Journal of Korean Medical Science
Vol. 9, No. 5, 388-393 October 1994

The changes in electrolytes and acid-base balance after artificially induced acute diarrhea by laxatives

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Following the acute diarrhea in patients(n=24) overnight with commonly used laxatives for bowel preparation, the changes in electrolytes and acid-base balance in blood and urine were investigated. Though no alterations of serum sodium or potassium concentrations were noted, mild but significant reduction of mean values(±SEM) of plasma pH and HCO_3 after diarrhea when compared to those before it developed(pH, from 7.42±0.01 to 7.39±0.01, $p<0.01$; HCO_3, from 25.8±0.6 to 23.7±0.6 mEq/L, $p<0.05$). However, significant reduction of concentration in spot urine sodium from 150±12.3 to 93±14 mEq/g of crea.($p<0.01$) and increase in spot urine potassium from 33±3.2 to 51±6.0 mEq/g of crea.($p<0.05$) following diarrhea were seen with significant reduction of urine pH from 6.67±0.21 to 5.5±0.13($p<0.001$). Also, with this effective urinary acidification following diarrhea, a significant reduction of urinary anion gap as well as significant increment of spot urine ammonium was accompanied(anion gap, from 80.4±11.1 to 44±8.5 mEq/g of crea. $p<0.001$; ammonium, from 87±18.5 to 229±37 mg/g of crea. $p<0.001$) in addition to the significant inverse correlation between these changes in spot urine from basal levels in 24 study subjects($y=-1.13x+61$, $r=0.7$, $p<0.001$). In conclusion, we observed that the acute diarrhea with laxatives used for bowel preparation caused a mild degree of metabolic acidosis with no changes in blood electrolytes. Also, the effective urinary acidification with hyperexcretion of ammonium functioned to mitigate the acute change of blood pH in extrarenal acidosis evoked by acute diarrhea overnight with laxatives, and urinary anion gap was confirmed again as an indirect marker for urinary ammonium.

Key Words : *Diarrhea, Laxative, Electrolyte, Acid-base Balance, Ammonium, Anion gap.*

INTRODUCTION

Diarrhea may be classified pathogenetically according to whether it is due primarily to osmotic, secretory, structural, or motility abnormalities(Weinberg et al., 1990). Many laxatives, besides bacterial endotoxins and neurohumoral agents, act as secretagogues(Dobbins, 1985) and induce secretory diarrhea by the stimulation of colonic electrolyte secretion. For example, studies have indicated that ricinoleic acid, an active component of castor oil,

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which classically was felt to work by enhancing bowel motility, is actually a potent colonic secretagogue through a cAMP-dependent mechanism(Ammon et al., 1974).

It has been well known that the fluid and electrolyte abnormalities associated with diarrhea include volume depletion, hypo- and hypernatremia, and usually metabolic acidosis(but a rare well-defined syndrome of metabolic alkalosis also occurs). However, the exact manifestations of final fluid and electrolyte changes depends on the underlying cause of diarrhea, its severity and chronicity. In laxative abuse, there are scattered and contradictory findings in the changes in electrolytes and acid-base balance. Chronic laxative abuse produces excessive fecal elimination of potassium without concurrent losses of bicarbonate. Thus normal acid-base homeostasis is typically preserved(Schwartz et al., 1953). Also, metabolic alkalosis along with inappropriate losses of urinary potassium has been described in association with laxative abuse(Fleischer et al., 1969). Furthermore, the previous studies regarding laxatives related diarrhea were confined mostly to chronic diarrhea due to chronic surreptitious intake(Schwartz et al., 1953 ; Cogill et al., 1959, LaRusso et al., 1975).

To the best of our Knowledge, the changes in fluid and electrolytes in acute diarrhea with laxatives have not been reported so far. Therefore, the aim of this study was to look for the changes in electrolytes and acid-base balance following acutely induced iatrogenic diarrhea overnight with commonly used laxatives in bowel preparation. We, also, evaluated the value of the recently proposed urinary anion gap(sodium plus potassium minus chloride) as an indirect index of ammonium excretion, which should increase by an appropriate renal response as part of the normal adaptation to gastrointestinal loss of bicarbonate in secretory diarrhea(Goldstein et al., 1986 ; Battle et al., 1988).

