

Guilty as charged: unmeasured urinary anions in a case of pyroglutamic acidosis

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ABSTRACT

A patient developed an unexplained metabolic acidosis with the characteristics of renal tubular acidosis. By correcting the serum anion gap for hypoalbuminaemia and analysing the urinary anions and cations, the presence of unmeasured anions was revealed. The diagnosis of pyroglutamic acidosis, caused by a combination of flucloxacillin and acetaminophen, was established. Strategies for solving complex cases of metabolic acidosis are discussed.

KEYWORDS

Anion gap, flucloxacillin, hypernatraemia, hypokalaemia, metabolic acidosis, urine osmolal gap

flucloxacillin was commenced. Her only additional medication was acetaminophen (one gram four times daily). During her recovery, she became somnolent on the 43rd day of admission. Her laboratory results now showed a metabolic acidosis, hypokalaemia, and hypernatraemia (table 1). The following parameters were also measured: γ -glutamyltransferase 45 U/l, alkaline phosphatase 139 U/l, serum phosphate 0.80 mmol/l, serum uric acid 0.20 mmol/l; urine was negative for ketones, glucose and protein. Initially, renal tubular acidosis was suspected. However, two days later, this diagnosis was revised, after a high serum anion gap became apparent and after an analysis of measured and unmeasured urinary anions and cations was performed, revealing a considerable

CASE REPORT

A 72-year-old woman (body weight 58 kg, height 170 cm) presented to the emergency room with back pain, fever and confusion. She had a previous history of lung emphysema, hepatitis A and B, breast cancer (treated with surgery and radiotherapy), and, more recently, a vertebral laminectomy for lumbar spinal canal stenosis. Her only medication consisted of bronchodilators and analgesics, including acetaminophen, non-steroidal anti-inflammatory drugs and morphine. At presentation, both vital signs (blood pressure 130/63 mmHg, pulse 94 beats/min and temperature 37.0°C) and physical examination were unremarkable. However, she had an infection (C-reactive protein 276 mg/l, leucocytes $19.3 \times 10^9/l$) and was admitted for further analysis. Magnetic resonance imaging showed an epidural abscess, and subsequent computed tomography revealed bilateral abscesses in the psoas muscles. *Staphylococcus aureus* was isolated from blood cultures and from one of the psoas abscesses. Treatment with long-term and high-dose (two grams six times daily) intravenous

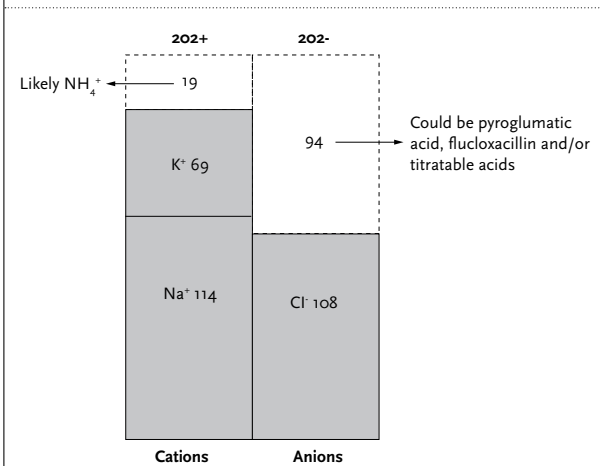
Table 1. Measurements and calculations in serum and urine

	Serum		Urine	
	Day 43	Day 45	Day 43	Day 45
C-reactive protein, mg/l	74	63	-	-
Leucocytes, $10^9/l$	16.5	18.1	-	-
Creatinine, $\mu\text{mol/l}$	46	50	-	2.2
Urea, mmol/l	4.6	4.2	-	96
Osmolality, mOsm/kg	308	-	-	500
Na ⁺ , mmol/l	150	151	66	114
K ⁺ , mmol/l	3.3	3.5	79	69
Cl ⁻ , mmol/l	120	123	87	108
pH	7.36	7.33	6.0	6.0
pCO ₂ , kPa (mmHg)	3.2 (25)	2.5 (19)	-	-
HCO ₃ ⁻ , mmol/l	16	10	-	-
Albumin, g/l	25	25	Negative	Negative
Lactate, mmol/l	0.9	0.6	-	-
Anion gap, mEq/l*	14	18	+ 58	+ 75
Corrected anion gap, mEq/l	18	22	-	-

*Reference range for the serum anion gap in our centre is 8 to 16 mEq/l.

concentration of unmeasured urine anions ($202 - 108 = 94$ mEq/l, *figure 1*). Pyroglutamic acid was suspected to be this unmeasured anion, because several risk factors (flucloxacillin, acetaminophen, ongoing infection, female gender) for pyroglutamic acidosis were present. Indeed, urine pyroglutamic acid was elevated (90.9 mmol/mmol creatinine, reference <0.1 mmol/mmol creatinine, absolute concentration 201.6 mmol/l). The serum acetaminophen concentration was not very high (2 $\mu\text{g/ml}$). She was transferred to the intensive care unit, where all medication was discontinued and where she was treated with sodium bicarbonate. After her acid-base and electrolyte disorders had been corrected, she recovered without sequelae and was discharged to a nursing home for further recovery.

Figure 1. Measured and unmeasured urinary anions and cations in a case of pyroglutamic acidosis



The number of anions and cations was calculated on day 45 using the following formula: $(\text{urine osmolality} - \text{urine urea})/2 = (500 - 96)/2 = 202$. The measured cations and anions are depicted in light grey boxes with solid lines; the unmeasured cations and anions are depicted in white boxes with dashed lines.

