NaHCO3 and NaC1 tolerance in chronic renal failure.

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Research Article

In patients with chronic renal failure, NaHCO3 therapy may correct or prevent acidemia. It has been proposed that the NaHCO3 required will not result in clinically significant Na retention comparable to that from similar increases in NaC1 intake. In each of ten patients with chronic renal failure, creatinine clearance (Ccr) range 2.5-16.8 ml/min, on an estimated 10-meq Na and C1 diet, electrolyte excretion was compared on NaHCO3 vs NaC1 supplements of 200 meq/day. Periods of NaHCO3 and NaC1 (in alternate order for successive patients) lasted 4 days, separated by reequilibration to base-line weight. Mean +/- SEM excretion (ex) of Na, C1, and HCO3 and deltaCcr and deltaweight (day 4-1) are compared below for the 4th day of NaC1 vs. NaHCO3 intake. Mean Ccr +/-SEM on day 4 of NaC1 and NaHCO3 were 10.8 +/-1.6 and 9.0 +/-1.4 ml/min, respectively (P less than 0.02). Mean systolic blood pressure (but not diastolic) increased significantly on NaC1 (P less than 0.05). No significant blood pressure changes were seen on NaHCO3. Net positive HCO3 balance occurred on NaHCO3 as indicated above and reflected a rise in mean serum HCO3 from 19 to 30 meq/liter (day 1 vs. 4) (P less than 0.01). Mechanisms for the greater excretion of Na on NaHCO3 may relate to C1 wasting as noted above on low C1 intake and […]

$NaHCO_3$ and NaCl Tolerance in Chronic Renal Failure

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ABSTRACT In patients with chronic renal failure, $NaHCO_3$ therapy may correct or prevent acidemia. It has been proposed that the $NaHCO_3$ required will not result in clinically significant Na retention comparable to that from similar increases in NaCl intake. In each of ten patients with chronic renal failure, creatinine clearance (C_{Cr}) range 2.5-16.8 ml/min, on an estimated 10-meq Na and Cl diet, electrolyte excretion was compared on $NaHCO_3$ vs. NaCl supplements of 200 meq/day. Periods of $NaHCO_3$ and NaCl (in alternate order for successive patients) lasted 4 days, separated by re-equilibration to base-line weight. Mean±SEM excretion (ex) of Na, Cl, and HCO_3 and ΔC_{Cr} and Δweight (day 4 − 1) are compared below for the 4th day of NaCl vs. $NaHCO_3$ intake.

	Na ex	Cl ex	HCO_3 ex	ΔWeight	ΔC_{Cr}
		meq/day		*lb*	*ml/min*
NaCl	170	156	6	+2.27	+0.45
	±9.5	±13	±3.4	±0.7	±0.2
$NaHCO_3$	203	62	92	−0.95	−0.88
	±9.5	±9	±11	±0.6	±0.3
P	<0.02	<0.001	<0.001	<0.01	<0.01

Mean C_{Cr} ±SEM on day 4 of NaCl and $NaHCO_3$ were 10.8±1.6 and 9.0±1.4 ml/min, respectively ($P < 0.02$). Mean systolic blood pressure (but not diastolic) increased significantly on NaCl ($P < 0.05$). No significant blood pressure changes were seen on $NaHCO_3$. Net positive HCO_3 balance occurred on $NaHCO_3$ as indicated above and reflected a rise in mean serum HCO_3 from 19 to 30 meq/liter (day 1 vs. 4) ($P < 0.01$). Mechanisms for the greater excretion of Na on $NaHCO_3$ may relate to Cl wasting as noted above on low Cl intake and limited HCO_3 reabsorptive capacity. Thus, Na excretion by day 4 was greater on $NaHCO_3$ than on NaCl, and only on $NaHCO_3$ did Na excretion near intake (210 meq/day).

