

Impaired Acidification of Urine in Children Aged Two Months to Two Years with Acute Gastroenteritis Complicated by Acidosis

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ABSTRACT

Background: In some children with acute gastroenteritis and acidosis, the urine pH may be abnormally high thus simulating distal Renal Tubular Acidosis (dRTA). This inability to acidify urine properly in the presence of metabolic acidosis has been shown to be due to poor delivery of sodium to the distal nephron which prevents full excretion of a hydrogen ion load, instead of an intrinsic defect in the ability of the distal tubule to acidify urine. The aim of this study is to determine the prevalence of transient urinary acidification defect in children aged two months to two years with acute gastroenteritis, dehydration and acidosis, and the relationship between urine pH and urine sodium concentration.

Method: A prospective study of children aged two months to two years admitted for the treatment of acute gastroenteritis and dehydration at the Children's Emergency Ward (CHEW) of the University of Port Harcourt Teaching Hospital, Rivers State

Results: Of the 196 children (140 males and 56 females) studied with spontaneous acidosis which developed as a result of acute gastroenteritis, seventy-three of them had impaired acidification of urine, giving a prevalence of 37.2%. There was no significant difference in the age, duration of symptoms, degree of acidosis, degree of dehydration and serum potassium concentration between the children with impaired and those with proper urine acidification. Those with impaired acidification of urine however had a significantly lower serum sodium and urine sodium concentrations and a significantly higher urine potassium concentration and urine anion gap than those children with proper urine acidification. All urine samples with sodium concentration less than or equal to 25mmol/L (52) had urine pH greater than 5.5.

Conclusion: Mere presence of acidosis and high urine pH should not lead to a diagnosis of Distal Renal Tubular Acidosis (dRTA). The urine anion gap (UAG) should be calculated using the formula: urine $[Na^+] + [K^+] - [Cl^-]$, and if negative, it suggests a high ammonium excretion, which makes the diagnosis of dRTA unlikely.

KEY WORDS: Gastroenteritis; Renal tubular acidosis; Acidification defect; Urine pH.

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INTRODUCTION

Diarrhoea is among the top three causes of childhood morbidity and mortality, especially in developing countries. The causes of mortality are dehydration, electrolyte and acid-base derangement, as well as undernutrition (especially if the diarrhea becomes persistent)^{1,2}. Frequently, the condition is also complicated by severe metabolic acidosis as a result of excessive loss of bicarbonate in diarrhoea stools, and over-production of organic acids from incomplete metabolism of carbohydrates^{1,3-7}. The kidneys usually respond to the acidemia by reclamation of filtered bicarbonate in the proximal tubule, distal secretion of hydrogen ion, augmentation of ammonium excretion, generation of new bicarbonate and excretion of an acidic urine with a pH less than 5.5^{5,8}.

In some children with acute gastroenteritis however, the urine pH is abnormally high, usually exceeding 5.5 even in the presence of acidosis^{5,6,9,10}. Such children had been erroneously thought to have distal renal tubular acidosis^{5,9}. This is because demonstration of a urinary pH greater than 5.5 in the presence of metabolic acidosis had been the only criterion used to diagnose dRTA¹¹⁻¹³. Inadequate delivery of sodium to the distal tubules was found to be the cause of this transient acidification defect. The poor delivery of sodium to the distal exchange site diminishes the luminal potential difference which is the driving force for hydrogen ion secretion^{5,14-16}.

The renal acid excretion, if distal acidification is intact, is usually in the form of ammonium and titratable acid^{5,6,8}. Laboratory estimation of urine ammonium is very difficult and not carried out by many hospitals. However, ammonium excretion can be estimated by calculating the urinary anion gap (UAG) using the formula: $UAG = [Na^+] + [K^+] - [Cl^-]$ ^{10,17,18}. If the urine anion gap is negative, this suggests a high urinary ammonium excretion, which means that the kidney is not the primary cause of the hyperchloraemic metabolic acidosis. If however the urine anion gap is positive, this represents an impaired ammonium excretion,

suggesting that the kidney is the cause of the hyperchloraemic metabolic acidosis^{6,8,19}. Inability to acidify urine makes it difficult to fully reclaim the bicarbonate escaping absorption at the proximal tubule, with resultant bicarbonaturia, even in the presence of acidosis. Also, ammonium excretion is impaired and hypokalaemia may worsen because of excessive potassium secretion (in place of hydrogen). Furthermore, metabolic acidosis worsens because hydrogen ions are not effectively secreted and excreted.

