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Case Report Open Access

Metabolic Acidosis with a Raised Anion Gap Associated with High 5-Oxoproline Levels; An Under-Recognized Cause for Metabolic Acidosis in Intensive Care

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Abstract

Metabolic acidosis is a common problem in ICU patients. Frequent causes of metabolic acidosis with a raised anion gap include lactic acidosis and ketoacidosis. In recent years high anion gap acidosis due to acquired 5-oxoprolinuria has been reported in association with chronic paracetamol use 1. There have been occasional reports of acidosis due to 5-oxoproline in an ICU setting 2 but to date there does not seem to be a general awareness of this phenomonen. 5-oxoproline is an amino acid derivative within the γ-glutamyl cycle within the liver, When gluathione stores are depleted γ-glutamycycteine synthase activity increases in an attempt to replenish the glutathione stores. However in the process excess glutamylcycteine is produced which is then converted into 5-oxoproline which can accumulate and cause a metabolic acidosis.

We present a case series of unexplained high anion gap metabolic acidoses in ICU associated with an acculumation of 5-oxoproline. These patients had a background history of alcohol abuse and/or malnutrition and had received paracetamol 4 g/day over periods of 2-3 weeks in ICU. Urinary 5-oxoproline levels were tested and were found to be abnormally high. In all these cases cessation of the paracetamol resulted in correction of the acidosis. It is likely that a combination of predisposing factors and prolonged paracetamol treatment resulted in depletion of glutathione stores in these patients.

ICU patients may have risk factors for depletion of glutathione stores. Prolonged use of paracetamol in these patients can further deplete gluathione and introduce the risk of developing metabolic acidosis due to 5-oxoproline.

Keywords: Paracetamol; Acetominophen; 5-oxoproline; Metabolic acidosis

Introduction

Metabolic acidosis is a common problem in the critically ill. Calculating the anion gap can differentiate between a metabolic acidosis caused by excess of anions from a metabolic acidosis caused by bicarbonate loss. Common causes of high anion gap metabolic acidosis include lactic acidosis and ketoacidosis [1]. Rarer causes include the accumulation of 5-oxoproline (pyroglutamic acid) an amino acid derivative of the γ-glutamyl cycle within the liver.

The γ-glutamyl cycle is responsible for the production of glutathione. When glutathione stores are depleted this metabolic cycle can become overdriven resulting in excess production and accumulation of 5-oxoproline. Acquired metabolic acidosis associated with high 5-oxoproline levels has been reported in association with prolonged paracetamol ingestion [2]. There have also been reports of metabolic acidosis due to 5-oxoproline in ICU patients [3]. In order to raise awareness of this condition and the circumstances in which it can occur we present two further case reports of a high anion gap metabolic acidosis caused by acculumation of 5-oxoproline in ICU patients

Case Report 1

The first case report is one of a 62 year old gentleman with a background history of Crohn's disease, complicated by an enterocutaneous fistula, and a history of alcohol excess with a weekly alcohol intake of 60-70 units. He underwent an elective total hip replacement in 2007 and developed a periprosthetic fracture two years later. He subsequently developed chronic infection of his hip with a chronically discharging sinus and was readmitted for investigations into the cause of the infection of the hip prosthesis, and for removal of the existing prosthesis.

At the time of admission he weighed 55 kg. Paracetamol 1 g four times daily was prescribed as part of his analgesia regimen. The hip prosthesis was removed, the hip cavity was washed out and a pin inserted for traction of that leg. Intraoperatively he required inotropic support and postoperatively, he was admitted to the ICU.

Three days postoperatively he developed an acute bowel perforation requiring emergency laporotomy and Hartmann's procedure. On his return to ICU, he was noted to have a lactic acidosis with pH 7.23, pCO_2 5.4 kPa, bicarbonate 17 mmol/L, base excess -10 and lactate 4.5. He also required 0.18 mcg/kg/min noradrenaline to maintain a mean arterial pressure greater than 65 mmHg. Following the optimization of his intravascular volume, his serum lactate returned to normal. However a high anion gap metabolic acidosis persisted, with pH 7.29,

pCO_2 3.5 kPa, bicarbonate 15, base excess -9, and anion gap 18 (corrected for albumin 17 g/l). Serum lactate at this time was normal, as was his renal function. A urine sample was sent for 5-oxoproline levels which were reported as being very markedly raised. Following this result, paracetamol use was discontinued. Within three days, the anion gap returned to within normal limits and his metabolic acidosis resolved. He subsequently made a full recovery.