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INTRODUCTION

In patients with chronic renal failure, $NaHCO_3$ therapy may correct or prevent acidemia. It has been observed that the $NaHCO_3$ required does not result in clinically significant sodium retention (as manifested by increased weight, blood pressure, or edema), comparable to that resulting from similar increases in NaCl intake. Seldin, Carter, and Rector stated that in their experience edema resulting from $NaHCO_3$ administration in patients with chronic renal failure is unusual (1). Carter stated further that alkali therapy as $NaHCO_3$ or sodium citrate does not usually aggravate edematous states (2). In a recent article, Kurtzman stated that $NaHCO_3$ is excreted much more readily than NaCl (3). Although these statements reflect clinical impressions we are not aware of systematic studies in humans comparing the excretion of sodium under controlled conditions when administered orally as $NaHCO_3$ or NaCl.

In the usual clinical setting, when faced with an edematous acidemic patient with chronic renal failure, NaCl restriction and $NaHCO_3$ therapy are often initiated simultaneously. To mimic these conditions, we compared sodium excretion rates when the fixed oral sodium intake was predominantly $NaHCO_3$ or NaCl. The results demonstrate higher rates of sodium excretion with $NaHCO_3$ under these conditions.

METHODS

Ten patients with renal failure (initial individual creatinine clearances ranging from 2.5 to 16.8 ml/min) and in a stable state were admitted to the Clinical Research Center of the University of Missouri Medical Center for these studies. The patients had been maintained on a sodium intake individualized so as to maintain stable weight and blood pressure and no more than trace edema. Protein intake was usually 40 g, potassium 40 meq, and fluid and

TABLE I

Patient Features and Study Order

Patient	Sex	Age	Creatinine clearance*	Study order		Diagnosis
				1st	2nd	
		yr	*ml/min*			
1	M	17	7.9	NaCl	$NaHCO_3$	Chronic glomerulonephritis
2	F	62	6.4	NaCl	$NaHCO_3$	End stage kidney disease (etiology unknown)
3	F	46	12.1	$NaHCO_3$	NaCl	Chronic glomerulonephritis
4	M	53	6.7	NaCl	$NaHCO_3$	Obstructive nephropathy
5	M	32	16.8	$NaHCO_3$	NaCl	Membranous nephropathy
6	M	45	13.7	NaCl	$NaHCO_3$	Chronic glomerulonephritis
7	F	53	2.5	$NaHCO_3$	NaCl	Polycystic kidney disease
8	F	67	10.5	NaCl	$NaHCO_3$	Obstructive nephropathy
9	M	47	12.5	NaCl	$NaHCO_3$	End stage kidney disease (etiology unknown)
10	M	76	15.4	$NaHCO_3$	NaCl	Obstructive nephropathy

* Day 1 of study.

caloric intake were ad lib. All patients were maintained on their base-line diets for at least 2 wk before the initiation of the controlled study periods. At the initiation of the studies all patients had zero to trace edema. During the start of each study period, all were placed on a 10 meq sodium diet (based on portion weights and usual food composition) (range, 13.0–16.5 meq/day by three random analytic verifications) for two separate 4-day study periods. Each period was supplemented with 207 meq/day of NaCl tablets or 201 meq/day of $NaHCO_3$ tablets, starting in alternate order for successive patients. During the study periods, daily 24-h urine volumes and serum samples were collected. All urines were collected under oil and concentrations of sodium, potassium, chloride, bicarbonate, creatinine, and urea nitrogen were determined in all samples. pH was measured in all urines. Daily intake and output, body weight, blood pressure, and the presence or absence of edema were monitored. Peripheral venous plasma renin activity was determined at the initiation and at the end of the sodium loading periods after 2 h in the upright position.

After a 4-day study period on a given salt, a period of 2 or 3 days was allowed for return to base-line weight. After the attainment of base-line status, a second study period similar to the first, but on the alternate salt, was initiated.

