Increased Anion Gap Metabolic Acidosis as a Result of 5-Oxoproline (Pyroglutamic Acid): A Role for Acetaminophen

Andrew Z. Fenves,* Haskell M. Kirkpatrick, III,* Viralkumar V. Patel,* Lawrence Sweetman,† and Michael Emmett*

*Department of Internal Medicine, †Metabolic Disease Center, BRI Baylor University Medical Center, Dallas, Texas

The endogenous organic acid metabolic acidoses that occur commonly in adults include lactic acidosis; ketoacidosis; acidosis that results from the ingestion of toxic substances such as methanol, ethylene glycol, or paraldehyde; and a component of the acidosis of kidney failure. Another rare but underdiagnosed cause of severe, high anion gap metabolic acidosis in adults is that due to accumulation of 5-oxoproline (pyroglutamic acid). Reported are four patients with this syndrome, and reviewed are 18 adult patients who were reported previously in the literature. Twenty-one patients had major exposure to acetaminophen (one only acute exposure). Eighteen (82%) of the 22 patients were women. Most of the patients were malnourished as a result of multiple medical comorbidities, and most had some degree of kidney dysfunction or overt failure. The chronic ingestion of acetaminophen, especially by malnourished women, may generate high anion gap metabolic acidosis. This undoubtedly is an underdiagnosed condition because measurements of serum and/or urinary 5-oxoproline levels are not readily available.

Clin J Am Soc Nephrol 1: 441–447, 2006. doi: 10.2215/CJN.01411005

The endogenous organic acid metabolic acidoses that occur most frequently in adults are lactic acidosis and ketoacidosis. Other organic acidoses that are encountered in adult patients are those that are caused by the metabolism of toxic substances such as methanol to formaldehyde or ethylene glycol to oxalic acid. Advanced renal failure causes a high anion gap acidosis as a result of the accumulation of both inorganic and organic acids. In the neonatal and pediatric population, a variety of inherited enzyme defects can generate various unusual forms of organic metabolic acidoses. The γ-glutamyl cycle produces glutathione, an antioxidant substance that is involved in many important biologic functions, including inactivation of free radicals, detoxification of many compounds, and amino acid membrane transport (Figure 1). Glutathione synthetase (GS) deficiency and 5-oxoprolinase (5-OPase) deficiency are two rare inherited enzyme defects that affect the γ-glutamyl cycle and result in massive urinary excretion of 5-oxoproline (pyroglutamic acid). Patients with GS deficiency also have high blood and cerebrospinal fluid 5-oxoproline levels and develop severe metabolic acidosis, hemolytic anemia, and central nervous system dysfunction (1). Heterozygous patients do not usually develop metabolic acidosis or severe 5-oxoprolinuria. Moderately increased urine excretion of 5-oxoproline also has been described in patients with propionic acidemia (2). Acquired 5-oxoprolinuria has been reported in infants who were fed the low-lactose preparation Nutramigen (3) and in patients who were taking acetaminophen (4); the anticonvulsant vigabatrin (5); or several antibiotics, including flucloxacillin and netilmicin (6).

In 1989, Creer *et al.* (7) reported a 52-yr-old woman with possible acquired 5-oxoproline metabolic acidosis. Urine drug screen revealed acetaminophen, but the significance of this finding was not apparent then. Within 1 yr, Pitt *et al.* (8) reported a second, similar case and proposed a possible contributory role for acetaminophen. In the second case, assays for GS and 5-OPase activity on cultured skin fibroblasts showed normal enzymatic activity (8). Pitt *et al.* also suggested that acetaminophen ingestion may have depleted intracellular glutathione stores, which then caused loss of feedback inhibition of γ-glutamylcysteine synthetase activity. This will increase production of γ-glutamylcysteine, which is partially converted to 5-oxoproline. Subsequently, a small number of additional cases were reported (9–14). All these patients were using acetaminophen. Normal assays for GS and 5-OPase enzyme assays were reported in some cases. Often, the cause of the metabolic acidosis was multifactorial.

Anion gap metabolic acidosis often develops in patients with acute acetaminophen hepatotoxicity and sometimes precedes the hepatic injury (15–17). Usually the metabolic acidosis is attributed to lactic acidosis and kidney failure. However, 5-oxoproline has not been measured routinely in either the plasma or the urine of these patients and may be a contributory factor.

