An unusual cause of severe metabolic acidosis

John V Peter, Natasha Rogers, Shailesh Murty, Rosemarie Gerace, Richard Mackay and Sandra L Peake

A 50-year-old man was transferred to the intensive care unit with high anion gap metabolic acidosis. Investigations suggested a diagnosis of pyroglutamic acidaemia. Factors contributing to the acidosis were medications (paracetamol and flucloxacillin), sepsis and renal failure. The acidosis resolved with supportive therapy and withdrawal of the drugs. It is important to recognise this treatable aetiology of metabolic acidosis. ***(MJA 2006; 185: 223-225)***

Clinical record

A 50-year-old man with cerebral palsy, intellectual impairment and epilepsy was referred to hospital with a 1-week history of fever, chills, rigors, haematuria and loin pain. His usual medications included phenytoin 300 mg/day, phenobarbitone 30 mg/day and carbamazepine 1200 mg/day. There was no history of prior renal disease.

At hospital admission (Day 1), he was conscious, in no obvious distress, and afebrile. He was dehydrated and tachypnoeic (respiratory rate, 22 breaths/minute), but haemodynamically stable. There was no pallor, jaundice or cyanosis. Cardiorespiratory examination was unremarkable. Abdominal examination revealed tenderness in the left renal angle, left loin and right upper quadrant with no features of peritonism.

Key initial (and subsequent) screening investigations are summarised in Box 1. Of note was neutrophilia and significant renal impairment (glomerular filtration rate, 28 mL/min by MDRD 4-variable equation). Urinalysis showed sterile pyuria, haematuria (dysmorphic red blood cells on microscopy) and proteinuria (3.46 g following 24-hour collection). A chest x-ray (CXR) showed mild generalised bronchial wall thickening, with no focal parenchymal opacity. Treatment with empirical broad-spectrum intravenous antibiotics (ceftriaxone and gentamicin) was initiated for suspected urinary tract infection following blood and urine cultures.

A computed tomography (CT) scan on Day 1 revealed a 2.3 cm simple cyst in the upper pole of the right kidney, multiple nodules in the lung bases and a small left pleural effusion. A vasculitic work-up, including assessment of antinuclear antibody, extractable nuclear antigen, antibodies to double-stranded DNA, antineutrophil cytoplasmic antibodies and complement levels, did not assist in diagnosis. Urine culture was negative, so a renal biopsy was performed to establish the aetiology of the acute nephritic syndrome, consistent with IgA nephropathy with mild activity (segmental crescents/necrotising lesions in two of 14 glomeruli), but without scarring. No treatment was indicated.

In view of the persistent fever on Day 3, a repeat CXR was performed. A small left-sided effusion was noted and pleural fluid aspirate was consistent with an exudate (pleural fluid white cell count [WCC], 16.6 × 10^9/L; 85% neutrophils; total protein, 37 g/L; lactate dehydrogenase [LDH], 420 U/L), which was presumed secondary to an underlying pneumonic process. Intravenous flucloxacillin was commenced at 2 g/day to broaden the gram-positive antibiotic cover and continued for 11 days. Blood, urine and pleural fluid cultures were negative.

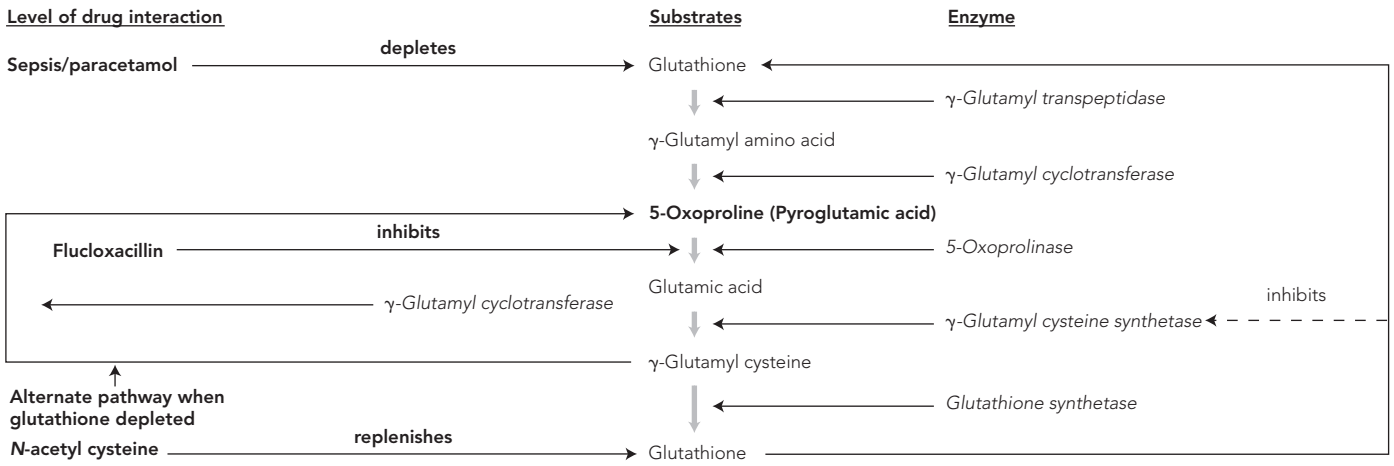
Despite initial clinical and laboratory improvement, the fever recurred on Day 7 with a radiographically visible increase in the

