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REVIEW ARTICLE

What is the clinical significance of 5-oxoproline (pyroglutamic acid) in high anion gap metabolic acidosis following paracetamol (acetaminophen) exposure?

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Context. Paracetamol (acetaminophen) ingestion is the most frequent pharmaceutical overdose in the developed world. Metabolic acidosis sometimes occurs, but the acidosis is infrequently persistent or severe. A growing number of case reports and case series describe high anion gap metabolic acidosis (HAGMA) following paracetamol exposure with subsequent detection or measurement of 5-oxoproline (also called pyroglutamic acid) in blood, urine, or both. Typically 5-oxoprolinuria or 5-oxoprolinemia occurs in the setting of inborn genetic errors in glutathione metabolism. It is unknown whether 5-oxoprolinemia in the setting of paracetamol exposure reflects an acquired or transient derangement of glutathione metabolism or previously unrecognized genetic defects. *Objective.* We reviewed the published cases of 5-oxoprolinemia or 5-oxoprolinuria among patients with HAGMA in the setting of paracetamol exposure. Our goal was to identify any consistent features that might increase our understanding of the pathophysiology, diagnosis, and treatment of similar cases. *Methods.* We searched the medical literature using PUBMED and EMBASE from inception to 28 August 2013 applying search terms (“oxoproline” OR “pyroglutamic acid” AND “paracetamol” OR “acetaminophen”). The intersection of these two searches returned 77 articles, of which 64 involved human subjects and were in English. Two articles, one each in Spanish and Dutch, were reviewed. An additional Google Scholar search was done with the same terms. We manually searched the reference lists of retrieved articles to identify additional four relevant articles. We focused on articles including measured 5-oxoproline concentrations in urine or blood. *Results.* Twenty-two articles included quantified 5-oxoproline concentrations. Several additional articles mentioned only qualitative detection of 5-oxoproline in urine or blood without concentrations being reported. Our manual reference search yielded four additional articles for a total of 24 articles describing 43 patients with quantified 5-oxoproline concentrations. The cases varied widely in paracetamol dose, duration and circumstances of paracetamol exposure, presence, and degree of elevation in transaminase activities, and when reported observed blood, serum, or urine 5-oxoproline concentrations. Concomitant use of flucloxacillin, another medication associated with oxoprolinemia or oxoprolinuria, confounded several of the cases. No clear dose–response relationship existed between the quantity of paracetamol ingested and the observed concentrations of 5-oxoproline. Clinical outcomes, including mortality, varied with no clear relationship to 5-oxoproline concentrations. *Conclusions.* In rare cases, HAGMA in the setting of paracetamol exposure is attributable to 5-oxoprolinemia. Clinicians should first exclude commoner and treatable causes of HAGMA, such as lactic acidosis, co-ingested drug administration, and ketoacidosis. It is likely that the propensity for HAGMA following paracetamol exposure may be genetically determined. The effects of acetylcysteine on 5-oxoproline concentrations or clinical outcome are unknown. When HAGMA is diagnosed, the 5-oxoproline concentration and the glutathione synthetase activity should be measured.

Keywords Metabolic; Paracetamol; 5-oxoproline; Pyroglutamic acid

Introduction

Paracetamol (acetaminophen) ingestion is the most common pharmaceutical overdose reported in the developed world.[1–3] Paracetamol is a common component of many over the counter analgesic products, cough and cold medications, and narcotic formulations.[4] Ingestions occur during both suicide attempts and therapeutic misadventures, when patients accidentally take multiple medications that contain paracetamol or accidentally ingest a supratherapeutic amount of paracetamol. Complications include nausea, vomiting, abdominal pain, renal failure, acute liver injury, and death.

Usually, 5-oxoproline, also called pyroglutamic acid, is a product of disordered glutathione metabolism. Glutathione is produced and degraded in the gamma glutamyl cycle (Fig. 1). Most commonly, 5-oxoproline is measured in pediatric patients with suspected inborn errors of metabolism, especially glutathione synthetase difficiency.[6,7] Several medications, such as flucloxacillin,[6,8] vigabatrin,[9] and netilmicin,[6] have been implicated as precipitating 5-oxoprolinemia.

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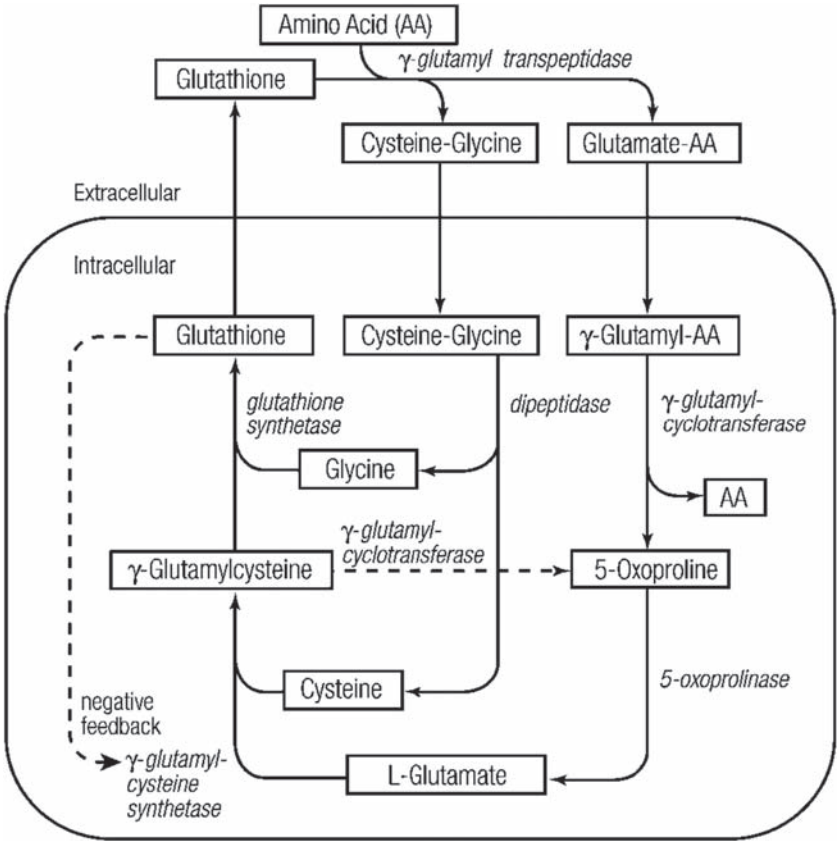

Fig. 1. Gamma-glutamyl cycle. Reproduced with permission from Duewall et al.[5]

High anion gap metabolic acidosis (HAGMA) occasionally complicates paracetamol poisoning and is a marker of poor prognosis. In some cases, the acidosis is a lactic acidosis.[10–12] However, a growing number of case reports and case series have documented that 5-oxoproline in the blood, urine, or both in cases of metabolic acidosis complicating paracetamol poisoning.[5,7,8,12–34]

Much remains unknown about 5-oxoprolinemia in paracetamol poisoning, including frequency, severity, and clinical significance. We review reports of patients with documented elevations of either serum or urine 5-oxoproline to elucidate the relationship between paracetamol and the formation of 5-oxoproline and the clinical utility of measuring 5-oxoproline concentrations patients with paracetamol poisoning.

