Comparision of Urine Anion Gap, Urine Osmolal Gap and Modified Urine Osmolal Gap in Assessing the Urine Ammonium in Metabolic Acidosis

CHALEOMSRI TAPANEYA-OLARN, M.D.*, WIWAT TAPANEYA-OLARN, M.D.*, RATIKORN PHUAKSUNGNERN, M.D.*, THANOM PETCHTHONG, B.Sc.**

Abstract

Twenty-four hour urine and spot urine samples from 29 patients with metabolic acidosis were collected for evaluation of urine ammonium in relation to urine anion gap, urine osmolal gap (OG) and modified urine osmolal gap (MOG).

Their underlying diseases included SLE in 8, RTA in 7, CRF in 6, RPGN in 2 (one with SLE), Lowe syndrome in 2, on acetazolamide in 2, gastroenteritis in 2, and CAH in one. Twenty-three patients had normal serum anion gap (< 14 mmol/L). Their mean CO_2 was 13.77 (9.4-17.9) mmol/L, net acid excretion (NAE) was 33.18±35.36 mmol/24 hour, NH^+_4 excretion was 29.16±31.97 mmol/24 hour.

Neither the 24-hour urine nor spot urine anion gap correlated with corresponding urine NH^+_4 with or without adding urine HCO^-_3 in the calculation.

Spot urine NH^+_4 correlated well with urine OG ($r^2 = 0.82$, $p < 0.001$) and less with MOG ($r^2 = 0.339$, $p < 0.006$). The urine osmolality was well correlated with the sum of 2 ($Na^+ + K^+ + NH^+_4$) + urea for both spot ($r^2 = 0.990$, $p < 0.001$) and 24 hour urine ($r^2 = 0.907$, $p < 0.001$) collection. Twenty-four hour urine NH^+_4 did not correlate with the OG or the MOG.

There was no correlation between spot urine NH_4/Cr ratio and 24 hour urine NH_4/Cr ratio ($r^2 = 0.243$, $p = 0.53$) nor between spot NAE/Cr ratio and 24 hour urine NAE/Cr ratio ($r^2 = 0.380$, $p = 0.014$).

Therefore in the presence of low urine NH^+_4 (< 100 mmol/L), urine osmolal gap may be used to determine urine NH^+_4 indirectly with good correlation. Twenty-four hour urine collection is still necessary to assess renal acidification.

Key word : Metabolic Acidosis, Urine Anion Gap, Urine Osmolal Gap, Urine Ammonium

* Department of Pediatrics,
** Research Center, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Metabolic acidosis is a common acid-base disturbance found in clinical practice. The causes of metabolic acidosis with normal plasma anion gap are from gastrointestinal cause such as diarrhea or from renal cause known as renal tubular acidosis. The causes of metabolic acidosis with wide anion gap are mainly from lactic acidosis, ketoacidosis, chronic renal failure or aspirin ingestion. The renal responses to metabolic acidosis are an increase in urine acid excretion mainly in the form of ammonium (NH^+_4).

The urine pH has been used to evaluate the renal acidification. It is considered to be abnormal if urine pH is ≥ 6 in the presence of metabolic acidosis. However the urine pH reflects free hydrogen ion present in the urine, not the total hydrogen ion (H^+). In the presence of metabolic acidosis, normal kidney excretes more H^+ that binds to the ammonia (NH_3) which is also increased.

If the NH_3 exceeds H^+, there will be less free H^+ despite huge amount of H^+ secreted, and the urine pH can become alkaline and can be misinterpreted as abnormal response[1]. Therefore measurement of urine NH^+_4 excretion is more reliable than urine pH alone in assessing the renal responses in acidosis.

Goldstein et al[2] and Battle et al[3] had attempted to use urine anion gap ($AG = Na^+ + K^+ - Cl^-$) as indirect measurement of NH^+_4 excretions. They found that in the absence of significant bicarbonaturia or ketonuria, negative AG indicated significant NH^+_4 excretion while positive AG indicated less NH^+_4 excretion. Halperin et al[4] had used urine osmolal gap (OG = measured urine osmolality – sum of urine NH^+_4, K^+, Cl^-, HCO^-_3, urea, glucose) to estimate the urine NH^+_4 in the presence of bicarbonaturia and ketonuria. Dyck et al[5] had used modified osmolal gap with better correlation and was confirmed by Kim et al[6].

$$MOG = \frac{\text{measured urine osmolality} - [2\ (Na^+ + K^+) + \text{urea} + \text{glucose}]}{2}$$

Since we do not routinely measure urine NH^+_4 and it was very difficult to obtain 24 hour urine in little children, the purposes of this study were, therefore to determine the correlation of urine AG, urine OG, and MOG with the urine NH^+_4, and net acid excretion (NAE) and to correlate the urine NH^+_4 from spot urine sample and 24 hour urine collection.

