Rare disease

Refractory metabolic acidosis in patients with sepsis following hemiarthroplasty for femoral neck fracture: a causative role for paracetamol and flucloxacillin?

Halima Amer,¹ Frances Dockery,¹ Nicholas Barrett,² Marc George,³ Karolina Witek,⁴ Jeremy Stanton,³ Diane Back³

¹Department of Ageing and Health, Guy's and St. Thomas' Foundation Trust, London, UK;

²Department of Critical Care, Guy's and St. Thomas' Foundation Trust, London, UK;

³Department of Orthopaedic Surgery, Guy's and St. Thomas' Foundation Trust, London, UK;

⁴Department of Metabolic Biochemistry, Guy's and St. Thomas' Foundation Trust, London, UK

Correspondence to Dr Halima Amer, h.amer@doctors.org.uk

Summary

The authors report two cases of pyroglutamic acidosis as a result of paracetamol and flucloxacillin therapy in patients with prosthesis infection following hemiarthroplasty for neck of femur fractures. Pyroglutamic acidosis is an important and often unrecognised cause of refractory metabolic acidosis that disproportionately affects older women, and can be caused by drugs such as paracetamol and flucloxacillin in the setting of sepsis, renal failure and malnutrition. Although relatively rare, the widespread use of these drugs in orthopaedic patients confirms the importance of this disorder.

BACKGROUND

Acquired pyroglutamic acidosis is a rare cause of high anion gap metabolic acidosis that results from the build up of pyroglutamic acid (5-oxoproline).¹ More common raised anion gap metabolic acidoses include those due to lactic acidosis, ketoacidosis and renal failure. Rarer causes include acidosis secondary to the ingestion of methanol, salicylic acid and paraldehyde. Although first reported

in an adult patient in 1989,² recently there have been a number of reports in the critical care literature highlighting its association with commonly prescribed drugs such as penicillins, paracetamol and antiepileptics.³ Given the drugs with which it has been associated, it is potentially an under-recognised problem. In addition to the ingestion of drugs such as paracetamol and flucloxacillin, key risk factors that have been identified include ongoing sepsis,

Figure 1 Organic acid gas chromatography-mass spectrometry (GC-MS) analysis for patient 1.

Figure 2 Organic acid gas chromatography-mass spectrometry (GC-MS) analysis for patient 2.

malnutrition, renal failure and female gender.⁴ Femoral neck fractures disproportionately affect older women, and postoperative infection has been reported as high as 16% of the total complication rate,⁵ affecting almost 5% of all procedures.⁶ Consequently the use of antibiotic therapy in older females following hemiarthroplasty is relatively common. Added to the widespread use of long-term paracetamol as the analgesia of choice in a patient population in which non-steroidal anti-inflammatories are unsuitable, the risk of pyroglutamate acidosis in older women following neck of femur fracture repair is potentially significant. Untreated, the acidosis is a major contributor to mortality.⁷ We present here two cases of refractory pyroglutamate acidosis in two patients within a 6-month period that developed sepsis following hemiarthroplasty for neck of femur fractures.

CASE PRESENTATION

Case 1

A female patient in her early 80s presented with a left intracapsular neck of femur fracture. A cemented Thompson's hemiarthroplasty was performed within 48 h of admission. Standard antibiotic cover was provided by three intravenous 1.5 g doses of cefuroxime. Her recovery was complicated by atrial fibrillation and an upper gastrointestinal bleed. There were no concerns regarding wound healing, and she was discharged home 11 days following the initial procedure. Seven days later, she was readmitted with fever and wound dehiscence. A washout and debridement were performed. *Staphylococcus aureus* was cultured from deep tissue samples. Intravenous flucloxacillin 2 g, four times daily was commenced. Regular paracetamol was continued for ongoing hip and wound pain. However, 14 days later the wound had again dehisced and a further washout was performed. Over the next few days the patient developed a severe hypokalaemia and

deteriorating renal function (table 1). Arterial blood gas sampling demonstrated a compensated metabolic acidosis with a base excess of -15.2 mmol/l and a raised anion gap of 28 mEq/l (table 1).