Rats that ingest a diet that contains 1% acetaminophen develop massive 5-oxoprolinuria, excreting up to 1 mol/L (18). 5-Oxoprolinuria could be prevented by feeding the animals methionine together with acetaminophen. The authors speculated that chronic acetaminophen ingestion leads to depletion of sulfur-containing amino acids, including cysteine, with a consequent depletion of

Received October 21, 2005. Accepted February 28, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

Address correspondence to: Dr. Andrew Z. Fenves, Nephrology Division, Baylor University Medical Center, 3500 Gaston, Dallas, TX 75246. Phone: 214-820-2350; Fax: 214-820-7367; E-mail: fenvesa@dneph.com

ISSN: 1555-9041/103-0441

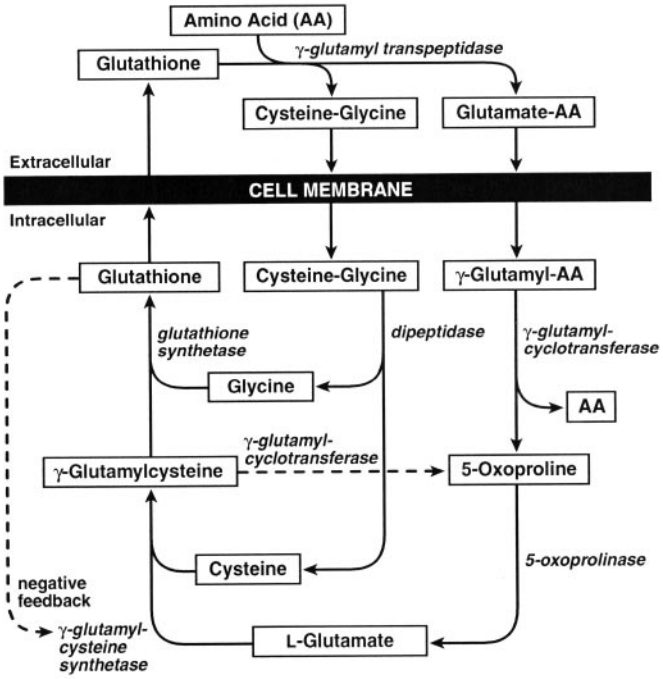

Figure 1. The γ-glutamyl cycle.

intracellular glutathione stores. This then generates 5-oxoprolinuria *via* the mechanism described above (see Figure 1).

We investigated four patients, three of whom presented with severe anion gap metabolic acidosis that was unexplained by lactic acid, ketoacidosis, the ingestion of methanol or ethylene glycol, or severe kidney failure. The fourth patient developed an unexplained high anion gap metabolic acidosis after hospital admission. Each patient had been regularly ingesting acetaminophen (generally on a daily basis) for relief of chronic pain, and each patient also had some degree of kidney dysfunction. In each case, markedly elevated levels of 5-oxoproline were documented in urine and/or plasma. We could not identify any other cause to account for the severity of their metabolic acidosis.

Case 1

A 36-yr-old white woman with a history of vaginal squamous cell carcinoma was transferred from another hospital in November 1990 with anuric renal failure. Nine months before this admission, she underwent a radical hysterectomy, bilateral pelvic lymphadenectomy, and bilateral salpingo-oophorectomy followed by radiation therapy without chemotherapy. Blood urea nitrogen (BUN), creatinine, and electrolytes all were within normal limits at that time. She was admitted for treatment of worse pelvic pain and was found to have acute renal failure. Bilateral hydronephrosis was found, and bilateral ureteral stents were placed. She developed generalized seizures, and oral phenytoin was started. A large retroperitoneal hemorrhage developed, and she required transfusion of 8 U of packed red blood cells. Gentamicin and vancomycin were initiated because of fever and presumed infection.

There was no history of diabetes, hypertension, or renal disease. She smoked one pack of cigarettes per day and denied use of alcohol or illicit drugs. Her outpatient medications included phenytoin 100 mg three times daily and propoxyphene/acetaminophen as needed for pain, which was used on a regular basis.

Laboratory studies on the day of transfer included a BUN of 123 mg/dl, creatinine of 5.9 mg/dl, glucose of 85 mg/dl, potassium of 3.6 mEq/L, sodium of 145 mEq/L, chloride of 90 mEq/L, CO_2 of 8 mEq/L, and an anion gap of 47 mEq/L. Renal failure was thought to be secondary to bilateral hydronephrosis. Radiation nephritis and possible acute tubular necrosis related to hemodynamic instability caused by massive retroperitoneal hemorrhage also were possible causative factors.

Evaluation of the high anion gap metabolic acidosis included two separate measurements of plasma lactic acid, both normal, and no detectable D-lactate acid. There was no evidence of ethanol, methanol, or ethylene glycol ingestion. Serum ketone assay was repeatedly negative. Although she had severe kidney failure, it was not thought that this could account for the severity of her high anion gap metabolic acidosis. The anion gap remained between 35 and 40 mEq/L.

A right percutaneous nephrostomy tube, placed because of persistent severe right-sided hydronephrosis, drained approximately 400 ml/d urine. Analysis of her urine for organic anions with gas chromatography–mass spectroscopy (GC-MS) revealed 0.7 mmol 5-oxoproline/mmol creatinine. The patient's medications during the hospital included vancomycin and gentamicin to treat blood culture–negative fevers, which resolved after the ureteral stents were removed.

