High Anion Gap Metabolic Acidosis Induced by concurrent use of Flucloxacillin and Paracetamol: a case report

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Objective

To describe a case of flucloxacillin and paracetamol induced 5-oxoprolinaemia leading to high anion gap metabolic acidosis (HAGMA).

Clinical Features

A 95-year-old female was admitted to hospital with dyspnoea and likely diuretic-induced kidney injury. Investigations revealed a HAGMA with an albumin adjusted anion gap of 36.3mmol/L (8-16mmol/L). Refer to Table 1.

The patient had been admitted prior to this for the treatment of methicillin susceptible *Staphylococcus aureus* (MSSA) bacteraemia complicated by L5/S1 discitis, likely permanent pacemaker infection, and suspected infective endocarditis. During her previous admission, she had been managed with intermittent administration of intravenous flucloxacillin 2g every 4 hours for four weeks followed by two weeks of continuous infusion of 12g per 24 hours via outpatient parenteral therapy service.

This presentation of HAGMA had occurred within two days of the oral therapy of flucloxacillin (day 51 in total) which had been prescribed as part of an oral tail with an intended step down to lifelong suppressive therapy. Paracetamol had been pre-morbidly prescribed prior to the initial presentation for chronic lower back pain and therapy had been maintained at this dose due to ongoing issues with pain.

Medications at the time of this episode included:

- Aspirin 100mg po once daily
- Colecalciferol 1000units po once daily
- Calcium carbonate 1500mg po once daily
- Enoxaparin 20mg subcutaneously daily
- Multivitamin po once daily
- Metoclopramide 10mg po three times daily
- Potassium SR 1200mg po once daily

Medications withheld on admission this episode included:

- Spironolactone 50mg po once daily
- Flucloxacillin 500mg po four times daily
- Furosemide 80mg po once daily
- Paracetamol 1330mg po three times daily

	Admission	Day 3	Day 7
Sodium (mmol/L)	142	141	142
Potassium (mmol/L)	2.5	3.2	4.0
Chloride (mmol/L)	98	108	110
Bicarbonate (mmol/L)	14	13	22
Creatinine (µmol/L)	156	121	71
eGFR (mL/min/1.73m^2)	24	33	63
Albumin (g/L)	15	18	19
Anion Gap (mmol/L)	36.3	25.5	15.3

Table 1: Biochemical investigations during the admission

Literature review

There are limited published case reports documenting this drug interaction.

It is theorised that the accumulation of 5-oxoproline (pyroglutamic acid) is driven by a synergistic mechanism. Chronic paracetamol exposure causes glutathione depletion, removing the feedback inhibition on gamma-glutamyl cysteine synthetase. This results in an increased production of 5-oxoproline. Flucloxacillin inhibits 5-oxoprolinase, thereby contributing to the levels of 5-oxoproline which lead to clinically significant 5-oxoprolinaemia.[1,2]

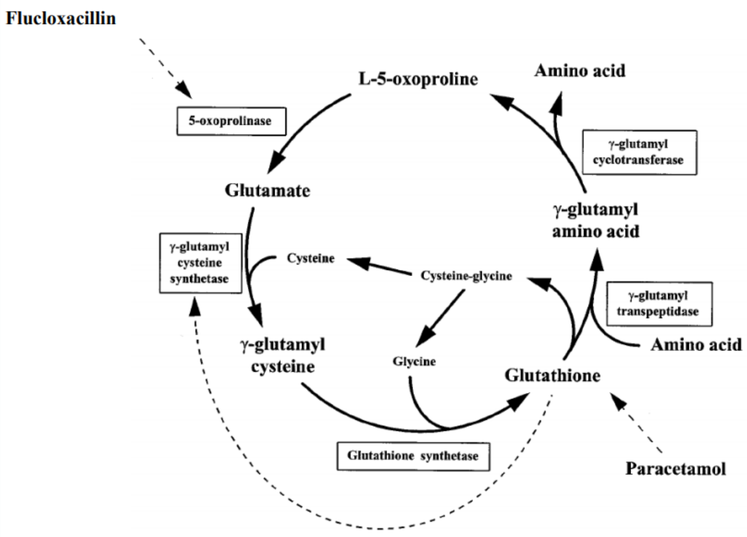

Figure 1: The gamma glutamyl cycle and proposed mechanism of 5-oxoprolinaemia[3]

Furthermore 5-oxoproline is cleared renally making renal impairment a significant risk factor in this mechanism. Other risk factors include age, and those relating to glutathione deficiency such as malnutrition, sepsis, and liver disease.[2]

Case progress and outcomes

The pharmacist identified the drug interaction and requested urinalysis to establish a diagnosis for the unexplained organic cause of metabolic acidosis. A urine metabolic screen showed pyroglutamic acid (5-oxoproline) 3+ on a semi-quantitative assay. On admission, flucloxacillin was ceased and changed to clindamycin.

Supportive therapies for metabolic acidosis such as sodium bicarbonate infusions and intravenous rehydration can be used to treat HAGMA and are low risk. In severe cases, haemodialysis has also be used to clear the accumulation of 5-oxoproline. N-acetylcysteine (NAC) infusions for paracetamol may also be used to treat chronic paracetamol toxicity.

In this case, nil intervention were required due to the resolution within 48 hours of admission of clinical symptoms and pathology, after the cessation of offending agents. Once the HAGMA had resolved, flucloxacillin was restarted at 500mg twice daily for lifelong suppressive therapy. Paracetamol had also been restarted prior to this at the same dose (3990mg/day).

A follow up urinalysis was ordered three weeks after the first, which showed an undetectable 5-oxoproline level.

Conclusion

This case highlights a rare drug-induced consequence from medications that are commonly concurrently prescribed. 5-oxoproline acidaemia is an underappreciated cause of HAGMA. Supportive measures for this drug-induced presentation are low risk and early recognition and withdrawal of causative agents are integral to management.

References

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