Acetaminophen, the missing anion gap in the patient with metabolic acidosis

Camilo Pena MD, Kenedy Brandon

Abstract

Acetaminophen intake is well-known but an often missed cause of high anion gap (AG) metabolic acidosis, and physicians must understand the metabolic pathway which increases the AG. Multiple mnemonics for common causes of metabolic acidosis have been developed and are widely taught in medical schools. Some of them, such as MUDPILES and KUSMALE, may not lead to an adequate workup and miss the diagnosis for the acidosis. More recently developed memory tools, such as GOLDMARK, provide a complete differential diagnosis for high AG metabolic acidosis. Pyroglutamic acid accumulates after alterations of the gamma-glutamyl cycle mediated by acetaminophen and glutathione deficiency in some patients. The lower capacity of 5-oxiprolinase to metabolize pyroglutamic acid into glutamate results in the gradual accumulation of oxoproline/pyroglutamic acid. Treatment is mainly supportive with the major aim of restoring glutathione levels, optimizing nutrition, and using N-acetylcysteine as needed. Different modalities of renal replacement therapy have also been used in these patients.

Keywords: metabolic acidosis, acetaminophen, anion gap, 5-oxoproline, pyroglutamic acid, gamma glutamyl cycle, glutathione

Managing metabolic acidosis is a frequent problem for internists, hospitalists, family physicians, intensivists, nephrologists, and even pediatricians. Due to the frequency of this metabolic disorder, many physicians have created their own step-wise approaches which have been validated by most medical organizations, including the American Society of Nephrology, which encourages this systematic approach (e.g., Boston approach, Copenhagen approach, Stewart Method).[1]

Evaluating a metabolic acidosis disorder must always include calculation of the unmeasured anions present in serum, including proteins, phosphate, sulfate, and organic anions.

Corresponding author: **Camilo Pena**
Contact Information: camilo.pena@ttuhsc.edu
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Anion Gap (AG) = $Na^+ - (Cl^- + HCO_3^-)$

This requires the assumption of a normal extracellular fluid volume (ECFV) and albumin levels. Otherwise, the AG must be corrected for the deviation of plasma albumin from the normal value of 4.0 gm/dL [a 1gm/dl reduction in albumin reduces the AG ~2.5-3 mEq/L]. An increased AG suggests the presence of an acid other than hydrochloric acid or its equivalent.

We were taught that after calculating and finding an abnormal AG, which ranges from 8-14, depending on the laboratory calibration and volume status, the next step should be correlating the increment of the gap with the decrement in bicarbonate and considering possible causes of the wide AG. Several

mnemonics have been developed to create a differential diagnosis. One of the most widely used is MUDPILES (also discussed by "Dr. House" during the second season of this TV show). However, some disorders in MUDPILES (methanol, uremia, diabetes ketoacidosis, phenformin, isoniazid, lactic acid, ethylene glycol, salicylates) occur infrequently. Others mnemonics, like KUSMALE (ketosis, uremia, salicylates, methanol, aldehydes, lactate, ethylene glycol), have become outdated with examples like aldehyde which refers to paraldehyde, an old sedative used in delirium tremens patients.

A newer mnemonic, GOLDMARK (Table 1), includes more common clinically important causes of AG metabolic acidosis[2]; this mnemonic includes an AG metabolic acidosis caused by 5-oxoproline/pyroglutamic acid and the potential contribution of acetaminophen.[3,4] This drug is sold over-over-the-counter worldwide for prices which range from few cents for single tabs to less than $10 dollars for a 250 pill bottle and can cause pyroglutamic/oxoproline acidosis (The "O" in GOLDMARK).[3,4]

Oxoprolinuria, as a cause of elevated AG metabolic acidosis, can present as an inherited disorder (Table 2),[5,6] resulting from mutations in enzymes in the gamma glutamyl cycle.[4] However, the most common presentation is an acquired disorder in malnourished patients given acetaminophen which unmasks the presence of glutathione deficiency (Figure 1).[7,8] Other drugs, such as vigabatrin (gamma-vinyl-GABA), an anticonvulsant used more frequently in pediatrics,

Table 1. GOLDMARK

G	Glycols
O	Oxoproline
L	L-lactic acid
D	D-lactic acid
M	Methanol
A	Aspirin
R	Renal failure
K	Ketoacidosis

Table 2. Hereditary forms of oxoprolinuria

Inactivating mutation	Function
5-Oxoprolinase	Conversion of pyroglutamic acid to glutamic acid
Gamma-glutamyl cysteine synthetase	Forms gamma-glutamylcysteine from cysteine plus glutamic acid
Glutathione synthetase	Forms glutathione (gamma-glutamylcysteinylgycine) from glycine plus gamma-glutamylcysteine
Gamma-glutamyl transpeptidase	Conversion of glutathione to cysteinylglycine and gamma-glutamyl-amino acid

dietary glycine deficiency from conditions, such as pregnancy, diabetes, malnutrition, and the use of antibiotics have also been reported as causes of glutathione deficiency.[7]

The mechanism for increased accumulation of anions and therefore high AG acidosis results from alterations in the gamma glutamyl pathway.[8] This pathway normally brings extracellular amino acids into the cytoplasm of the cell. Although glutathione is formed inside of the cell, it exerts feedback inhibition of the rate limiting enzyme: gamma-glutamyl cysteine synthetase (GGCS). If a patient is deficient in glutathione from, for example, malnutrition, and then ingests acetaminophen, which requires glutathione as part of its metabolism, the patient loses the inhibitory effect on GGCS. This inhibition increases the levels of gamma glutamylcysteine which moves through a shunt pathway to form endogenous pyroglutamic acid. Oxoprolinuria leads to the loss of bicarbonate as part of the buffer system, accompanied by the salt of the acid in this case sodium pyroglutamate.