While receiving oral sodium bicarbonate (Bicitra 30 ml orally twice daily) and regular hemodialysis, her anion gap remained in the 32- to 41-mEq/L range. At this time, she continued to ingest large daily doses of propoxyphene/acetaminophen for pain. The patient's invasive squamous cell carcinoma could not be controlled, and she died in January 1991.

Case 2

A 46-yr-old white woman was admitted to Baylor University Medical Center (BUMC) in May 1997 with severe metabolic acidosis and respiratory failure. For >1 yr, she had recurrent episodes of nausea and vomiting approximately once per month. She had been hospitalized several times with these complaints. On each admission, she was noted to have a mild high anion gap metabolic acidosis that promptly resolved with administration of intravenous glucose and fluids. She also had mild elevations of her liver function tests. She admitted to the frequent use of acetaminophen, and plasma acetaminophen levels were in the therapeutic range. Five days before this admission, the patient again developed severe nausea and vomiting.

Her medical history was remarkable for migraine headaches for >30 yr. She also had a 6-yr history of hypertension. She had had an abdominal hysterectomy many years before and laparoscopic cholecystectomy 1 mo before admission. Home medications included enalapril 10 mg/d, Premarin 0.625 mg/d, and acetaminophen either alone or in combination with Propoxyphene as needed for pain.

On admission to BUMC, the patient was in respiratory distress and had orthostatic hypotension. Admission laboratory tests included arterial blood gas on room air: pH 6.88, Pco_2 28 mmHg, and Po_2 145 mmHg. White blood cell count was 20,000 with 15% bands and 93% total polysegmented neutrophils. Hemoglobin was 10.1 g/dl, and hematocrit was 32.2%. Glucose was 534 mg/dl, sodium was 131 mEq/L, potassium was 4.0 mEq/L, chloride was 90 mEq/L, and bicarbonate was 8 mEq/L, with an anion gap of 33 mEq/L. Serum ketone assay was negative. Serum creatinine was 2.0 mg/dl. γ-Glutamyl transferase was 1100 U/L, serum glutamic oxaloacetic transaminase was 2200 U/L, serum glutamate pyruvate transaminase was 900 U/L, lactate dehydrogenase was 2000 U/L, and creatinine phosphokinase was normal at

159 U/L. The ammonia level was 48 μmol/L. Lactic acid level was 15.2 mEq/L. Erythrocyte sedimentation rate was 1 mm/h. Admission drug screen was positive for opioids but negative for amphetamines, barbiturates, cocaine, methadone, or PCP. Salicylate level on admission was <3 mg/dl, and acetaminophen level was 6.8 μg/ml, confirming that the patient was taking acetaminophen-containing medications. Alcohol level was undetectable. Lumbar puncture was unremarkable. Urine, blood, and cerebrospinal fluid cultures all were negative.

During the next 48 h, treatment with intravenous fluids and supportive therapy produced general overall improvement, and her lactate level fell to the normal range. However, the anion gap remained very high, >32 mEq/L over the next 3 d, and her metabolic acidosis persisted. Plasma 5-oxoproline level by GC-MS was 6.4 mmol/L and was characterized further as the L-isoform, which probably excludes a major contribution of bacterial origin.

Acetaminophen was discontinued. Renal function initially worsened, and her serum creatinine increased to 3.7 mg/dl but then stabilized and improved. At that time, her anion gap metabolic acidosis also resolved. Two weeks after this episode, the patient consented to a skin biopsy. GS activity in cultured fibroblasts was in the supranormal range.

Case 3

A 74-yr-old white woman presented with nausea, vomiting, labored breathing, and progressive mental deterioration over 5 d. A large anion gap metabolic acidosis was noted, and she was admitted to the intensive care unit.

Her medical history was significant for severe chronic obstructive pulmonary disease, peripheral vascular disease, chronic pain, breast cancer, atrial fibrillation, and osteoporosis. Medications included acetaminophen/hydrocodone as needed for pain, diltiazem 180 mg/d, digoxin 0.125 mg/d, Trental 400 mg/d, furosemide 20 mg twice daily, albuterol inhaler, and ipratropium bromide inhaler. She also had a history of ongoing alcohol abuse and previous tobacco use. On admission, the patient was in respiratory distress with markedly labored breathing. Admission laboratory was remarkable for an arterial blood gas on room air: pH 7.16, Pco_2 14 mmHg, and Po_2 111 mmHg. White blood cell count was 14,500/UL with 84% polysegmented neutrophils. Hemoglobin was 16.1 g/dl, hematocrit was 46.2%, and platelets were 546,000/UL.