Gamma glutamyl cycle

The gamma-glutamyl cycle is a six-enzyme cycle that is the primary pathway for glutathione synthesis and degradation (Fig. 1).[36] Glutathione is essential for maintaining cellular homeostasis by regulating oxidant stress and detoxifying drugs.[7,37] While rarely, children with deficiencies of either glutathione synthase or 5-oxoprolinase will present with a metabolic acidosis or other abnormalities from the accumulation of 5-oxoproline.[22,38] Glutathione is produced by the enzymes glutathione synthetase and γ-glutamylcysteine synthetase.[24] Gamma-glutamylcysteine synthetase combines glutamate and cysteine to form γ-glutamylcysteine, which is then converted to glutathione by glutathione synthetase.[6] Formation of glutathione results in the feedback inhibition of γ-glutamylcysteine synthetase stopping further production of glutathione.[7,24] Glutathione deficiency removes the feedback inhibition of γ-glutamylcysteine synthetase resulting in the formation of γ-glutamylcysteine.[6] Elevated concentrations of γ-glutamylcysteine lead to the formation of 5-oxoproline, which is degraded to glutamate by 5-oxoprolinase.[12,24] The enzyme 5-oxoprolinase catalyzes the rate-limiting step in the cycle leading to the accumulation of 5-oxoproline.[6]

Glutathione is transported to the extracellular space where γ-glutamyl transpeptidase catalyzes the first step in glutathione degradation.[39] The resulting glutamate is bound to other amino acids for transport back to the intracellular space.[6,12] In the intracellular space, γ-glutamyl cyclotransferase converts glutamate into 5-oxoproline and regenerates amino acids.[12,37] Gamma-glutamyl cyclotransferase is also the enzyme responsible for converting γ-glutamylcysteine to 5-oxoproline.[6,7]

Methods

We searched the medical literature using PUBMED and EMBASE from inception to 28 August 2013 applying search terms ("oxoproline" OR "pyroglutamic acid") AND ("paracetamol" OR "acetaminophen"). The terms "oxoproline" OR "pyroglutamic acid" returned 2,752 articles between the two

databases, while the terms "paracetamol" OR "acetaminophen" returned 83,867 articles. The intersection of these two searches returned 77 articles, of which 64 involved human subjects and were in English. Two articles with English abstracts were translated from Spanish and Dutch. A secondary search using the same terms in Google Scholar located five additional publications describing four patients (one duplicate publication), for whom 5-oxoproline concentrations were reported in two cases. Quantified 5-oxoproline concentrations were reported in 22 unique articles. In several additional cases, 5-oxoproline was detected in urine or blood without concentrations being reported.[35,39–46] Attempts via email were made to contact the corresponding authors of these reports; however, none were able to provide supplementary data. A manual search of references provided an additional four articles for a total of 26 articles describing the cases of 43 patients (Table 1) with quantified 5-oxoproline concentrations.

Case summaries

Reports including only urine 5-oxoproline concentrations

In 2011, Reddi and Kunadi[13] described a 50-year-old woman with a history of hypertension, depression, cervical and lumbosacral disc disease, and chronic obstructive pulmonary disease with a chief complaint of shortness of breath. Her history was significant for therapeutic paracetamol dosing of 750 mg every 8 h, as needed. She presented with HAGMA and an anion gap of 16 mEq/L with normal lactate and ketone concentrations. The urine 5-oxoproline concentration was $>$ 11,500 mmol/mol creatinine, and a qualitative urine test for paracetamol was positive. Her transaminase activities were normal, and she improved with intravenous fluids and sodium bicarbonate. The authors concluded that the HAGMA was secondary to chronic paracetamol use and oxoprolinuria.

Tailor et al.[7] reported a 40-year-old man who presented with six episodes of HAGMA during an 8-month period. His past medical history included chronic back pain, depression, hypertension, and childhood asthma. He reported taking several medications including hydrocodone/paracetamol before each admission except the 5th encounter. The presenting symptom for most of the visits was dyspnea with or without fatigue, abdominal pain and confusion. On the 1st visit, his serum amylase and lipase activities were elevated to 1127 U/L and 1503 U/L, respectively. Upon his 5th admission, he was diagnosed with and surgically treated for cholecystitis. His urine showed elevated concentrations of 5-oxoproline on the 3rd, 4th, and 6th admissions with concentrations of 20,700, 11,200, and 8,900 mmol/mol creatinine, respectively, which corresponded with therapeutic range paracetamol concentrations. After his 6th admission with HAGMA, he had several more admissions without evidence of an elevated anion gap. The paracetamol screens were negative on these subsequent admissions. Interestingly, the authors were able to elicit a negative history of glutathione synthetase deficiency in the patient and his family, and his glutathione synthetase activity was in the normal range. The authors concluded that this patient's 5-oxoprolinuria was associated with paracetamol use.

Table 1. Characteristics of patients included in the review.

Types of paracetamol ingestion	$n = 43$
Overdose	5
Therapeutic use	33
Unknown dosing	5
Co-administration of flucloxacillin	6
Elevated AST or ALT activity	8
Multiple presentations of metabolic acidosis without other identified cause	3

In a letter to the editor, Yale and Mazza[14] described a healthy 44-year-old woman who was prescribed oxycodone/paracetamol for a month of back pain and presented with HAGMA. Her paracetamol concentration was 15 mg/L, her ketone and lactate levels were normal, her ethanol and salicylate screens were negative, and her anion gap was 25 mEq/L. A urine sample obtained 2 days later showed a 5-oxoproline concentration of 554 mmol/mol creatinine. The authors state that they believe their patient is a heterozygote for glutathione synthetase deficiency but did not report if testing was done to demonstrate this.