SUBJECTS AND METHODS

This study was carried out in the Children Emergency ward of University of Port Harcourt Teaching Hospital. Included in the study were children aged two months to two years with acute watery diarrhea, clinical signs of dehydration, metabolic acidosis with serum bicarbonate less than 18mmol/L, normal serum creatinine level and whose parents or caregiver gave their consent after the nature of the study had been explained to them.

Excluded were those with a history of previous renal disease or raised creatinine level at any time during hospitalization, children with severe malnutrition (marasmus or kwashiorkor), children with dysentery, those who received steroids or frusemide during the study, and those in whom urine sample could not be collected within four hours of the blood sample collection. The minimum sample size of 174 was determined using a prevalence rate of 87% acidification defect in children with acute gastroenteritis, dehydration and acidosis from a previous study⁹, with the formula: $n = z^2 (p \times q) / e^2$

The children were examined by both the registrar on duty and one of the investigators, and the level of dehydration determined using the guidelines in the WHO programme for assessing the diarrhea patient²⁰.

Treatment protocol: Those whose clinical assessment showed "some dehydration" were rehydrated using treatment plan B (75mls/kg of ORS solution or intravenous Ringer's Lactate Solution, 70mls/kg if the vomiting is persistent, and given over the first four hours). Intravenous half-strength Darrows solution was also used in place of intravenous Ringer's Lactate Solution if the latter was not available, or if the patient had severe hypokalaemia with hypotonia and paralytic ileus. Those with severe dehydration were rehydrated using treatment plan C (intravenous Ringer's Lactate or if not available, normal saline, 100mls/kg given as 30mls/kg in the first one hour and 70mls/kg over the next five hours for infants, and for an older child, 30mls/kg in the first 30 minutes, followed by 70mls/kg over two and

half hours)²¹.

The patients were reassessed hourly (for those with severe dehydration) until there was a definite improvement (strong radial pulse, improved skin turgor, passage of urine, improved level of consciousness), and four hourly (for those with some dehydration). In the maintenance phase, the ongoing losses (continuing stool losses and vomiting) was replaced, using either ORS or 4.3% dextrose/0.18 normal saline depending on the tolerability of oral fluids, until diarrhoea stops. Feeding of the patient was also recommenced and the amount gradually increased as the child could tolerate. Other fluids like breast milk, fruit juices or beverages were also allowed.

Laboratory protocol: On admission, two milliliters of venous blood sample was withdrawn into a lithium heparin bottle by one of the investigators, and the patient commenced on the appropriate treatment protocol. The blood was then sent to the laboratory where it was centrifuged immediately (within one hour of collection) and the serum analyzed for sodium, potassium, chloride, bicarbonate, urea and creatinine. Urine sample was also collected within 4 hours of the blood collection, during the rehydration therapy but before the dehydration had been corrected. The urine was collected either by a clean catch into a universal urine bottle, or with the aid of a sterile urine collector applied to the vulva (females) or around the penis (males). The urine so collected was immediately analyzed for pH using Medi-Test Combi 9 multistix (Machery-Nagel, Postfach 101352, D-52313) The urine was then sent to the laboratory where it was analyzed for sodium and potassium (flame photometer) and chloride (radiometer) concentration. Urinary acidification defect was diagnosed if urine pH was more than 5.5 in the presence of acidosis (serum bicarbonate less than 18mmol/L). Urinary sodium less than 25mmol/L would suggest inadequate distal sodium delivery¹⁰. The urinary anion gap (UAG) was calculated using the formula: $UAG = \text{urine } [Na^+] + [K^+] - [Cl^-]$ (normal = 0), and this was used as an index of ammonium excretion.

Ethical consideration: The Ethics Committee of the University of Port Harcourt Teaching Hospital gave approval for the study and an informed signed consent was also obtained from the parents/guardians.

Statistics: The raw data were collated into a master sheet. Only data from patients who fulfilled the inclusion criteria was analyzed. Qualitative data was assessed using chi-square test and quantitative data by Student's t-test. A p - value of 0.05 or less was

considered as being statistically significant. Data are expressed as mean (\pm S.D) and was analyzed using SPSS 10 statistical package.