The patient was transferred to the high dependency unit where potassium replacement and 1.26% sodium bicarbonate was administered. A provisional diagnosis of pyroglutamate acidosis secondary to concurrent flucloxacillin and paracetamol administration, potentiated by ongoing sepsis, was made. Urine testing for organic acids subsequently confirmed the diagnosis, demonstrating a gross increase in excretion of pyroglutamate (figure 1). Paracetamol and associated metabolites were also detected. Intravenous flucloxacillin and paracetamol both of which had been given for 38 days, were ceased. Urine and blood cultures were positive for *Enterococcus faecalis*, and treatment with daptomycin was commenced. Although the acidosis improved over the ensuing 5 days, the underlying hip sepsis did not resolve, and 65 days after the initial hemiarthroplasty, the prosthesis was removed. Despite this, the sepsis persisted; there was a further deterioration in renal function, and 3 weeks later the patient died.

Case 2

A female patient in her late 80s presented with a left intracapsular neck of femur fracture. A cemented Thompson's hemiarthroplasty was performed the following day. Perioperative antibiotic prophylaxis was provided by three intravenous 1.5 g doses of cefuroxime. Six days postoperatively, the wound continued to discharge serosanguinous fluid, and oral flucloxacillin 500 mg, four times daily was commenced. Ultrasound of the left hip 14 days postoperatively showed deep fluid collections in the soft tissues, and a washout and debridement was performed the following day. Deep tissue sample cultures grew *S aureus*, and the

Table 1 Measured and calculated serum values

	Patient 1 Day 51	Patient 2 Day 30
pH (7.35 to 7.45)	7.38	7.36
PCO ₂ (10.67 to 13.33 kPa)	1.68	3.37
HCO ₃ ⁻ (22 to 28 mmol/l)	7.3	14.0
Base excess (-2.0 to 2.0 mmol/l)	-15.2	-14.3
Corrected anion gap (8 to 16 mEq/l)*	28	21
Albumin (40 to 52 g/l)	22	22
Na ⁺ (135.0 to 145.0 mmol/l)	148.7	134.4
K ⁺ (3.5 to 5.0 mmol/l)	2.86	2.34
Cl ⁻ (98.0 to 107.0 mmol/l)	113.8	99.2
Lactate (0.4 to 2.2 mmol/l)	0.8	1.3
Urea (1.7 to 8.3 mmol/l)	8.6	4.9
Creatinine (45 to 84 µmol/l)	145	64
C reactive protein (<5 mg/l)	72	207
Leucocytes (4.0 to 11.0 × 10 ⁹ /l)	8.5	10.9

Normal ranges are indicated in brackets.

*Electrolyte values from arterial blood gas sampling were used to calculate the corrected anion gap.

flucloxacillin was changed to 1 g, four times daily intravenously. Regular paracetamol 1g, four times daily was also prescribed. A further washout and debridement was performed 20 days following the original hemiarthroplasty. Although there was clinical improvement of the hip, at day 30 postoperatively the patient had an unresponsive episode. She was found to have new onset atrial fibrillation, thought to be secondary to hypokalaemia. All blood results are presented in table 1. It was thought that the patient had ongoing sepsis from the prosthesis, and an excision hemiarthroplasty was scheduled. Pyroglutamic acidosis was considered as a cause for the ongoing metabolic acidosis, and flucloxacillin and paracetamol stopped. Intravenous flucloxacillin had been given for a total of 26 days. Bicarbonate was administered and the corrected anion gap improved. The patient required an excision arthroplasty 43 days postoperatively, but died 5 days later. Urine testing for organic acids received post mortem showed an increase in excretion of pyroglutamate (figure 2). There was also an increased level of 4-hydroxyphenyllactate in keeping with liver stress.

