Impaired Urinary Ammonium Excretion in Patients With Isolated Proximal Renal Tubular Acidosis[1]

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ABSTRACT

During previous studies in patients with isolated proximal renal tubular acidosis (pRTA), the rates of urinary ammonium excretion were considered inappropriately low for their state of chronic metabolic acidosis. These observations were made while the patients were on a normal diet as well as when they were undergoing a short ammonium chloride test. Because these findings suggested an impaired ability to excrete maximal amounts of ammonium, the response to the 3-day acid loading test was evaluated in eight patients with isolated pRTA and in 10 normal control subjects. Plasma creatinine, acid-base, and electrolyte values were analyzed before and after 3 days of ingesting 2 mmol/kg·24 h of ammonium chloride. Twenty-four–hour urine specimens were collected the day before and on the third day of acid loading to determine urine pH, as well as the rate of excretion of NH_4^+ and titratable acid in milliequivalents per 24 h per 1.73 m^2. During the basal state, all patients with pRTA had hyperchloremic metabolic acidosis and they excreted urine of lower pH (5.51 ± 0.18 versus 6.00 ± 0.13; $P < 0.05$) and greater titratable acid (29.1 ± 4.3 versus 21.8 ± 1.4; $P < 0.05$); however, they had rates of NH_4^+ excretion similar to those of controls. On the third day of acid loading, they excreted urine of lower pH (4.66 ± 0.03 versus 5.00 ± 0.03; $P < 0.05$) and equivalent amounts of titratable acid, whereas their NH_4^+ excretion was significantly less than that of controls (47.7 ± 4.4 versus 76.3 ± 5.7; $P < 0.05$). These results show that patients with isolated pRTA have an impaired excretion of urinary ammonium and suggest that a decreased supply of NH_3 to the distal tubular fluid may contribute to their urine of lower pH.

Key Words: *Acid balance, acid loading, titratable acid, urinary pH*

In proximal renal tubular acidosis (pRTA), also known as "Type 2" or "bicarbonate wasting" renal tubular acidosis, reduced rates of bicarbonate reabsorption by the proximal tubule lead to a large fraction of filtered bicarbonate to be excreted in the urine. This bicarbonate wasting produces a state of hyperchloremic (normal anion gap) metabolic acidosis, and when the plasma bicarbonate concentration drops to levels below its renal threshold, the urine pH falls below 5.3.

The Fanconi syndrome is a generalized disorder of proximal tubular transport in which there is bicarbonate wasting as well as glycosuria, aminoaciduria, and increased clearance of phosphate. This syndrome is frequently cited as the prototype of pRTA (1). In contrast to this clinical entity, Rodriguez-Soriano *et al.* (2) first described in two children an isolated type of pRTA where the only renal functional abnormality was a decreased bicarbonate reabsorption, with no other evidence of proximal or distal tubular disorder. In 1977, we reported nine members of a family with a similar defect of isolated pRTA, persisting through adult life and without a detectable defect in other proximal or distal tubular functions (3). In two of these subjects, Lemann *et al.* (4) demonstrated that their net acid excretion (NH_4^+ + titratable acidity − HCO_3) was sufficient to compensate for the usual daily acid production of a normal diet. These same studies also showed that, in spite of their chronic metabolic acidosis, they sustain a normal calcium and phosphorous balance with no detectable bone disease. However, in spite of an adequate excretion of the endogenous acid produced by their diet, we observed that the rate of urinary ammonium excretion was inappropriately low for their chronic state of hyperchloremic acidosis. Furthermore, when challenged with an acute oral ammonium chloride load, they produced sufficient urinary net acid, as compared with normal subjects, but the contribution of ammonium to this quantity was usually smaller than that of titratable acid (TA) (3).

To investigate if these previous observations were evidence of an impaired ability to excrete maximal

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amounts of urinary ammonium, we submitted them to the 3-day NH_4Cl loading test as described by Elkinton *et al.* (5). The data to be reported in this article indicate that this sustained acid challenge to patients with isolated pRTA resulted in a lower rate of excretion of NH_4^+, despite a more severe acidosis and a lower pH of the urine than were observed in a control population.