Hodgman et al.[15] reported a severe case of HAGMA in a 58-year-old woman who presented with confusion and poor diet, diminished hearing, hypothermia and tachypnea. She had a history of analgesic and diazepam abuse, alcoholism, anxiety, depression, an eating disorder, COPD and migraines. Her arterial blood gases on presentation were as follows: pH, 7.02; pCO2, 10 mmHg; and pO2, 104 mmHg. Measured serum bicarbonate concentration was 5 mEq/L, and her paracetamol concentration was 49 mg/L; however, based on elevated AST (1308 U/L) and ALT (348 U/L) activities, she was started on oral acetylcysteine. Her lactate was moderately elevated to 3.1 mmol/L. Her serum was negative for ethanol, acetone, methanol, ethylene glycol, and salicylate. Urine dipstick was negative for ketones. A urine organic acid screen obtained on day 1 showed a 5-oxoproline concentration reported as 2350 mmol/mol creatinine. Their patient made a full recovery with supportive care.

In 2010, Howie et al.[16] described a pregnant 21-year-old woman who presented at full term with 2 weeks of shortness of breath and was diagnosed with a lower respiratory tract infection. She had been taking approximately 3g/day of paracetamol regularly over the past year for temperomandibular joint pain. She had also taken amoxicillin and erythromycin in the previous week. She decompensated after admission with tachypnea and HAGMA. Her bicarbonate was 4.2 mEq/L, and her anion gap was calculated at 25.8 mEq/L despite a lactate of 1.6 mmol/L. Her paracetamol concentration was 14 mg/L. A urine organic acid screen was positive for a 5-oxoproline to creatinine ratio of 4970 mmol/mol creatinine. She underwent urgent cesarean section due to prolonged decelerations on a fetal heart monitor, and she remained intubated in the intensive care unit. Further treatment consisted of antibiotics, blood transfusion, hemofiltration, and vitamin B supplementation. Her condition

improved and a convalescent urine sample showed no elevation in urine organic acids including 5-oxoproline.

Zand et al.[17] record two cases of HAGMA in the setting of paracetamol ingestion. The first patient was a 19-year-old woman with no significant medical history who ingested 225 tablets of 500mg of paracetamol (total dose, 112.5g). Her paracetamol plasma concentration was 216 mg/L, and she had severe acidosis with a pH of 7.0 on an arterial blood gas and an anion gap of 27 mEq/L. Her AST was 475 U/L and ALT was 358. She was treated with an acetylcysteine infusion and underwent evaluation for her elevated anion gap. The usual causes such as lactate, ketones, toxic alcohols, and salicylates were ruled out. However, a urine organic acid analysis revealed an elevated 5-oxoproline concentration of 260 mmol/mol creatinine. Her acidosis resolved over the pursuing 8 days, and she did not require liver transplantation.

The second patient was a 67-year-old woman with alcohol abuse, cirrhosis, chronic pancreatitis, recurrent cholecystitis and recurrent gastrointestinal tract hemorrhages who was admitted for a severe GI bleed. She underwent resection of a GI stromal tumor. On post-operative day 4, she began receiving scheduled doses of paracetamol 1000mg every 6 h. After 15 days (cumulative dose of 60g of paracetamol), she developed a mild anion gap metabolic acidosis. By day 30 of paracetamol therapy, she had become gradually more confused. Her pH was 7.32 and her anion gap was 29 mEq/L which prompted a diagnostic workup for ketones, salicylates, L-lactate, and D-lactate which were all absent. Her urine organic acid screen detected a 5-oxoproline concentration in excess of 27,000 mmol/mol creatinine. Paracetamol was discontinued, and she was started on an infusion of sodium bicarbonate and acetylcysteine. Her acidosis and mental status improved 3 days after stopping the paracetamol.

Humphreys et al.[18] report on a 41-year-old man with autosomal dominant polycystic kidney disease and follicular B-cell lymphoma with transformation to aggressive large cell lymphoma who was admitted for chemotherapy. He had already undergone 3 prior chemotherapy regimens, but had progressive disease complicated by malignant pleural and pericardial effusions. He was started on ifosfamide, mesna, etopside, and cytarabine for the first 5 days of admission. On day 4, he developed a non-anion gap hyperchloremic metabolic acidosis with a bicarbonate concentration of 14 mEq/L. This was attributed to ifosfamide-induced type II renal tubular acidosis and was complicated by nonoliguric acute renal failure with a serum creatinine rise from 1.5 to 2.7 mg/dL. He remained neutropenic and had daily fevers over the 10-day period from hospital day 7 to 17 for which he was treated with therapeutic doses of paracetamol reaching a cumulative dose of 20.8g. During this 10-day period, he developed a progressive anion gap metabolic acidosis which was not due to lactate, ketones, or salicylates. A urine organic acid screen showed a marked elevation in 5-oxoproline concentrations to 5,800 mmol/mol creatinine. Eventually, a blood culture grew *Candida albicans,* and despite aggressive supportive management, he suffered a cardiac arrest and expired.

Romero and Htyte[19] described a 68-year-old man with osteoarthritis and hypertension and a history of chronic paracetamol use for his pain. He presented to the emergency department (ED) with 4 days of malaise, nausea, vomiting, and worsening shortness of breath. On presentation, he was tachycardic, hypotensive, and tachypneic. Laboratory studies showed his pH to be 7.12 and his anion gap to be 28 mEq/L. His lactate was slightly elevated at 2.9 mmol/L, and his paracetamol concentration was 47 mg/L. Further testing showed no detectable alcohol, salicylates, and ketones. Due to his clinical conditions, he was intubated and transferred to the intensive care unit where he received supportive care and a sodium bicarbonate infusion. He improved after one day of treatment. It was recognized that this patient had previous admissions for acidosis and serum organic acid testing was done. His urine 5-oxoproline concentration was 14,200 mmol/mol creatinine.

Green et al.[12] described a 43-year-old woman with a history of recurrent nephrolithiasis, cocaine and alcohol abuse, and epilepsy who presented with altered mental status. Friends reported that she ingested large amounts of paracetamol in the days prior to presenting to the hospital. Her physical examination was significant for cachexia and a GCS of 14, but otherwise normal. Laboratory evaluation was significant for a metabolic acidosis with a pH of 7.11, pCO2 of 14 mmHg, anion gap of 34 mEq/L, paracetamol concentration of 60.3 mg/L, creatinine of 2.47 mg/dL, BUN of 30 mg/dL, AST of 61 U/L, ALT of 213 U/L, and a normal lactate of 1.7 mmol/L. She received intravenous fluids, sodium bicarbonate, fomepizole, thiamine, folate, ceftriaxone, and acetylcysteine, and required dialysis for her profound acidosis. She recovered completely and was discharged 4 days later. A urine sample obtained during her initial presentation resulted in a 5-oxoproline concentration of 17,292 mmol/mol creatinine.