PATIENTS AND METHOD

Twenty-four-hour urine and samples of the last 24-hour urine specimens (spot urine) were collected under mineral oil from pediatric patients who had untreated metabolic acidosis, with plasma $CO_2 \leq 18$ mmol/L.

Urine glucose and ketone were measured by Labstix™ (Bayer, Australia), urine pH by pH meter, urine osmolality by the Advanced™ micro-osmometer model 3 MO (Advanced Instruments, USA), urine Na^+, K^+ by Flame Photometer 480 (Corning), urine Cl^- by Chloride Analyzer 925 (Corning), urine urea by enzyme urease, urine titratable acid (TA) and urine NH^+_4 by Jorgensen K[6]. Urine CO_2 tension were measured by urine carbondioxide (by Harleco CO_2 apparatus set), and urine HCO^-_3 were calculated from urine CO_2 tension.

Since we did not measure urine glucose quantitatively, urine osmolal gap was not, therefore, estimated in any urine specimen with glucosuria.

Statistics

The r^2 value was tested for significance using a single tailed *t* test.

RESULTS

There were 29 (11 males, 18 females) patients enrolled in this study. The demographic data and underlying diseases are shown in Table 1.

Most patients had underlying renal diseases: renal tubular acidosis (RTA) in 7, chronic renal failure (CRF) in 6, systemic lupus erythematosus (SLE) in 8 including one with rapidly progressive glomerulonephritis (RPGN), RPGN in 2, Lowe syndrome in 2, on acetazolamide in 2, gastrointestinal causes in 2, congenital adrenal hyperplasia (CAH) in one. Mean serum CO_2 was 13.77 (9.4-17.9) mmol/L, NAE was 33.18±35.36 mmol/24 hours, NH^+_4 excretion was 29.16±31.97 mmol/24 hours, and TA was 12.59±8.97 mmol/24 hours.

Table 1. Characteristics of the subjects.

Variable	
Age mean (range)	6 yrs. 10 mo. (2 mo. - 16 yrs.)
Sex	
Male	11 (38%)
Female	18 (62%)
Underlying diseases	
Lupus nephritis*	8
Renal tubular acidosis	7
Chronic renal failure	6
RPGN	2
Lowe's syndrome	2
On acetazolamide	2
Gastroenteritis	2
Congenital adrenal hyperplasia	1
Total serum CO_2 mean (range, mmol/L)	13.77 (9.4 - 17.9)
Serum anion gap	
Normal anion gap (< 14 mmol/L)	23
Wide anion gap (≥14 mmol/L)	3

* one with RPGN

Twenty-three patients had normal serum AG (< 14 mmol/L) and none had ketonuria. Although spot urine anion gap seemed to correlate with 24 hour urine AG (Fig. 1), there was no correlation of urine AG and urine NH^+_4, neither from spot urine nor 24 hour urine with or without adding urine HCO^-_3 in the calculation ($r^2 = 0.005$, $p = 0.221$).

The spot urine OG was well correlated with urine NH^+_4 as shown in Fig. 2 ($r^2 = 0.82$, $p < 0.001$), but the spot urine MOG was less correlated with urine NH^+_4 ($r^2 = 0.339$, $p < .006$). However when the modified urine osmolal gap was correlated with urine NH^+_4, the urine osmolality correlated with the sum of 2 ($Na^+ + K^+ + NH^+_4$) + urea. It is well correlated for both spot urine (Fig. 3, $r^2 = 0.990$, $p < 0.001$) and 24 hour urine collection (Fig. 4, $r^2 = 0.907$, $p < 0.001$). The 24 hour urine OG were not correlated well with urine NH^+_4 ($r^2 = 0.004$, $p = 0.753$).

There were no correlation between spot urine NH_4/Cr ratio ($r^2 = 0.243$, $p = 0.53$) nor spot NAE/Cr ratio and 24 hour urine NAE/Cr ratio ($r^2 = 0.380$, $p = 0.014$).