Chemical analysis. Sodium and potassium were measured in serum and urine with an Instrumentation Laboratory (Lexington, Mass.) flame photometer. Serum and urinary chloride were quantified with an American Instrument Co. (Travenol Laboratories Inc., Silver Spring, Md.) chloride titrater. Bicarbonate concentrations in serum and urine were determined with titration by a micromodified Segal method (4). Urine pH was determined by an Instrumentation Laboratory pH meter on specimens kept under oil. True creatinine concentrations in serum and urine were measured by a previously described method (5). Urea nitrogen concentrations in serum and urine were measured by the urease-Nesslerization colorimetric method (6). Renin was determined by a radioimmunoassay (7) and expressed as nanograms/milliliter per hour angiotensen II.

Calculations. Clearances (milliliters/minute) of urea and creatinine were calculated as: (urine/plasma concentrations) × (24-h urine volume [milliliters/day]/1,440 [minutes/day]). For these clearance calculations, the plasma at the beginning and the end of the 24-h collection period. Daily sodium, potassium, chloride, and bicarbonate excretion rates were calculated as urine concentration times 24-h urine volume and expressed as milliequivalents/day. Blood pressures were recorded after 15 min supine and 5 min upright, twice a day. Mean systolic and diastolic blood pressure recordings were calculated from all these measure- value utilized was the mean of the plasma concentration ments for each day. Sodium balances were calculated as total sodium intake (dietary plus tablet) minus urinary losses. Dietary intake was calculated from the actual portions ingested and usual food composition. Measured and calculated values obtained during respective days of NaCl and $NaHCO_3$ loading were compared by paired-t analysis for these ten patients. Differences were considered nonsignificant when $P > 0.05$.

RESULTS

Table I shows selected clinical features of the patients and order of the study salt administered. Six patients were started on sodium chloride first and four started on sodium bicarbonate first. Two patients started on bicarbonate first (after patient 1 and after patient 8) did not complete the study satisfactorily and are not included in Table I or in the analysis. The first received some $NaHCO_3$ during the NaCl loading and the second, a poorly controlled diabetic, had markedly varying urine volumes associated with intermittent glucosuria. Mean (±SEM) urine pH values on day 4 on NaCl and by day 4 on $NaHCO_3$ were 6.1±0.2 and 7.7±0.1 ($P <$ 0.001 by paired-t analysis).

Fig. 1 shows the mean values of daily sodium excretion in all patients. Sodium excretion values were significantly higher only on days 3 and 4 of $NaHCO_3$ ingestion, as compared to days 3 and 4 on NaCl.

Fig. 2 shows the mean daily sodium balance for all patients. Only on days 3 and 4 on $NaHCO_3$ loading were the daily sodium balances significantly less than on cor-

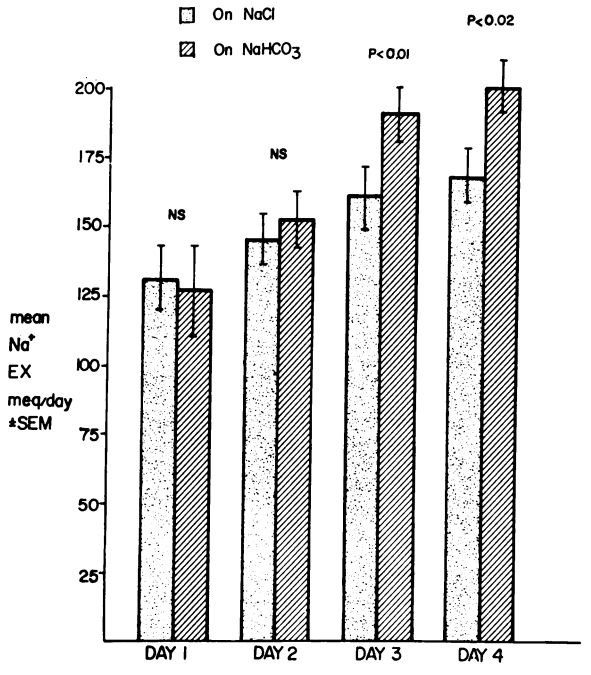

FIGURE 1 Mean daily values of sodium excretion are shown for respective study days on NaCl vs. $NaHCO_3$. $n = 10$.

responding days on NaCl. Only on $NaHCO_3$ was sodium balance approached.