Glucose was 166 mg/dl, sodium was 143 mEq/L, potassium was 4.7 mEq/L, chloride was 114 mEq/L, and bicarbonate was <5 mEq/L, yielding an anion gap of >24 mEq/L. Albumin was 3.0 g/dl, total bilirubin was 1.0 mg/dl, alkaline phosphatase was 138 U/L, ALT was 74 U/L, AST was 195 U/L, prothrombin time was 15.9 s, and partial thromboplastin time was 42.2 s. Serum osmolality measured at 318 mOsm/kg (calculated 300). Lactic acid was 2.5 mmol/L, semiquantitative serum ketone testing was negative, salicylate was <25 mg/L, and ethanol and methanol were negative. Plasma 5-oxoproline level was 2.8 mmol/L, and urine contained 1 mmol/mmol creatinine (both by GC-MS).

During the next 24 h, the patient's status worsened. She became progressively more dyspneic and obtunded. Creatinine increased, respiratory acidosis complicated her metabolic acidosis, and she died secondary to ventricular asystole approximately 24 h after her admission.

Case 4

A 55-yr old black woman with a history of diabetes, morbid obesity, and bilateral knee replacement surgery presented to her local hospital with an infected prosthetic right knee joint. The prosthesis was removed, and the wound was débrided. She then was transferred to BUMC for further care. On presentation to BUMC, she was a severely obese woman with an infected right knee surgical wound. Her serum creatinine was 1.5 mg/dl, erythrocyte sedimentation rate was 72 mm/h, and serum albumin was 2.7 g/dl. Electrolytes were normal. Several days after admission, mild metabolic acidosis developed and was attributed to renal insufficiency. During the third week of her BUMC hospitalization, a high anion gap metabolic acidosis developed. During her hospitalization, she required multiple surgical débridements, received multiple parenteral antibiotics (levofloxacin, linezolid, and voriconazole), and underwent hyperbaric oxygen therapy. She was given hydrocodone/acetaminophen combination for pain relief. Five weeks after admission and 2 d after her final débridement, her condition acutely worsened. She became increasingly tachypneic and was transferred to the intensive care unit. Sodium was 145 mEq/L, potassium was 4.4 mEq/L, chloride was 102 mEq/L, bicarbonate was 8 mEq/ L, BUN was 15 mg/dl, creatinine was 2.2 mg/dl, and anion gap was 35 mEq/L. Arterial blood gas (on supplemental oxygen) were as follows: pH 7.44, Pco_2 14 mmHg, and Po_2 256 mmHg. White blood cell count was 30, 600 with 74% polysegmented neutrophils and 10% bands. Glucose was 159 mg/dl, serum lactate was 4.3 mmol/L, and plasma ketone test was negative. Blood and urine cultures were positive for *Pseudomonas aeruginosa*, and her antibiotic coverage was broadened. Intravenous sodium bicarbonate was administered. She stabilized, and the serum lactate level fell to the normal range; however, a high anion gap acidosis persisted. Upon review of the patient's medications, we calculated that she had received 107 g of acetaminophen during the 6-wk hospital course (averaging 2.7 g/d). Acetaminophen was stopped, and both urine and whole blood were analyzed with GC-MS for organic anions. This revealed high plasma and urine 5-oxoproline levels of 10.5 mmol/L and 24.7 mmol/mmol Cr, respectively. The metabolic acidosis slowly corrected.

Discussion

Metabolic acidosis that is caused by 5-oxoproline results from disruption of the γ-glutamyl cycle, which is shown in Figure 1. Several inherited enzyme defects that have been characterized are extremely rare and usually present at a very early age with neurologic and hematologic abnormalities. GS deficiency is an autosomal recessive disorder and is characterized by mental retardation, ataxia, hemolytic anemia, and chronic metabolic acidosis in the homozygous patients (1). With GS deficiency, reduced glutathione levels increase γ-glutamylcysteine synthetase activity, and the resulting high γ-glutamylcysteine levels are partially converted to 5-oxoproline. 5-Oxoprolinase deficiency is a second rare autosomal recessive disorder that presents with 5-oxoprolinuria (19). It is interesting that these patients often develop kidney stones at a young age.

Acquired 5-oxoprolinuria has been described in adults. Several contributory factors include malnutrition (20,21), pregnancy (22,23), and strict vegetarian diet (24). Limited glycine availability may be a common precipitating cause. Increased urinary 5-oxoproline excretion also has been described in patients with type 2 diabetes (25). Severe 5-oxoproline aciduria and acidemia has been described in patients who use several different medications. These include acetaminophen (paracetamol) (4,7,8–14), vigabatrin (5), and the antibiotics flucloxacillin and/or netilmicin (6). Glycine deficiency and these other clinical conditions all may result in depletion of glutathione. This is proposed as the explanatory mechanism for the development

of excess 5-oxoproline generation. This critically important tripeptide, which contains glutamic acid, cysteine, and glycine, has major reducing and antioxidant effects, participates in transhydrogenation reactions and amino acid transport, modulates immune function, and detoxifies many drugs and poisons. Cysteine and glycine are required for the synthesis of glutathione (Figure 1).