Case Report 2

The second case report is one of a 45 year old 60 kg man with a background history of hypertension, multiple previous deep venous thromboses and pulmonary emboli with an inferior vena cava filter in situ, chronic pancreatitis and a weekly alcohol intake of 50-60 units. His regular medications included metoprolol, thiamine and pancrelipase. He was admitted to ICU following the development of acute-on-chronic pancreatitis. He developed a systemic inflammatory response syndrome and multiorgan failure, requiring inotropic support, ventilatory support renal replacement therapy. Multiple intraabdominal collections were drained using CT guidance. Paracetamol was prescribed as required for pain and pyrexia. In spite of continuing antibiotic therapy and drainage of intraabdominal collections he remained septic.

On admission to the ICU, there was a metabolic acidosis which was attributed to the buildup of organic acids with the acute kidney injury. With the commencement of renal replacement therapy, this resolved. Over the following number of weeks however a further metabolic acidosis developed, with pH 7.33, pCO_2 3.3 kPa, bicarbonate 16 mmol/L, base excess -10 and anion gap increasing to 23 (corrected for albumin 11 g/l). By this time his renal function had improved and renal replacement therapy had been discontinued. Due to persistent pyrexias, paracetamol had been administered at frequent intervals for the previous 22 days. A urine sample was sent for 5-oxoproline levels which were reported as being markedly elevated. Following this result, paracetamol use was discontinued and there was a subsequent fall in the anion gap and an increase in pH to 7.42 over the following 4 days. However the patient had a further deterioration culminating in haemodynamic instability and lactic acidosis, resulting in death 20 days later.

Discussion

The γ-glutamyl cycle in the liver is involved in transport of amino acids across the cell membrane and in the synthesis of glutathione - an antioxidant peptide involved in inactivation of free radicals and detoxification of many compounds including N-acetyl-p-benzo-quinone-imine (NAPQI) the toxic metabolite of paracetamol. Within the γ-glutamyl cycle glutamic acid combines with cysteine to form γ-glutamyl cysteine some of which combines with glycine to form glutatione and some of which is converted to 5–oxoproline (Figure 1). In the normal state when gluatione stores are adequate gluathione exerts a negative feedback inhibition on the enzyme γ-glutamyl cysteine synthase which regulates the cycle. However when gluathione stores are depleted this negative feedback is lost and there is increased production of γ- glutamyl cysteine in an attempt to replenish the glutathione stores. The increased γ-glutamyl cysteine leads in turn to an increased production of 5-oxoproline. 5-oxoproline is converted to glutamic acid by the enzyme 5-oxoprolinase. However this step is rate limited thus when the rate of 5-oxoproline production exceeds the rate at which it is metabolised it will accumulate.

