Submitted February 2019; Accepted October 2019

CASE REPORT

Severe metabolic acidosis induced by 5-oxoproline accumulation after paracetamol and flucloxacillin administration

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Keywords - **metabolic acidosis, pyroglutamic acid, 5-oxoproline, paracetamol, acetaminophen, flucloxacillin**

Abstract

In this case report we present a singular case of metabolic acidosis seen in a 78-year-old female who was admitted to the intensive care unit (ICU) with dyspnoea, tachypnoea and tachycardia due to paracetamol and flucloxacillin usage. Laboratory examination revealed a high anion gap metabolic acidosis caused by accumulation of 5-oxoproline, otherwise known as pyroglutamic acid. Treatment consisted of discontinuation of the offending drugs and supportive care with sodium bicarbonate, inotropic medication and mechanical ventilation. Seven days after ICU admission, treatment was complicated by recurrence of metabolic acidosis after discontinuation of sodium bicarbonate. Our patient also developed 5-oxoproline-associated metabolic encephalopathy. We demonstrate that the elimination of 5-oxoproline will take longer than expected. Furthermore, this case clearly illustrates the potentially unexpected delayed clearance of 5-oxoproline. We also briefly discuss treatment modalities.

Introduction

High anion gap metabolic acidosis is a subcategory of metabolic acidosis. Differentiating normal anion gap metabolic acidosis from high anion gap metabolic acidosis is an essential step in the diagnostic work-up of a patient presenting with metabolic acidosis, as the treatment is very different.[1] Causes of high anion gap metabolic acidosis include ketoacidosis, lactic acidosis, methanol and ethylene glycol intoxication and chronic renal failure. A less common cause that should nonetheless be included in the differential diagnosis is 5-oxoprolinaemia. It can be caused by simultaneous usage of paracetamol and flucloxacillin.[2]

Clinically, patients may present with tachypnoea, tachycardia, headache, confusion, weakness and fatigue, nausea and vomiting. Adverse effects primarily include decreased cardiac output, arterial dilatation, altered oxygen delivery, predisposition to arrhythmias and impairment of the immune response.[3]

5-oxoprolinaemia is thought to be a rare disorder, but its true frequency is unknown. It is probable that many cases are missed.[4] Based on previous case reports, 5-oxoprolinaemia is a severe disorder frequently requiring ICU admission.[2] Furthermore, there is not much evidence on the treatment, course and clearance of 5-oxoprolinaemia. Our case illustrates various risk factors for the development of 5-oxoprolinaemia and provides a discussion on the different treatment modalities.

Case history

A 78-year old woman was admitted due to spondylodiscitis of intervertebral disc C6-C7. The diagnosis was confirmed with positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI). Obtained blood cultures showed *S. Aureus* bacteraemia. Flucloxacillin treatment was initiated at six grams per 24 hours by continuous intravenous infusion. Additionally, the patient received one gram doses of oral paracetamol four times per day for analgesia. Past medical history included a lumpectomy, bronchial hyperreactivity, neurogenic claudication and cholecystectomy. Her hospitalisation was complicated by diarrhoea and excessive vomiting. On day 13 of hospital admission and continuous administration of paracetamol and flucloxacillin, she developed dyspnoea in combination with a lowered oxygen saturation. A pulmonary focus was not found and there was no evidence of

scattering of *S. aureus*. The dyspnoea worsened and our rapid response team was consulted. Physical examination showed an exhausted patient. She was 63 kg in weight with a height of 1.53 meter. She had tachypnoea of 35/min and an oxygen saturation of 92%, with a non-rebreather mask supplying 90% oxygen, a heart rate of 140 beats/min, blood pressure of 150/75 mmHg, a Glasgow Coma Scale of 15 and temperature of 36.9 °C. The patient was admitted to our ICU and intubated. Further physical examination showed no cardiac, abdominal or pulmonary abnormalities; there was, however, significant skin mottling. Arterial blood gas analysis showed a severe metabolic acidosis prior to intubation (pH 6.89; pCO2 3.5 kPa; pO2 33.9 kPa; bicarbonate 5.0 mmol/l). Laboratory analysis further revealed an elevated serum creatinine of 143 mmol/l, leucocytosis of 32.3 x 109/l and a slightly elevated CRP of 25 mg/l. Ketonuria and increased lactate levels were absent. Further abnormal laboratory findings can be found in *table 1*.