The liver has one of the highest organ contents of glutathione, and it is known that hepatic glutathione stores are depleted in patients with acetaminophen toxicity (26). N-acetyl benzoquinonimine, an acetaminophen metabolite, binds irreversibly to glutathione (26,27). *In vitro* studies show that the intracellular glutathione content of liver cells must fall to <20% of control values before acetaminophen toxicity develops (28).

High anion gap metabolic acidosis occurs frequently in patients with acetaminophen toxicity (15,29,30). This generally is attributed to lactic acidosis and kidney failure. However, in some cases, the anion gap cannot be explained (30,31). These patients often have less severe toxicity and a history of chronic acetaminophen ingestion.

Pitt (4) measured urine 5-oxoproline excretion in patients who ingested acetaminophen compared with control subjects. Urine 5-oxoproline excretion in the acetaminophen group was >100 times higher than that in the control group, although still much lower than occurs in patients with inherited GS deficiency and most of the reported cases of acquired 5-oxoproline acidosis (3).

Chronic acetaminophen ingestion is associated with reduced plasma glutathione levels (32). Review of the literature revealed 18 *adult* cases of acquired, often transient, 5-oxoprolinuria and high anion gap metabolic acidosis associated with chronic "therapeutic" ingestion of acetaminophen (this excludes pediatric patients and patients with acute acetaminophen poisoning). The patient characteristics and biochemical findings of the previously reported patients and four new patients whom we report are summarized in Tables 1 and 2.

It is interesting that all of our patients, as well as 14 of the 18 previously described patients, were women. The activity of several isoenzymes in the γ-glutamyl cycle are know to be different in men and women (33,34). These differences may increase the susceptibility of women to develop this disorder.

It should be emphasized that acetaminophen ingestion alone probably does not generate clinically significant 5-oxoprolinuria or metabolic acidosis. In most cases, synergistic interaction between acetaminophen ingestion and multiple other factors exists (9). All of these patients had underlying or preceding illnesses, and most were malnourished. This probably depleted hepatic glutathione stores. This undoubtedly increases the susceptibility to toxic effects of chronic acetaminophen use. Many but not all of the patients had abnormal liver function tests. Several also had a history of chronic alcohol abuse, which also is known to reduce glutathione levels (35).

Healthy individuals who ingest diets that are depleted of cysteine, methionine, or glycine increase their excretion of

Table 1. Patient demographics and clinical characteristics of 20 patients with 5-oxoproline–induced high anion gap metabolic acidosis[a]

Patient	Reference	Age (yr)	Gender	Nutritional Status	Infection	Hypotension	Nausea/Vomiting
1	Creer *et al.* (7)	52	F	Alb low, s/p Billroth II	None	+	None
2	Pitt *et al.* (8)	34	F	Vegetarian	Post mortem lung culture *S. Pneumonia*	−	+
3	Pitt and Hauser (9)	33	F	Pregnant	Blood culture *S. Pneumonia*	−	−
4	Pitt and Hauser (9)	54	F	Alcohol abuse	UTI	−	+
5	Pitt and Hauser (9)	60	F	Subtotal gastrectomy	None	−	+
6	Pitt and Hauser (9)	57	F	Multiple abdominal operations	None	−	+
7	Pitt and Hauser (9)	17	F	Spina bifida	Infected V-P shunt	+	−
8	Pitt and Hauser (9)	73	F		None	+	−
9	Pitt and Hauser (9)	84			SBE	+	−
10	Pitt and Hauser (9)	57		Alcohol abuse	None	−	−
11	Dempsey *et al.* (10)	80	F	Chronic infection	Septic arthritis, bilateral psoas abscess	+	−
12	Dempsey *et al.* (10)	60	F	Gastrectomy	None	−	
13	Dempsey *et al.* (10)	64	F	Lymphoma	None	−	
14	Dempsey *et al.* (10)	54	F	Alcohol abuse	None	+	−
15	Humphreys *et al.* (11)	41			None	−	−
16	Yale and Mazza (12)	44	F		None	−	−
17	Tailor *et al.* (13)	40			None	+	+
18	Foot *et al.* (14)	57	F	Kidney transplant, sepsis	Yes	+	+
19	Current report	36	F	Metastatic cancer	None	−	−
20	Current report	46	F	Intractable nausea	None	+	+
21	Current report	74	F	Alcohol abuse	None	+	+
22	Current report	55	F	Low albumin, poor oral intake	None	−	+

[a]Alb low, low albumin; Billroth II, partial gastrectomy; UTI, urinary tract infection; V-P, peritoneal shunt; SBE, endocarditis.