METHODS

The control subjects were seven men and three women, all members of the medical and nursing staff of our hospital. Their ages ranged from 22 to 58 yr. The eight subjects with isolated pRTA, four men and four women, included six patients of the previously described family (3), plus two newly found members detected after the original report. They were from 22 to 60 yr of age, well nourished, and entirely asymptomatic. The two new members as well as the other six reported cases, fulfilled the criteria of isolated pRTA as described in Table 1. Informed consent was obtained from all participants, and these studies were done with the approval of the Committee on Human Research of Hospital San Juan de Dios and in accordance with the principles of the Declaration of Helsinki. No medication was taken for at least 2 wk before these studies, and all participants were instructed to adhere to their regular diet, consume fluids *ad libitum*, and perform their daily activities as usual. The protocol had two phases; the first consisted of a basal period, and the second phase followed the ingestion of ammonium chloride for 3 days. On the first day of the study, the collection of a 24-h urine specimen was started after the 6:00 a.m. sample was discarded. All urine samples were preserved under thymol and mineral oil in tightly capped and refrigerated bottles. During the first morning, between 8:00 and 9:00 a.m. and while the subjects were in the fasting state, an arterialized blood sample was obtained to determine their basal plasma creatinine, acid-base, and electrolyte composition. After this procedure, each subject ingested 2.0 mmol/kg·24 h of ammonium chloride, which was dispensed in gelatin capsules and administered in four divided doses throughout the day.

On the third day of ammonium chloride loading, another 24-h urine specimen was collected. The protocol ended on the following morning after another arterialized blood sample was obtained.

TABLE 1. Criteria for selection of patients as having isolated pRTA

Creatinine Clearance (mL/min·1.73 m^2)	>75
Plasma Bicarbonate (mEq/L)	<18
Plasma pH	<7.37
Plasma Anion Gap (mEq/L)	8 to 16
Plasma K (mEq/L)	3.5 to 4.8
FEFB[a] at Plasma (HCO_3) of 23 mEq/L (%)	>15
Tubular Reabsorption of Phosphate (%)	>85
Glucosuria	Absent
Aminoaciduria	Absent
Hypercalciuria	Absent
Nephrocalcinosis	Absent
Urine pH at Plasma (HCO_3) of <18 mEq/L (U)	<5.3
Maximal Urine Osmolality (mosM/kg H_2O)	>800

[a] Fractional excretion of filtered bicarbonate; HCO_3, bicarbonate concentration.

Analytical Techniques

Analytical methods for electrolytes, creatinine, and ammonium were done as previously reported (3). Blood pH and P_{CO_2} were determined anaerobically at 37°C with a Corning 168 pH/Blood Gas Analyzer (Medfield, MA), whereas plasma bicarbonate was calculated from these values according to the Henderson-Hasselbalch equation, with a carbon dioxide solubility coefficient of 0.0301 and a pK'_a of 6.1.

Urine pH and titratable acidity were measured at room temperature with an automatic titrator (RTS 822; Radiometer, Copenhagen, Denmark).

Data Analysis

The plasma data pertaining to each subject are shown during the basal state and after 3 days of acid loading. The urine pH, together with the excretion rates of phosphate, ammonium (NH_4^+), and TA, is given for all of the participants before and on the third day of ammonium chloride ingestion.

The mean and SE of each set of plasma and urinary values were calculated for both groups. The differences between the means of the two groups were compared, as were those corresponding to the two phases of the study within each group. The differences between mean values were analyzed by the *t* test for paired and unpaired data as appropriate. Significance was designated as $P < 0.05$. All statistics were done with the Stat View® Program (Brain Power Inc., Calabasas, CA).

RESULTS

All 18 subjects tolerated the ammonium chloride capsules without incident. The values obtained in the 10 control subjects for plasma creatinine, phosphate, acid-base, and electrolytes before and after the ingestion of NH_4Cl are provided in Table 2. All values in the basal state fall in the usual normal range; we emphasize that their blood pH, P_{CO_2}, and plasma bicarbonate were the same as previously reported from our laboratory for the normal adult population of San Jose, Costa Rica, which is at an alti-

tude of 1,200 m (6). After the third day of acid loading, all subjects had a significant fall in their plasma pH and bicarbonate with an increase in chloride concentration, whereas no appreciable changes were observed in plasma creatinine, phosphate, sodium, potassium, or anion gap.

