured by the following procedure: 20 cc. of ferric sulphate and 3 cc. of concentrated sulphuric acid were added to 10 gram samples. The mixtures were dried in an oven and then ashed in a muffle furnace. The ash was taken up in 10 cc. of distilled water and 3 cc. aliquots were analyzed for sodium by the method employed for blood (3).

The potassium content of the feces in Case A. K. was determined as follows: 2.0 gram samples of feces were dried in an oven and then ashed in a muffle furnace. The ash was taken up in 10 cc. of distilled water and 1.0 cc. aliquots were analyzed by the procedure used for blood (4).

Twenty-four hour collections of urine were obtained throughout the study. The urine was voided directly into a bottle containing toluene as a preservative and a layer of mineral oil to prevent the escape of CO_2 (5). The urine was kept in an icebox and analyzed at the end of each collection for the following: (*a*) pH, using the Beckman pH meter, (*b*) chloride (6), (*c*) calcium, (*d*) phosphate, and (*e*) amino-nitrogen plus ammonium salts (7).[3]

The sodium content of the urine in Case A. K. was measured by the same technique employed for blood, modified as to the volume used; ferric salt was added in amounts sufficient to prevent interference by phosphates. The urinary potassium was determined as follows: 2.0 cc. samples of urine were ashed in a muffle furnace and the ash taken up in 10 cc. of distilled water; 2.0 cc. aliquots then were concentrated and analyzed by the method employed for blood.

Simultaneous studies were made of the serum electrolytes. Venous blood drawn under oil was utilized for the following analyses: chloride, CO_2 (8), pH (9), calcium, and phosphorus. Oxalated blood was used for the measurement of the blood urea nitrogen (10). The following additional data were obtained in Case A. K.: cell volume, serum water (11), blood sodium, potassium, and total base (12), and the urea clearance (13).

After control values had been established, the effects of calcium carbonate, aluminum phosphate, and aluminum hydroxide were studied in individual periods. A 4 to 5 day interval for adjustment to the added medication was allowed prior to the analyses. Calcium carbonate was administered in 2.0 gram amounts 10 times daily: 80 grams (400 m.eq.) were thus given in a 4-day period, containing 32 grams of calcium ion. One hundred and five cc. of aluminum phosphate were administered daily in divided doses; a total of 420 cc. (35 m.eq. HPO_4) in a 4-day period containing, by analysis, 386 mgm. of chloride, 4368 mgm. of phosphate, and 2625 mgm. of aluminum (14). One hundred and five cc. of aluminum hydroxide were given daily in divided doses; a total of 420 cc. in a 4-day period containing 386 mgm. of chloride and 4716 mgm. of aluminum. Complete mineral balances were not obtained since no attempt was made to measure the loss in the insensible perspiration or sweat. This loss presumably was constant, however, through the various periods in each case, since fairly constant conditions were maintained. The results are considered exclusively in relation to the individual control values.

RESULTS

The complete data are recorded in Tables III and IV.

DISCUSSION

(*1*) *Calcium carbonate*

The ingestion of 400 m.eq. daily, as calcium carbonate, was roughly accounted for by increase in total outgo, almost entirely in the stools. The increase in excretion in the urine was, for the patient A. K., only 7.3 m.eq., and for the other 2 patients, C. D. and W. G., 13.9 m.eq. and 14.1 m.eq., respectively. As was to be expected with the large addition to calcium excretion in the stools (15), there was an increase of HPO_4 in the feces. For A. K. and W. G., the outgo in the stools was about double the fore-period values. These increments were, however, somewhat more than offset by a decrease in the removal of HPO_4 in the urine. The increase in calcium and decrease in HPO_4 excretion in the urine together markedly reduced the requirement for ammonium production as noted in Table III. Other compounds of acid-base excretion, however, are related to the change in ammonium production. For the patient A. K., a small increase in Na and decrease in Cl, and a considerable reduction of K, were found. The re-

[3] Referred to in the text as "ammonia" for the purpose of simplicity.