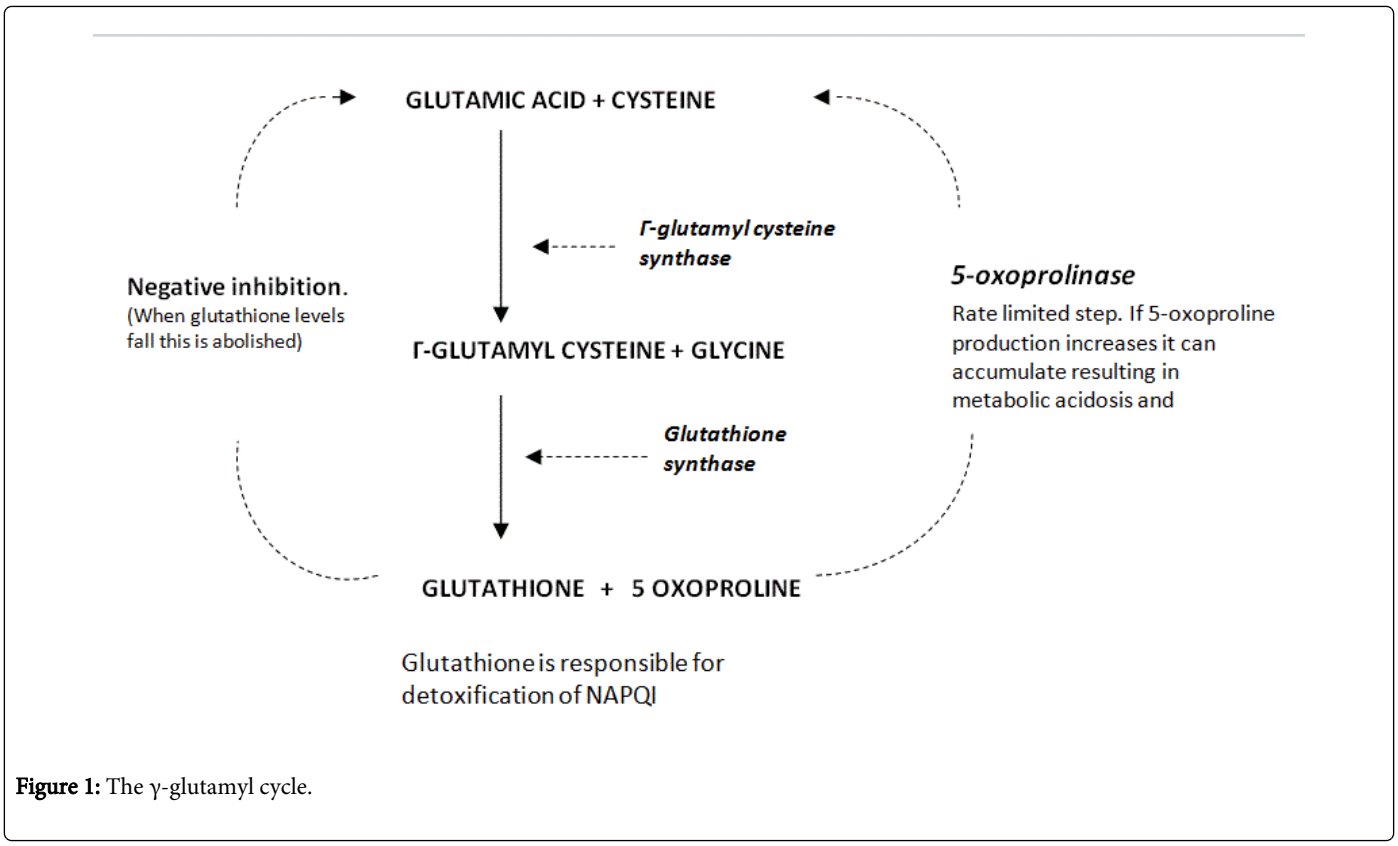

Figure 1: The γ-glutamyl cycle.

Acquired metabolic acidosis due to accumulation of 5-oxoproline was first described in adults in 1989 [4]. This was followed closely by a second case report which suggested a possible contributory role for paracetamol [5]. Since then there have been a number of case reports of acquired 5-oxoproline metabolic acidosis in patients who were taking paracetamol [2]; the anticonvulsant vigabatrin [6] or flucloxacillin [7].Although there are reports of metabolic acidosis with a raised anion gap with acute paracetamol overdose [8], the majority of the published case reports involved patients who received only therapeutic doses of paracetamol for pain or pyrexia. The patient demographics, clinical characteristics and biochemical findings of the previously reported patients along with two new patients whom we report are summarized in Table 1.

Patient	Reference	Age	Gender	Nutritional status/ comorbidities	pH	Anion Gap	Lactate	Urine 5-Oxoproline[a]
		(yrs)				(mEq/l)	(mmol/l)	(mmol/mmol Creatinine)
1	Creer et al. [4]	52	F	Albumin low, partial gastrectomy	7.17	27	2.2	15
2	Pitt et al. [5]	34	F	Vegetarian	7.17	N/A	N/A	13
3	Pitt and Hauser [9]	33	F	Pregnant	7.12	33	N/A	17
4	Pitt and Hauser [9]	54	F	Alcohol abuse	7.23	26	N/A	13.8
5	Pitt and Hauser [9]	60	F	Subtotal gastrectomy	7.14	39	N/A	11
6	Pitt and Hauser [9]	57	F	Multiple abdominal surgeries	7.16	31	N/A	10
7	Pitt and Hauser [9]	17	F	Spina bifida	7.38	31	N/A	20.4
8	Pitt and Hauser [9]	73	F		7.31	31	N/A	22
9	Pitt and Hauser [9]	84	M		7.15	21	N/A	23.6
10	Pitt and Hauser [9]	57	M	Alcohol abuse	7.09	37	N/A	5.7
11	Dempsey et al [12]	80	F	Chronic infection	7.27	35	0.5	Elevated
12	Dempsey et al. [12]	60	F	Gastrectomy	7.14	38	1.6	13.7
13	Dempsey et al. [12]	64	F	Lymphoma	6.8	33	1	4
14	Dempsey et al. [12]	54	F	Alcohol abuse	7.26	22	1.1	13.8
15	Humphreys et al. [18]	41	F		N/A	29	Normal	Elevated
17	Tailor et al. [19]	40	F		7.24-7.32	20-36	1.5-5.2	8.9-20.7
18	Foot et al. [20]	57	F	Kidney transplant	6.99	31	1.6	[370mm/L]
19	Fenves et al. [10]	36	F	Metastatic cancer	N/A	47	N/A	7
20	Fenves et al. [10]	46	F		6.88	33	N/A	N/A
21	Fenves et al. [10]	74	F	Alcohol abuse	7.16	24	2.5	1
22	Fenves et al. [10]	55	F	Albumin low, poor oral intake	7.44	35	4.3	24.7