Fig. 3 shows the mean values of chloride excretion in all patients. Chloride excretions were significantly higher on NaCl as compared to periods on $NaHCO_3$ for days 2, 3, and 4. Mean daily chloride excretions on

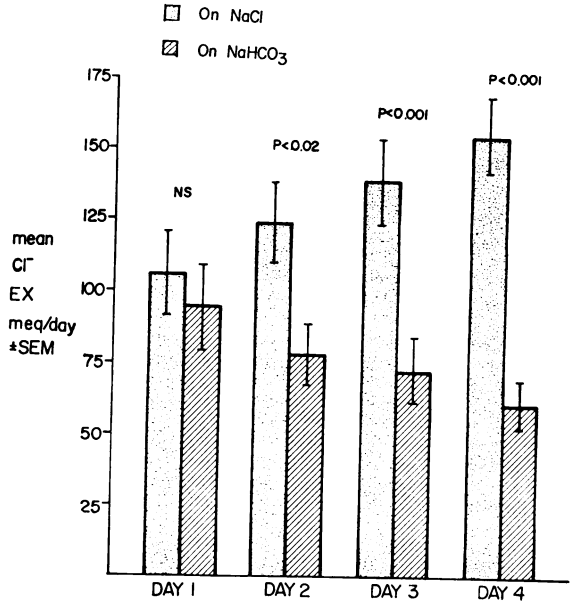

FIGURE 3 Mean daily chloride excretions are shown for respective days on NaCl and $NaHCO_3$. $n = 10$.

$NaHCO_3$ are well above the estimated intake of 10 meq/day.

Fig. 4 shows the mean bicarbonate excretion in milliequivalents/day in all patients. Bicarbonate excretions were greater during $NaHCO_3$ ingestion for days 2, 3, and 4 than during NaCl ingestion. Bicarbonate excretion on NaCl was minimal. During the 4 days on $NaHCO_3$, bicarbonate excretion did not reach the bicarbonate intake of 200 meq/day. This positive bicarbonate balance was in accord with an increase in serum bi-

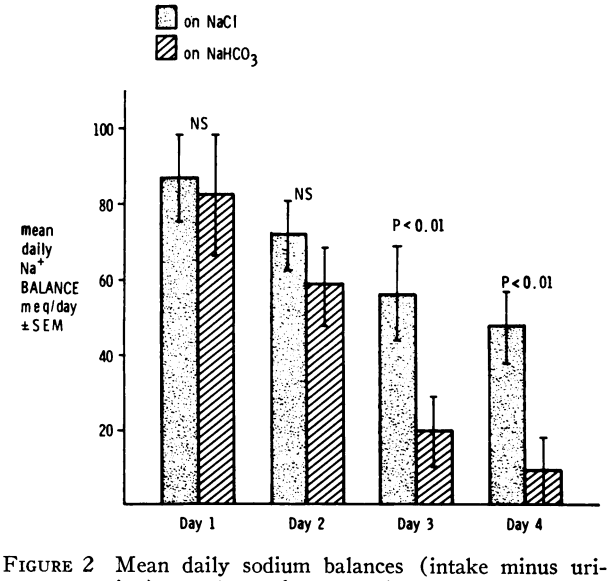

FIGURE 2 Mean daily sodium balances (intake minus urinary excretion) are shown for respective days on NaCl and $NaHCO_3$. $n = 10$.