TABLE III

Effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide on mineral excretion in man

Subject	Periods of study (4-day)	Urine							Feces					Total outgo				
		pH	NH_4	Na	K	Ca	HPO_4*	Cl	Na	K	Ca	HPO_4*	Cl	Na	K	Ca	HPO_4*	Cl
		m.eq. per 24 hours							*m.eq. per 24 hours*					*m.eq. per 24 hours*				
A. K. Unit No. 148736 Female Age 63 Gastric ulcer	Fore-period, I	6.16	34.3	54.5		11.6	31.2	72.8	1.3		30.6	10.5	2.0	55.8		42.2	41.7	74.8
	Fore-period, II	6.27	35.6	59.0	63.3	12.6	30.5	82.3	0.9	6.6	41.3	10.9	2.0	59.9	69.9	53.8	41.4	84.3
	Average	6.21	35.0	55.7	63.3	12.1	30.9	77.6	1.1	6.6	36.0	10.7	2.0	57.9	69.9	48.0	41.6	79.6
	$CaCO_3$, I (400 m.eq.)	6.56	20.6	58.8	49.1	20.5	12.1	71.0	1.7	11.9	356.0	24.9	4.1	60.5	61.0	376.5	37.0	75.1
	$CaCO_3$, II	6.75	21.0	69.3	52.1	20.2	10.4	81.2	1.9	12.1	394.0	24.8	3.9	71.2	64.2	414.2	35.2	85.1
	$CaCO_3$, III	6.63	26.2	49.5	50.2	17.5	12.7	73.2	0.7	12.0	378.0	20.5	4.0	50.2	62.2	395.5	33.2	77.2
	Average	6.65	22.6	59.2	50.5	19.4	11.7	74.8	1.4	12.0	376.0	23.8	4.0	60.6	62.5	395.4	35.1	79.1
	Change	+ 0.44	− 12.4	+ 3.5	− 12.8	+ 7.3	− 19.2	− 2.8	+ 0.3	+ 5.4	+ 340.0	+ 12.7	+ 2.0	+ 2.7	− 7.4	+ 347.4	− 6.5	− 0.5
	After-period	5.92	36.6	70.5	60.6	8.6	30.4	85.2	2.0	10.6	38.8	9.7	2.7	72.5	71.2	47.4	40.1	87.9
C. D. Unit No. 255381 Male Age 37 Duodenal ulcer	Fore-period	5.76	67.5			12.0	26.7	66.6			54.3	14.4	2.5			66.3	41.4	69.1
	$CaCO_3$ (400 m.eq.)	6.24	37.2			25.9	8.9	23.7?			484.0	17.8	2.9			509.9	16.7	26.6
	Change	+ 0.48	− 30.4			+ 13.9	− 17.8	− 42.9			+ 429.7	+ 3.4	+ 0.4			+ 443.6	− 24.7	− 42.5
	Aluminum phosphate, I (35 m.eq. HPO_4)	5.42	88.4			9.5	24.5	87.1			46.3	41.1	4.3			55.8	65.6	91.4
	Aluminum phosphate, II (35 m.eq. HPO_4)	5.43	77.2			8.9	29.6	76.0			51.4	42.7	4.6			60.3	72.3	80.6
	Average	5.42	82.8			9.2	27.1	81.6			48.9	41.9	4.5			58.1	69.1	86.0
	Change	− 0.34	+ 15.3			− 2.8	+ 0.4	+ 17.0			− 5.4	+ 27.5	+ 2.0			− 8.2	+ 27.7	+ 16.9
	Aluminum hydroxide	5.93	46.8			12.1	7.3	60.5			51.9	33.2	3.9			64.0	40.5	64.4
	Change	+ 0.17	− 20.7			+ 0.1	− 20.7	− 6.1			− 2.4	+ 18.8	+ 1.4			− 2.3	− 0.9	− 4.7

TABLE III—*Continued*

Subject	Periods of study (4-day)	Urine							Feces					Total outgo				
		pH	NH_4	Na	K	Ca	HPO_4*	Cl	Na	K	Ca	HPO_4*	Cl	Na	K	Ca	HPO_4*	Cl
		m.eq. per 24 hours							*m.eq. per 24 hours*					*m.eq. per 24 hours*				
W. G. Unit No. 144032 Male Age 51 Gastric ulcer	Fore-period	5.16	73.0			6.3	24.5	75.0			54.3	17.5	2.9			60.6	42.0	77.9
	$CaCO_3$ (400 m.eq.)	6.06	38.9			20.4	8.2	57.7			520.0	30.3	5.3			540.4	38.5	63.0
	Change	+ 0.9	− 34.1			+ 14.1	− 16.3	− 17.3			+ 465.7	+ 12.8	+ 2.4			+ 479.8	− 3.5	− 14.9
	Aluminum phosphate (35 m.eq.)	5.12	86.7			5.5	24.5	80.5			40.2	38.7	8.7			45.7	63.2	85.2
	Change	− 0.04	+ 13.7			− 0.8	± 0.0	+ 5.5			− 14.1	+ 21.2	+ 1.8			− 14.9	+ 21.2	+ 7.3
	Aluminum hydroxide	5.59	43.3			5.5	8.1	73.3			43.8	25.0	4.8			49.3	33.1	78.1
	Change	+ 0.47	− 29.7			− 0.8	− 16.4	− 1.7			− 10.5	+ 7.5	+ 0.9			+ 11.3	− 8.9	+ 0.2

* HPO_4 is here taken as univalent for the reason that at the usual pH of urine its base equivalence is approximately 1.0.
The values for "change" are derived by comparison with the fore-period values.