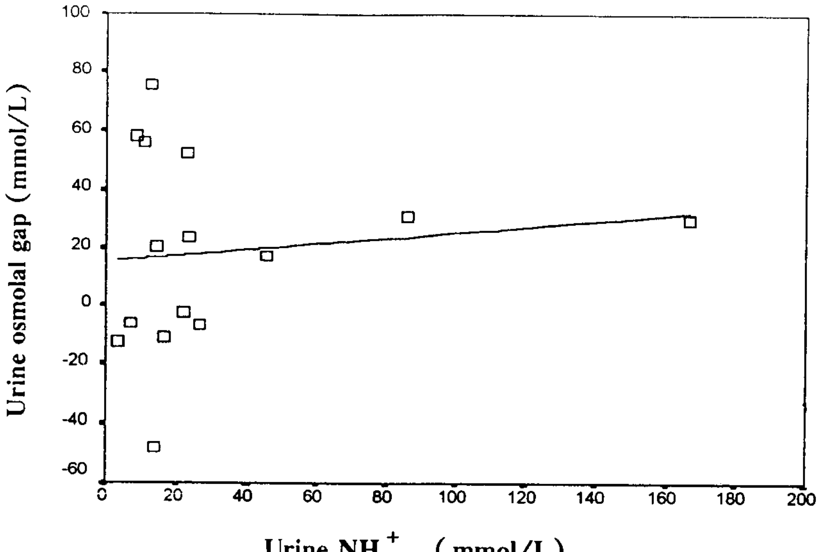

Fig. 1. Correlation of 24-hour urine anion gap and spot urine anion gap ($r^2 = 0.696$, $p < 0.001$).

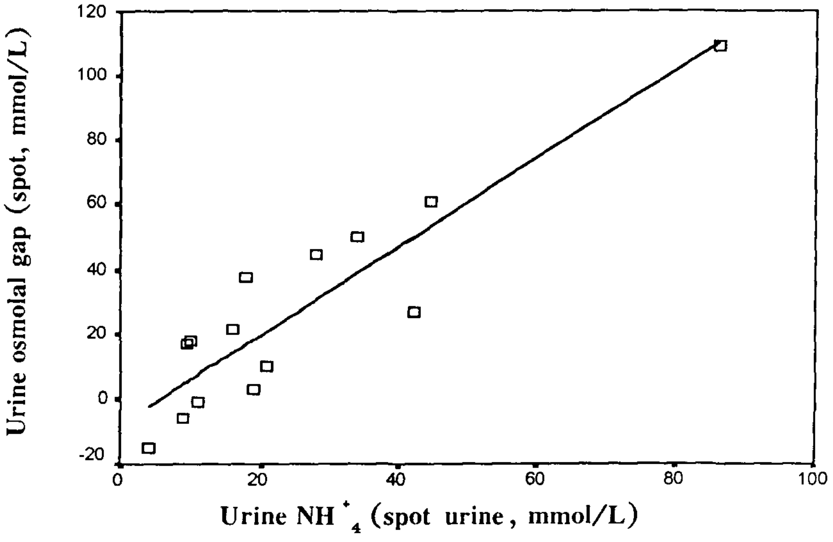

Fig. 2. Correlation of spot urine osmolal gap and urine NH^+_4 ($r^2 = 0.821$, $p < 0.001$).

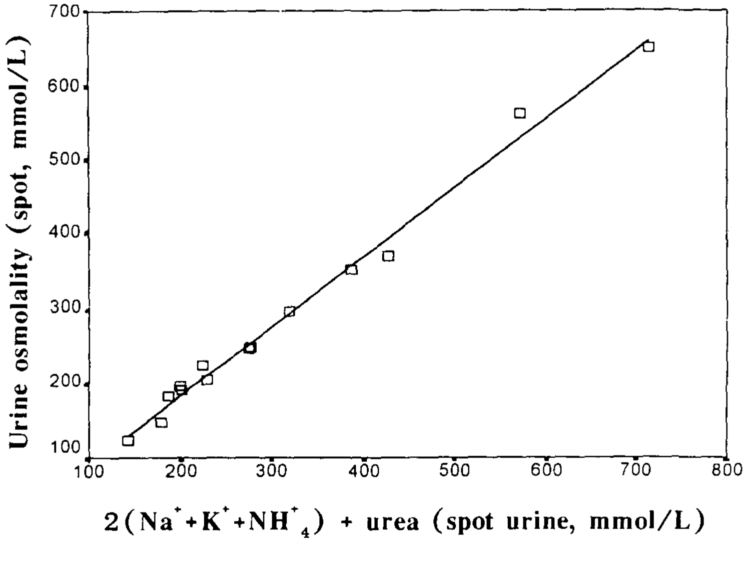

Fig. 3. Correlation of spot urine osmolality and the sum of 2 (Na^+ + K^+ + NH^+_4) + urea (spot urine, mmol/L) ($r^2 = 0.990$, $p < 0.001$).