Duewall et al.[5] described a 39-year-old woman with a past medical history of bipolar disorder, previous suicide attempts, and chronic pain who was brought to the ED with altered mental status. She took an unknown amount of paracetamol/hydrocodone on a regular basis for pain control. On arrival to the hospital, she was obtunded and was emergently intubated. Her initial laboratory evaluation was significant for a metabolic and respiratory acidosis with a pH of 7.09, pCO2 of 28 mmHg, anion gap of 22 mEq/L, an paracetamol concentration of < 3 mg/L, creatinine level of 3.6 mg/dL, BUN of 59 mg/dL, and a normal lactate level at 0.4 mmol/L; transaminases were not reported. The urine 5-oxoproline concentration at admission was 8,555 mmol/mol creatinine. Acetoacetate, 3-hydoxybutyrate and 2-hydroxybutyrate were also elevated, consistent with a starvation ketosis. She received intravenous fluids containing dextrose, and was extubated and discharged a few days later.

Myall et al.[20] described a 50-year-old woman with a history of epilepsy who presented to the hospital with hip pain. Synovial and blood cultures were positive for *Staphylococcus aureus*; she was treated with flucloxacillin and paracetamol. Her condition deteriorated and she was transferred to the intensive care unit. Laboratory evaluation revealed

a new metabolic acidosis with pH of 7.27, pCO2 of 1.31 kPa (10 mmHg), and an anion gap of 30.1 mEq/L. Neither a paracetamol concentration nor transaminase activities were reported. Her renal function remained normal. She had a mild ketosis attributed to malnutrition. Urine organic acid testing showed a 5-oxoproline concentration of 16,500 mmol/mol creatinine. At this point, paracetamol and flucloxacillin were discontinued and acetylcysteine was started. Her antibiotic was changed to meropenem, her acidosis improved, and she made a complete recovery.

O'Brien et al.[21] described a 54-year old woman with a history of gastric bypass surgery requiring a revision, alcohol abuse with hepatic steatosis, and recent paracetamol abuse who presented with altered mental status. She was cachectic and obtunded. Laboratory evaluation showed a pH of 7.10 (CO_2 not reported) and an anion gap of 28 mEq/L. Her AST and ALT activities were 332 U/L and 365 U/L, respectively. Her paracetamol concentration was 24 mg/L. Her serum creatinine was reported as normal. A lactate concentration was initially elevated at 5.2 mmol/L but normalized with fluid resuscitation; however, her HAGMA persisted. Blood cultures were negative. Urine organic acids testing showed a 5-oxoproline concentration of $>$2,000 mmol/mol creatinine. She died from multi-organ failure.

Rolleman et al.[8] described a 72-year-old woman with a history of emphysema, hepatitis A and B, breast cancer, and recent laminectomy who presented to the hospital for fever, back pain, and altered mental status. She received NSAIDs, paracetamol, and morphine for pain. On presentation, she had altered mental status with otherwise unremarkable physical examination and stable vital signs. Evaluation detected *Staphylococcus aureus* epidural and psoas abscesses, which were treated with flucloxacillin. Paracetamol was continued for pain control. She developed a metabolic acidosis with a pH of 7.36, pCO2 of 25 mmHg, an anion gap of 18 mEq/L, HCO3 of 16 mEq/L, and a creatinine of 50 µmol/L (0.57 mg/dL), and was transferred to the intensive care unit. The reported paracetamol concentration was 2 mg/L, and transaminases were not reported. The lactate concentration was 0.9 mmol/L. Urine organic acid testing returned with a 5-oxoproline concentration of 90,900 mmol/mol creatinine with a normal gamma-glutamyl transferase of 45 U/l. Paracetamol and flucloxacillin were discontinued, and she was treated with sodium bicarbonate. She recovered and was discharged.

Foot et al.[22] report on a 57-year-old woman with an extensive past medical history who presented with lethargy, anorexia, and worsening dyspnea over the prior 2 days. She had a renal transplant which was failing despite immunosuppression, complicated by recurrent renal calculi formation. A small bowel obstruction 8 months prior to presentation required operative management and was complicated by wound breakdown and sinus formation. Her medications included tacrolimus, mycophenolate, prednisolone, amlodipine, sodium bicarbonate, calcitriol, caltrate, and multivitamins. She also took unknown quantities of aspirin, codeine, and paracetamol for chronic abdominal pain. On presentation, she was tachycardic, hypotensive, confused, and had Kussmaul breathing at a rate of 32 breaths/minute. Paracetamol concentration was 20 mg/L, within the therapeutic range. AST and ALT levels were within normal limits. Her pH was 6.99, HCO3 was 2 mEq/L, and anion gap of 31 mEq/L. Despite a large anion gap, her lactate was 1.6 mmol/L. Urine organic acid analysis revealed a 5-oxoproline concentration of 3700 mmol/L. In communication with the author, no creatinine-normalized data could be provided. It was determined by arthrocentesis of her knee that she had MRSA septic arthritis with bacteremia. Despite a month of maximal therapy, the patient died.

In a recent abstract at the Society for Critical Care Medicine, Prasad[23] described a 58-year-old alcoholic woman who presented with nausea, vomiting, diarrhea, altered mental status, and leukocytosis with a history of taking over 4 g/day of paracetamol for chronic pain. Her anion gap was 33 mEq/L, and her paracetamol concentration was 27.3 mg/L. Lactate, ammonia, serum osmolality, ketones, salicylate, and ethanol were reported as normal. The 5-oxoproline urine concentration was $>$5000 mmol/mol creatinine. She improved with supportive care, mechanical ventilation and intravenous fluids, and was prescribed antibiotics and acetylcysteine.

Reports including blood 5-oxoproline concentrations with or without urine concentrations

In the earliest reported case of paracetamol associated 5-oxoprolinemia, Creer et al.[24] described a 52-year-old woman who presented with progressive tachypnea and disorientation. Her past medical history included living-donor kidney transplant secondary to membranoproliferative glomerulonephritis, hypertension, total hysterectomy with right oophorectomy and a Bilroth II gastrojejunostomy for treatment of peptic ulcer disease. Her medications included prednisone, azathioprine, clonidine, propranolol, furosemide, ranitidine, doxepin, and propoxyphene. Her initial treatment included intravenous fluids and dopamine followed by 5% dextrose in normal saline with sodium bicarbonate and oxygen by facemask. Her laboratory studies showed HAGMA with an anion gap of 27 mEq/L. Serum lactate was normal, and her screens for ketones, salicylate, methanol, and ethylene glycol were negative. No D-lactate was detected in her blood or urine, despite the risk of intestinal bacterial overgrowth following her gastric bypass procedure. A qualitative urine drug analysis showed the presence of paracetamol, propoxyphene, and norpropoxyphene. A gas chromatography–mass spectrometry analysis found a plasma 5-oxoproline concentration of 12.6 mmol/L and 24-hurinary excretion of 5-oxoproline in the range of 0.91–1.60 g/day. She was treated with intravenous sodium bicarbonate, and her symptoms gradually resolved.