Table 2. Biochemical data of 20 patients with 5-oxoproline–induced high anion gap metabolic acidosis and significant acetaminophen exposure[a]

Patient	pH	Anion Gap	Lactic Acid (mmol/L)	Alkaline Phosphatase	GGT	Renal Insufficiency (Cr)	Urine 5-Oxoproline (mmol/mmol Cr)[b]	Plasma 5-Oxoproline (mmol/L)[c]	Acetaminophen Exposure
1 (7)	7.17	27	2.2	158/344	344	(2.1)	15	12.6	1 mo
2 (8)	7.17	N/A	N/A	N/A	N/A	N/A	13	16	+
3 (9)	7.12	33	N/A	520	N/A	N/A	17	N/A	2 wk
4 (9)	7.23	26	N/A	227	732	N/A	13.8	6.7	3 d
5 (9)	7.14	39	N/A	240	692	N/A	11	6.6	Acute
6 (9)	7.16	31	N/A	147	197	N/A	10	6.6	1 wk
7 (9)	7.38	31	N/A	N/A	304	+	20.4	N/A	Approximately 22 d
8 (9)	7.31	31	N/A	126	N/A	N/A	22	16	Long history 4 g/d
9 (9)	7.15	21	N/A	158	137	N/A	23.6	11.3	+
10 (9)	7.09	37	N/A	218	254	N/A	5.7	2.3	1 wk
11 (10)	7.27	35	0.5	109	27	(1.5)	Elevated	Elevated	+
12 (10)	7.14	38	1.6	240	692	(1.1)[d]	13.7	6.6	+
13 (10)	6.80	33	1.0	N/A	N/A	(2.6)	4.0	8.0	+
14 (10)	7.26	22	1.1	N/A	N/A	(2.7)	13.8	6.7	+
15 (11)	N/A	29	Normal	N/A	N/A	(1.5)	Elevated	N/A	20.8 g/10 d
16 (12)	N/A	25	0.9	N/A	N/A	N/A	0.55	N/A	+
17 (13)[e]	7.24 to 7.32	20 to 36	1.5 to 5.2	N/A	N/A	1.2 to 2.3	8.9 to 20.7	N/A	+/+/+
18 (14)	6.99	31	1.6	240	158	3.4	(370 mm/L)	N/A	+
19	N/A	47	N/A	N/A	N/A	(5.9)	7	N/A	1 mo +
20	6.88	33	N/A	N/A	N/A	(2.0)	N/A	6.4	+
21	7.16	24	2.5	138	N/A	(1.8)	1	2.8	+
22	7.44	35	4.3	223	N/A	(2.2)	24.7	10.5	2.7 g/d

[a]Cr, creatinine; GGT, γ-glutamyl transferase; N/A, not applicable.
[b]Reference range <0.070 mmol/mmol Cr.
[c]Reference range <0.1 mmol/L.
[d]History of chronic renal insufficiency.
[e]Six sequential admissions, three with documented high urine oxoproline levels.

5-oxoproline (36). Patient 2 in Table 1 was a vegetarian, and patient 3 was pregnant (21–23). Many of the reported patients also had infection or sepsis. The cause of high anion gap metabolic acidosis with sepsis often cannot be elucidated (37–39). Glutathione synthetic rates in critically ill septic children fall by approximately 60% (40). Furthermore, some antibiotics (fludoxacillin and netilmicin) have been implicated in the development of this syndrome.

All our patients and many of those previously reported had renal insufficiency or failure. A reduction of kidney function will reduce urine excretion of 5-oxoproline and therefore may cause greater systemic accumulation.

The course of our case 4 (patient 22 in Tables 1 and 2) illustrates the critical role of acetaminophen in the development of otherwise unexplained high anion gap metabolic acidoses in some patients. She had multiple comorbid conditions that contributed to depleted glutathione stores, and she received large doses of acetaminophen for pain. This patient developed severe 5-oxoproline metabolic acidosis during her hospitalization in response to therapeutic administration of acetaminophen. Chronic renal insufficiency may have contributed to higher plasma 5-oxoproline levels. The observation that the high anion gap metabolic acidosis resolved with cessation of the drug is very important.

We believe that treatment of this unusual form of metabolic acidosis should focus on the recognition of its presence and cessation of acetaminophen intake. The importance of treatment of sepsis and renal and/or hepatic dysfunction is self-evident. N-acetylcysteine has been used with some effectiveness in patients with GS deficiency because it is thought to increase the low intracellular glutathione and cysteine concentrations (41). One adult patient with the acquired syndrome of high anion gap metabolic acidosis as a result of 5-oxoprolinemia was treated with intravenous N-acetylcysteine and improved (the only other reported patient who was treated was a 5.8-yr-old child, who also improved). In view of N-acetylcysteine's low toxicity and theoretical benefit, its use seems reasonable until better studies become available.

A prospective study of 23 patients who were in the intensive care unit with unexplained high anion gap metabolic acidosis failed to identify any patient with high 5-oxoproline levels (42). This entity undoubtedly is rare but very important to recognize because it can be treated by withdrawing a very common therapeutic agent.