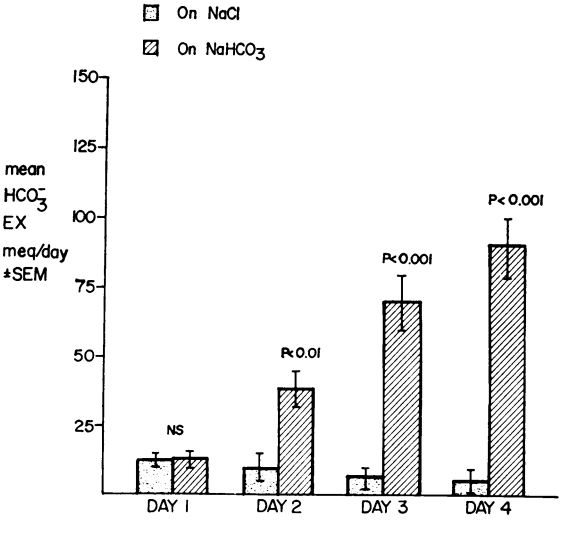

FIGURE 4 Mean daily bicarbonate excretions are shown for respective days on NaCl and $NaHCO_3$. $n = 10$.

TABLE II

Mean±SEM Values of Serum Electrolytes, Creatinine, and Urea Nitrogen at Start and End of Study

Supplement	A.M. day	Serum				Creatinine	Urea nitrogen
		Na	K	Cl	HCO_3		
		meq/liter				*mg/dl*	
NaCl	1	139.5	4.94	104.1	20.2	9.0	64.7
		±2.3	±0.4	±4.8	±1.2	±1.2	±5.9
	5	141.3	5.07	110.7	19.7	8.4	59.2
		±0.8	±0.3	±2.2	±1.8	±1.1	±5.2
P		NS	NS	<0.02	NS	<0.001	<0.02
$NaHCO_3$	1	139.1	5.2	106.7	18.9	9.0	62.2
		±1.5	±0.3	±1.7	±1.7	±1.1	±6.1
	5	142.1	4.4	93.6	30.4	9.0	57.9
		±1.2	±0.2	±2.5	±2.4	±1.1	±5.7
P		<0.02	<0.02	<0.001	<0.001	NS	<0.02
P (NaCl vs. $NaHCO_3$)							
Day 1 vs. day 1		NS	NS	NS	NS	NS	NS
Day 5 vs. day 5		NS	<0.01	<0.001	<0.01	<0.05	NS

carbonate from 18.9 to 30.4 meq/liter. This and other serum changes are shown in Table II. Serum sodium increased significantly while on $NaHCO_3$ and serum potassium decreased significantly from day 1 to day 5. Serum potassium was significantly higher on day 5 of NaCl compared to $NaHCO_3$ loading, but there were no significant differences on day 1. On NaCl, serum chloride concentrations increased significantly, and on $NaHCO_3$, serum chloride decreased. Mean serum chloride differences between the two groups were not significant on day 1, but differences were significant for day 5.

Mean serum creatinine and urea nitrogen values both decreased ($P < 0.001$, $P < 0.02$) with NaCl loading. With $NaHCO_3$, there were no significant differences in serum creatinine, but serum urea nitrogen decreases ($P < 0.02$) were noted. Table III shows that the total fluid intake was not significantly different for the two loading periods. Urine volumes were greater on $NaHCO_3$ even on day 1 ($P < 0.01$). Although starting weights were not significantly different, increases on NaCl ($P < 0.02$) occurred.

TABLE III

Comparisons of Mean±SEM Values for Fluid Intake, Output, Clearances, and Potassium Excretion