DISCUSSION

Our data do not demonstrate the good correlation of urine anion gap and urine NH^+_4 as previous report[2,3]. This is probably due to low urine NH^+_4 excretion (29.16±31.97 mmol/24 hour) in most of our patients as pointed out by Dyck et al[5] that urine NH^+_4 is closely related to urine AG when it is above 100 mmol/L. The other possibility of the poor correlation is due to the significant bicarbonaturia in most of our patients. When we add urine HCO^-_3 in the calculation of urine AG

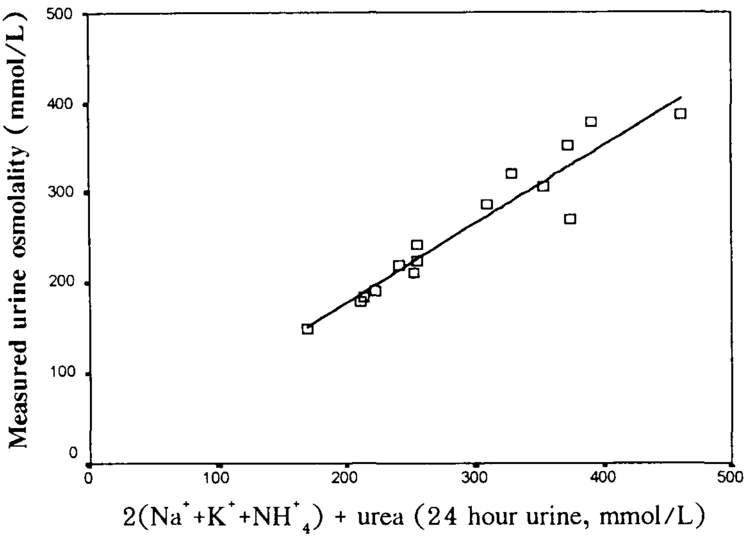

Fig. 4. Correlation of 24 hour urine osmolality and the sum of 2 (Na^+ + K^+ + NH^+_4) + urea (24 hours urine, mmol/L) (r^2 = 0.907, $p < 0.001$)

the correlation was not improved. However, most of our patients who had low urine NH^+_4 excretion also had positive urine AG, same as previous report(2-4,6).

Our data demonstrates that urine osmolality is directly related in a linear fashion with the sum of uncharged solutes which included urea, ketone and glucose plus twice the positive ion charges. Since we excluded patients with glucosuria and none of our patients had ketonuria, urine osmolality should, therefore, relate to the sum of urine urea plus twice of the urine Na+, K+ and NH^+_4. However, most of our patients had low urine NH^+_4 excretion (29.16±31.97 mmol/day), low urine OG and low urine MOG less than 100 mmol/L which were lower than those of RTA patients of Kim et al's report(6), (< 200 mmol/L). This would mean that urine NH^+_4 contributed only small portions in urine osmolality as compared to urine Na (51+31 mmol/L), urine K (22+71 mmol/L) and urine urea (91.64+46.73 mmol/L). Therefore, in the presence of low urine NH^+_4 excretion, urine NH^+_4 correlated better with the urine osmolal gap than the modified osmolal gap as in Fig. 2, 3.

In conclusion, in the absence of ketonuria and glucosuria with presence of small amount of urine NH^+_4 (less than 100 mmol/L), urine osmolality was correlated with the sum of urine urea and twice urine Na^+ + K^+ + NH^+_4. Positive urine AG indicated low urine NH^+_4 excretion.

The urine NH^+_4 correlated better with urine OG than with urine MOG and AG. Neither the spot urine NH^+_4 nor NAE correlated with 24 hour urine collections.

(Received for publication on October 15, 1999)

REFERENCES

1. Richardson RMA, Halperin ML. The urine pH : a potentially misleading diagnostic test in patients with hyperchloremic metabolic acidosis. Am J Kidney Dis 1987; 10:140-3.
2. Goldstein MB, Bear R, Richardson RMA, Marsden PA, Halperin ML. The urine anion gap : a clinically useful index of ammonium excretion. Am J Med Sci 1986; 292:198-202.
3. Battle DC, Hizon M, Cohen MD, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med 1988; 318:594-9.
4. Halperin ML, Margolis BL, Robinson LA, Halperin RM, West ML, Bear RA. The urine osmolal gap : a clue to estimate urine ammonium in 'hybrid' types of metabolic acidosis. Clin Invest Med 1988; 11:198-202.
5. Dyck RF, Asthana S, Kalra J, West ML, Massey KL. A modification of the urine osmolal gap : An improved method for estimating urine ammonium. Am J Nephrol 1990; 10:359-62.
6. Kim GH, Han JS, Kim YS, Joo KW, Kim S, Lee JS. Evaluation of urine acidification by urine anion gap and urine osmolal gap in chronic metabolic acidosis. Am J Kidney Dis 1996; 27:42-7.
7. Jorgensen K. Titrimetric determination of the net excretion of acid/base in urine. Scan J Clin Lab Invest 1957; 9:287-91.