Table 3 gives similar types of data for the eight subjects with isolated pRTA. During the basal state, they had hyperchloremic metabolic acidosis, but the other plasma values were no different from those of control subjects. A similar effect of ammonium chloride loading was also observed in these individuals, because after the third day, a greater degree of hyperchloremic metabolic acidosis was present with no significant alterations in the other plasma components.

The urinary pH, as well as the excretion rates for TA ammonium (NH_4^+), and phosphate, is given in Table 4 for all 18 participants. It also shows the mean ± SE of these determinations for both groups of subjects and for each phase of the study, along with the statistical significance of the differences between means.

Table 4 demonstrates that, during the basal state, both groups had similar rates of phosphate excretion, but the patients with pRTA produced more TA because of lower urine pH (5.51 versus 6.00). On the other hand, despite their stated chronic acidosis, they had NH_4^+ excretion rates similar to those of control subjects.

On the third day of ammonium chloride ingestion, the two groups had similar rates of phosphate and

TABLE 2. Plasma values in 10 control subjects before (B) and after (A) 3 days of NH_4Cl loading

NH_4Cl No.	Creatinine (mg/dL)		pH		P_{CO_2} (mm Hg)		HCO_3^- (mEq/L)		Na^+ (mEq/L)		K^+ (mEq/L)		Cl^- (mEq/L)		P (mmol/L)	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	0.7	0.8	7.44	7.36	32	29	21.3	16.1	139	137	4.2	4.0	100	105	1.2	1.4
2	1.2	1.1	7.40	7.37	37	36	22.6	20.7	136	138	3.5	3.9	103	110	1.3	1.1
3	1.0	0.8	7.43	7.35	38	40	25.3	21.6	137	136	4.6	3.6	100	102	0.9	1.3
4	0.6	1.4	7.44	7.38	37	35	25.5	20.4	144	140	3.7	4.6	107	109	1.2	1.4
5	1.0	1.0	7.41	7.32	35	39	24.1	19.5	136	136	4.0	3.6	100	102	1.5	1.2
6	1.1	1.4	7.42	7.35	41	39	26.5	21.4	137	140	3.7	4.4	104	111	1.4	1.4
7	0.9	0.7	7.44	7.38	35	33	23.4	19.1	142	138	3.6	3.6	104	106	1.0	1.3
8	0.6	1.1	7.41	7.31	32	31	20.5	15.3	135	138	4.6	4.0	99	108	1.1	1.5
9	0.9	0.8	7.38	7.38	42	32	24.5	18.2	136	137	4.2	4.6	100	106	1.3	1.1
10	1.1	0.7	7.39	7.32	35	36	20.6	18.6	138	140	4.4	3.7	104	108	0.9	1.1
Mean	0.9	1.0	7.42	7.35[a]	36	35	23.4	19.1[a]	138	138	4.1	4.0	102	107[a]	1.2	1.3
SE	0.1	0.1	0.01	0.01	1.0	1.2	0.7	0.7	1	0.5	0.1	0.1	0.8	1	0.07	0.04

[a] Different from B at the $P < 0.05$ level.

TABLE 3. Plasma values in eight subjects with isolated pRTA, before (B) and after (A) 3 days of NH_4Cl loading

NH_4Cl No.	Creatinine (mg/dL)		pH		P_{CO_2} (mm Hg)		HCO_3^- (mEq/L)		Na^+ (mEq/L)		K^+ (mEq/L)		Cl^- (mEq/L)		P (mmol/L)	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	0.8	0.9	7.28	7.21	27	20	12.1	7.8	139	138	3.5	4.1	117	117	1.0	1.4
2	0.6	0.9	7.35	7.24	28	33	15.2	13.7	142	140	4.2	3.9	111	113	1.4	1.3
3	0.9	0.8	7.29	7.31	35	30	16.8	14.8	137	136	4.0	3.8	109	110	1.3	1.0
4	1.1	1.4	7.34	7.34	32	24	17.0	12.3	136	140	3.8	3.6	111	114	1.2	1.4
5	1.1	1.1	7.32	7.21	30	33	14.9	12.6	139	141	4.0	4.3	112	116	1.0	0.9
6	0.6	1.0	7.36	7.30	30	26	16.5	12.2	140	140	3.6	3.9	110	113	1.5	1.2
7	0.9	0.7	7.36	7.32	24	19	13.2	9.2	137	138	4.1	4.0	111	117	1.1	1.1
8	1.2	1.5	7.31	7.28	34	27	16.6	12.3	138	141	3.6	4.0	112	116	1.2	1.5
Mean	0.9	1.0	7.33	7.28[a]	30	26	15.3	11.9[a]	139	139	3.9	3.9	111	115[a]	1.2	1.2
SE	0.1	0.1	0.01	0.02	1.3	1.9	0.1	0.8	0.6	0.6	0.1	0.1	1	1	0.06	0.08

[a] Different from B at the $P < 0.05$ level.

