Case Report

5-Oxoproline acidosis caused by acetaminophen and flucloxacillin treatment – a case report

P van Montfort, F Helmich, GJM Mostard & DJL van Twist

Abstract

High anion gap metabolic acidosis (HAGMA) is a common diagnosis in the emergency department, which requires a systematic work-up in order to identify and treat the underlying cause. We present an unusual case of HAGMA due to 5-oxoproline accumulation caused by prolonged treatment with both acetaminophen (paracetamol) and flucloxacillin. This paper describes the diagnostic work-up of HAGMA and emphasizes on the approach and initial treatment in case the underlying etiology is unclear.

Keywords

Acidosis, 5-oxoproline, flucloxacillin, acetaminophen

Key points

- Diagnosis and treatment of metabolic acidosis requires a systematic approach.
- 5-Oxoproline is a rare, but potentially lethal cause of metabolic acidosis.
- Concomitant usage of flucloxacillin and acetaminophen (paracetamol) can result into accumulation of 5-oxoproline acid.
- Treatment of 5-oxoproline acidosis consists of supportive care and IV treatment with N-acetylcysteine. Hemodialysis can be considered.

Case

A 77-year-old patient was referred to the emergency department because of severe respiratory distress. His medical history included obesity, hypertension, and hypercholesterolemia. Recently, he was hospitalised because of *Staphylococcus aureus* bacteraemia and infected hip prosthesis for which he still received high dose acetaminophen (paracetamol), flucloxacillin, and rifampicin intravenously.

Physical examination revealed tachypnoea (28 breaths/ minute), mild tachycardia (95 bpm) and an oxygen saturation of 98% on room air. Lung auscultation was unremarkable. An electrocardiogram and chest x-ray showed no abnormalities. Blood gas analysis, however, revealed a severe metabolic acidosis (Table 1).

Plasma urea (6.5mmol/l; reference 3.5-7.5) and lactate levels (1.14 mmol/l; reference 0.6-1.8) were low. Urine analysis indicated very mild ketonuria (5.0 mmol/l). Since the patient was still hospitalised in a rehabilitation centre, used no salicylates, and had no history of suicide attempts, intentional poisoning was considered to be unlikely. However, as he still received high doses of acetaminophen, flucloxacillin, and rifampicin intravenously as a treatment for the infected hip prosthesis, we hypothesised that this combination may have resulted into accumulation of 5-oxoproline and subsequently a 5-oxoproline acidosis.

Unfortunately, detection of 5-oxoproline in urine or plasma was not routinely available.[1] Under the working diagnosis of 5-oxoproline induced acidosis, the patient was admitted to the intensive care unit and treated with both sodium bicarbonate and N-acetylcysteine. Flucloxacillin and acetaminophen treatment were discontinued immediately. However, as his physical condition deteriorated quickly, the patient and his relatives decided to discontinue further treatment. The patient died shortly after.

Table 1. Arterial blood gas analysis at admission (on room air)

	Reference value	Patient's value
pH	7.35 – 7.45	7.16
pCO2 (kPa)	4.7 – 6.4	1.5
pO2 (kPa)	9.2 – 13.0	14.8
HCO3- (mmol/L)	23.0 – 28.0	3.9
Base Excess (mmol/L)	-3.0 – 3.0	-22.6
Sodium (mmol/L)	135 – 145	146
Potassium (mmol/L)	3.5 – 5.0	3.0
Chloride (mmol/L)	95 – 107	122
Glucose (mmol/L)	3.6 – 6.1	4.8
Lactate (mmol/L)	0.6 – 1.8	1.19
Anion gap (mmol/L)	8 – 16	19.60

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Table 2. Overview of popular mnemonics used to remember the major causes of high anion gap metabolic acidosis.[6]

Mnemonic	Meaning
MUD PILES	Methanol, Uraemia, Diabetes, Paraldehyde, Iron (and Isoniazid), Lactate, Ethylene glycol, and Salicylate.
KUSSMALE	Ketoacidosis, Uraemia, Salicylate, Methanol, Aldehyde, Lactate, and Ethylene glycol.
GOLD MARK	Glycols (ethylene and propylene), Oxoproline, L-lactate, D-lactate, Methanol, Acetylsalicylate, Renal failure, and Ketoacidosis

Several weeks after admission, the results of extensive urine analysis confirmed high concentrations of 5-oxoproline (4,372 mmol/ mmol creatinine; reference <65) and metabolites of acetaminophen (1,224 mmol/ mmol creatinine; reference < 28) next to minor elevated levels of ketones and lactate.

