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Case Report

Successful Early Treatment of 5-Oxoproline Metabolic Acidosis with N-Acetylcysteine: A Case Report

Ayman El Idrissi[#1], Pomme IHG Simons[#1], Jannic van Leendert[1], Astrid MP Demandt[1,2], Marlies van Wolfswinkel[1], Fabienne JH Magdelijns[*1]

[1]Internal Medicine, Division of General Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

[2]Department of Internal Medicine, Division of Hematology, GROW school for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands

[#]Equal contribution

***Corresponding authors:** Fabienne Magdelijns, Department of Internal Medicine, Maastricht University Medical Centre, P Debyelaan 25 6229HX, Maastricht, The Netherlands

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Abstract

Background: 5-oxoproline intoxication is an often-iatrogenic cause of a high-anion gap metabolic acidosis [1]. The most common cause is the combined use of high dose flucloxacillin with acetaminophen. Treatment primarily involves discontinuation of provoking agents and administering intravenous bicarbonate. However, N-acetylcysteine may represent a promising alternative treatment option. **Case presentation:** We present a case of 5-oxoproline intoxication induced by the concurrent use of flucloxacillin and acetaminophen. Upon diagnosis, discontinuation of provocative agents and administration of intravenous bicarbonate was started, however without improvement of the metabolic acidosis. Promptly, N-acetylcysteine was administered, resulting in noticeable improvement. **Conclusion:** N-acetylcysteine may represent a promising supplementary treatment option for 5-oxoproline metabolic acidosis.

Keywords: N-acetylcysteine; 5-oxoproline; metabolic acidosis; bicarbonate

Abbreviations: PET: Positron Emission Tomography; DAIR: Debridement, Antibiotics and Implant Retention

Introduction

5-oxoproline intoxication is a rare and often iatrogenic cause of a high-anion gap metabolic acidosis [1]. The most common cause is the combined use of high dose flucloxacillin with acetaminophen. Current treatment primarily involves discontinuation of provoking agents and administering intravenous bicarbonate. However, N-acetylcysteine – a precursor for glutathione – may represent a promising supplementary treatment option. Here we present a case of 5-oxoproline intoxication induced by the concurrent use of flucloxacillin and acetaminophen for a prosthetic joint infection. Upon diagnosis of 5-oxoproline intoxication, discontinuation of provocative agents and administration of intravenous bicarbonate was started, however without improvement of the metabolic acidosis. Promptly, N-acetylcysteine was administered, resulting in noticeable improvement in the metabolic acidosis.

Case presentation

A 72-year-old man with a history of primary myelofibrosis and arthroplasty of the right knee, presented at the emergency department with malaise, lower back pain and redness, swelling and pain of the right knee. Laboratory tests revealed a C-reactive protein level of 172 mg/L (normal range <10mg/L). A prosthetic joint infection was suspected and ceftriaxone 2 grams daily

was started intravenously. The knee joint was surgically treated with debridement, antibiotics and implant retention (DAIR). Acetaminophen was prescribed in the dose of 1000mg four times daily, ibuprofen 200mg three times daily and oxycodone extended release 20mg twice daily for pain management.

The day following admission, meticillin-sensitive Staphylococcus aureus was isolated from blood and synovial fluid cultures. Antibiotic treatment was switched to intravenous flucloxacillin with a loading dose of 2 grams followed by 12 grams per day continuously. A positron emission tomography (PET) scan showed the prosthetic joint infection of the knee and lumbar spondylodiscitis of L2 and L3, congruent with the lower back pain. Endocarditis could not be excluded. Therefore, flucloxacillin dose was maintained at 12 grams daily.

On the 24th inpatient day, the patient developed dyspnea. Arterial blood gas analysis revealed a high anion gap metabolic acidosis with respiratory compensation (pH 7.31, pCO2 1.0kPa, bicarbonate 3.5mmol/L, base excess -20.3, albumin 17.4g/L). Additionally, the patient experienced acute kidney injury, with creatinine levels rising from 114 µmol/L to 232 µmol/L. We evaluated all possible causes of a high anion gap metabolic acidosis using the acronym 'GOLDMARK' and concluded that 5-oxoprolin intoxication, potentially aggravated by renal failure, was the cause. Urinary measurements confirmed our diagnosis, revealing elevated 5-oxoproline levels (Figure 1).

Acetaminophen and flucloxacillin were discontinued (cefazolin was started as alternative antibiotic treatment) and intravenous bicarbonate was administered both as bolus and continuously. This temporarily ameliorated the acid base balance. However, bicarbonate and base excess levels deteriorated again, prompting the early initiation of intravenous N-acetylcysteine (Figure 1). Subsequently, pH levels improved and stabilized around 7.40. Despite correction of metabolic acidosis, the patient's condition further deteriorated due to progression of his underlying disease. Palliative sedation was initiated, and the patient passed away 12 days after the diagnosis of 5-oxoproline intoxication.

