PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 145, 222–226 (1974)

Effect of Oral Calcium Carbonate on Urinary Excretion of Ca, Na and Mg in Advanced Renal Disease (37782)

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Intravenous load of calcium in patients with chronic renal failure is associated with augmented excretion rates of calcium, sodium and magnesium (1). Although it has been demonstrated that oral intake of calcium carbonate in normal subjects and in patients with renal disease produces an increase in urinary calcium (2), its effect on urinary sodium and magnesium has not been studied as yet. Oral calcium carbonate has been reported to correct acidosis and hypocalcemia (2, 3) and to decrease serum levels of immunoreactive parathyroid hormone in patients with chronic renal disease (4). In view of the frequent use of calcium carbonate in chronic renal failure, further evaluation of its various actions is warranted. The present study was undertaken to evaluate the effect of oral calcium carbonate on serum levels and renal handling of calcium, sodium, and magnesium in patients with advanced renal disease.

Materials and Methods. Ten patients with chronic kidney disease of diverse etiology were studied (Table I). The patients were on reduced protein diet (40 g protein/day) with constant amounts of sodium, potassium, calcium, and phosphorus throughout the study. Patient M. C. with salt-wasting nephropathy was receiving salt supplements (total sodium intake 200 milliequivalents in 24 hr) to balance excessive urinary losses of sodium. None of the patients were treated with diuretics or with vitamin D, and none were dialyzed.

Inulin clearances were recorded in each patient at the beginning and upon the completion of the study. During the remainder of the study, clearances of endogenous creatinine were measured almost every day. Calcium, magnesium, and sodium concentrations were measured in the urine and in the serum specimens daily in most patients during the whole study period, and the respective clearances were calculated. Serum phosphorus and bicarbonate were measured every day. The clearances of calcium and magnesium were determined in terms of ultrafiltrable fractions of these ions. Inulin (5), creatinine, and bicarbonate (7) were determined by a Technicon Autoanalyzer. Sodium was measured with an Instrumentation Laboratory flame photometer, Model 143. Total and ultrafiltrable calcium and magnesium were measured with Norelco Unicam Atomic Absorption Spectrophotometer. Ultrafiltrates of serum were prepared with the use of colloidian bags (8). Inorganic phosphorus was measured utilizing the methodology developed by the American Monitor Company (9).

Following determination of control values, aluminum hydroxide gel (Amphojel) was given in an initial dose of 30 ml every hour. As serum concentration of phosphorus approached 5 mg/100 ml, Amphojel was discontinued, and calcium carbonate powder was started in an initial amount of 2.5–5.0 g every hour. The dose of calcium carbonate was adjusted to maintain serum calcium concentration in excess of 9 mg/100 ml. This level of serum calcium was recorded in each patient for at least 20 consecutive days. The initial administration of aluminum hydroxide gel to reduce serum phosphorus level was used as a safety measure to avoid excessively

TABLE I. Clinical Data of All Patients.[a]

Patient	Age	Sex	Diagnosis	C_{IN} (ml/min)	C_{Cr} (ml/min)
R.C.	39	F	Chr. Gn.	2.0	4.0
P.R.	45	F	Polyc. K.	1.4	2.3
D.D.	35	M	K-W	4.3	8.0
C.J.	74	F	Polyc. K.	3.7	3.8
V.F.	40	F	Chr. GN.	5.3	8.0
M.S.	21	F	Chr. PN.	5.4	8.2
H.L.	35	F	Chr. GN.	9.1	12.0
M.L.	34	M	K-W	4.9	7.6
J.E.	49	F	Chr. PN.	4.3	5.4
M.C.	54	M	Med. C.	4.0	4.5

[a]Abbreviations: C_{IN}, inulin clearance; C_{Cr}, endogenous creatinine clearance; F, female; M, male; Chr. GN., Chronic glomerulonephritis; Polyc. K., polycystic kidney disease; K-W, diabetic nephropathy; Chr. PN., chronic pyelonephritis; Med. C., medullary cystic kidney disease.

high calcium phosphorus products and their possible adversery effects.

Results. Both control inulin and endogenous creatinine clearances of each individual patient are listed in Table I. The initial and final serum concentrations of calcium, magnesium, phosphorus bicarbonate and inulin clearances are listed in Table II. There were no significant changes or fluctuations in glomerular filtration rates as estimated by clearances of inulin and creatinine throughout the study.[1]