Corrected for albumin, the anion gap was 23 mmol/l, reference value of 8±3 mmol/l. The osmol gap was 3.8 mOsm/kg, reference value of <10 mOsm/kg. Our patient therefore had a high anion gap metabolic acidosis without an elevated osmol gap.

Table 1. Abnormal laboratory values at admission to the intensive care unit

Measurement	Value	Reference range	Unit
Chloride	122	(94 - 109)	mmol/l
Creatinine	143	(50 - 95)	µmol/l
GFR (CKD-EPI)	31	(60 -)	ml/min
Lactate dehydrogenase	325	(- 247)	U/l
Creatine kinase	289	(- 145)	U/l
Brain natriuretic peptide	77	(- 28.9)	pmol/l
Albumin	20	(31 - 45)	g/l
Magnesium	0.53	(0.69 - 1.04)	mmol/l
Lipase	95	(14 - 43)	U/l

Aetiology of high anion gap metabolic acidosis

Differentiating between causes of high anion gap metabolic acidosis can be challenging. Evaluation requires different laboratory and clinical findings. 'GOLD MARK' is a helpful mnemonic to remember the causes of high anion gap metabolic acidosis.[1] This mnemonic represents Glycols, Oxoproline, L-lactate, D-lactate, Methanol, Aspirin, Renal failure and Ketones. Glycols and methanol were ruled out in our case because an osmol gap was not present. There was no evidence of ketonuria or lactic acidosis. Our patient's kidney function had decreased during her stay in the orthopaedic ward because of sepsis, vomiting and diarrhoea but serum creatinine values were recovering before ICU admission. Renal dysfunction may have contributed to her high anion gap metabolic acidosis but was regarded as unlikely to have been the sole attributor.

This narrowed our differential diagnosis down to acetylsalicylic acid intoxication or 5-oxoproline accumulation.[5] We had no clinical suspicion of acetylsalicylic acid over-ingestion and thus decided to discontinue paracetamol and test for 5-oxoprolinaemia. This test had to be sent to a laboratory in Nijmegen, the Netherlands.

Five days after initial ICU admission we received results from the laboratory. 5-oxoproline concentrations measured by gas chromatography-mass spectrometry (GC-MS) in the urine were as high as 22.1 mmol/l. The urine creatinine value was 2.01 mmol/l, this corresponds with a 5-oxoproline concentration of 11000 µmol/mmol creatinine, reference value of <75 µmol/mmol creatinine.[6] GC-MS also measured peaks corresponding to an antibiotic and paracetamol in the urine sample, but quantification and specification was not performed.

Treatment and progress

As previously mentioned, treatment consisted of discontinuing paracetamol and administering bicarbonate in order to correct the metabolic acidosis. Intubation was required due to exhaustion, and sedation was commenced in order to start controlled ventilation. After an evaluation of the literature we discovered the possible role of flucloxacillin in 5-oxoprolinaemia, so we switched to clindamycin. Three days after ICU admission we stopped administering bicarbonate, after which our patient developed acidosis with a pH of 7.32. We also tried to taper off the sedative medication but stopping proved impossible due to persistent neurological agitation. The diagnosis of encephalopathy was confirmed by electroencephalography. After cerebrospinal fluid samples showed no evidence of causative bacterial or viral pathogens, we interpreted it as metabolic encephalopathy induced by 5-oxoprolinaemia, possibly in combination with delirium. The clinical condition of the patient deteriorated in the following days. Her temperature rose to 39.0°C and serum leucocytes to 36.3 x 109/l, without a focus. Aetiologies such as sinusitis, meningitis, pneumonia, urinary tract infection, abdominal infection and an arterial line infection were excluded. Mechanical ventilation parameters had to be increased, inotropic medication was started and sedatives were uptitrated. Chest radiography showed an infiltrate that wasn't very well defined and pulmonary oedema, which was not caused by cardiac dysfunction. Our differential diagnosis of non-cardiac pulmonary oedema was acute respiratory distress syndrome (ARDS), pulmonary (viral) infection, drug induced oedema and pulmonary embolism. After negative sputum cultures, tests for viral microbes and an earlier CT angiography, ARDS remained the most likely diagnosis. Even at admission there was a need for high levels of oxygen, which is not generally expected in respiratory failure due to metabolic acidosis, but could possibly be attributed to ARDS. We tried to reduce the pulmonary oedema by continuous administration of furosemide, optimisation of position and ventilation.

