Metabolic acidosis and elevated pyroglutamic acid in a patient with multiple organ dysfunction syndrome and chronic acetaminophen use

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Abstract. We report a case of a critically ill patient with a high anion-gap metabolic acidosis and liver failure due to chronic acetaminophen use and alcohol abuse. The metabolic acidosis on admission was explained by the high lactate level, but further investigation showed high levels of pyroglutamic acid contributing to the metabolic acidosis. Withdrawal of acetaminophen and treatment with N-acetylcysteine and haemofiltration lead to a rapid decline in pyroglutamic acid levels.

Introduction
High anion-gap metabolic acidosis is a frequently encountered problem in the ICU. The main causes of a high anion-gap metabolic acidosis are organic acids, renal failure with the retention of anions, and metabolism of toxic substances. There is a poor correlation between the level of anion gap and quantification of identifiable organic acids [1]. Even in patients with acidosis and an increased lactate level, lactate accounts for only 20% of the acidosis [2]. In presenting this case we draw attention to the less common and probably underestimated contribution of pyroglutamic acid to high anion-gap metabolic acidosis caused by chronic acetaminophen use and critical illness.

Case report
A 51-year-old female presented herself to the emergency department with progressive abdominal distension and pain, diarrhoea, and a three-week history of weakness. Her medical history consisted of alendronate, calcium-carbonate, temazepam and acetaminophen. In order to control her abdominal pain she used acetaminophen 2 gr/day. The estimated time of ingestion of her last acetaminophen was less than 6 hours before admission. She used to drink 3-4 bottles of wine a week but had stopped drinking one week prior to admission. Despite 15 l/min via an oxygen mask, her respiratory rate was 40/min. On admission saturation was 95% but after a few hours this declined and mechanical ventilation was required. She was confused and her Glasgow Coma Score was E3M5V3. Her systolic blood pressure was 80 mmHg, and she had a sinus tachycardia of 110/min. Examination of heart and lungs was normal. Her core temperature was 32 degrees Celsius. A shifting dullness and jaundice was present but vascular distension of heart and lungs was normal. Her systolic blood pressure was 86 mmHg, and partial thromboplastin time 31.4 s (range 10-12.2 s), and partial thromboplastin time 66.2 s (range 23.3-30 s), antithrombin III level 10% (range 80-140%) and ammonia 142 µmol/l (range 0-50 µmol/l). Serum creatinine was 60 µmol/l (range 50-95 µmol/l). Plasma acetaminophen level was 10 mg/l. Plasma pyroglutamic acid level 1430 µmol/l (range 0-160 µmol/l).

Arterial blood gas analysis before mechanical ventilation: Ph 7.05, \(pCO_2\) 15 mmHg, \(pO_2\) 86 mmHg, bicarbonate 4.0 mmol/l, BE -24.4, \(O_2\) sat. 92%. Anion gap; \([(Na^+ + K^+) - ([Cl^- + (HCO_3^-)] = 37.3 \text{ mmol/l.}\)

Anion gap corrected (mmol/l): \([Na^+]_{\text{observed}} + 0.25 \times ([Na^+] - [Na^+]_{\text{normal}}) - ([Cl^- + (HCO_3^-)] = 41.8 \text{ mmol/l.}\)

Serum osmolality calculated \(275 \text{ mOsm/kg}\) and measured \(275-295 \text{ mOsm/kg}\), osmol gap 13 mOsm/kg.

Strong ion difference apparent (SIDapp); \([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - ([Cl^-] + [lactate]) = 21.1 \text{ mmol/l.}\)

SID effective (SIDeff); \([Na^+]_{\text{observed}} + 0.123 \times [\text{PCO}_2] + 0.4 \times [\text{H}^+] - ([Cl^-] + [\text{HCO}_3^-] + [\text{H}_2\text{CO}_3]) = 4.1 \text{ mmol/l.}\)

Testing for ascites showed <0.1*10.6 leukocytes/l. Blood, tracheal aspirate and ascites cultures revealed no microorganisms. Ultrasonography showed a nodular liver and increased echogenicity consistent with cirrhosis. Ascites was present. The spleen was of normal size.

The admitting diagnosis was acute on chronic liver failure due to chronic alcohol and acetaminophen abuse resulting in multiple organ failure (SOFA score 15). At first glance, the metabolic acidosis was explained as a pure metabolic acidosis with a high anion gap. To narrow the possible causes of the high anion gap, the osmol gap was calculated and found not to be elevated. Due to the normal osmol gap the ethanol level was not measured and the high anion gap metabolic acidosis was explained by the high lactate level. Treatment was initiated with fluid resuscitation, IV glucose suppletion, vasopressors, mechanical ventilation, thiamine, fentanyl and IV N-acetylcysteine (NAC) until acetaminophen levels were known. Early high volume continuous venovenous haemofiltration was initiated (50