TABLE IV

Effect of calcium carbonate, aluminum phosphate, and aluminum hydroxide on various constituents of the blood plasma

Subject	Periods of study (4-day)	Cl	CO_2	pH	P	Ca	K	Na	Total base	BuN	Urea clearance	Cell volume	Serum water
		mM./L.			*mM./L.*		*m. eq./L.*			*mgm. per cent*	*per cent average normal*	*per cent*	*grams per cent*
A. K. Unit No. 148736 Female Age 63 Gastric ulcer	Fore-period I	101.9	30.9	7.43	1.26	4.9	5.30	143.0	155.3	15.4	66	40.4	91.1
	Fore-period II	102.2	31.8	7.47	1.29	4.7	5.20	144.3	153.3	14.6	81	37.0	90.97
	Calcium carbonate I	100.7	31.7	7.50	1.35	5.75	5.20	147.9	160.0	17.0	44	41.0	90.42
	Calcium carbonate II	100.5	31.9	7.44	1.19	5.35	5.00	145.2	158.5	17.8	65	41.5	90.68
	Calcium carbonate III	103.1	29.7	7.47	1.22	5.1	5.30	145.0	156.1	15.5	65	37.5	91.14
	After-period	100.2	30.9	7.43	1.13	5.1	5.30	143.8		13.2	76	37.2	91.06
C. D. Unit No. 255381 Male Age 37 Duodenal ulcer	Fore-period	101.7	29.6	7.46	1.32	5.05				9.4			
	Calcium carbonate	99.6	29.6	7.46	0.97	5.15				13.5			
	Aluminum phosphate I	103.4	28.4	7.48	1.0	5.7				12.0			
	Aluminum phosphate II	100.5	29.8	7.46	1.22	5.5				10.0			
	Aluminum hydroxide	102.4	28.5	7.47	1.13	5.25				15.4			
W. G. Unit No. 144032 Male Age 51 Gastric ulcer	Fore-period	96.7	28.6	7.43	1.42	4.65				14.2			
	Calcium carbonate	95.6	29.9	7.43	1.35	5.1				13.8			
	Aluminum phosphate	106.9	28.2	7.42	1.40	4.75				16.3			
	Aluminum hydroxide	101.6	27.4	7.41	1.40	5.05				14.0			

maining components, Mg, SO_4, and organic acids were not measured. The accuracy of ammonium adjustment is shown by the slight extent of change in urine pH. For the patient W. G., a considerable, and for C. D., a much larger, reduction of chloride in the urine was found. Excretion of this anion in the urine is known to fluctuate widely even in the presence of a constant intake (16, 17).

The changes in mineral excretion induced by calcium carbonate occurred within 24 hours after the addition of the alkali to the regimen. Mineral excretion returned to original levels almost equally soon after the discontinuation of calcium carbonate therapy.

The use of calcium carbonate did not alter the electrolyte constitution of the blood plasma (Table IV).

(2) *Aluminum phosphate*

The ingestion of 35 m.eq. HPO_4 as aluminum phosphate caused a roughly equivalent increase in the stools and had no appreciable effect on HPO_4 output in the urine. Calcium excretion in the stools was to a slight extent reduced. There was no appreciable change in the calcium output in the urine. Some increase in chloride and, also, ammonium excretion in the urine was found. A relationship of these changes to phosphate ingestion was not apparent. No alterations were noted in the electrolyte components of the blood plasma.

(3) *Aluminum hydroxide*

Aluminum hydroxide caused a considerable increase in HPO_4 excretion in the stools, as demon-

strated by the data from the two periods of study. This finding is in agreement with the results obtained by other workers (18). A roughly equivalent decrease of the excretion of HPO_4 in the urine was found and, along with it, the to be expected reduction of ammonium. For patient C. D., this was exactly equivalent to the decrease of HPO_4. The total outgo of HPO_4 was not increased. Aluminum hydroxide did not alter the electrolytes of the blood plasma, thus confirming previous observations (19).

CONCLUSION

The ingestion of calcium carbonate, aluminum phosphate, or aluminum hydroxide, in the quantities used in the treatment of peptic ulcer, places no appreciable burden on the processes of acid-base metabolism. The necessary adjustments of acid-base excretion are relatively small and are accomplished with a remarkable precision.

The electrolyte constitution of the blood plasma is not disturbed.

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