Fenves et al.[25] reported four cases of 5-oxoprolinuria with concomitant paracetamol exposure. The first case was of a 36-year-old woman who had undergone a radical hysterectomy, bilateral pelvic lymphadenectomy, bilateral salpingo-oophorectomy, and pelvic radiation therapy due to vaginal squamous cell carcinoma. Nine months after this procedure, she presented in anuric renal failure with bilateral

hydronephrosis and had bilateral ureteral stents placed. She also required 8 units of packed red blood cells secondary to a large retroperitoneal hemorrhage. Her home medications included phenytoin and propoxyphene/paracetamol as needed for pain. Initial chemistry tests showed a creatinine concentration of 5.9 mg/dL and an anion gap of 47 mEq/L. Workup for both D- and L-lactate, toxic alcohols, and ketones was negative. Urine organic analysis using GC–MS revealed 5-oxoproline concentration of 700 mmol/mol creatinine. She continued to take "large daily doses" of propoxyphene/paracetamol. She received hemodialysis and oral bicarbonate supplementation but died from her invasive squamous cell carcinoma.

The second case was a 46-year-old woman who was admitted for severe metabolic acidosis with respiratory failure. Her history was significant for migraine headaches for which she took paracetamol with or without propoxyphene. She had been admitted multiple times over the past year with nausea and vomiting and HAGMA, which promptly resolved with intravenous fluids and glucose. The patient again acknowledged frequent paracetamol use prior to this admission and had a plasma paracetamol concentration within the therapeutic range. Her initial pH was 6.88, and her anion gap was 33 mEq/L. Her GGT, AST, and ALT activities were all elevated to 1100 U/L, 2200 U/L, and 900 U/L, respectively. Serum ketones levels were negative, however; her lactate was elevated to 15.2 mEq/L. With intravenous fluids over the following 48 h, her condition improved and her lactate normalized, but her anion gap remained elevated. A plasma analysis using GC–MS showed a 5-oxoproline concentration of 6.4 mmol/L. After discontinuation of paracetamol, the patient eventually improved. Interestingly, 2 weeks after convalescence, the patient consented to a skin biopsy and had glutathione synthetase activity that was supranormal in cultured fibroblasts.

The third case was a 74-year-old woman who presented with 5 days of progressive mental status decline, nausea, vomiting, and dyspnea. She was diagnosed with HAGMA and admitted to the intensive care unit. Her medical history consisted of COPD, peripheral vascular disease, chronic pain, breast cancer, atrial fibrillation, and osteoporosis. She was taking paracetamol/hydrocodone as needed for pain among other medications. An arterial blood gas drawn from the patient while on room air showed a pH of 7.16, and her anion gap was calculated at >24 mEq/L. Her lactate concentration was 2.5 mmol/L, and her ketones, toxic alcohols, and salicylate tests were negative. Analysis of plasma using GC–MS demonstrated a 5-oxoproline concentration of 2.8 mmol/L, and the urine concentration was 1000 mmol/mol creatinine.

The fourth case was a 55-year-old woman with diabetes and morbid obesity who was admitted for removal of an infected right prosthetic knee arthroplasty. Several days later, she developed a mild metabolic acidosis. She required surgical debridement of her infected right knee wound and received several courses of parenteral antibiotics. Pain was controlled with hydrocodone/paracetamol orally. Five weeks after admission, she acutely decompensated, became tachypneic, and was transferred to the intensive care unit. She was noted to have an elevated anion gap despite a normal pH of 7.44 on an ABG. The serum lactate concentration was moderately elevated to 4.3 mmol/L, but serum ketone levels were negative. Her blood cultures grew *Pseudomonas aeruginosa* and her antibiotic coverage was adjusted. Review of her medications revealed that she had received 107g of paracetamol in a 6-week period, corresponding to an average of 2.7g/d. Paracetamol was discontinued and her metabolic acidosis slowly resolved. GC–MS analysis of her plasma and urine revealed 5-oxoproline concentrations of 10.5 mmol/L and 24,700 mmol/mol creatinine, respectively.

Dempsey et al.[26] reported four cases of 5-oxoproline acidosis in the setting of paracetamol use. The first was an 80-year-old woman who was treated in an intensive care unit for methicillin-sensitive *Staphylococcus aureus* septic arthritis of a right hip arthroplasty. She received flucloxacillin and imipenem. She developed respiratory failure, oliguria, and hypotension requiring inotropic support. Blood tests showed HAGMA with a pH of 7.27 and anion gap of 35 mEq/L. L-Lactate, D-lactate, and β-hydroxybutyrate were all negative. Paracetamol metabolites were detected in the urine. A qualitative screen for urine organic acids revealed a high concentration of 5-oxoproline; however, no quantitative measurements, nor blood testing was performed. She received intravenous bicarbonate infusions and her acidosis resolved after 8 days. Convalescent urine organic acid testing was negative for 5-oxoproline.

The second patient was a 60-year-old woman with COPD, congestive heart failure, and history of a partial gastrectomy who presented with 4 days of malaise, nausea, vomiting, and dyspnea. She had been discharged 5 days previously after being admitted twice over a 1-month period for similar symptoms. She was on several medications including paracetamol. Her serum concentrations of paracetamol and theophylline were 22.2 mg/L and 10.7 mg/L, respectively, but ethanol, methanol, ethylene glycol, and salicylates were undetectable. She had a pH of 7.14 and an anion gap of 38 mEq/L. Urine and blood 5-oxoproline assays were significant for 13,700 mmol/mol creatinine and 6.6 mmol/L, respectively. After cessation of paracetamol and administration of intravenous bicarbonate, all metabolic disturbances resolved and the patient was discharged 15 days later.

The third case was a 64-year-old woman with chronic renal failure who presented to the ED with general malaise. Paracetamol was among the medications she took and its concentration was 6 mg/L. Her initial laboratory studies showed a severe anion gap metabolic acidosis with a pH of 6.8 and an anion gap of 33 mEq/L. Despite aggressive supportive treatment and intravenous bicarbonate administration, the patient died 3 days after admission. Urine and blood 5-oxoproline concentrations were 4000 mmol/mol creatinine and 8.0 mmol/L, respectively.

The fourth patient, a 54-year-old woman, presented with 10 days of malaise, cough, and sore throat. Her medical history was significant for alcohol and analgesic abuse, analgesic nephropathy, renal scarring, and kidney stones. Her regular medications included paracetamol/codeine.