TABLE 4. Urine values in all 18 subjects before and on the third day of NH_4Cl loading[a]

No.	10 Control Subjects								8 Patients With Isolated pRTA							
	Basal				3rd Day of NH_4Cl				Basal				3rd Day of NH_4Cl			
	UpH (U)	TA (r)	NH_4^+ (r)	P (r)	UpH (U)	TA (r)	NH_4^+ (r)	P (r)	UpH (U)	TA (r)	NH_4^+ (r)	P (r)	UpH (U)	TA (r)	NH_4^+ (r)	P (r)
1	5.77	23.3	32.4	22.2	4.76	38.0	48.4	25.2	5.65	23.0	16.0	20.8	4.60	38.4	29.2	26.2
2	5.90	21.5	17.8	23.8	5.02	41.6	62.2	29.7	5.05	19.0	28.0	16.9	4.55	46.3	55.0	26.9
3	5.35	26.4	37.4	22.3	5.08	39.6	50.3	28.1	5.10	32.0	31.5	22.4	4.71	48.6	52.2	29.4
4	6.50	24.5	30.1	32.4	5.00	42.5	68.8	42.5	5.50	23.0	26.0	21.5	4.60	44.8	42.0	27.9
5	6.35	15.5	12.3	24.1	5.00	45.8	90.4	32.7	6.60	27.0	20.0	42.6	4.65	66.8	66.2	48.2
6	5.70	25.2	25.0	27.7	5.10	53.4	92.8	38.9	5.60	22.0	23.0	20.8	4.70	48.6	40.8	34.4
7	5.55	24.6	38.0	23.6	4.88	48.8	83.0	33.5	5.00	57.0	42.0	35.6	4.80	55.7	58.8	41.1
8	6.25	25.6	51.3	36.6	5.02	54.5	86.5	38.9	5.55	29.4	29.4	26.2	4.70	38.5	37.4	28.6
9	6.30	14.7	29.6	24.8	5.12	57.6	99.5	42.0								
10	6.35	16.3	33.0	25.4	5.04	37.2	80.7	28.6								
Mean	6.00	21.8	30.7	26.3	5.00	45.9	76.3	34.1[b]	5.51[c]	29.1[c]	27.0	25.9	4.66[d]	48.5	47.7[d]	32.8[b]
SE	0.13	1.4	3.5	1.5	0.03	2.3	5.7	2.0	0.18	4.3	2.8	3.8	0.03	3.3	4.4	2.8

[a] r, rates of excretion = TA and NH_4^+ in milliequivalents and phosphate (P) in millimoles per 24 h/1.73 m^2. UpH = urinary pH.

[b] Different from basal period at $P < 0.05$.

[c] Different from basal control subjects at $P < 0.05$.

[d] Different from control subjects on the third day of NH_4Cl at $P < 0.05$.

TA excretion, even though the patients with pRTA had a lower urine pH (4.66 versus 5.00). If one considers that phosphate has a pK_2' of 6.8, it can be calculated quite easily that any fall in urine pH below 5.5 will produce very little TA for each millimole of phosphate excreted. For a simpler calculation of the contribution of this phenomenon, see reference 14. However, the most important observation in this phase of the study was the fact that the patients with pRTA excreted less NH_4^+ than the controls, even though they had a more sustained and severe acidosis as well as a urine of lower pH.

DISCUSSION

Previous studies in subjects with isolated pRTA have shown normal values for most renal functions, such as GFR, as well as their ability to reabsorb amino acids, glucose, and phosphate. Distal tubular functions have been found normal by the capacity of subjects with isolated pRTA to excrete urine with a pH below 5.3 and to achieve maximum and minimum urine osmolality under appropriate stimuli (2,3,7). It had also been demonstrated that these subjects were able to lower urinary sodium concentration to less than 10 mEq/L when a low-sodium diet was ingested (8). Previous metabolic studies, done in two subjects included in this work, attest to their normal acid, calcium, and phosphorus balance (4).