On day 7, after once again ceasing bicarbonate administration, the metabolic acidosis re-occurred with a pH of 7.28. Measured

5-oxoproline levels still reached toxic levels of 2650 µmol/mmol creatinine corresponding with a concentration of 6.2 mmol/l which explained the recurrence of acidosis. With a treatment delay of eight days we initiated intravenous acetylcysteine treatment with a bolus of 9000 mg in one hour and one gram per hour for the following day. From day 10 to 12, 5-oxoproline concentrations decreased to non-toxic concentrations. *Figure 1* shows 5-oxoproline urine concentrations, measured by GC-MS at four different time points with corresponding blood pH values. From day 12 onwards, we saw a rapid neurological amelioration. Sedative medications could be stopped and the patient regained a maximum score on the Glasgow Coma Scale with intubation. Agitation persisted, but was under control with haloperidol and thereafter with risperidone, and was attributed to delirium. The condition of our patient improved slowly in the following days. A tracheostomy was required due to excessive mucus production. Physiotherapy was started in order to improve her general condition. Progress continued and she was discharged 36 days after ICU admission.

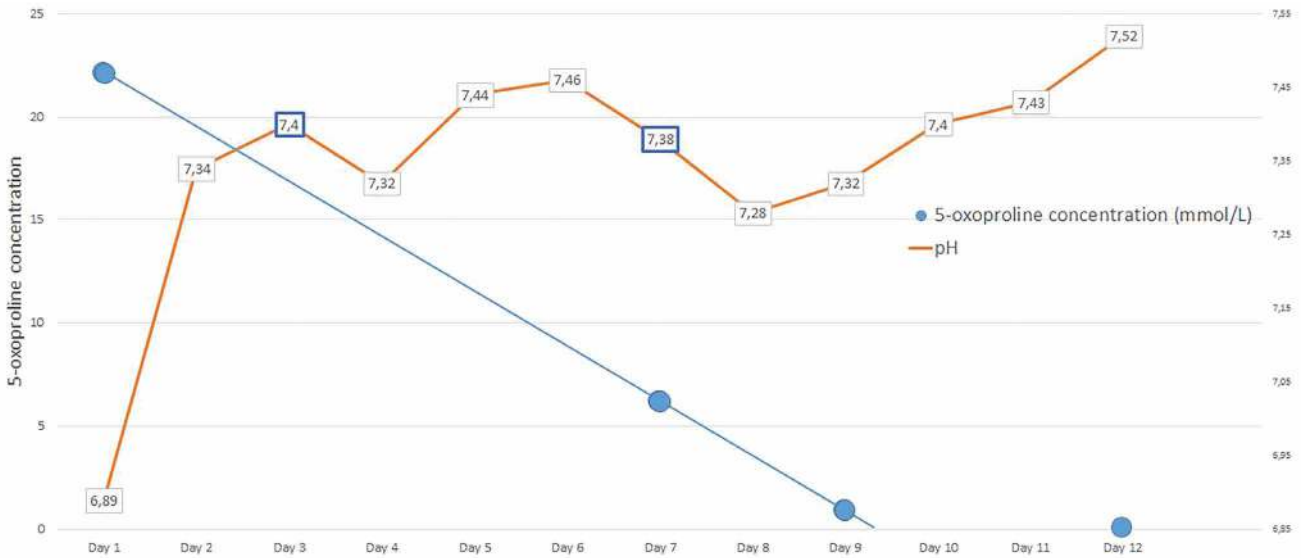

Figure 1. 5-oxoproline urine concentrations and blood pH
Highlighted boxes = discontinuation or lowering of bicarbonate treatment