1 Investigations*

	Day 1 Hospital admission	Day 18 ICU admission	Day 63 On recovery	Reference range
Haematology				
Haemoglobin (g/L)	125	**115**	120	135–175
White cell count (× 10^9/L)	13.6	24.7	7.82	4–11
Neutrophil count (× 10^9/L)	**11.1**	**22.75**	6.09	1.8–7.5
International normalised ratio	1.2	**7.6**	1.0	0.8–1.2
APTT (s)	27	**65**	26	24–37
Fibrinogen level	—	**5.7**	—	1.5–4.0
D-dimer FDP	—	**2.15**	—	< 2.0
Biochemistry				
Sodium (mmol/L)	134	138	137	137–145
Potassium (mmol/L)	3.9	2.8	4.1	3.5–4.9
Chloride (mmol/L)	97	93	99	100–109
Bicarbonate (mmol/L)	23	**6**	29	22–32
Urea (mmol/L)	**9.1**	**18.6**	2.7	2.7–8.0
Creatinine (mmol/L)	**0.210**	**0.541**	0.100	0.05–0.12
Gamma GT (U/L)	**152**	**92**	**116**	0–60
Albumin (g/L)	25	17	23	34–48
Lactate dehydrogenase (U/L)	**252**	**293**	210	110–230
Serum amylase (U/L)	—	**119**	—	20–100
C-reactive protein (mg/L)	**290**	**160**	**47**	< 10
Anion gap (mmol/L)	18	**42**	13	7–17
Lactate level (mmol/L)	—	0.7	—	0.2–2.0
Serum pyroglutamic acid level† (μmol/L)	—	**11 010**	—	15–215
Urine pyroglutamic acid level† (μmol/mmol creatinine)	—	**20 495**	**13 103**	< 100

* Platelet count, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and creatinine kinase were normal when measured.
† Initial serum and urine pyroglutamic acid levels were measured 36 hours after admission to the intensive care unit, and repeat urine test was performed on Day 10. Serum and urine pyroglutamic acid levels not measured at discharge.
— = Not measured. Bold indicates highly abnormal results.
APTT = activated partial thromboplastin time.
FDP = fibrinogen degradation products.
GT = glutamyl transpeptidase. ICU = intensive care unit. ◆

2 The γ-glutamyl cycle: mechanism of oxoprolinuria



Sepsis and paracetamol reduce glutathione levels, lifting feedback inhibition of γ-glutamyl cysteine synthetase. Excess γ-glutamyl cysteine is converted by γ-glutamyl cyclotransferase to 5-oxoproline, the build-up of which leads to acidaemia and oxoprolinuria. Flucloxacillin may inhibit further the rate-limiting enzyme 5-oxoprolinase. ◆

pleural effusion size. Repeat pleural aspirate confirmed an empyema (pleural fluid pH 6.4; LDH, 833 U/L; glucose, 0.2 mmol/L) requiring intercostal catheter insertion. However, there was minimal further drainage, despite intrapleural streptokinase administration.

On Day 14, ceftriaxone and gentamicin were changed to empirical timentin and ciprofloxacin because of persistent fever and rising WCC. Flucloxacillin was increased to 4 g/day. Oral paracetamol (1 g every 6 hours as required) and subcutaneous fentanyl were administered for pain relief. On Day 18, deteriorating renal function and conscious state necessitated transfer to the intensive care unit (ICU).