การเปรียบเทียบค่า anion gap, osmolal gap และ modified osmolal gap ในปัสสาวะเพื่อประเมินค่าแอมโมเนียมในภาวะ metabolic acidosis

เฉลิมศรี ตปนียโอฬาร, พ.บ., วิวัฒน์ ตปนียโอฬาร, พ.บ.*,*
รติกร เผือกสูงเนิน, พ.บ., ถนอม เพ็ชร์ทอง, วท.บ.***

ได้ศึกษาผู้ป่วยเด็ก 29 รายที่มีภาวะ metabolic acidosis ด้วยการเก็บปัสสาวะแบบสุ่ม และเก็บแบบ 24 ชม. เพื่อหาค่าแอมโมเนียม (NH^+_4) เทียบกับ anion gap (AG), osmolal gap (OG) และ modified osmolal gap (MOG) ผู้ป่วยเป็นโรค systemic lupus erythematosus 8 ราย, renal tubular acidosis 7 ราย, chronic renal failure 6 ราย, rapidly progressive glomerulonephritis 2 ราย (ร่วมกับ SLE 1 ราย), Lowe syndrome 2 ราย, ได้รับยา acetazolamide 2 ราย, อุจจาระร่วง 2 ราย และ congenital adrenal hyperplasia 1 ราย, ผู้ป่วย 23 รายมี serum AG ปกติ (< 14 mmol/L) มีค่าเฉลี่ย serum total CO_2 content เป็น 13.77 (9.4–17.9) mmol/L, urine net acid excretion (NAE) มีค่า 33.18 $\pm$ 35.36 mmol/24 hours, urine NH^+_4 excretion มีค่า 29.16 $\pm$ 31.97 mmol/24 hours พบว่า urine AG ไม่มีความสัมพันธ์กับ urine NH^+_4 ไม่ว่าจะเพิ่มค่า urine HCO^-_3 ในการคำนวณหรือไม่ทั้งในปัสสาวะ 24 ชม. หรือแบบสุ่ม ค่า urine NH^+_4 มีความสัมพันธ์กับค่า urine OG ในปัสสาวะที่เก็บแบบสุ่ม (r^2 = 0.82, $p < 0.001$) แต่มีความสัมพันธ์ไม่ดีนักกับ urine MOG (r^2 = 0.339, $p < 0.006$) ค่า urine osmolality มีความสัมพันธ์เป็นอย่างดีกับค่า 2 ($Na^+ + K^+ + NH^+_4$) + urea ในทั้งปัสสาวะแบบสุ่ม (r^2 = 0.990, $p < 0.001$) และปัสสาวะเก็บ 24 ชม. (r^2 = 0.907, $p < 0.001$) ค่า NH^+_4 ในปัสสาวะ 24 ชม. ไม่มีความสัมพันธ์กับ OG หรือ MOG ไม่พบความสัมพันธ์ระหว่างค่า NH^+_4/Cr ในปัสสาวะแบบสุ่ม กับค่า NH^+_4/Cr ในปัสสาวะที่เก็บ 24 ชม. (r^2 = 0.243, p = 0.53) รวมทั้งไม่พบความสัมพันธ์ระหว่างค่า NAE/Cr ในปัสสาวะที่เก็บแบบสุ่ม กับปัสสาวะ 24 ชม. (r^2 = 0.380, p = 0.014)

โดยสรุปในภาวะที่มี urine NH^+_4 ต่ำกว่า 100 mmol/L อาจใช้ค่า osmolal gap ในการหาค่า NH^+_4 โดยทางอ้อม แต่การเก็บปัสสาวะ 24 ชม. ก็ยังมีความจำเป็นในการประเมินการขับกรดของไต

คำสำคัญ : Metabolic Acidosis, Urine Anion Gap, Urine Osmolal Gap, Urine Ammonium

* ภาควิชากุมารเวชศาสตร์,

** สำนักงานวิจัย, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพฯ 10400