Conclusion

High anion gap metabolic acidosis secondary to 5-oxoproline accumulation very likely is an underrecognized and underreported condition in adult patients, particularly among women. Patients who have malnutrition, sepsis, chronic alcohol use, underlying liver disease, and/or renal insufficiency and also ingest acetaminophen can develop acquired high anion gap

metabolic acidosis as a result of 5-oxoproline accumulation in serum and massive 5-oxoprolinuria.

Acknowledgments

We thank Dr. James J. Pitt (Melbourne, Australia) for measurements of 5-oxoproline as the L-isoform, and Dr. Owen Griffith (Milwaukee, WI) for measurements of glutathione synthetase in cultured skin fibroblasts.

References

1. Meister A, Larsson A: Glutathione synthetase deficiency and other disorders of the gamma-glutamyl cycle. In: *The Metabolic and Molecular Basis of Inherited Metabolic Disease*, 7th Ed., edited by Scriver CR, Beaudet AL, Sly WS, Valle D, New York, McGraw-Hill, 1995, pp 1461–1477
2. Morishita H, Nagaya S, Nakajima T, Kawase A, Ohya A, Sugiyama S, Kamiya K, Watanabe I, Togari H, Suzuki Y, *et al.*: Pyroglutamic aciduria in propionyl CoA carboxylase deficiency. *J Inherit Metab Dis* 7: 139–140, 1984
3. Nakanishi T, Shimizu A, Saiki K, Fujiwara F, Funashashi S, Hayashi A: Quantitative analysis of urinary pyroglutamic acid in patients with hyperammonemia. *Clin Chim Acta* 197: 249–256, 1991
4. Pitt J: Association between paracetamol and pyroglutamic aciduria. *Clin Chem* 36: 173–174, 1990
5. Bonham JR, Rattenbury JM, Meeks A, Pollit RJ: Pyroglutamic aciduria from vigabatrin. *Lancet* 1: 1452–1453, 1989
6. Croal BL, Glen AC, Kelly CJ, Logan RW: Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult patient receiving antibiotic therapy. *Clin Chem* 44: 336–340, 1998
7. Creer MH, Lau BWC, Jones TD, Chan KM: Pyroglutamic acidemia in an adult patient. *Clin Chem* 35: 684–686, 1980
8. Pitt JJ, Brown GK, Clift V, Christodoulou J: Atypical pyroglutamic aciduria: Possible role of paracetamol. *J Inherit Metab Dis* 13: 755–756, 1990
9. Pitt JJ, Hauser S: Transient 5-oxoprolinuria and high anion gap metabolic acidosis: Clinical and biochemical findings in eleven patients. *Clin Chem* 44: 1497–1503, 1998
10. Dempsey GA, Lyall HJ, Corke CF, Scheinkestel CD: Pyroglutamic acidemia: A cause of high anion gap metabolic acidosis. *Crit Care Med* 28: 1803–1807, 2000
11. Humphreys BD, Forman JP, Zandi-Nejad K, Bazari H, Seifter J, Magee CC: Acetaminophen-induced anion gap metabolic acidosis and 5-oxoprolinuria (pyroglutamic aciduria) acquired in hospital. *Am J Kidney Dis* 46: 143–146, 2005
12. Yale SH, Mazza JJ: Anion gap acidosis associated with acetaminophen. *Ann Intern Med* 133: 752–753, 2000
13. Tailor P, Raman T, Garganta CL, Njalsson R, Carlsson K, Ristoff E, Carey HB: Recurrent high anion gap metabolic acidosis secondary to 5-oxoproline (pyroglutamic acid). *Am J Kidney Dis* 46: E4–E10, 2005
14. Foot CL, Fraser JF, Mullany DV: Pyroglutamic acidosis in a renal transplant patient. *Nephrol Dial Transplant* 20: 2836–2838, 2005
15. Gray TA, Buckley BM, Vale JA: Hyperlactataemia and metabolic acidosis following paracetamol overdose. *Q J Med* 65: 811–821, 1987
16. Roth B, Woo O, Blanc P: Early metabolic acidosis and coma after acetaminophen ingestion. *Ann Emerg Med* 33: 452–456, 1999
17. Flanagan RJ, Mant TG: Coma and metabolic acidosis early in severe acute paracetamol poisoning. *Hum Toxicol* 5: 179–182, 1986
18. Ghauri FY, McLean AE, Beales D, Wilson ID, Nicholson JK: Induction of 5-oxoprolinuria in the rat following chronic feeding with N-acetyl 4-aminophenol (paracetamol). *Biochem Pharmacol* 46: 953–957, 1993
19. Larsson A, Mattson B, Wauters EAK, van Gool JD, Duran M, Wadman SK: 5-Oxoprolinuria due to hereditary 5-oxoprolinase deficiency in two brothers: A new inborn error of the gamma-glutamyl cycle. *Acta Paediatr Scand* 70: 301–308, 1981
20. Persaud C, Forrester T, Jackson AA: Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. *J Nutr* 126: 2823–2830, 1996
21. Jackson AA, Badaloo AV, Forrester T, Hibbert JM, Persaud C: Urinary excretion of 5-oxoproline (pyroglutamic acid) as an index of glycine insufficiency in normal man. *Br J Nutr* 58: 207–214, 1987
22. Jackson AA, Persaud C, Werkmeister G, McClelland IS, Badaloo A, Forrester T: Comparison of urinary 5-L-oxoproline (L-pyroglutamate) during normal pregnancy in women in England and Jamaica. *Br J Nutr* 77: 183–196, 1997
23. Persaud C, McDermott J, De Benoist B, Jackson AA: The excretion of 5-oxoproline in urine, as an index of glycine status, during normal pregnancy. *Br J Obstet Gynaecol* 96: 440–444, 1989
24. Jackson AA, Persaud C, Meakins TS, Bundy R: Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased in normal adults consuming vegetarian or low protein diets. *J Nutr* 126: 2813–2822, 1996
25. Forrester TE, Badaloo V, Bermett FI, Jackson AA: Excessive excretion of 5-oxoproline and decreased levels of blood glutathione in type II diabetes mellitus. *Eur J Clin Nutr* 44: 847–850, 1990
26. Lu SC: Regulation of hepatic glutathione synthesis. *Semin Liver Dis* 18: 331–343, 1998
27. James LP, Mayeux PR, Hinson JA: Acetaminophen-induced hepatotoxicity. *Drug Metab Dispos* 31: 1499–1506, 2003
28. Richman PG, Meister A: Regulation of gamma-glutamylcysteine synthetase by nonallosteric feedback inhibition by glutathione. *J Biol Chem* 250: 1422–1426, 1975
29. Zabrodski RM, Schunurr LP: Anion gap acidosis with hypoglycemia in acetaminophen toxicity. *Ann Emerg Med* 13: 956–959, 1984
30. Record CO, Iles RA, Cohen RD, Williams R: Acid-base and metabolic disturbances in fulminant hepatic failure. *Gut* 16: 144–149, 1975
31. Black M, Cornell J, Rabin L, Shachter N: Late presentation of acetaminophen hepatotoxicity. *Dig Dis Sci* 27: 370–374, 1982
32. Trenti T, Bertolotti M, Castellana CN, Ferrari A, Pini LA, Sternieri E: Plasma glutathione level in paracetamol daily abuser patients. Changes in plasma cysteine and thiol groups after reduced glutathione administration. *Toxicol Lett* 64–65: 757–761, 1992
33. Butera L, Feinfeld DA, Bhargava M: Sex differences in the