Figure 1 depicts a direct relationship between diffusible serum calcium and its clearance in each individual patient. The open circles represent the lowest (control) and the closed circles the highest concentrations of diffusible serum calcium at the end of the study in each patient. The control concentration of diffusible serum calcium (DS_{Ca}) for the whole group of twelve patients was (Mean $\pm$ standard deviation) 4.18 $\pm$ 0.61 mg/100 ml, whereas after sustained normocalcemia and normophosphatemia the concentration was 5.54 $\pm$ 0.58 mg/100 ml ($P < 0.005$). The corresponding calcium clearance rates (C_{Ca}) were 0.57 $\pm$ 0.38 and 1.21 $\pm$ 0.62 ml/min ($P < 0.005$). Total and diffusible serum magnesium decreased to below the control values in every patient (Table II). The clearances of magnesium increased in a parallel fashion to those of calcium. The control value of magnesium clearance for all patients was 2.03 $\pm$ 0.51, and after sustained normocalcemia the mean rate was 2.40 $\pm$ 0.57 ml/min ($P < 0.005$). The correlation between the clearance rates of both divalent ions in ten patients is shown in Fig. 2. Likewise, sodium clearances rose proportionately with the increase in calcium clearances as shown in Fig. 3. The mean control value for sodium clearance (C_{Na}) was 0.48 $\pm$ 0.32, and after sustained normocalcemia the rate was 0.63 $\pm$ 0.40 ml/min ($P < 0.005$). The effect of increasing urinary excretion of calcium on the

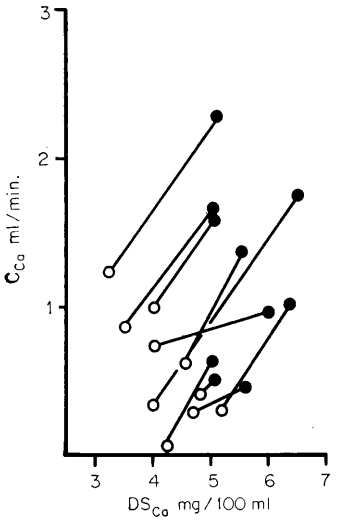

FIG. 1. The relation between the changes in diffusible serum calcium concentrations (DS_{Ca}) and calcium clearance rates (C_{Ca}) in ten patients.

[1] A portion of present data pertinent to renal handling of phosphorus were listed in a previous publication (4).

TABLE II. Serum Concentrations of Calcium (S_{Ca}), Magnesium (S_{Mg}), Phosphorus (S_p) and Bicarbonate ($SH_{CO_3}^-$) Before and at the End of the Study.[a]

Patient		S_{Ca} (mg/100 ml)	S_{Mg} (mg/100 ml)	S_p (mg/100 ml)	$SH_{CO_3}^-$ (mequiv/liter)	C_{IN} (ml/min)
	C	8.4	2.3	9.5	21	2.0
R.C.	N	10.5	1.8	3.3	29	2.1
	C	7.8	2.1	8.0	—	1.4
P.R.	N	11.2	1.7	2.4	—	1.2
	C	8.0	2.8	7.1	22	4.3
D.D.	N	10.5	1.8	3.1	30	5.5
	C	8.1	2.8	8.5	—	3.7
C.J.	N	10.4	2.0	2.1	—	3.5
	C	7.0	2.1	5.9	21	5.3
V.F.	N	10.0	1.8	3.0	23	4.8
	C	8.5	3.5	6.2	24	5.4
M.S.	N	10.2	2.0	3.4	23	5.8
	C	8.5	1.9	5.3	18	9.1
H.L.	N	10.5	1.4	2.4	20	8.0
	C	6.0	1.6	7.4	20	4.9
M.L.	N	9.0	1.0	2.1	23	5.8
	C	8.3	3.0	8.2	20	4.3
J.E.	N	9.7	2.4	2.9	24	4.6
	C	8.0	2.2	5.6	10	4.0
M.C.	N	9.9	1.0	2.2	14	4.7
	C	7.86	2.43	7.17	19.50	4.77
		0.79	0.57	1.39	4.20	2.25
Mean ± SD						
	N	10.19	1.69	2.69	23.25	4.60
		0.59	0.44	0.57	5.00	1.95
P		<0.0005	<0.0005	<0.0005	<0.025	NS

[a]Abbreviations: C, control; N, after sustained normocalcemia; *P*, significance of the difference between C and N values as determined by *t* test; NS, not significant.

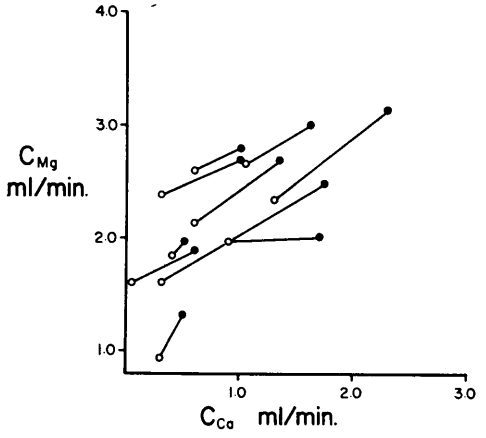

FIG. 2. The relation between the changes in calcium clearances (C_{Ca}) and magnesium clearances (C_{Mg}) in ten patients.

excretion of sodium was most striking in patient M. C. with salt-wasting nephropathy. The strong natriuretic response to oral calcium induced extracellular volume depletion with clinical manifestations necessitating vigorous replacement of sodium (Fig. 4).