Investigations at ICU admission (Box 1) revealed a severe high anion gap (42 mmol/L) metabolic acidosis. Arterial blood gas analysis (on 100% inspired oxygen) showed a pH of 7.31, PaO_2 242 mmHg, $PaCO_2$ 12 mmHg, and HCO_3 5.6 mmol/L. Flucloxacillin and paracetamol were ceased, and intravenous vancomycin was commenced. Intravenous bicarbonate infusion (25 mL/hour), commenced in the ward for the acidosis, was continued. With supportive therapy (fluids, oxygen, antibiotics), the patient improved over the next 36 hours and the metabolic acidosis resolved.

Following stabilisation, the patient underwent decortication of the left pleura. Histopathology was consistent with an organising fibrinous pleuritis. No bacteria were seen. Decortication was complicated by significant bleeding, requiring massive transfusion. After surgery, the patient's renal function, respiratory function and conscious state steadily improved; he was extubated 5 days after decortication. Recovery was complicated by protracted vomiting. Endoscopy confirmed a Barrett's oesophagus and small hiatus hernia; he improved with a proton-pump inhibitor. In the absence of further respiratory compromise, he was discharged home.

Diagnosis

The cause of the high anion gap metabolic acidosis at ICU admission was not immediately apparent. Serial evaluation of biochemical markers showed worsening renal function. However, even with a creatinine level of 0.541 mmol/L, the expected level of unmeasured anions was only 10–19 mmol/L and was insufficient to explain an anion gap of 42 mmol/L and the severity of the metabolic acidosis. Lactate (0.7 mmol/L) and blood glucose levels (6.1 mmol/L) were not elevated, and urinalysis was negative for ketones, suggesting that lactic or keto-acidosis were unlikely causes (blood ketones were not measured). There was no history of salicylate administration or ethylene glycol, ethanol or methyl alcohol consumption.

Case-note review indicated that the patient had received a total of 8 g of paracetamol and 16 g of flucloxacillin in the 4 days before ICU admission. Ongoing sepsis and worsening renal failure, in combination with these drugs, suggested a possible diagnosis of pyroglutamic acidaemia (PGA).

Urine pyroglutamic acid levels, highly elevated 36 hours after ICU admission (Box 1) remained elevated 10 days later, although the values had decreased significantly. Plasma pyroglutamic acid levels were also markedly elevated 36 hours after ICU admission (Box 1). The very high urine and plasma pyroglutamic acid levels supported our diagnosis of PGA. Red cell glutathione synthetase activity was normal (5.6 μmol/g haemoglobin; reference range, 4.2–9.8 μmol/g haemoglobin), suggesting that it was unlikely that this patient had a hereditary disorder of the γ–glutamyl cycle.

Discussion

High anion gap metabolic acidosis is frequently encountered in critical care practice. Recently, there have been several reports of high anion gap acidosis resulting from excess production of 5-oxoproline, and termed "pyroglutamic acidaemia".[1-5] This acidaemia is most frequently reported with paracetamol therapy,[1] but has also been associated with flucloxacillin[2] and vigabatrin,[3] particularly in the setting of severe sepsis, renal or hepatic dysfunction.[4]

The reported inciting dose of paracetamol has been variable: 8 g of paracetamol daily for 3 weeks in one study,[6] and a cumulative dose of 20.8 g of paracetamol over 2 weeks in another.[7] In a series of 11 patients with transient oxoprolinuria, all patients were taking paracetamol, with most receiving therapeutic dosages.[8] A serum paracetamol level of > 200 μmol/L was seen in only one of the eight patients in whom paracetamol levels were checked. Our patient

received a cumulative dose of 8 g of paracetamol over 4 days, and it is likely that PGA was precipitated by a combination of factors, including sepsis, renal dysfunction, and co-administration of flucloxacillin.

PGA also occurs with genetic deficiency of either glutathione synthetase or 5-oxoprolinase.[5] However, not all causes of 5-oxoprolinuria are necessarily associated with acidaemia.

The mechanism of non-hereditary PGA is probably multifactorial. Suppression of glutathione levels because of sepsis, as seen in animal models of polymicrobial sepsis,[9] may have contributed to the development of PGA in our patient. Flucloxacillin could have further compounded this acidosis by inhibiting the breakdown of pyroglutamic acid by 5-oxoprolinase.[2] The role of paracetamol in PGA is more complex.