Three days before admission her general practitioner prescribed amoxicillin and stopped her antihypertensive medication due to relative hypotension. The day after admission her mental status declined and she developed respiratory distress. Urinary drug testing was positive for benzodiazepines, paracetamol, and quinine/quinidine. After the administration of 8.4% sodium bicarbonate, she improved significantly and her respiratory effort and mental status returned to normal. Urinary and blood testing for 5-oxoproline showed concentrations of 13,800 mmol/mol creatinine and 6.7 mmol/L, respectively.

Leung et al.[27] reported a case of 5-oxoprolinemia after an intentional overdose of paracetamol. A 30-year-old woman with a history of alcoholism ingested 150g of crushed paracetamol tablets approximately 15 h before arrival to the Accident and Emergency Department. Her initial symptoms were drowsiness and confused speech. On ABG, her initial pH was 7.211 and her bicarbonate was 6.2 mEq/L. The calculated anion gap was initially 30.8 mEq/L. Her serum lactate was elevated to 9.0 mmol/L, but the authors did not attribute her entire anion gap solely to lactic acidosis. Urine and serum organic acid testing revealed elevated concentrations of 5-oxoproline. GC–MS showed a urine concentration of 1250 mmol/mol creatinine and a plasma concentration of 0.22 mmol/L. This patient received activated charcoal by mouth, and intravenous sodium bicarbonate and acetylcysteine. During the admission, her AST and ALT activities both peaked at $>3{,}000$ U/L (upper limit of quantification at the author's hospital laboratory). She recovered without any serious hepatic sequelae.

In 2007, Alados Arboledas et al.[28] described a 16-month-old boy who was suffering from hemolytic uremic syndrome after a gastrointestinal infection. He had renal failure, anemia, and abdominal pain with distension. During the first few weeks of admission, he required peritoneal dialysis, venovenous hemofiltration, and hemodialysis. Three weeks later, his urine output improved. However, after suspension of the hemofiltration, he developed a HAGMA with anion gap peaking at 42–45 mEq/L. Urine and serum were sent for organic acid testing and showed 5-oxoproline concentrations of 392 mmol/mol creatinine and 9.8 mmol/L, respectively. Over the preceding 3 weeks, he had received 75–100 mg/kg/day of paracetamol.

Pitt and Hauser[29] reported 11 cases of HAGMA with transient oxoprolinuria. The authors gave very limited information about each case, but all patients had paracetamol or metabolites detected in their urine and/or serum. Urine and plasma organic acid analyses were done using gas chromatography–mass spectrometry. Table 2 summarizes the available laboratory values for the 11 cases.

The first patient was a 33-year-old pregnant woman at an estimated gestational age of 32 weeks who presented with respiratory distress and HAGMA. She had been taking paracetamol for back pain prior to arrival. She was diagnosed with pneumococcal sepsis and started on penicillin, but lost the fetus in utero. She was later diagnosed with sacroiliac osteomyelitis. Upon convalescence, she was challenged with paracetamol and did not suffer any adverse effects.

The second patient was a 54-year-old woman who presented with constitutional symptoms, hematemesis, and a urinary tract infection. She had been taking paracetamol for 3 days due to back pain. She was started on unstated intravenous antibiotics and slowly recovered after 6 days.

The third patient was a 60-year-old woman who presented with intermittent episodes of vomiting, anorexia, malaise, and confusion over the prior month. Her medical history was extensive and included chronic obstructive pulmonary disease, congestive heart failure, and a subtotal gastrectomy. She had recently been admitted twice to another hospital for unexplained metabolic acidosis. Prior to this admission, she had consumed paracetamol. She was treated for metabolic acidosis with sodium bicarbonate and was discharged after 15 days.

The fourth patient was a 56-year-old woman who presented with a 7-day history of abdominal pain treated with paracetamol and opiate analgesia. She had a history of hypothyroidism and multiple abdominal surgeries, and had been vomiting for about 12 h prior to arrival. She underwent a negative laparotomy and was admitted to the intensive care unit for metabolic acidosis, pulmonary edema, and myxedemic crisis. Her acidosis resolved over the next 7 days.

The fifth patient was a 64-year-old woman with diabetes and schizophrenia who overdosed on paracetamol. She was found hypothermic and in a "semicomatose" state. Her pH was 6.8 and her anion gap was 38.3 mEq/L. She was placed on hemofiltration but died despite treatment.

The sixth patient was a nearly 6-year-old girl with right lower lobe pneumonia, fever, vomiting, lethargy, and abdominal pain. She received IV penicillin but deteriorated shortly after admission. She developed encephalopathy, hypoglycemia, coagulopathy, and her AST peaked at 10,888 U/L. Paracetamol toxicity was suspected, and she was treated with acetylcysteine. Her transaminase activities returned to normal over the next 10 days and she was discharged.

The seventh patient was a 17-year-old girl with a history of spina bifida, hypertension, bilateral vesicoureteric reflux who presented with an infected ventriculoperitoneal shunt. She had been prescribed paracetamol for pain after a shunt revision and developed compensated metabolic acidosis. After 2 days, she developed septic shock requiring cardiovascular

Table 2. Laboratory values from 11 patients in case series of Pitt and Hauser.[29]

Subject	1	2	3	4	5	6	7	8	9	10	11
Anion gap (mmol/L)	33.1	26.3	38.8	31.3	38.3	29.0	31.2	16.4	30.5	20.8	37.1
Plasma 5-oxoproline (mmol/L)	N/A	6.7	6.6	6.6	8.0	N/A	N/A	N/A	16.0	11.3	2.3
Urine 5-oxoproline (mmol/mol creatinine)	17,000	13,800	11,000	10,000	4,000	5,900	20,400	600	22,000	23,600	5,700

and respiratory support. Her metabolic acidosis persisted for 22 days while being administered paracetamol and resolved after codeine was substituted for analgesia.

The eighth patient was a 1-year-old girl who initially presented with a 1-day history of fever, lethargy, and diarrhea. She was intubated for presumed septic shock. She had received paracetamol and unstated intravenous antibiotics. Her anion gap was 16.4 mEq/L which was the smallest out of Pitt and Hauser's series, and her urine 5-oxoproline concentration of 600 mmol/mol creatinine was the lowest they recorded. Her blood cultures remained negative and she rapidly recovered.

The ninth patient was a 73-year-old woman with a history of recurrent abdominal pain from presumed diverticulitis who presented with 3 days of abdominal pain. She had been taking approximately 4 g of paracetamol daily prior to admission. She underwent a laparotomy which did not show diverticulitis. Postoperatively in the intensive care unit, she developed a HAGMA, fever, and hypotension. She was taken back to the operating room for a second laparotomy, but no ischemic bowel was discovered.