Discussion

Acidosis is a frequent finding in acute internal medicine and its underlying cause can be rapidly found in most cases using a systematic diagnostic approach.[2] Based on the blood gas analysis, the type of acidosis (metabolic, respiratory, or combined acidosis) should be identified first. Metabolic acidosis is characterised by a reduced level of bicarbonate, eventually resulting in a reduction of blood pH. The partial pressure of carbon dioxide (pCO_2) is reduced as well due to the respiratory compensation mechanism, which we clearly observed in this patient.

Diagnostic work-up

The anion gap is an important tool in the initial work-up of metabolic acidosis. The anion gap is calculated with a simple formula: ($[Na^+] - [Cl^-] + [HCO_3^-]$).[2] An elevated anion gap (>10 mmol/L) indicates accumulation of organic acids rather than a loss of bicarbonate. The organic acids most commonly causing high anion gap metabolic acidosis (HAGMA) can be remembered with the aid of a mnemonic. Several mnemonics have been proposed such as 'MUD PILES', 'KUSSMALE', and most recently 'GOLD MARK' (Table 2), with the latter representing Glycols (ethylene and propylene), Oxoproline, L-lactate, D-lactate, Methanol, Acetylsalicylate, Renal failure,

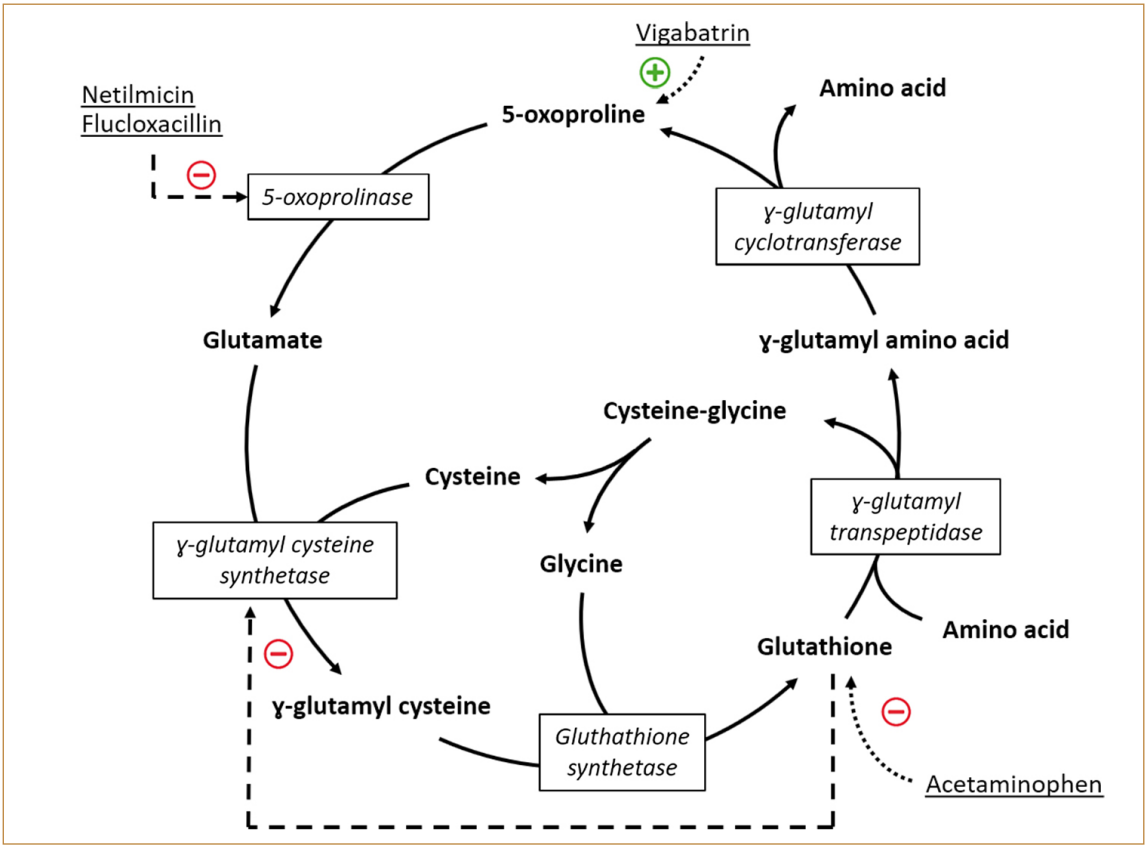

Figure 1. The gamma-glutamyl cycle and mechanisms resulting in 5-oxoproline accumulation