The metabolite of paracetamol, *N*-acetyl benzoquinoneimine, reacts irreversibly with glutathione. Under normal circumstances, glutathione depletion leads to increased γ-glutamyl cysteine synthetase activity and excessive production of γ-glutamyl cysteine (Box 2). However, under altered conditions, glutathione synthetase activity becomes rate-limiting, leading to the conversion of γ-glutamyl cysteine to 5-oxoproline by γ-glutamyl cyclotransferase.[5] Our patient's antiepileptic medications, which are known hepatic enzyme inducers and metabolised via CYP2E1, may have further compromised glutathione availability by decreasing glutathione stores and competing with paracetamol for metabolism.

Renal impairment may also be important. Renal tubular epithelial dysfunction may impair intracellular glutathione re-formation (a high ATP-requiring state), leading to accumulation of 5-oxoproline and prompt excretion (because of its small molecular size) into the urine, peritubular capillaries and systemic circulation.

The use of *N*-acetyl cysteine to treat PGA has been advocated to replenish glutathione stores by supplying cysteine for glutathione synthesis. Another theoretical treatment option is the use of cysteamine, which increases cytosolic cysteine and restores substrate availability for the glutamate pathway, normalising pyroglutamic acid levels.

As PGA can be easily missed in a critically ill patient, where several factors may contribute to a metabolic acidosis, a high index of suspicion is required to diagnose this condition. PGA should be considered in the differential diagnosis of high anion gap acidosis, especially when the levels of organic acids do not sufficiently account for the degree of anion gap and when there is co-administration of drugs such as paracetamol and flucloxacillin. Where PGA is suspected, the offending drugs should be withdrawn and treatment with *N*-acetyl cysteine considered.

Competing interests

None identified.

Author details

John V Peter, MD, DNB, FRACP, Reader[1]
Natasha Rogers, MB BS, Registrar, Renal Medicine[2]
Shailesh Murty, MB BS, MD, Registrar, Intensive Care Unit[2]
Rosemarie Gerace, BSc, Scientist, Newborn Screening Unit[3]
Richard Mackay, FRACP, Registrar[3]
Sandra L Peake, BM BS, FJFICM, PhD, Senior Consultant, Intensive Care Unit[2]

1 Medical Intensive Care Unit, Christian Medical College and Hospital, Vellore, Tamil Nadu, India.
2 Queen Elizabeth Hospital, Adelaide, SA.
3 Women's and Children's Hospital, Adelaide, SA.

Correspondence: peterjohnvictor@yahoo.com.au

References

1 Pitt JJ, Brown GK, Clift V, et al. Atypical pyroglutamic aciduria: possible role of paracetamol. *J Inherit Metab Dis* 1990; 13: 755-756.
2 Croal BL, Glen AC, Kelly CJ, et al. Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult patient receiving antibiotic therapy. *Clin Chem* 1998; 44: 336-340.
3 Bonham JR, Rattenbury JM, Meeks A, et al. Pyroglutamicaciduria from vigabatrin. *Lancet* 1989; 1: 1452-1453.
4 Dempsey GA, Lyall HJ, Corke CF, et al. Pyroglutamic acidemia: a cause of high anion gap metabolic acidosis. *Crit Care Med* 2000; 28: 1803-1807.
5 Pitt JJ, Hauser S. Transient 5-oxoprolinuria and high anion gap metabolic acidosis: clinical and biochemical findings in eleven subjects. *Clin Chem* 1998; 44: 1497-1503.
6 Sanap M. A 37 year old man with intermittent abdominal pain and a non-lactic, non-ketone, high anion gap metabolic acidosis. *Crit Care Resusc* 2003; 5: 66-68.
7 Humphreys BD, Forman JP, Zandi-Nejad K, et al. Acetaminophen-induced anion gap metabolic acidosis and 5-oxoprolinuria (pyroglutamic aciduria) acquired in hospital. *Am J Kidney Dis* 2005; 46: 143-146.
8 Mayatepek E. 5-Oxoprolinuria in patients with and without defects in the gamma-glutamyl cycle. *Eur J Pediatr* 1999; 158: 221-225.
9 Villa P, Saccani A, Sica A, et al. Glutathione protects mice from lethal sepsis by limiting inflammation and potentiating host defense. *J Infect Dis* 2002; 185: 1115-1120.

(Received 2 Dec 2005, accepted 11 May 2006) ❑