Discussion. The increase in sodium clearance following gradual rise in filtered load of calcium as noticed in the present study is similar to previous observations in which the filtered load was augmented acutely with calcium infusions both in normal subjects (10) and in patients with advanced chronic renal insufficiency (1). The clinical consequence of this observation was apparent in patient M. C. who developed symptoms of extracellular volume depletion during the course of the study. Additional observations based on com-

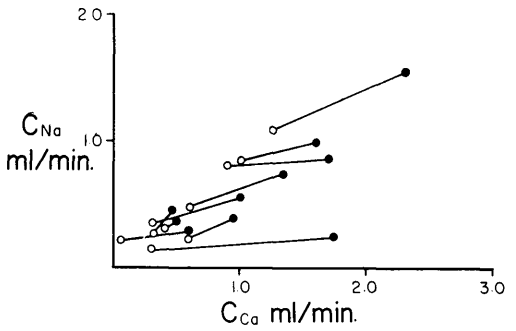

FIG. 3. The relation between the changes in calcium clearances (C_{Ca}) and sodium clearances (C_{Na}) in ten patients.

plete balance studies may define in more detail the clinical importance of the observed natriuretic effect of oral calcium carbonate.

The observed decrease in the concentration of magnesium in the serum in all our patients is not well understood; however, several possible contributing factors are worth mention: (a) losses of magnesium through increased urinary excretion, (b) decreased intestinal absorption of magnesium as a result of large oral loads of calcium (11), and (c) suppression of parathyroid activity with increased incorporation and retention of magnesium in the bone.

The increase in the clearances of sodium and magnesium associated with the rising filtered load of calcium, as noticed in our patients, is consistent with the possibility that the proposed common renal reabsorptive mechanism(s) for calcium, sodium and magnesium is operating also in chronically diseased kidneys (12, 13).

Summary. The effect of oral calcium carbonate on serum levels and urinary excretion of calcium sodium and magnesium was evaluated in 10 patients with advanced renal disease. A rise in serum calcium which was observed in all patients was associated with increased urinary excretions of calcium, sodium and magnesium, suggesting that common reabsorptive mechanism(s) are underlying the renal handling of these ions also in advanced renal disease. A decrease in serum magnesium which was noticed in all patients could be explained by a decreased intestinal absorption, an increased urinary loss, or both.

This study was partly supported by a Grant FR-51 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

1. Popovtzer, M. M., Massry, S. G., Coburn, J. W., and Kleeman, C. R., J. Lab. Clin. Med. **73**, 763 (1967).

2. Clarkson, E. M., McDonald, S. J., and DeWardener, H. E., Clin. Sci. **30**, 425 (1966).

3. Makoff, D. L., Gordon, A., Franklin, S. S., Gerstein, A. R., and Maxwell, M. H., Arch. Intern. Med. **125**, 15 (1969).

4. Popovtzer, M. M., Pinggera, W. F., Hutt, M. H., Robinette, J., Halgrimson, C. G., and Starzl, T. E., J. Clin. Endocrin. **35**, 213 (1972).

5. Galli, A., Path. Biol. (Paris) **14**, 911 (1966).

6. Autoanalyzer Methodology. File N-11A, Technicon Instruments Corporation, Chauncey, New York (1963).

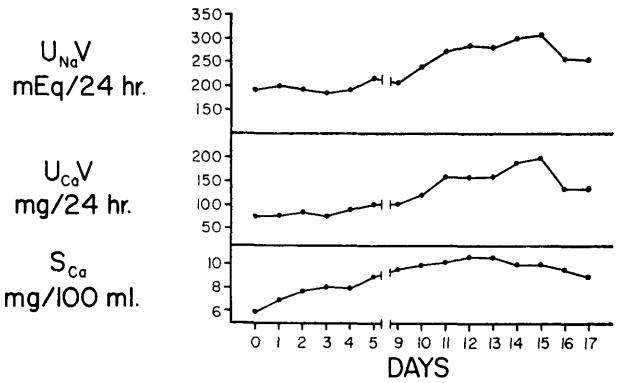

FIG. 4. Sequential changes in the excretion rates of calcium ($U_{Ca}V$), sodium ($U_{Na}V$), and magnesium ($U_{Mg}V$) in patient M. C.

7. Skeggs, L. T., Jr., Hochstrassen, H., Clin. Chem. **10**, 918 (1964).

8. Toribara, T. Y., Terepka, A. R., and Dewey, R. A., J. Clin. Invest. **36**, 738 (1957).

9. Kuby, S. A., J. Biol. Chem. **235**, 2830 (1960).

10. Levitt, M. F., Halpern, M. H., Polimeros, D. P., Sweet, A. Y., and Gribetz, O., J. Clin. Invest. **37**, 294 (1958).

11. Heaton, F. W., Hodgkinson, A., and Rose, G. A., Clin. Sci. **27**, 31 (1964).

12. Walser, M., Amer. J. Physiol. **200**, 1099 (1961).

13. Samiy, A. H. E., Brown, J. L., Globus, D. L., Kessler, R. H., and Thompson, D. D., Amer. J. Physiol. **198**, 599 (1960).

Received Sept. 4, 1973. P.S.E.B.M., 1974, Vol. 145.