Discussion

As demonstrated in our case, elimination of 5-oxoproline may take a number of days to weeks. Toxic concentrations may persist for days, even after eliminating the offending drugs. *Figure 1* illustrates a constant decrease of 5-oxoproline concentrations in the urine and lowered pH values in the blood, which persisted longer than expected. Patient-specific factors such as kidney dysfunction may play a role in the plasma elimination. In our case, urine concentrations of 5-oxoproline decreased from 22.1 mmol/l to 6.2 mmol/l within seven days with a persistent acidosis. There is no available literature that describes a relapse of metabolic acidosis due to persistent high levels of 5-oxoproline. Furthermore, there is no evidence describing the elimination speed of 5-oxoproline, nor concentrations over time. That is why it is recommended to frequently measure the level of 5-oxoproline. There is no association between 5-oxoproline concentrations and morbidity or mortality.[2]

Elevated levels of paracetamol have been observed in 5-oxoprolinaemia although in most cases plasma concentrations tend to be in the low-normal therapeutic range.[2,4,7,8] Known risk factors for 5-oxoprolin metabolic acidosis include female sex, malnutrition, sepsis, chronic alcohol use, underlying liver disease and renal insufficiency. Applicable risk factors for our patient were: gender, renal insufficiency and malnutrition due to strict adherence to a diet. Her renal insufficiency was exacerbated due to excessive vomiting and diarrhoea.[8] 5-oxoprolinaemia can occur after a prolonged period of flucloxacillin and paracetamol usage. Paracetamol can induce glutathione synthetase deficiency, which in turn leads to increased γ-glutamylcysteine levels and glutathione depletion. γ-glutamylcysteine is thereafter metabolised to 5-oxoproline. Flucloxacillin inhibits 5-oxoprolinase, which ultimately leads to accumulation of 5-oxoproline, as illustrated in *figure 2*.[9] The time to onset, in an overview of the reports sent to the Netherlands Pharmacovigilance Centre Lareb, ranges between 9 days to 2 months which is in concordance with our case in which metabolic acidosis occurred after 13 days of therapy.[10]

Treatment mainly consists of supportive care whilst plasma elimination of 5-oxoproline takes place. Bicarbonate administration, inotropy or mechanical ventilation can all be used as in our case. Acetylcysteine can be used to replenish both glutathione and cysteine. Glutathione and cysteine deficiencies