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and Ketoacidosis.[3] In most cases HAGMA is caused by either lactate or ketones.[2]

5-Oxoproline

5-Oxoproline, or pyroglutamic acid, is an intermediate of the gamma-glutamyl cycle (Figure 1), a pathway synthesising glutathione. Glutathione is an antioxidant that plays a key role in the neutralisation of toxic (acetaminophen) metabolites. However, several factors could disrupt the gamma-glutamyl cycle, leading to accumulation of 5-oxoproline. For example, hereditary enzyme deficiencies or mutations reducing enzyme activity have been described.[4] More common, however, is glutathione depletion associated with the use of acetaminophen.

Depletion of glutathione interrupts the negative feedback loop resulting in accumulation of γ-glutamyl-cysteine, which on its turn is metabolised into 5-oxoproline. Next to acetaminophen, other drugs (netilmicin, vigabatrin) interfere with the gamma-glutamyl cycle as well. For example, the anticonvulsant vigabatrin is metabolised into 5-oxoproline. Furthermore, the antibiotics flucloxacillin and netilmicin inhibit 5-oxoprolinase, the enzyme involved in oxidation of 5-oxoproline.

Other risk factors for 5-oxoproline accumulation are renal failure (resulting in diminished excretion) and malnutrition. Interestingly, most patients with 5-oxoproline acidosis are female, suggesting a gender-specific mechanism. However, this may also be the result of confounding caused by higher incidences of anorexia nervosa and acetaminophen poisoning in women.[5, 6]

Treatment of metabolic acidosis

The cornerstone in treating metabolic acidosis is to identify and treat the underlying cause. However, with hundreds of possible acids of which only a few being routinely measured, a specific acid may not (yet) be identified at the emergency department. In such cases treatment is limited to supportive care including fluid resuscitation, nutritional and ventilatory support, and/or renal replacement, while performing additional analysis to identify the primary cause.[1]

Treatment with sodium bicarbonate is controversial due to a lack of evidence for improving morbidity and mortality. Moreover, if administered, there is a risk for overshoot metabolic alkalosis and volume overload, which may lead to an adverse outcome.[2]

In case of 5-oxoproline acidosis, treatment with N-acetylcysteine has been suggested to restore depleted glutathione levels and thereby reducing the production of 5-oxoproline.[1] Toxic concentrations of 5-oxoproline may persist for days to weeks, but hemodialysis may accelerate its elimination.[7]

Conclusion

High anion gap metabolic acidosis (HAGMA) is a common diagnosis in the emergency department, which requires a systematic work-up in order to diagnose and treat the underlying cause. If the primary condition is not identified immediately, treatment is limited to supportive care while performing additional analysis.

Concomitant usage of acetaminophen and flucloxacillin over a long period may result into a severe, potentially lethal HAGMA caused by 5-oxoproline accumulation. Therefore, clinicians need to be aware of the risk of 5-oxoproline acidosis and should consider caution with this drug combination. Especially in patients with impaired renal function or low body weight, a regular check of creatinine and bicarbonate blood levels should be considered.

Declaration of competing interests

Nothing to declare.

References

1. Morris CG, Low J: Metabolic acidosis in the critically ill: Part 2. Causes and treatment. *Anaesthesia* 2008;**63(4)**: 396-411.
2. Kraut JA, Madias NE: Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol* 2010;**6(5)**: 274-285.
3. Mehta AN, Emmett JB, Emmett M: GOLD MARK: an anion gap mnemonic for the 21st century. *The Lancet* 2008;**372(9642)**: 892.
4. Ristoff E, Larsson A: Patients with genetic defects in the gamma-glutamyl cycle. *Chem Biol Interact* 1998;**111-112**: 113-121.
5. Schurmans W, Lemahieu W, Frans E: High anion gap metabolic acidosis: use the proper acronym, discard the red herrings and thou shall find the culprit. *Clin Kidney J* 2014;**7(3)**: 320-322.
6. Hundemer GL, Fenves AZ: Acquired 5-oxoproline acidemia successfully treated with N-acetylcysteine. *Proc* (Bayl Univ Med Cent) 2017;**30(2)**: 169-170.
7. Luyasu S, Wamelink MM, Galanti L, et al.: Pyroglutamic acid-induced metabolic acidosis: a case report. *Acta Clin Belg* 2014;**69(3)**: 221-223.

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