subunits of glutathione-S-transferase iso-enzyme from rat and human kidney. *Enzyme* 43: 176–182, 1990
34. McLellan LI, Hayes JD: Sex specific constitutive expression of the preneoplastic marker glutathione S-transferase, YfYf, in mouse liver. *Biochem J* 245: 399–406, 1987
35. Ookhtens M, Kaplowitz N: Role of the liver in interorgan homeostasis of glutathione and cyst(e)ine. *Semin Liver Dis* 18: 313–329, 1998
36. Metges CC, Yu Y-M, Cai W, Lu X-M, Wong S, Regan MM, Ajami A, Young VR: Oxoproline kinetics and oxoproline urinary excretion during glycine- or sulfur amino acid-free diets in humans. *Am J Physiol Endocrinol Metab* 278: E868–E876, 2000
37. Rackow EC, Mecher C, Astiz ME, Goldstein C, McKee D, Weil MH: Unmeasured anion during severe sepsis with metabolic acidosis. *Circ Shock* 30: 107–115, 1990
38. Mecher C, Rackow EC, Astiz ME, Weil MH: Unaccounted for anion in metabolic acidosis during severe sepsis in humans. *Crit Care Med* 19: 705–711, 1991
39. Mizock BA, Mecher C: Pyroglutamic acid and high anion gap: Looking through the keyhole? *Crit Care Med* 28: 2140–2141, 2000
40. Lyons J, Rauh-Pfeiffer A, Ming-Yu Y, Lu X-M, Zurakowski D, Curley M, Collier S, Duggan C, Nurko S, Thompson J, Ajami A, Borgonha S, Young VR, Castillo L: Cysteine metabolism and whole blood glutathione synthesis in septic pediatric patients. *Crit Care Med* 29: 870–877, 2001
41. Martensson J, Gustafsson J, Larsson A: A therapeutic trial with N-acetylcysteine in subjects with hereditary glutathione synthetase deficiency (5-oxoprolinuria). *J Inherit Metab Dis* 12: 120–130, 1989
42. Mizock BA, Belyaev S, Mecher C: Unexplained metabolic acidosis in critically ill patients: The role of pyroglutamic acid. *Intensive Care Med* 30: 502–505, 2004