MATERIALS AND METHODS

Twenty four patients(initially thirty but six patients were excluded in the analysis data due to underlying organic colonic diseases) admitted to the gastrointestinal service of Hanyang university hospital without acute diarrhea were studied. Sixteen patients had irritable bowel syndrome, 5 had chronic gastritis, and the remaining 3 had peptic ulcer disease as final diagnosis on discharge.

These 24 patients scheduled for either colonoscopy or barium enema at 9 AM the next day were given castor oil, 1.5ml/kg and bisacodyl. 1 tablet per every ten kg of body weight as laxatives for bowel preparation at 9 PM, two hours after a light evening meal, followed by 12 hour-over night fasting. Frequent waterry diarrhea, mostly more than 3 times and 100 grams of stool weight in each bowel movement, was observed in each study subject before the morning procedures.

All 24 subjects underwent blood and spot urine collections twice before laxative-intakes(8PM) and the next day before the procedures(8AM). Measurements of serum and urine electrolytes, urinary pH and arterial blood gas analysis were performed by automated multiple analysis system. Spot urinary ammonium concentration was determined as previously described(Cunnarro et al., 1974).

The serum anion gap defined by the sodium value minus the sum of the chloride and bicarbonate values was used(Oh et al., 1977). The urinary anion gap in urinary pH less than 6.5 indicating no or trivial bicarbonaturia was calculated by subtracting the chloride value from the sum of the sodium and potassium values. If the urinary pH is above 6.5, however, the anion gap was calculated by substracting the sum of the chloride and bicarbonate values from the sum of the sodium and potassium values(Goldstein et al., 1986 ; Battle et al., 1988). This formula was applied in eight patients before laxatives, and no one after laxatives out of twenty four patients recruited for this study because their urinary pH was below 6.5. All values of urinary parameters were expressed per gram(g) of creatinine in urine, concentration of which was measured simultaneously from spot urine.

Statistical analysis of the data was performed with Student's *t* test, and p value of less than 0.05 was considered statistically significant. Results are expressed as mean±SEM.

RESULTS

Changes in mean levels of electrolytes, anion gap and pH of blood and "spot" urine before and after acute diarrhea by laxatives(Table 1, 2)

After acute diarrhea during 12 hours following the intake of laxatives, serum concentrations of sodium, potassium and chloride did not change significantly from normal baseline values. Although still in normal

range, mild but significant reduction after acute diarrhea when compared to those before it developed in bicarbonate(from 25.8±0.6 to 23.7±0.6mEq/L, $p<0.05$) and arterial pH(from 7.42±0.01 to 7.39±0.01, $p<0.01$). No significant difference in the serum anion gap was found before or after acute diarrhea with laxatives(Table 1).

In contrast to mildly reduced blood pH and bicarbonatemia, i.e, mild metabolic acidosis, and no other significant changes in electrolytes or anion gap of blood after acute diarrhea, urinary sodium excretion decreased(from 150±12.3 to 93±14mEq/g of crea. $p<0.01$), urinary potassium increased(from 33±3.2 to 51±6.0mEq/g of crea. $p<0.05$), and urinary pH fell significantly(from 6.67±0.21 to 5.5±0.13) with notable decrease in urinary anion gap(80.4±11.1 to 44±8.5mEq/g of crea.) (Table 2).

Changes in mean values of urinary ammonium and urinary anion gap before and after acute diarrhea by laxatives, and the relationship beween changes of both variables from baseline levels following acute diarrhea(Table 2, Fig. 1)

With the significant reduction in urinary pH and anion gap, significant increment of mean urinary ammonium excretion was accompanied following acute diarrhea (from 87±18.5 to 229±37mg/g of crea. $p<0.001$)(Table 2). When individual subjects of a total 24 patients were considered, all except two showed reduced urinary anion gap with negative values(less than zero) in the change from basal levels following acute diarrhea, and simultaneous increases in the change from basal levels of urinary ammonium excretion were noticed. The mean of de-

Table 1. Changes in mean levels(±SEM) of electrolytes, anion gap and pH of blood following acute diarrhea with intake of laxatives

	Na^+ (mEq/L)	K^+ (mEq/L)	Cl (mEq/L)	HCO_3 (mEq/L)	Anion gap* (mEq/L)	pH
Before laxatives	139 ±0.6	4.0 ±0.08	107 ±0.6	25.8 ±0.6	9.6 ±0.5	7.42 ±0.01
After laxatives	138 ±0.8	4.1 ±0.12	106 ±0.8	23.7 ±0.6	10.3 ±1.1	7.39 ±0.01
p value	NS	NS	NS	<0.05	NS	<0.01

Na^+=serum sodium concentration.
K^+=serum potassium concentration.
Cl=serum chloride concentration.
HCO_3=serum bicarbonate concentration.
*: Anion gap of blood=$Na^+-(Cl+HCO_3)$.