Although chronic NH_4Cl loading was not performed in other studies, the rates of NH_4^+ and TA excretion after an acute acid load test have been considered adequate when compared with those of normal controls (9–11). In fact, until now, the only abnormal renal function detected in subjects with isolated pRTA was a greatly reduced tubular reabsorption of bicarbonate, which undoubtedly causes their metabolic acidosis. We had pointed out in earlier publications that these urinary NH_4^+ values, although adequate for normal individuals, were inappropriately low when compared with those for normal subjects submitted to chronic metabolic acidosis (12–14). However, despite an inappropriately low rate of NH_4^+ excretion, patients with isolated pRTA, as previously demonstrated, live in a normal acid balance (4). In this study, a similar conclusion is implied by comparing the net acid excretion of the two groups during the basal state. As discussed before, their lower urine pH produced a greater TA than controls and was thus able to compensate for their inappropriately low NH_4^+ excretion. It is during the third day of NH_4Cl loading that a definite impairment in urinary NH_4^+ excretion was clearly demonstrated. The 10 controls had a mean excretion rate of 76 mEq/24 h·1.73 m^2, which is not significantly different from that of 10 subjects receiving similar doses in the report of Elkinton *et al.* (5). On the other hand, the subjects with isolated pRTA had a lower NH_4^+ excretion of 48 mEq/24 h·1.73 m^2, despite the same amount of acid loading, a greater degree of acidosis, and urine with a lower pH. These findings during the third day of loading reveal that both NH_4^+ excretion and urine pH are decreased

in the pRTA group. On the other hand, the controls show higher urine pH and rates of NH_4^+ excretion.

Classically, the response to an acute acid load has been regarded as an inverse correlation between urine pH and NH_4^+ excretion (10,11). In other words, there is a concomitant decrease in urine pH along with an increased NH_4^+ excretion. Because other investigators have found the opposite, *i.e.*, a direct correlation between urine pH and ammonium excretion, during chronic acid loading or when only the experimental values are analyzed (9,12), the importance of NH_3 as the predominant buffer modifying the urine pH has become evident. In this study, the association of a lower urine pH in the subjects with pRTA and with a clear demonstration of an impaired ammonium excretion makes it seem logical to ascribe the low urine pH to a decreased ammonia buffer. The control of ammonium excretion by the kidney has been recently reviewed (15,16). This control is achieved by its rate of production, predominantly in the proximal tubule cells, from whence it is preferentially secreted into the tubule lumen across the apical membrane.

The active absorption of NH_4^+ by the thick ascending limb of Henle's loop allows the accumulation of ammonium, by countercurrent multiplication, into the renal medullary interstitium. Finally, ammonium enters the collecting duct mainly through the diffusion of NH_3 along gradients established by proton secretion. In view of the normal renal functions previously described in subjects with isolated pRTA, it would seem unlikely that the distal tubule or other structures within the renal medulla were the cause of an inadequate supply of NH_3 to the final urine. Instead, as originally suggested (3), a defect in ammonia production within the proximal tubule cells would be a more likely explanation. Also, because a decreased bicarbonate reabsorption by the proximal tubule could render a fluid of higher pH at this site than in the acidotic controls, this could lead to a decrease in NH_3 trapping.

Another explanation for a decreased ammonium secretion in the proximal tubule would be an impairment in the apical Na^+/NH_4^+ exchange mechanism.

More recently, Halperin *et al.* (17) have suggested an interesting hypothesis to explain both the decreased renal threshold for bicarbonate reabsorption and the impaired ammonium excretion seen in these subjects with isolated pRTA. They proposed that in spite of the patients' chronic state of metabolic acidosis, the intracellular fluid (ICF) pH of their proximal convoluted tubules might be more alkaline than in normal subjects.

This decrease in ICF hydrogen ion concentration would lead to a lesser activity of the Na/H ion antiporter, and thus to a decreased bicarbonate reabsorption (18). Because the main stimulus for ammonium production is a low ICF pH of the proximal tubular cells (19), they have proposed that this relative alkalinity of the proximal tubular cells could also explain the lower rates of ammonium excretion, even under NH_4Cl loading.

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