Supplement	Day	Intake	Urinary output	Weight	C_{Cr}	C_{urea}	K excretion
		ml/day		*lb*	*ml/min*		*meq/day*
NaCl	1	2,801	1,766	144.9	10.5	6.2	31
		±323	±109	±10.0	±1.5	±0.9	±5.0
	4	2,401	1,939	147.2	10.8	6.6	26
		±148	±129	±9.6	±1.6	±0.9	±4.0
P		NS	NS	<0.02	NS	NS	NS
$NaHCO_3$	1	2,745	2,227	144.6	9.9	6.3	29.1
		±253	±165	±9.6	±1.4	±0.0	±5.5
	4	2,730	2,415	143.7	9.0	6.3	28.3
		±272	±160	±9.2	±1.4	±0.9	±3.8
P		NS	NS	NS	<0.01	NS	NS
P							
Day 1 vs. day 1		NS	<0.02	NS	NS	NS	NS
Day 4 vs. day 4		NS	<0.02	<0.01	<0.02	NS	NS

C_{Cr}, creatinine clearance; C_{urea}, urea clearance.

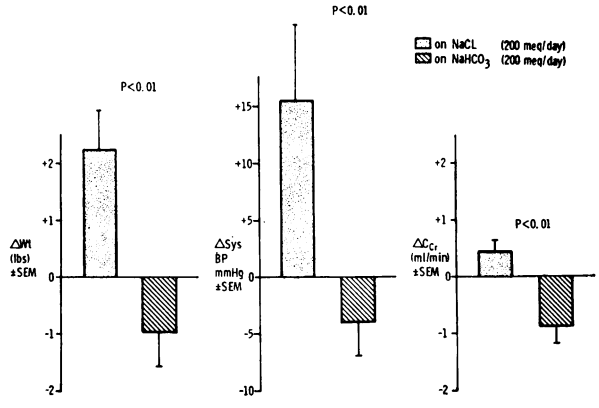

FIGURE 5 Mean changes (day 1 to day 5) in weight, systolic blood pressure (Sys BP), and creatinine clearance (C_{Cr}) are shown for NaCl and $NaHCO_3$.

Peripheral venous plasma renin activity on days 1 and 5 of NaCl were 2.9±0.6 and 1.8±0.6 ng/ml per h; on days 1 and 5 of $NaHCO_3$ values were 2.67±0.91 and 7.0±2.0 ng/ml per h. These changes from the morning of day 1 to the morning of day 5 were different from one another by paired-*t* analysis ($P < 0.05$). Creatinine clearance decreased significantly ($P < 0.01$) from day 1 to day 4 on $NaHCO_3$ loading, but not with NaCl loading.

Fig. 5 shows the relative changes of weight, systolic blood pressure, and creatinine clearance on NaCl vs. $NaHCO_3$. These changes on $NaHCO_3$, as compared to NaCl for these parameters, were all significantly different and in opposite directions. There were no significant changes noted in the diastolic blood pressure on either loading period.

DISCUSSION

The greater excretion rates of sodium during $NaHCO_3$ ingestion support clinical impressions that, under some circumstances, sodium is excreted more readily as $NaHCO_3$ than as NaCl. Although stools were not analyzed, it is unlikely that either sodium salt was not readily absorbed since sodium excretion reached intake on $NaHCO_3$ and in all studies weight changes correlated highly ($r = 0.86$) with calculated sodium balance. The cumulative sodium balance was still positive, however, in those losing weight on bicarbonate (see Fig. 2), reflecting in part the anticipated overestimate of sodium balance when nonurinary losses are neglected. However, the magnitude of the increase in serum sodium concentration on HCO_3 in association with greater urine volumes and slight weight loss is best explained by a negative fluid balance and some sodium retention. On NaCl, cumulative sodium retention was much greater and was coupled with fluid retention and weight gain.

Mechanisms. The mechanisms for greater sodium excretion rates on $NaHCO_3$ cannot be delineated precisely from these studies. Since bicarbonate excretion was negligible during NaCl ingestion, no major bicarbonate wasting as in proximal renal tubular acidosis was demonstrable.

However, increased sodium excretion on $NaHCO_3$ may relate in part to reduced maximum bicarbonate reabsorption (milliequivalents/minute per GFR) in bicarbonate-loaded patients with chronic renal failure (8). This has been attributed to high tubular fluid flow per nephron (8). Also parathyroid hormone decreases HCO_3 reabsorption and is usually increased in chronic renal failure (9, 10). Decreases in ionized calcium subsequent to increasing alkalemia could further increase parathyroid hormone levels.