RESULTS

Two hundred and fifteen children aged between 2 months and 2 years, who were hospitalized for acute watery diarrhoea and dehydration were seen within the study period. One hundred and ninety-six children (140 males and 56 females) however were used for the final analysis. The male: female ratio was 2.5:1. Of the 19 children excluded, urine could not be collected within 4 hours of the blood collection in 9 of them, and 10 did not meet the inclusion criteria (7 had raised creatinine levels ($>65\mu\text{mol/L}$) and 3 had normal bicarbonate levels ($>18\text{mmol/L}$). One hundred and sixty-four children (83.7%) had signs of "some" dehydration and 32 (16.3%) had clinical signs of "severe" dehydration as previously defined (Table I).

Fifty-two (26.5%) of the children had very low urine sodium ($<25\text{mmol/L}$), and the urine anion gap was negative or 0 with a mean of -50.36mmol/L (± 37.47). The serum sodium concentration was less than 130mmol/L in 4 children (2%) and 150mmol/L and above in 12 children (6.1%). One child with hypernatremia had two episodes of seizures, whereas the others were without symptoms. Twenty-six children (13.3%) had serum potassium concentration less than 3mmol/L . None of the children had hyperkalaemia. All the children had plasma anion gap within normal range.

Urinary acidification defect

Seventy-three children had impaired acidification of urine (i.e. pH greater than 5.5 in the presence of acidosis), giving the prevalence of transient urinary acidification defect in children with acute gastroenteritis of 37.2%. Forty-one (29.3%) of the 140 males and 32 (57.1%) of the 56 females had impaired acidification of urine. This difference in prevalence among males and females was statistically significant ($\chi^2 = 13.27$; $df = 1$; $p < 0.05$). Sixty-one of the children had "some" dehydration whereas 12 of them had severe dehydration. None of the children with severe dehydration and clinical signs of hypovolemic shock had impaired acidification defect. Defective urine acidification was also not seen amongst the thirteen youngest patients aged 2-3 months (Fig.2). All the 52 children with inadequate distal delivery of sodium (urine sodium $=25\text{mmol/L}$) had urine pH above 5.5. Table II compares the mean age, serum and urine electrolytes of children with normal and those with impaired urine

acidification. There was no significant difference in the age ($t = 0.093$; $df = 194$; $p > 0.05$), serum potassium ($t = 0.544$; $df = 194$; $p > 0.05$) and the serum bicarbonate ($t = -0.138$; $df = 194$; $p > 0.05$) in the two groups. The serum sodium, serum chloride, urine sodium and urine chloride were however significantly lower in the children with impaired urine acidification than in those with normal urine acidification. The mean urine potassium and mean urine anion gap of the children with impaired urine acidification were higher than those of the children with normal acidification, and the differences were statistically significant. The difference in their degree of dehydration was not significant ($\chi^2 = 0.03$, $df = 1$; $p > 0.05$ using Yates correction).

Relationship between urinary sodium and urinary pH.

Figure 1 shows the relationship between the pH of the urine and the urinary sodium. The urine pH was high in the patients with low urine sodium. Table III shows the serum and urinary electrolyte, UAG and pH values according to urine sodium concentration. The serum sodium was significantly lower and the urine pH, urine potassium and urine anion gap significantly higher in the group of children with urine sodium $=25\text{mmol/L}$ when compared to the group of children with urine sodium above 25mmol/L . The age, duration of symptoms, degree of dehydration and degree of acidosis did not differ significantly in the two groups of children.

Table I. Characteristics of the patients on admission.

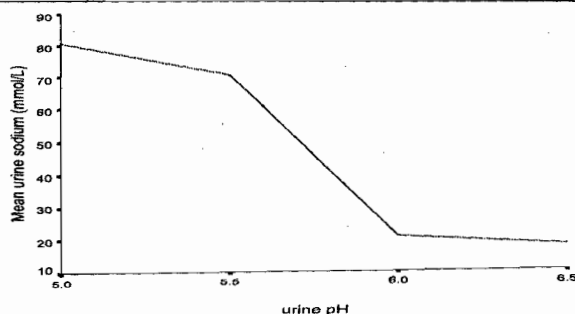
Characteristics	mean (\pm S.D) n = 196
Age (months)	9.73 (5.14)
Weight (Kg)	7.89 (2.39)
Duration of diarrhea (days)	3.24 (2.38)
No. of stools / day	5.74 (2.09)
Male : Female. No (%)	140:56 (71.4:28.6)
Degree of dehydration. No (%)	
"some"	164 (83.7)
"severe"	32 (16.3)

Table II. Comparison of the age, serum and urine electrolytes in those with normal and impaired urine acidification.