Table 2. Changes in mean levels(±SEM) of electrolytes, ammonium, anion gap and pH of spot urine following acute diarrhea with intakes of laxatives

	Na^+	K^+	Cl	Anion gap *	NH_4	pH
	(mEq/g of crea.)				(mg/g of crea.)	
Before laxatives	150 ±12.3	33 ±3.2	120 ±12.4	80.4 ±11.1	87 ±18.5	6.67 ±0.21
After laxatives	93 ±14	51 ±6.0	110 ±14	44 ±8.5	229 ±37	5.5 ±0.13
p value	<0.01	<0.05	NS	<0.001	0.001	<0.001

Na^+=urine sodium concentration.
K^+=urine potassium concentration.
Cl=urine chloride concentration.
NH_4=urine ammonium concentration.
*: Anion gap of urine=Na^++K^+-Cl when urine pH<6.5 or
$Na^++K^+-(Cl+HCO_3)$ when urine pH>6.5

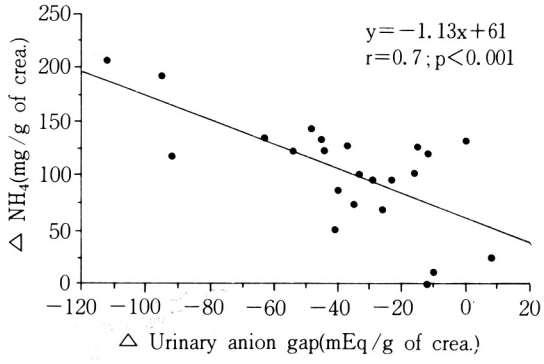

Fig. 1. The relationship between both changes in ammonium($\triangle NH_4$) and anion gap of spot urine from each basal levels after inducing acute diarrhea with laxatives in 24 individual subjects.
(The one of 24 values in this figure was doubled)

creased values from each basal level in the spot urine anion gap was −37.4±6.0mEq/L(range, −112 to 8mEq/g of crea.) and that of increased values in the ammonium excretion of spot urine was 103.2±10.1mg/g of crea. (range, 0 to 207mg/dL). Furthermore, there was a significant inverse correlation between changes in urinary ammonium and those in urinary anion gap from each baseline level($y=-1.13x+61$, $r=0.7$, $p<0.001$). Thus, the higher the change in urinary anion gap, the lower the change in urinary ammonium excretion from it was seen after acute diarrhea by laxatives(Fig. 1).

DISCUSSION

The secretory diarrheas are, generally, characterized by loss of diarrheal fluid that has a sodium content similar to that of plasma(Weinberg et al., 1990). Despite isotonic sodium loss, the resulting volume depletion in severe cases of secretory diarrhea is a non-osmotic stimulus for ADH release when blood volume contracts by more than 8 to 10 percent, leading to water retention by the kidneys with liberal water intake and a tendency to produce hyponatremia(Andreoli, 1988). None of these study subjects, however, developed marked volume loss or thirst related increased water intake during the overnight study. Therefore, the mean value of serum sodium after acute diarrhea by laxatives did not change from the normal baseline value, and compensatory renal sodium retention for extrarenal loss of sodium loss from acute diarrhea was observed in view of significantly reduced urinary sodium excretion as compared to that before the induction of acute diarrhea(Table 1 and 2).