DISCUSSION

Pyroglutamic acidosis is most commonly secondary to an inborn deficiency of glutathione synthetase. This causes a reduction in glutathione levels and activation of an alternative metabolic pathway, resulting in the formation of pyroglutamate from the precursor to glutathione, γ -glutamyl cysteine. Low glutathione levels have a negative feedback effect, resulting in increased production of γ -glutamyl cysteine synthetase, and ultimately, pyroglutamate. 5-oxoprolinase oxidises pyroglutamate, or 5-oxoprolinone, to glutamate, which can be reconverted to γ -glutamyl cysteine. Sepsis, chronic alcohol excess, paracetamol and malnutrition all deplete glutathione stores. Some antibiotics (flucloxacillin and netilmicin) and some anticonvulsants (vigabatrin) inhibit the oxidation of pyroglutamate. Hence a combination of flucloxacillin and paracetamol can result in significant accumulation

of pyroglutamate, potentiated by impaired clearance in renal failure.⁸ In the cases discussed here, high levels of urinary pyroglutamic acid were detected following long-term treatment with flucloxacillin and paracetamol, after which metabolic acidosis was observed (table 1). In addition to its direct measurement in urine, pyroglutamic acid is an unmeasured anion in the serum and contributes to a raised serum anion gap. Both of the patients discussed had a high anion gap metabolic acidosis. Common causes for this disorder include lactic acidosis, diabetic ketoacidosis, renal failure and ingestion of toxic substances such as methanol. Recently paracetamol and penicillins have become recognised as causative for high anion gap acidosis.⁹ Both cases presented here had a degree of renal impairment that will have contributed to the raised anion gap but was not solely responsible for it. In both cases, there was no evidence of ketosis or history of ingestion of toxic substances or other drugs potentially responsible for raised anion gap acidosis. Following discontinuation of paracetamol and flucloxacillin, the metabolic acidosis resolved. In view of the history, a score of 7 on the Naranjo scale suggests that the effects were probably due to use of this drug combination.

Although the depletion of glutathione stores is undoubtedly multifactorial, it is important to consider the risks and benefits of paracetamol in each patient. Both patients did have detectable paracetamol in their urine, although its significance is unclear. Interestingly, both patients were persistently hypokalaemic and required significant potassium replacement therapy. Hypokalaemia has long been recognised as a side effect of high-dose antibiotic therapy, although often in the setting of metabolic alkalosis. Penicillin derivatives act as a non-reabsorbable anion and more sodium is reabsorbed at the expense of potassium, resulting in low serum potassium. It is likely that this phenomenon contributed to the observed hypokalaemia. As metabolic acidosis is the most common acid-base disorder in intensive care and high dependency units, many of the cases secondary to pyroglutamate acidosis have been reported in this setting. However pyroglutamic acidosis has been recognised in medical and orthopaedic patients.¹⁰ The risk factors for the acquisition of pyroglutamic acidosis in the absence of congenital enzyme deficiency are that patients are commonly older, have risk factors for glutathione depletion, are on medications known to prevent pyroglutamic acid breakdown and have mild renal impairment. All of these factors were present in our patients.

The optimal management strategy for pyroglutamic acidosis has yet to be defined. However, the reported management strategies have all included ceasing the flucloxacillin and paracetamol. Clearly, consideration for an alternative non-penicillin antibiotic therapy will be required. Fluid resuscitation and general supportive care including electrolyte supplementation is important. The role of *N*-acetylcysteine for glutathione replenishment is ill-defined but would appear to have potential benefit and minimal associated harm.

Learning points

- ▶ Pyroglutamic acidosis is a relatively rare cause of high anion gap metabolic acidosis, but its risk is increased with use of common concurrent medications such as paracetamol and penicillin.
- ▶ Pyroglutamic acidosis should be considered in older patients receiving concurrent paracetamol and penicillin therapy following joint surgery with refractory high anion gap acidosis.
- ▶ If suspected, immediate substitution of non-penicillin antibiotics would be advisable and supportive management commenced. *N*-acetylcysteine may be considered.
- ▶ It is worth reappraising the advisability of long-term paracetamol in older patients.

Competing interests None.

Patient consent Not obtained.

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