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production of gamma-glutamyl-cysteine, which under the altered cysteine synthetase in the gamma-glutamyl cycle. This will increase through the glutathione leads to reduced feedback inhibition of one is produced in the glutamyl cycle (Figure 1). Deficiency of glutathione as the cause of metabolic acidosis in acetaminophen [4]. Glutathione, uric acid, and organic acids account for another small part of the SIG, acid normally accounts for less than 0.2% of the SIG. Amino acids, contributions to the metabolic acidosis (8% of the SIG) although it does not have a high degree of sensitivity in the evaluation of anions and cations in low concentrations. In contrast with the anion gap, the SIG is not affected by alkalosis, hypoaalbuminaemia or dehydration. Normally the SIG is zero; a positive increase in the gap identifies the presence of unmeasured strong anions other than lactate, and provides information on their concentration. Due to the history of chronic acetaminophen use, positive SIG and altered mental status (cardinal feature as it is reported in most cases of pyroglutamic acidemia), the diagnosis of pyroglutamic acidemia was suspected and then confirmed. This is in accordance with the observation that hyperlacticaemia is usually accompanied by metabolic acidosis, but lactate is only responsible for a small percentage of the acidosis and unmeasured anions account for most of the acidosis [2]. According to the increase observed in the SIG of 17 mmol/l, the pyroglutamic acid level of 1.43 mmol/l thereby contributes to the metabolic acidosis (8% of the SIG) although it does not completely account for it. In patients with sepsis, pyroglutamic acid normally accounts for less than 0.2% of the SIG. Amino acids, uric acid, and organic acids account for another small part of the SIG, whereas most of the unmeasured anions are still unidentified [3]. Pitt et al. were the first to suggest the role of glutathione depletion as the cause of metabolic acidosis in acetaminophen [4]. Glutathione is produced in the glutamyl cycle (Figure 1). Deficiency of glutathione leads to reduced feedback inhibition of gamma-glutamyl-cysteine synthetase in the gamma-glutamyl cycle. This will increase production of gamma-glutamyl-cysteine, which under the altered conditions resulting from acetaminophen ingestion, leads to overproduction and accumulation of pyroglutamic acid (5-oxoproline) (Figure 1) [5]. Acetaminophen causes a glutathione deficiency by binding of N-acetyl-p-benzoquinone-imine (NAPQI), a toxic metabolite of acetaminophen metabolized by cytochrome P-450, and by disrupting the glutathione cycle [6]. Specific conditions, such as pregnancy [7], certain medications (vigabatrin, flucloxacinil, and netilmicin) [8], malnutrition [9] strict vegetarian diet [10] and sepsis, may also lead to glutathione deficiency independently of acetaminophen and thereby increase the chance of acetaminophen effects at lower doses. In critically ill septic children, glutathione synthesis is known to decrease by 60% [11]. The common mechanism seems to be a deficiency of one of the three amino acids necessary for the formation of glutathione. Although glutamate, cysteine and glycine are all required for the synthesis of glutathione, the cellular availability of cysteine has been considered to be the rate-limiting factor in the synthesis of glutathione [12]. Females appear to be more likely to develop pyroglutamic acidemia, which can be explained by the fact that glutathione-S-transferases are involved in the conjugation of acetaminophen with glutathione and the activity of a number of these iso-enzymes is known to be gender related [13]. Our patient was female, a chronic acetaminophen user and critically ill. We assumed that malnutrition due to her chronic alcohol abuse could also have played a role in her glutathione deficiency [14,15].

The acetaminophen level on admission was 10 mg/l. According to the Rumack-Matthew nomogram, hepatotoxicity is normally not expected when an estimated time of ingestion is < 6 hours before admission and when an acetaminophen level is 10 mg/l. However, chronic alcoholics have an increased risk of hepatotoxicity due to induction of CYP 450 leading to enhanced generation of NAPQI. Together with the above-mentioned causes of glutathione depletion, acetaminophen toxicity in this case was certainly possible. The antidote of choice for the treatment of acetaminophen poisoning is NAC which is a glutathione precursor and increases the low intracellular glutathione and cysteine concentrations. By increasing the glutathione concentration, it increases the negative feedback inhibition of gamma-glutamyl-cysteine synthetase leading to the reduction in pyroglutamic acid...
formation. Another possible mechanism to decrease pyroglutamic acid levels is haemofiltration. Pyroglutamic acid has a low molecular weight and would be expected to be easily removed by haemofiltration although as far as we know there are no data on pyroglutamic acid and haemofiltration at present. After initiation of NAC and CVVH therapy, pyroglutamic acid level decreased rapidly (Figure 2).

In conclusion, it is recommended that any patient with a high anion-gap metabolic acidosis which cannot be adequately explained, and if the patient is known to use acetaminophen, they should be investigated for the presence of pyroglutamic acid in urine or plasma, especially if the patient’s mental status is altered. If used, acetaminophen agents should be withdrawn and treatment with N-acetylcysteine should be considered.

References