23	Kortmann et al. [11]	72	F	Albumin low, poor oral intake	7.12	30	0.7	16.6
24	Kortmann et al [11]	56	F	Alcohol abuse	7.2	28	1.3	4.1
25	Kortmann et al. [11]	79	F	Chronic infection	7.29	29	1.6	N/A
26	Howie et al. [17]	21	F	Pregnant	7.26	25	1.6	4.9
27	Green et al. [21]	43	F	Eating disorder, opioid abuse	7.11	34	1.7	17.2
28	Duewell et al. [22]	39	F	Chronic infections	7.09	22	0.4	8.5
29	McGregor et al. [3]	63	F	Pancreatitis, poor oral intake	7.03	37	1.5	Elevated
30	McGregor et al. [3]	83	F	Alcohol abuse, poor oral intake	7.39	29	1	Elevated
31	Current report	62	M	Crohn's disease, chronic infection	7.37	18	1.3	Elevated
32	Current report	62	M	Alcohol abuse, poor oral intake	7.24	23	2.1	Elevated
[a]Normal reference range for urine 5-Oxoproline<0.1 mmol/mmol Creatinine								

Table 1: Patient demographics and biochemical data of 32 patients with 5-oxoproline-associated high anion gap matabolic acidosis.

The suggested mechanism of the development of this 5-oxoproline associated metabolic acidosis is that prolonged paracetamol use can lead to a depletion of glutathione stores particularly in patients who may have other risk factors for glutathione depletion. The glutathione depletion then causes loss of the feedback inhibition of γ-glutamylcysteine synthase activity resulting in an increased production of γ-glutamylcysteine and 5-oxoproline as outlined above resulting in a metabolic acidosis with a raised anion gap.

Patients with pre-existing depletion of glutathione stores may be more susceptible to developing 5-oxoproline related metabolic acidosis following paracetamol exposure. Contributory factors include malnutrition [9], pregnancy [9], liver disease [10], female gender [11], and alcohol abuse [12]. There is also some evidence that glutathione levels may be decreased in critical illness and in sepsis [13,14].

To date paracetamol-induced metabolic acidosis has been reported predominantly in female patients, which has been thought to indicate distinct gender-dependant differences in the enzymes of this metabolic pathway [15]. However both of our patients with a documented raised anion gap metabolic acidosis associated with high urinary 5-oxoproline levels were male. In both cases there was a background history of significant alcohol intake, malnourishment and regular paracetamol administration over a number of weeks all-factors likely to result in patients having depleted glutathione stores.

Whilst 5-oxoproline is converted to glutamic acid by 5-oxoprolinase, excess 5-oxoproline is excreted unchanged in the urine. In one series of patients with 5-oxoproline associated anion gap metabolic acidosis, renal dysfunction accompanied the diagnosis in 3 out of 4 patients [16]. Reduced renal function may worsen the situation by reducing the excretion of 5-oxoproline.

In conclusion paracetamol is a common therapy for pain or pyrexia in ICU. Whilst the consequences of acute paracetamol overdose are well known, it is often prescribed at maximal therapeutic doses and is otherwise considered an innocuous drug. The association between paracetamol intake, elevated 5-oxoproline levels and a raised anion gap metabolic acidosis has been highlighted in case reports however the incidence of metabolic acidosis caused by excess 5-oxoproline is unknown. It is important to be aware that ICU patients may have several risk factors for depletion of glutathione stores and in fact that critical ilness [13] and sepsis [14] may themselves be associated with reduced glutathione. We suspect that this may be an underrecognized cause for metabolic acidosis in the ICU and we would agree with the suggestion that 5-oxoproline excess should be routinely considered in the differential diagnosis for a cause for a metabolic acidosis [17].

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