The tenth patient was an 84-year-old man with a history of severe mitral regurgitation and mitral valve prolapse who presented after a collapse. He was diagnosed with subacute bacterial endocarditis after his blood cultures grew coagulase-negative *Staphylococcus*. He was started on dicloxacillin and paracetamol. He developed a HAGMA and paracetamol was discontinued. Acetylcysteine was given intravenously and he recovered rapidly.

The eleventh patient was a 57-year-old man with a history of alcoholic pancreatitis who presented with acute abdominal pain after a week of epigastric pain. He had been taking paracetamol for his epigastric pain. He had a HAGMA and was treated with acetylcysteine after discontinuation of paracetamol.

Pitt et al.[30] published a case report in 1990 of a 34-year-old woman without significant past medical history who presented to the hospital with fever, vomiting, and dyspnea. On her initial presentation, she had a metabolic acidosis with a pH of 7.17 and base excess of − 22 mmol/L with no pCO2 reported. She had a "moderate" lactic acidosis, which did not completely account for her anion gap. Urine and serum 5-oxoproline concentrations were 13,000 mmol/mol creatinine and 16 mmol/L, respectively. Glutathione synthetase and oxoprolinase activities were normal. They detected paracetamol (concentration not reported). Other abnormalities included positive sputum and lung cultures for streptococcus pneumonia. The patient suffered a cardiac arrest and could not be resuscitated.

Peter et al.[31] described a 50-year-old man with a history of cerebral palsy and epilepsy who presented with fever, hematuria, and low back pain. On his initial evaluation, he had a mild leukocytosis of 13.6×10^9/L, urinalysis showing sterile pyuria, hematuria and 3.46 g of protein over 24 h, an anion gap of 18 mEq/L, and a small pleural effusion. He was empirically started on treatment with unnamed antibiotics. Flucloxacillin was added on day 3. He also received paracetamol during his hospitalization for analgesia. He had a complicated hospital course with progressive deterioration of his renal function (attributed to IgA nephropathy) and his mental status requiring admission to the intensive care unit. He developed an acidosis with a pH of 7.31, pCO2 of 12 mmHg, and an anion gap of 42 mEq/L with a lactate of 0.7 mmol/L upon his transfer to the ICU. His creatinine was 0.541 mmol/L (6.1 mg/dL) and BUN was 18.6 mmol/L (50 mg/dL). Transaminase and paracetamol concentrations were not reported. There were no ketones in his urine. Urine and serum organic acid panels were obtained, and flucloxacillin and paracetamol were discontinued. His urine and serum 5-oxoproline concentrations were markedly elevated to 20,495 mmol/mol creatinine and 11.01 mmol/L, respectively. He received intravenous fluids, bicarbonate, vancomycin, and oxygen. He recovered and was discharged to home.

Armenian et al.[32] described a 27-year-old woman with a history of chronic abdominal pain, *H. pylori,* colonic polyps, and chronic use of paracetamol who presented to the hospital with abdominal pain and persistent vomiting. Her initial vital signs were stable, and physical examination was only significant for mild, diffuse abdominal tenderness. Her laboratory evaluation revealed a metabolic acidosis with a pH of 7.12, pCO2 of 16 mmHg, HCO3 of 7 mEq/L, and anion gap of 22 mEq/L, with a normal serum lactate at 2.0 mmol/L and negative serum ketones. Her creatinine and hepatic enzymes were within normal limits. Paracetamol concentration was 3 mg/L. She received intravenous fluids and sodium bicarbonate. Due to concerns for malnutrition and chronic paracetamol use, organic acid testing was obtained. Serum and urine organic acids were sent 48 h after admission and treatment with intravenous acetylcysteine 150mg/kg bolus followed by oral NAC at a rate of 70mg/kg every 4 h for 24 h. Urine and serum 5-oxoproline concentrations were elevated at 650 mmol/mol creatinine and 35.8 mmol/L, respectively.

Kortmann et al.[33] published a series of three cases of anion gap metabolic acidosis with elevated 5-oxoproline. The first patient was a 72-year-old woman with a history of hypertension, renal insufficiency, and osteoarthritis who was admitted with septic arthritis. She was treated with flucloxacillin and paracetamol for pain. She decompensated and developed a metabolic acidosis with a pH of 7.12, HCO3 of 3.5 mEq/L, and an anion gap of 30.75 mEq/L. Her paracetamol concentration was 3.2 mg/L. Further testing did not reveal a lactic or ketoacidosis. Organic acid testing was obtained which revealed elevated urine and plasma concentrations of 5-oxoproline at 16,623 mmol/mol creatinine and 6.573 mmol/L, respectively. Paracetamol was discontinued, and she recovered.

The second patient was a 56-year-old woman with a history of HIV, renal insufficiency, alcohol abuse, and a recent urinary tract infection who was receiving norfloxacin and paracetamol for pain. She presented with dyspnea, and on physical examination, she was tachypneic and cachectic. Laboratory evaluation was remarkable for a metabolic acidosis with pH of 7.20, pCO2 of 27 mmHg, HCO3 of 10 mEq/L, and anion gap of 28 mEq/L. Lactate was normal and ketones were negative. Her paracetamol concentration was 12 mg/L. Testing revealed elevated plasma and urine

5-oxoproline concentrations of 2.292 mmol/L and 4,184 mmol/mol creatinine, respectively.

The last patient was a malnourished 79-year-old woman with a history of COPD, osteoporosis, diabetes, and recent spondylodiscitis treated with flucloxacillin and paracetamol. During her hospitalization, she developed dyspnea and was found to have metabolic acidosis with pH of 7.29, HCO3 at 10.9 mEq/L, and anion gap at 29 mEq/L with a normal lactate concentration. She also had renal insufficiency with creatinine at 183 μmol/L (2.07 mg/dL) as well as elevated liver enzymes with ALP at 39 U/L and GGT at 523 U/L. Organic acids testing revealed an "elevated" urine 5-oxoproline concentration (serum concentration was not recorded). Paracetamol and flucloxacillin were stopped, and she was treated with sodium bicarbonate and intravenous acetylcysteine in a dose of 600mg every 8 h. Unfortunately, she did not improve and passed away.