However, even though sodium excretion on $NaHCO_3$ neared intake, bicarbonate excretion remained well below that ingested. Therefore, any mechanisms decreasing bicarbonate reabsorption cannot entirely account for all of the sodium excretion seen on $NaHCO_3$.

It seems unlikely that greater degrees of extracellular or plasma volume expansion account for higher sodium excretion rates on $NaHCO_3$. The changes in weight, blood pressure, peripheral renin, and clearances described favor greater expansion on NaCl.

Another mechanism for increased sodium excretion on $NaHCO_3$ may relate to the persistently high chloride excretion. Since the chloride content of the diet utilized approximates that of sodium (11), the chloride excretion values during bicarbonate ingestion suggest a negative balance of chloride. This is supported by a decrease in serum chloride concentration (day 1 to day 5) from 106.7 to 93.6 meq/liter ($P < 0.001$) (Table II) in the face of minimal change in weight. Also, during NaCl ingestion, chloride excretion never exceeded chloride ingestion as tablets, again suggesting little to no chloride in the diet. Thus, although dietary chloride content was not determined directly in these studies, the above arguments support the presence of chloride wasting during bicarbonate ingestion.

The ability of patients with chronic renal failure to reduce chloride excretion in the face of chloride restriction is unknown. Patients with chronic renal failure have been shown to have impaired ability to reduce sodium concentrations in the urine, subsequent to sodium restriction (12). Chloride concentrations were not determined in these studies, however, and it is not known whether the inability of patients with chronic renal failure to reduce sodium concentrations in the urine might be secondary to a primary defect in reducing chloride concentrations. This is a reasonable possibility since certain portions of the nephron, namely the loop of Henle, are now thought to transport chloride actively

(13, 14). Luke, Schmidt, Khanh, and Galla have shown that chloride-depleted rats may tend to waste sodium (15).

In essence, the study shows that the tolerance of the diseased kidney to variations in chloride intake is very limited. On chloride loading the mean maximum chloride excretion was 9.1% of the filtered chloride. On chloride restriction, mean minimum chloride excretion was 5.1% of filtered chloride in the same patients. Thus, when large amounts of chloride are administered the maximum renal excretion will be exceeded and chloride (along with sodium when administered as NaCl) will be retained. In contrast, when chloride intake is negligible chloride will still be excreted and the patient will waste chloride and associated cations.

The situation with respect to bicarbonate differs. Sodium bicarbonate administration results in an increase in serum bicarbonate so that bicarbonate filtration rate exceeds the reabsorptive capacity of the diseased kidney. Mean bicarbonate reabsorption at the end of bicarbonate loading in these studies was 23.3 meq/liter of GFR well below the 30.4 meq of bicarbonate per liter of filtrate. Since these patients are unable to conserve chloride, chloride is wasted on $NaHCO_3$ with chloride restriction; since the reabsorptive capacity for HCO_3 is exceeded, bicarbonate is excreted. The combination of these two events results in greater sodium excretion in the bicarbonate-treated patients than when these patients were treated with NaCl alone.

Clinical implications. In some patients, under the conditions of these studies, the limiting factor for sodium bicarbonate administration may be increasing plasma bicarbonate concentration secondary to bicarbonate retention rather than positive sodium balance. The daily ingestion of $NaHCO_3$ was much greater in our studies than usually required clinically, but was chosen purposely to examine the tolerance to large amounts of sodium administered as $NaHCO_3$ over 4 days.

In many clinical settings, it is common practice to initiate $NaHCO_3$ therapy simultaneously with severe NaCl restriction. Further studies will be necessary to determine if greater sodium excretion rates can be achieved with $NaHCO_3$ as compared to NaCl in the absence of associated NaCl restriction.

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