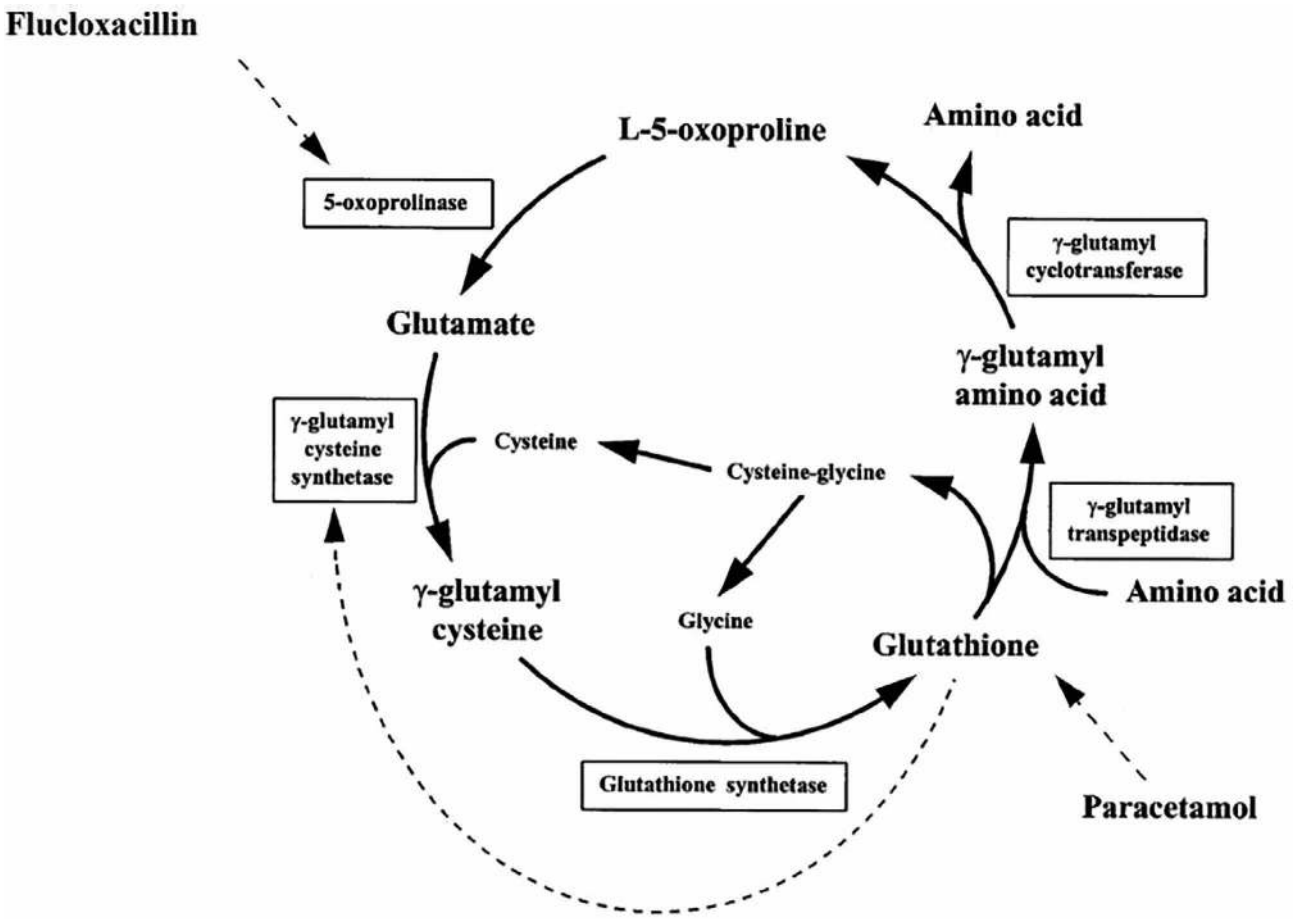

Figure 2. The γ-glutamyl cycle, illustrating the proposed mechanism of 5-oxoproline accumulation as a result of concomitant use of flucloxacillin and paracetamol [10]

can cause accumulation of 5-oxoproline through an ATP-depleting futile 5-oxoproline cycle.[4] Acetylcysteine is indicated and has been studied for instances of paracetamol overdose.[11] Acetylcysteine in 5-oxoprolinaemia is commonly employed to replenish glutathione and cysteine deficiencies although its effect as a substrate for γ-glutamylcysteine synthetase could theoretically increase 5-oxoproline levels.[2,12] Usage of haemodialysis to accelerate the elimination process is described and was successfully applied in two case reports.[13,14] It has been described in case reports that a 5-oxoproline induced metabolic acidosis can cause metabolic encephalopathy.[4,15] Treatment can be complicated by metabolic encephalopathy. Motor agitation and restlessness can interfere with supportive treatment/ventilatory efforts.

5-oxoprolinaemia is a diagnosis that could frequently be missed due to lack of in-house diagnostic tests. In our case there was a delay of five days because assays had to be conducted in a laboratory in Nijmegen, the Netherlands. Further research still needs to be carried out to ascertain more information regarding elimination rate, risk factors and possible therapies.

Conclusion

5-oxoproline high anion gap metabolic acidosis can be caused by concurrent paracetamol and flucloxacillin usage. It is a severe and rare disorder with risk factors such as female gender, malnutrition, renal insufficiency, sepsis, chronic alcohol use, liver disease and renal insufficiency. If suspicion of 5-oxoprolinaemia arises, possible offending drugs must be discontinued immediately. Toxic concentrations may persist for a number of days or weeks onwards, requiring follow-up of arterial blood pH and concentrations of 5-oxoproline in the urine. 5-oxoprolinaemia may even induce chemical encephalopathy which will impede recovery. Treatment is mainly supportive in nature. The role of acetylcysteine is unclear although it is often given empirically. Haemodialysis has proven effective in several case reports. Our patient was discharged 36 days after ICU admission.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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