Most recently, Milosevic et al.[34] described in Australia a 28-year-old woman who had been taking 1 g of paracetamol four times daily for 2 weeks for abdominal pain. She returned with vomiting, loose stools, and continued abdominal pain. Arterial blood gases obtained in response to a low serum bicarbonate concentration revealed a pH of 7.20. Lactate and beta-hydroxybutyrate concentrations were normal. Plasma amino acid analysis revealed high concentrations of glutamate (440 μmol/L; reference range, 10–50 μmol/L) and 5-oxoproline (1570 μmol/L; reference range, <70 μmol/L). Her 5-oxoproline urine concentration was $>5{,}000$ mmol/mol creatinine (normal, <100). The authors speculated that she had a genetic deficiency of glutathione synthetase. She recovered uneventfully after discontinuing paracetamol.

In Northern Ireland, Chestnutt et al.[35] described an 83-year-old woman with diabetes and renal insufficiency who developed a wound infection after left hip hemiarthroplasty. She received flucloxacillin 2 g four times per day. One week later, she had surgery to wash out the wound, and paracetamol 1 g four times per day was added. Over the course of another week, she developed HAGMA with hyperkalemia (6.2 mmol/L), a serum carbon dioxide concentration of 9 mmol/L, and a pH of 7.32. She continued to receive flucloxacillin and paracetamol. Her pH further decreased to 7.26 with a serum carbon dioxide concentration of 5 mmol/L and an anion gap of 27 mmol/L. She had a plasma lactate concentration of 2.6 mmol/L and a normal beta hydroxybutyrate. She received oral sodium bicarbonate for her HAGMA. Urine organic acid analysis then showed a "large, abnormal amount" of 5-oxoproline. Flucloxacillin and paracetamol were both discontinued, and she recovered over the course of the next week.

Possible genetic cause for excess 5-oxoproline production

Tokatli et al.[46] described a 9-month-old infant who received paracetamol 15 mg/kg every six h for 2 days during an apparent acute illness. She developed metabolic acidosis which persisted despite administration of intravenous fluids and sodium bicarbonate. Serum aminotransferase activity rose, and paracetamol was discontinued. AST and ALT activities peaked at 3034 U/L and 1402 U/L, respectively (treatment with acetylcysteine is not mentioned). Subsequent analysis of urinary organic acids showed "massive" oxoprolinuria (concentration not reported). Analysis of glutathione synthetase activity showed that she had 5% of the expected activity. Genetic analysis of the infant, whose parents were first cousins, found that she was homozygous for a mutation (419G>A) in the gene coding for glutathione synthetase. The authors opined that the dehydration from acute illness and exposure to paracetamol contributed to the clinical appearance of her glutathione synthetase deficiency and oxoprolinuria. They speculated further that heterozygous patients might also be at high risk of hepatotoxicity following paracetamol exposure.

Authors of several papers speculated that their patients also had enzyme deficiencies, although they did not specifically test for genetic mutations.[7,14,17,22,24,34]

Several rare enzyme deficiencies have been described in the synthesis and metabolism of glutathione.[47] Of these the most frequently reported is glutathione synthetase deficiency. At least 10 different point mutations have been identified.[48] The hallmarks of glutathione synthetase deficiency include hemolytic anemia, metabolic acidosis, and 5-oxoprolinuria. Severity depends upon the specific mutation. The known point mutations are autosomal recessive, and humans who are heterozygous have both glutathione synthetase activity and glutathione concentrations which are approximately 55% of those seen in normal people.[48]

Deficiency of 5-oxoprolinase is much rarer with about eight published cases.[47] Isolated 5-oxoprolinuria without acidosis typifies this deficiency, but other developmental or metabolic abnormalities may or may not be present.[47]

Role of acetylcysteine

It is unknown what role, if any, acetylcysteine plays in the evolution or treatment of 5-oxoprolinemia associated with paracetamol. Several of the case reports included empiric use of acetylcysteine. However, it is unclear whether acetylcysteine has beneficial, harmful, or no effect on 5-oxoprolinemia. It is possible that acetylcysteine, as a substrate for γ-glutamylcysteine synthetase, would increase production of 5-oxoproline by γ -glutamylcyclotransferase.

Recommended evaluation of a patient with HAGMA in the setting of paracetamol exposure

It appears that 5-oxoproline is a rare cause of HAGMA in the setting of paracetamol exposure, although the true incidence is unknown. Clinicians should first exclude commoner and treatable causes of HAGMA, such as lactic acidosis, co-ingested drug (e.g. salicylates, toxic alcohols, iron, and metformin), and diabetic or alcoholic ketoacidosis. If clinical suspicion for 5-oxoprolinemia still exists, a pediatric hospital laboratory that tests for inborn metabolic errors is likely to be a useful resource. If elevated concentrations of 5-oxoproline exist in blood and/or urine, genetic testing for

polymorphism for glutathione synthetase and 5-oxoprolinase is warranted.

Limitations of the review

The literature described has multiple limitations. The cases reported are very heterogeneous in that some were likely associated with chronic supratherapeutic ingestions of paracetamol or paracetamol combination products while many cases were associated with therapeutic dosing of paracetamol. Also, some patients were exposed to other medications, such as flucloxacillin, which are independently associated with 5-oxoprolinemia. The amount of information given, including how the 5-oxoproline concentrations were reported, also varied between reports and was often limited making interpretation difficult.

These cases also suffered from a spectrum and publication bias. Obtaining 5-oxoproline concentrations is not part of the standard practice in evaluating patients that present after supratherapeutic paracetamol ingestions or in those who have HAGMA. As such, we cannot be sure how often this occurs since it requires unique or special circumstances to measure 5-oxoproline concentrations and access to laboratories that can do the appropriate testing. It is likely that many physicians do not consider 5-oxoproline when evaluating patients with HAGMA, which significantly decreases the chances of making the correct diagnosis and publishing a case report or series. We also do not know whether 5-oxoprolinemia occurs independently of HAGMA or whether it occurs with smaller ingestions in patients that are not systemically ill. If significant 5-oxoproline formation does occur in these situations, our estimate of its incidence may be greatly underappreciated.

Conclusions

Multiple case reports and case series associate paracetamol with 5-oxoprolinemia. The case reports and series taken together suggest sporadic occurrence of HAGMA and high concentrations of 5-oxoproline (pyroglutamic acid) found in blood or urine following paracetamol exposure. No clear dose–response relationship emerges from these cases. This suggests the possibility of an inherited enzyme deficiency within the gamma-glutamyl cycle. A few case reports document investigation into the enzyme activity and associated genetic mutation but do not come to a conclusion regarding the role of this enzyme in paracetamol-related HAGMA with 5-oxoprolinemia. Further research is required to determine the incidence of 5-oxoprolinemia, clarify its clinical significance and relationship to acute or chronic paracetamol ingestions, and ascertain the optimal management of 5-oxoprolinemia in paracetamol poisoning.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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