	Urine pH		p
	=5.5 (n=123)	>5.5 (n=73)	
Age (months)	9.76 (5.35)	9.68 (4.81)	NS
Serum values (mmol/L)	mean (±S.D)		
Sodium	140.16 (7.14)	133.86 (4.06)	<0.000
Potassium	3.6 (0.65)	3.5 (0.66)	NS
Chloride	114.15 (8.01)	105.81 (12.01)	<0.000
Bicarbonate	14.36 (2.75)	14.41 (2.33)	NS
Urine values (mmol/L)	mean (±S.D)		
Sodium	77.90 (43.98)	20.42 (12.75)	<0.000
Potassium	9.43 (6.54)	16.30 (15.30)	<0.000
Chloride	142.78 (49.65)	77.99 (20.54)	<0.000
Urine anion gap	-55.82 (44.57)	-44.15 (17.29)	<0.008

Table III. Serum and Urinary electrolyte, UAG and pH values according to urine sodium concentration

	Urine sodium (mmol/L)		p
	= 25 (n=52)	>25 (n=144)	
Serum values (mmol/L)	mean (±S.D)		
Sodium	133.65 (4.03)	139.32 (5.45)	<0.000
Potassium	3.36 (0.63)	3.60 (0.647)	<0.022
Chloride	104.94 (13.78)	113.25 (7.97)	<0.000
Bicarbonate	14.58 (2.16)	14.31 (2.74)	NS
Urine values (mmol/L)	mean (±S.D)		
Sodium	13.98 (7.14)	71.85 (43.34)	<0.000
Potassium	17.69 (17.52)	9.93 (6.62)	<0.000
Chloride	73.79 (19.45)	134.85 (50.30)	<0.000
Urine anion gap	-41.96 (18.53)	-53.39 (41.92)	<0.059
pH	6.19 (0.25)	5.27 (0.37)	<0.000


Fig 1. Urine pH in relation to mean urine sodium concentration in 196 children with diarrhoea.

DISCUSSION

The prevalence of impaired urinary acidification in this study was 37.2%. This is much lower than the 87% reported by Izraeli et al.⁹ The difference may be due to the methodology employed. In that study, urine samples were analyzed for pH using a Radiometer gas analyzer, which is more sensitive and accurate in detecting pH. Also, children whose urine samples were tested on the second day of admission were included in their determination of the prevalence. In this study however, urine pH was tested using a multistix, which is not as sensitive in detecting finite pH values, and only the urine values obtained within four hours of admission were used to determine the prevalence.

There was no significant difference in the mean ages of those who had acidification defect and those who were able to acidify their urine properly. This is consistent with the findings in previous studies^{9,22} which showed that very young infants are capable of acidifying their urine. Immaturity of the kidneys therefore did not seem to be the cause of the acidification defect.

Potassium depletion results in inability to establish a normal blood to tubular fluid hydrogen ion gradient. This is because potassium depletion enhances renal ammonia production, and the excessive ammonia presented to the distal tubules combines with any available hydrogen ion to form ammonium ion. The elevation in the urine pH is thus primarily due to increase in ammonia diffusion into the urine, rather than an acquired renal tubular acidosis^{9,23}. Only ten out of twenty-six children whose initial serum potassium concentration was less than 3.0mmol/L developed impaired urine acidification. There was no significant difference in the serum potassium concentration in the two groups of patients. This agrees with the study done by Izraeli and co-workers⁹ but however differs from the findings of Battle et al¹⁰ where the potassium concentration of the study group with diarrhoea, although within the normal range, was significantly lower than the potassium concentration in normal subjects. In the study done by Tanen²³ on normal human subjects to determine the effects of potassium depletion on urine acidification, it was found that the urine pH was significantly higher during potassium deficiency if sufficient potassium depletion had been induced. In that study, the degree of potassium depletion may have been greater, because not only were the subjects receiving low potassium diet, the addition of Kayexalate to the protocol may have provided a much greater potassium-depleting stress than acute gastroenteritis. It thus suggests that the

urine pH is more likely to be increased with larger degrees of potassium depletion due to a concomitant increase in ammonium diffusion into the urine that results from increased renal ammonia production²³.