DISCUSSION

Pyroglutamic acidosis is increasingly being recognised as an important cause of high anion gap metabolic acidosis.¹ Because Kortmann *et al.* have already covered the pathophysiology of pyroglutamic acidosis in this issue of the Journal,² our objective in this discussion is to focus on the diagnostic challenges associated with metabolic acidosis due to an unmeasured anion.

Initially, we diagnosed our case as renal tubular acidosis, because of the apparent hyperchloraemic non-anion gap metabolic acidosis, high urine pH, positive urine anion gap, presence of hypokalaemia, and the absence of common disorders causing high-anion gap acidosis.³ However, a critical reappraisal, which consisted of appropriately

adjusting the serum anion gap for hypoalbuminaemia and an analysis of urinary cations and anions (*figure 1*), suggested unmeasured anions. This reappraisal generated several teaching points (summarised in *table 2*).

Table 2. Teaching points

- Pyroglutamic acidosis is a cause of high anion gap metabolic acidosis
- Pyroglutamic acid can be 'overproduced' in the setting of glutathione depletion (acetaminophen, sepsis, liver dysfunction, malnutrition) or 'undersecreted' due to inhibition of its enzyme (flucloxacillin, vigabatrin)
- When hypoalbuminaemia is present, the serum anion gap should be adjusted downward (2.5 mEq decrease in anion gap for each 10 g/l decrease in albuminaemia)
- The urine anion and osmolal gaps can be used to assess urinary ammonium excretion:
 - Urine anion gap: $\text{urine Na}^+ + \text{K}^+ - \text{Cl}^-$
 - Urine osmolal gap: $\text{measured} - \text{calculated}$ ($2 * [\text{Na}^+ + \text{K}^+] + \text{urea} + \text{glucose}$) urine osmolality
 - Estimated urinary NH_4^+ excretion: $(\text{urine osmolal gap})/2$
- The urine anion gap cannot differentiate between renal tubular acidosis and metabolic acidosis due to an unmeasured anion
- Analysis of urine cations and anions can be useful to detect the presence of unmeasured anions when the serum anion gap is inconclusive

First, the serum anion gap must be adjusted downward in patients with hypoalbuminaemia, because the negative charges on the serum proteins primarily determine the serum anion gap.⁴ Nevertheless, even the adjusted serum anion gap may be difficult to interpret, because its expected normal values range so widely (~ 8 to 16 mEq/l when not including K^+) and also depend on the measurement characteristics of the laboratory.⁵

Second, in cases in which the serum anion gap is 'borderline' and the cause of the acidosis is not obvious from the clinical context, the analysis of the urinary composition may be useful. Traditionally, three urinary tests have been utilised to differentiate metabolic acidosis, including the urine pH, the urine anion gap and the urine osmolal gap.⁶ Although the urine pH is expected to be high (generally >5.5) in renal tubular acidosis (due to urine bicarbonate loss or impaired ammoniogenesis), this test is limited by the use of semiquantitative dipsticks, dietary factors, and presence of urinary pathogens.⁷

Both the urine anion and osmolal gaps provide an estimate of urinary ammonium excretion.^{8,9} The urinary ammonium excretion can be used to assess whether the kidneys are attempting to 'rid the acid' (high urinary ammonium excretion) or if the problem resides within the kidneys (failure to excrete ammonium), as for example in distal renal tubular acidosis.

The urine anion gap is an indirect measure of urine ammonium excretion, because ammonium is usually excreted as ammonium chloride.⁸ However, the urine anion gap cannot differentiate between renal tubular acidosis and metabolic acidosis due to unmeasured anions.^{6,8} In both of these settings the urine chloride concentration will be relatively low and therefore the anion gap positive, but for different reasons. In renal tubular acidosis, ammonium excretion is impaired and therefore little ammonium chloride is excreted. In metabolic acidosis due to an unmeasured anion, the kidneys will respond appropriately to the acidosis by increasing urinary ammonium excretion, but ammonium will be excreted with the unmeasured anions instead of with chloride.

The urine osmolal gap is a direct and semiquantitative index of the urinary ammonium concentration, because it estimates the concentration of this unmeasured cation (*figure 1, table 2*).⁹ The estimated urinary ammonium excretion in our patient was 19 mEq/l, which is approximately the cut-off value between an appropriate and an inappropriate renal response to metabolic acidosis.⁹ Although one would expect this value to be higher, the recent onset and relatively mild degree of metabolic acidosis likely produced the modest urine osmolal gap. More convincingly, however, was the large proportion of unmeasured anions, which prompted us to pursue the search for unmeasured anions. In theory (and for added complexity), these anions could also be urine bicarbonate, for example in proximal renal tubular acidosis; although this concentration of urine bicarbonate would seem rather high, there were no other signs of proximal tubular dysfunction, and treatment with bicarbonate would not have resolved the acidosis so easily.

Finally, we propose the following explanations for the hypokalaemia and hypernatraemia. Hypokalaemia could have been caused by a non-reabsorbable anion, which can stimulate potassium secretion in the renal collecting duct. Both pyroglutamic acid and flucloxacillin can act as non-reabsorbable anions,^{10,11} and flucloxacillin may therefore also have contributed to the unmeasured urinary anions (*figure 1*). Hypernatraemia may have been caused by a positive sodium balance (large sodium content administered with flucloxacillin¹²) and/or a solute diuresis combined with reduced water intake.¹³

CONCLUSION

We have presented yet another case of pyroglutamic acidosis to illustrate the importance of having an index of suspicion for this diagnosis in unexplained cases of a high anion gap metabolic acidosis, especially because discontinuation of the offending factors can easily reverse this condition. Moreover, this case was presented to illustrate the utility of analysing unmeasured urinary anions to assist in the diagnosis of challenging cases of metabolic acidosis.

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