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Case Report

Pyroglutamic acidosis caused by the combination of two common medicines prescribed in everyday practice

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Abstract

We present the case of a 71-year-old female treated for infective endocarditis with flucloxacillin and paracetamol. Her clinical course became complicated by a blood-gas demonstrating a raised anion gap metabolic acidosis. The patient was diagnosed with pyroglutamic metabolic acidosis. This is a rare interaction between high dose flucloxacillin and paracetamol, and is an important complication to recognize.

INTRODUCTION

Pyroglutamic acidosis (PGA) is a rare complication of co-prescribed penicillin (isoxazolyl) and paracetamol. The risk of PGA is increased by polypharmacy as well as multiple co-morbidities. If not recognized and addressed, PGA can contribute significantly towards poorer patient outcomes [1, 2].

CASE REPORT

A 71-year-old lady with a background history of hypertension was transferred for step-down care on intravenous antibiotics. She was diagnosed with L5 discitis and suspected infective endocarditis complicating a *Staphylococcus aureus* blood stream infection (BSI). Transoesophageal echo had shown a mobile echo density on the aortic valve and the diagnosis of discitis was confirmed on magnetic resonance imaging (MRI). There was no clear source of the bacteraemia. The patient reported a significant history of chills and fevers for 1 week post coronavirus disease-2019 (COVID-19) vaccination. There was no evidence of collection at the site of vaccination. The *S.aureus* blood culture isolate was susceptible to flucloxacillin. She was commenced on 2 g of flucloxacillin 4 hourly along with 1 g of IV paracetamol four times daily for analgesia. This regimen continued for 2 weeks with an appropriate response clinically and biochemically. The only side-effect of treatment noted was persistent nausea, developing around Day 10.

The patient's condition began to deteriorate on Day 16, with increasing nausea and several episodes of vomiting. She became hypotensive, dyspnoeic and developed a reduction in her urine output. The biochemistry results demonstrated a new acute kidney injury (AKI) with creatinine rising from 78 to 160 μmol/L. Blood gas showed a pH of 7.29, pCO_2 of 2.3 kPa and a bicarbonate of 15 mmol/L. Lactate was normal. These results were consistent with a high anion gap acidosis (HAGMA) of 26 mEq/L. Alternative causes of acute deterioration with these symptoms and biochemistry, such as sepsis, were considered and excluded. PGA was suspected due to the treatment regimen alongside the biochemical indices. The nausea and vomiting were a response to low pH and the dyspnoea was an attempt to eliminate CO_2 as compensation for the acidosis.

Diagnosis of PGA was confirmed with urine showing the presence of inorganic acids. Paracetamol was stopped and flucloxacillin was changed to a cephalosporin (Cefurxime). The patient's symptoms resolved and blood gas parameters normalized after 48 hours. However, she developed significant adverse reactions such as bone marrow suppression and an allergic reaction to second- and third-line antimicrobial agents. These also had inadequate or suboptimal anti-staphylococcal cover and her inflammatory markers began to rise. Noscomial infection was ruled out at this stage with appropriate screening tests. A repeat MRI at 6 weeks demonstrated ongoing active infection at the L5 region. A reintroduction of flucloxacillin without paracetamol was successful and the patient completed another 6 week course with no further complications. Repeat MRI showed significant improvements in discitis.

DISCUSSION

The risk of PGA secondary to the interaction between flucloxacillin and paracetamol is poorly recognized in clinical practice and literature [2, 3]. The causes of a HAGMA can be summarized by the acronym GOLD-MARK [4] (glycols, oxoproline, lactate, D-lactate, methanol, aspirin, renal failure and ketoacidosis).

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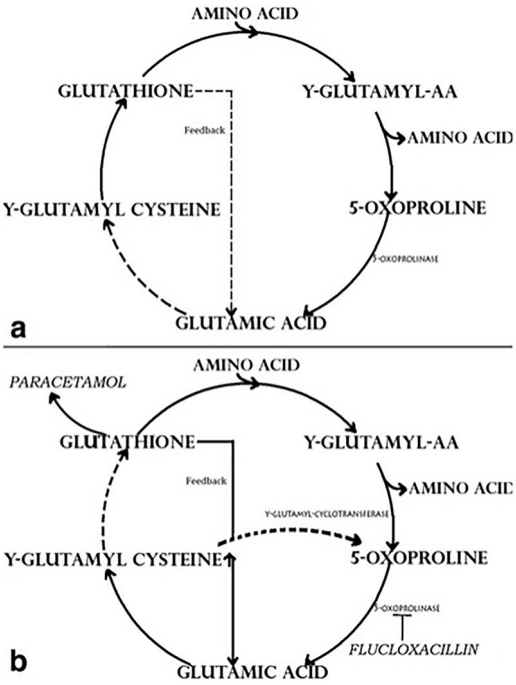

Figure 1. Glutamyl cycle (**a**) and effect of paracetamol and flucloxacillin on the y-glutamyl cycle (**b**). In the γ-glutamyl cycle, the rate-limiting step is the conversion of glutamic acid to γ-glutamyl-cysteine by γ-glutamyl-cysteine synthetase.

Pyroglutamic acid (5-oxoproline) is an intermediate metabolite of the gamma-glutamyl cycle [1, 5]. Both paracetamol and flucloxacillin interact with the gamma-glutamyl cycle as outlined below and in Figure 1:

1) Paracetamol contributes to cysteine deficiency through direct conjugation. The paracetamol metabolite, N-acetyl-P-benzoquinonimine binds irreversibly to glutathione. When glutathione levels are depleted, the feedback inhibition is removed resulting in the formation of γ-glutamylcysteine and the formation of 5-oxoproline [5, 6].
2) Flucloxacillin inhibits 5-oxoprolinase, preventing degradation of pyroglutamic acid to glutamate. This leads to higher concentrations of 5-oxoproline [5].

Pyroglutamic acid is renally excreted. This patient had an AKI, which exacerbated the accumulation of toxic metabolites in the kidneys and further impacted renal function [6].

Anecdotally, we have seen an increase in the number of patients presenting with discitis following a prolonged period of fevers and chills following COVID-19 vaccination. Nationally, the rate of community acquired *S. aureus* BSI has increased [7]. We could postulate that this is related to an indirect effect on the immune system from infection with COVID-19 or COVID-19 vaccination, or that prolonged rigors related to vaccination could lead to bacterial translocation [8].

In summary, an increased awareness of the possible interaction between these two commonly co-prescribed medications is essential in recognizing PGA. This, along with clinical signs and biochemical indices, could alert clinicians to PGA as a cause of the acutely deteriorating patient on this commonly prescribed regimen. Finally, this paper also outlines how there should be more awareness among clinicians for this phenomenon.

CONFLICT OF INTEREST

The authors have no interests to declare.

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