In this study, the urine potassium concentration was significantly higher in children with impaired urine acidification. This differs from that found by Izraeli *et al*⁹ and Battle *et al*¹⁰ where the urine potassium concentration was higher in those with proper acidification of urine although the difference was only statistically significant in the subjects studied by the latter authors. The reason for this different finding cannot be readily explained. However, it has been shown that the higher the urine pH, the more bicarbonate will appear in urine accompanied by loss of cations, chiefly, sodium and potassium, and that this potassium wasting is further accentuated by the secondary hyperaldosteronism which follows extracellular volume contraction^{5,24}. Serum aldosterone level was not measured in the subjects in this study to ascertain if those with impaired acidification had a more profound hyperaldosteronism. The fact that only children with normal serum concentrations of creatinine were included in this study, excludes renal impairment as the cause of the improper urinary acidification.

Impaired urinary acidification was related to the concentration of sodium in urine. All those with urine sodium less than 25mmol/L had acidification defect. This agrees with the study by Battle *et al*¹⁰ where urine pH could not be reduced below 5.3 when the urine sodium was less than 25mmol/L. This finding could be explained with the findings of earlier studies by Battle *et al*,¹⁴ De Sousa *et al*²⁵ and Schwartz *et al*.²⁶ These authors showed that the urine pH is related to the amount of sodium delivered to the distal tubules for reabsorption, especially if there has been sodium depletion. Sharifi *et al*²⁷ compared the results of oral versus intravenous rehydration therapy in children with severe gastroenteritis. That study showed that the children treated with oral rehydration solution took in significantly more sodium, potassium and bicarbonate, and their hyperchloraemic acidosis was more rapidly corrected than in those who were rehydrated with intravenous fluid. The urinary electrolytes however were not studied, and so, it is difficult to convincingly establish the fact that their earlier correction of acidosis may be related to their earlier correction of sodium deficit, hence increased distal sodium delivery. The fact that oral rehydration salt solution may be superior to intravenous fluid in correcting electrolyte and acid-base abnormalities more rapidly could not be substantiated in

this study, since all the children received oral rehydration salt solution at some point, including those who were initially rehydrated with intravenous fluid.

The urine anion gap was 0mmol/L or negative in all the patients in this study. This agrees with previous works by Battle *et al*¹⁰ and Rodriguez-Soriano and Vallo²⁸ which showed that in gastroenteritis, ammonium excretion is high. This excludes Renal Tubular acidosis as the cause of the impaired urinary acidification. Kim *et al*²⁹ also demonstrated an inverse relationship between the urine anion gap and ammonium excretion i.e. the more negative the urine anion gap, the higher the ammonium excretion. In this study, the urine anion gap was significantly higher (i.e. less negative) in children with impaired urine acidification, suggesting that in them, their ammonium excretion, and hence net acid excretion was lower than in children with proper acidification of urine. A similar finding was obtained in the study by Battle *et al*¹⁰ where the urine anion gap became more negative and the urine pH became more acidic following a single dose of frusemide to some of the subjects to increase distal delivery of sodium.

Impaired acidification of urine was significantly more among females than males in this study. This might be an incidental finding, since it has not been previously reported that impaired ability to acidify urine properly during acidosis was commoner in girls. The sex difference was not considered by the other workers^{9,22}.

This study has thus highlighted the point that the urine pH must always be evaluated in conjunction with the urinary sodium and the urinary ammonium content in order to properly assess the distal acidification process. In the presence of acidosis, a high urine pH in association with a low urine sodium and high ammonium content (as suggested by a negative urine anion gap) rules out an intrinsic defect in distal urinary acidification. Improvement of sodium delivery to the distal acidification sites will usually ensure adequate excretion of the additional acid load with correction of the acidosis. Those with intrinsic acidification defect from distal Renal Tubular Acidosis will however require bicarbonate supplements for life for the correction of the acidosis. Further studies would be required to validate the fact that the superiority of oral rehydration salt solution over intravenous electrolyte solution in correcting the acidosis and hypokalaemia following acute gastroenteritis was as a result of better delivery of sodium to the distal tubule.

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