Occasionally, hypokalemia is also noted as a characteristic feature of diarrhea. However, unlike sodium losses, which increase linearly with the amount of diarrheal stool, potassium losses increase less dramatically with increasing volumes of diarrheal stool. Therefore, although potassium losses during large-volume diarrheal states do not increase as dramatically with stool volume as do sodium losses, fecal potassium losses can be a significant cause of body potassium loss, potentially exceeding 100mEq/day in severe diarrheal states(Fordtran, 1967). Though insufficient data are available to permit firm conclusions for the possible contributory role of renal potassium losses to the hypokalemia in diarrhea, certainly the stimulation of the renin-aldosterone axis secondary to volume depletion can promote renal potassium losses. Therefore, the patients with chronic laxative abuse without the evidence of severe diarrhea may present for evaluation of hypokalemia of unknown etiology (Schwartz et al., 1953). With acute diarrhea following intake of laxatives in this study, significant increase of mean value of urinary potassium excretion was noted as expected with lower gastrointestinal fluid losses. A normal range of mean serum potassium concentration, however, was well maintained even after acute diarrhea and these documented urinary potassium losses. We may explain this normokalemia possibly by a complex interplay of the potassium homeostastic mechanism with transcellular shifting by either the presence of metaboblic acidosis or other factors involved in internal balance despite the low total body potassium contents with urinary and intestinal potassium losses by acute diarrhea(Sterns, 1981).

The typical acid-base disturbance associated with diarrhea is a hyperchloremic metabolic acidosis equivalent to normal anion gap metabolic acidosis because stool bicarbonate is high, and chloride low, relative to blood. As expected, though the degree of metabolic acidosis was mild in this study, we observed significant reduction of mean levels of blood pH and serum bicarbonatemia with a still normal mean range of serum anion gap, In response to this diarrhea related extrarenal acidosis, an increase in ammonium excretion is an important feature of an appropriate renal response(Tannen, 1983). Normally, the rate of ammonium excretion

can increase to as much as five to ten times higher than baseline levels as with an acidemic stimulus (Lemann et al., 1966). In this study, mean urinary ammonium excretion after overnight acute diarrhea increased two and half times from mean baseline level before the intake of laxatives(from 87±18.5 to 229±37mg/g of crea. Table 2). Also, the urinary anion gap equal to the sum of sodium plus potassium minus the sum of chloride plus bicarbonate(bicarbonate negligible at urine pH<6.5) known as a useful indirect marker of urinary ammonium excretion with inverse correlation between both (Battle, 1988 ; Goldstein, 1986) was decreased significantly in mean value following acute diarrhea. Despite this expected similar observation of a decreased urinary anion gap after acute diarrhea, the mean value of the urinary anion gap of the present study after it was positive rather than negative value of previous studies by Battle et al., 1988(44±8.5 vs.−20± 5.7mEq/L). We may reason that it would be related to the acute nature and short period of iatrogenically induced diarrhea rather than chronic diarrhea as in previous studies. However, the reduction of the urinary anion gap from basal levels of 24 study subjects except two was obviously noted with the mean reduction of −37.4±6.0mEq/g of crea. The reason remains unclear in these 2 out of 24 patients with no decrease in urinary anion gap from basal levels following acute diarrhea despite the increase in the changes of urinary ammonium excretion to 25 and 132mg/g of crea. respectively(Fig. 1). However, we confirmed again the similar inverse relationship between the changes in urinary ammonium excretion and those in urinary anion gap of all 24 study subjects before and after acute diarrhea following the intake of laxatives.

The urine pH in patients with severe hyperchloremic metabolic acidosis and volume depletion with diarrhea is often increased to 6.0 or more, a finding that may confuse the diagnostic process by suggesting the presence of distal renal tubular acidosis. This indicates that tubular secretion of protons can be impaired if sodium is delivered to proton-secreting sites in quantities inadequate to generate a sufficiently high electrical gradient(Battle et al., 1987). But, we observed that the individual urinary pH of all patients except two after acute diarrhea fell simultaneously as urinary acidification with increased urinary ammonium excretion, and urinary sodium excretion was decreased significantly, but not to less than 15mEq/L in any study subject(not shown in data).

In conclusion, following overnight acute diarrhea with laxatives, a mild degree of normal anion gap metabolic acidosis without significant changes in serum electrolytes, but with significant fall in urinary pH and significant urinary ammonium excretion were observed. This suggests that the effective urinary acidification with mainly increased ammonium excretion mitigated the acute change in blood ph in extra-renal acidosis evoked by acute diarrhea. Also, we confirmed again that the urinary anion gap calculated using readily available laboratory data, namely the urinary electrolytes, can be used as an indirect marker of urinary ammonium in the evaluation of extrarenal acidosis such as diarrhea.

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