Pyroglutamic acidosis due to therapeutic paracetamol: an under-recognised cause of metabolic acidosis

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Introduction

Elevated anion gap metabolic acidosis is a common finding in critical illness. Causes include lactic acidosis, ketoacidosis, advanced renal failure and ingestion of toxic alcohols. Here we report 2 cases of an under-recognised cause, accumulation of 5-oxoproline (pyroglutamic acid) secondary to therapeutic doses of paracetamol.

Case 1

A 44 year old woman arrived by ambulance after being unwell at home for 8 days. She complained of chest and abdominal pain and was admitted with suspected pancreatitis. She had a profound metabolic acidosis and starvation ketosis was suspected. She denied overdose yet serum paracetamol was detected and she was treated with N-acetyl cysteine. It was suspected that 5-oxoproline was contributing to the degree of acidosis.
Urine sent for organic acid analysis showed a grossly elevated level of 5-oxoproline, mild ketoaciduria, mild lactic aciduria, and the presence of paracetamol.

Biochemistry:

	Day 0	Day 2	Day 3	Units	Reference Range
Na	140	146	146	mmol/L	(133-146)
K	3.5	3.8	3.4	mmol/L	(3.5-5.3)
Cl	97	117	112	mmol/L	(95-108)
HCO_3	6	19	22	mmol/L	(22-29)
Anion Gap	37	10	12	mEq/L	(5-25)
pH	7.10	7.5			(7.35-7.45)
pCO_2	<1.60	3.0		kPa	(4.30-6.40)
O_2 sat	98.7	96.9		%	(94.0-98.0)
Creatinine	200	36	32	umol/L	(45-85)
CRP	404			mg/L	(0-5)
Glucose	5.3			mmol/L	(3.0-7.7)
Amylase	1343		359	U/L	(0-53)
Lacate	1.2	0.9		mmol/L	(0.0-1.3)
Ketones	3			mmol/L	(<0.6)
Paracetamol	37			mg/L	

Case 2

A 64 year old woman was admitted with an adnexal mass which necessitated bilateral nephrostomies. She had been on paracetamol throughout her admission and was being treated with flucloxacillin for suspected endocarditis. On day 25 she developed a metabolic acidosis which was treated with sodium bicarbonate. Paracetamol and flucloxacillin were stopped, but haemodialysis was required to resolve the acidosis.
Urine organic acid analysis showed a gross elevation of 5-oxoproline, moderate ketoaciduria, mild lactic aciduria, and the presence of paracetamol.

Anion gap metabolic acidosis

Updated mnemonic of causes most likely to be encountered[1].

G	Glycols (ethylene, propylene)
O	5-oxyproline (pyroglutamic acid)
L	L-lactate
D	D-lactate
M	Methanol (and other alcohols)
A	Aspirin (salicylic acid)
R	Renal failure
K	Ketosis (diabetic, alcoholic, starvation)

Discussion

The γ-glutamyl cycle imports amino acids across cell membranes and creates glutathione, a critically important anti-oxidant[2]. Disruption of this cycle leads to metabolic acidosis due to the build up of 5-oxoproline (figure 1). Rare inherited deficiencies of the enzymes glutathione synthetase and 5-oxoprolinase are known to result in massive urinary excretion of 5-oxoproline[2]. However acquired deficiencies of cellular glutathione and cysteine act to remove negative feedback on the enzyme γ-glutamyl-cysteine synthase leading to a futile over-activation of this cycle and the build-up of 5-oxoproline. Chronic paracetamol use can result in depletion of glutathione, particularly in combination with sepsis, chronic alcoholism, chronic liver failure or malnutrition. The antibiotics flucloxacillin and netilmicin inhibit another enzyme in this cycle, 5-oxoprolinase whose role is to break down 5-oxoproline.

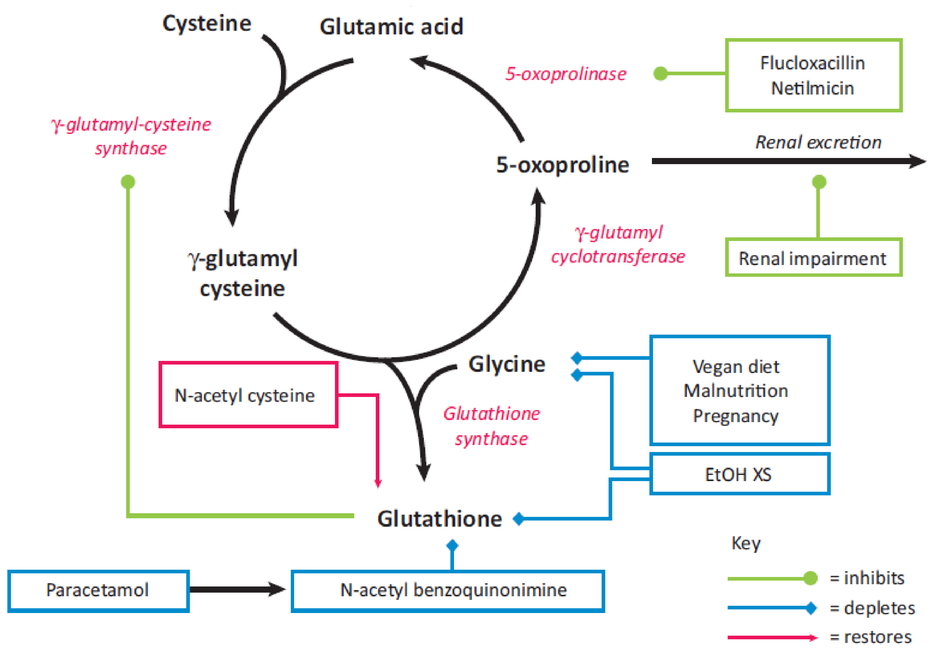

Figure 1.
The γ-glutamyl cycle.
Hunter *et al*[β]

Contributory factors[2,3]

Paracetamol use	Flucloxacillin/netilmicin
Sepsis	Pregnancy
Renal impairment	Hepatic impairment
Female gender	Vigabatrin
Malnutrition, strict vegetarian diet, chronic alcoholism	

Conclusion

Pyroglutamic acidosis is a rarely diagnosed cause of metabolic acidosis, however its prevalence is likely to be underestimated. It should be suspected in patients with an anion gap metabolic acidosis who are on therapeutic doses of paracetamol, particularly if long-term and there are contributing factors present. Consideration should also be given in patients with a known cause of metabolic acidosis (e.g. renal impairment) where the degree of acidosis and anion gap cannot be accounted for.
5-oxoproline is detected in urine organic acid testing which is available in regional metabolic laboratories. Treatment entails stopping paracetamol and other causative medications, and giving N-acetyl cysteine to restore glutathione stores[2,3]. Urine organic acids should be retested after cessation of paracetamol to ensure the abnormality has resolved.

References

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