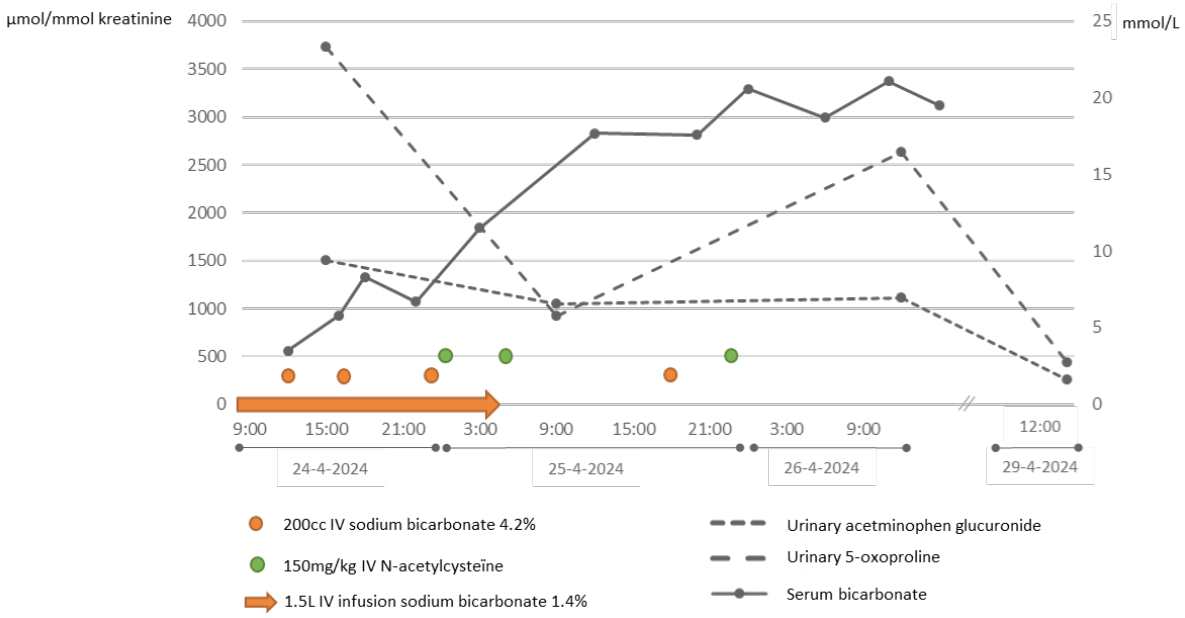

Figure 1: Course of urinary acetaminophen glucuronide, urinary 5-oxoproline, and serum bicarbonate levels, along with the corresponding times of intervention with sodium bicarbonate or N-acetylcysteine.

Discussion and conclusions

5-oxoproline intoxication is characterized by the accumulation of 5-oxoproline (also known as pyroglutamic acid), an intermediate in the gamma-glutamyl cycle [1]. The gamma-glutamyl cycle comprises a series of enzymatic reactions in which glutamate is combined with cysteine and glycine to form the tripeptide glutathione. Glutathione is subsequently broken down to form 5-oxoproline (Figure 2). Glutathione impedes the gamma-glutamyl cycle, and plays a crucial role in amino acid transport and the detoxification of reactive oxygen species [1].

In the presenting case, accumulation of 5-oxoproline results from two main factors: depletion of glutathione and reduced breakdown of 5-oxoproline. Gluthathione depletion is a common side effect of acetaminophen, as its downstream product N-acetyl-p-benzoquinone binds to glutathione and removes it from the gamma-glutamyl cycle. This effect is exacerbated in conditions such as malnutrition, alcohol abuse, kidney disease, liver disease or sepsis. Additionally, flucloxacillin inhibits 5-oxoprolinase which converts 5-oxoproline to glutamate [1]. This dual mechanism leads to the accumulation of 5-oxoproline.

Treatment of 5-oxoproline intoxication primarily involves discontinuation of provocative agents, e.g. acetaminophen and/or flucloxacillin, and improving concomitant factors like kidney disease and malnutrition. To our knowledge, only five case-reports mention N-acetylcysteine as a treatment option, and large-scale studies demonstrating its clinical efficacy are lacking [2-6]. N-acetylcysteine is metabolized to cysteine – a precursor for glutathione synthesis (Figure 2) – thereby replenishing glutathione levels. Moreover, evidence supporting the use of N-acetylcysteine for 5-oxoproline intoxication can be found in patients with hereditary glutathione synthase deficiency, a condition resembling the phenotype of 5-oxoproline intoxication [7].

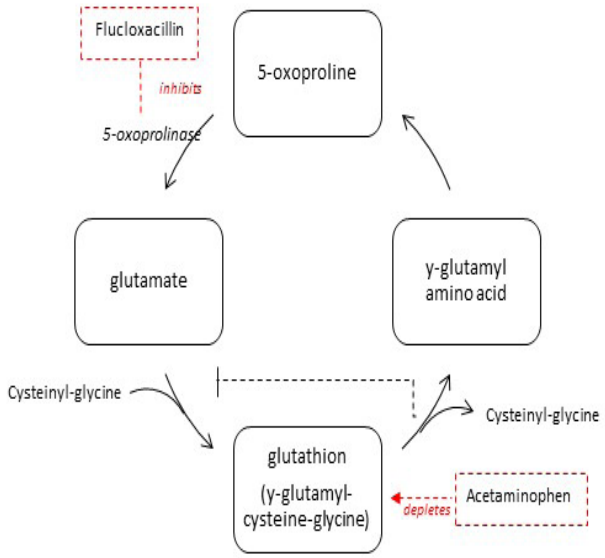

Figure 2: Schematic overview of the gamma-glutamyl cycle and the effects of flucloxacillin and acetaminophen on this cycle.

In conclusion, N-acetylcysteine seems a promising treatment option for 5-oxoproline intoxication, as illustrated in this case. Although, larger studies are necessary to further evaluate its clinical efficacy.

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