$$H^+ Anion^- + NaHCO_3 \leftrightarrow Na^+ Anion^- + H_2O + CO_2$$

With the accumulation of pyroglutamic acid in the setting of a low capacity 5-oxiprolinase to metabolize pyroglutamic acid into glutamate, there will be an "overwhelmed" enzyme unable to maintain a balance

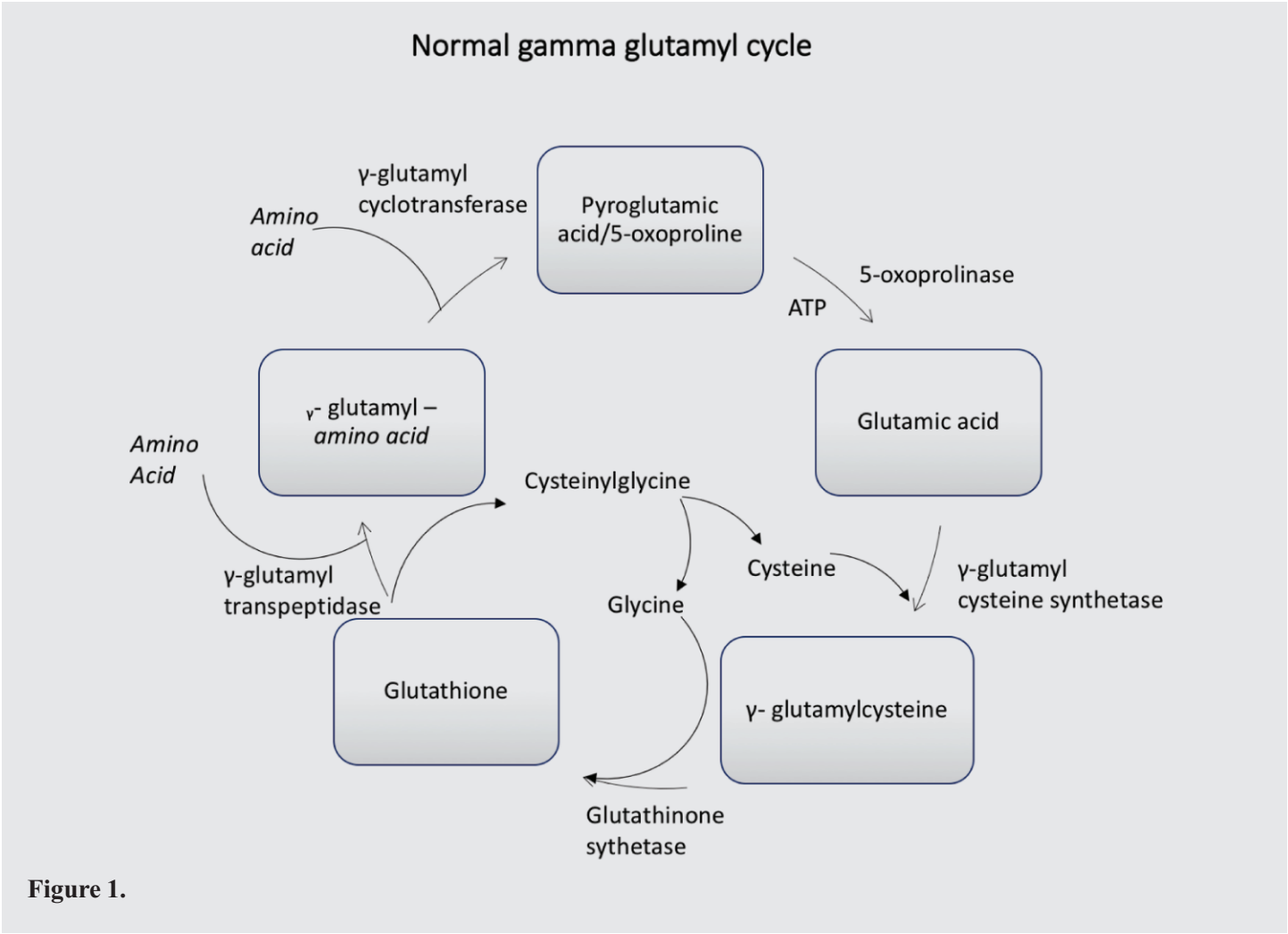

Figure 1.

between production and conversion, thus gradually building-up levels of oxoproline/pyroglutamic acid (Figure 2).[9]

With kidney disease (either acute or chronic) the clearance of oxoproline will decrease and thus worsen this process.[10] Serum levels of acetaminophen can be measured in blood, but they might not be elevated or even detectable in these patients. Some specialized laboratories can measure 5-oxoproline in urine and/or plasma by gas chromatography and mass selection. Most reported cases of pyroglutamic aciduria are caused by repeated therapeutic acetaminophen doses, usually in the setting of sepsis, pregnancy, or failure to thrive; typical clinical presentations are described in Table 3.

Stopping the offending agent and maintaining adequate diuresis with good hydration are the first steps in management. Expert opinion suggests the use of N-acetylcysteine to regenerate glutathione in addition to the use of bicarbonate if the pH is less than 7. Different modalities of renal replacement therapy using standard dialysis criteria, such as CVVH, CVVHD, CVVHDF, and IHD have been.[11] The best way to help our patients' quick recovery requires a proper differential diagnosis for a high AG acidosis (GOLDMARK) and early intervention.

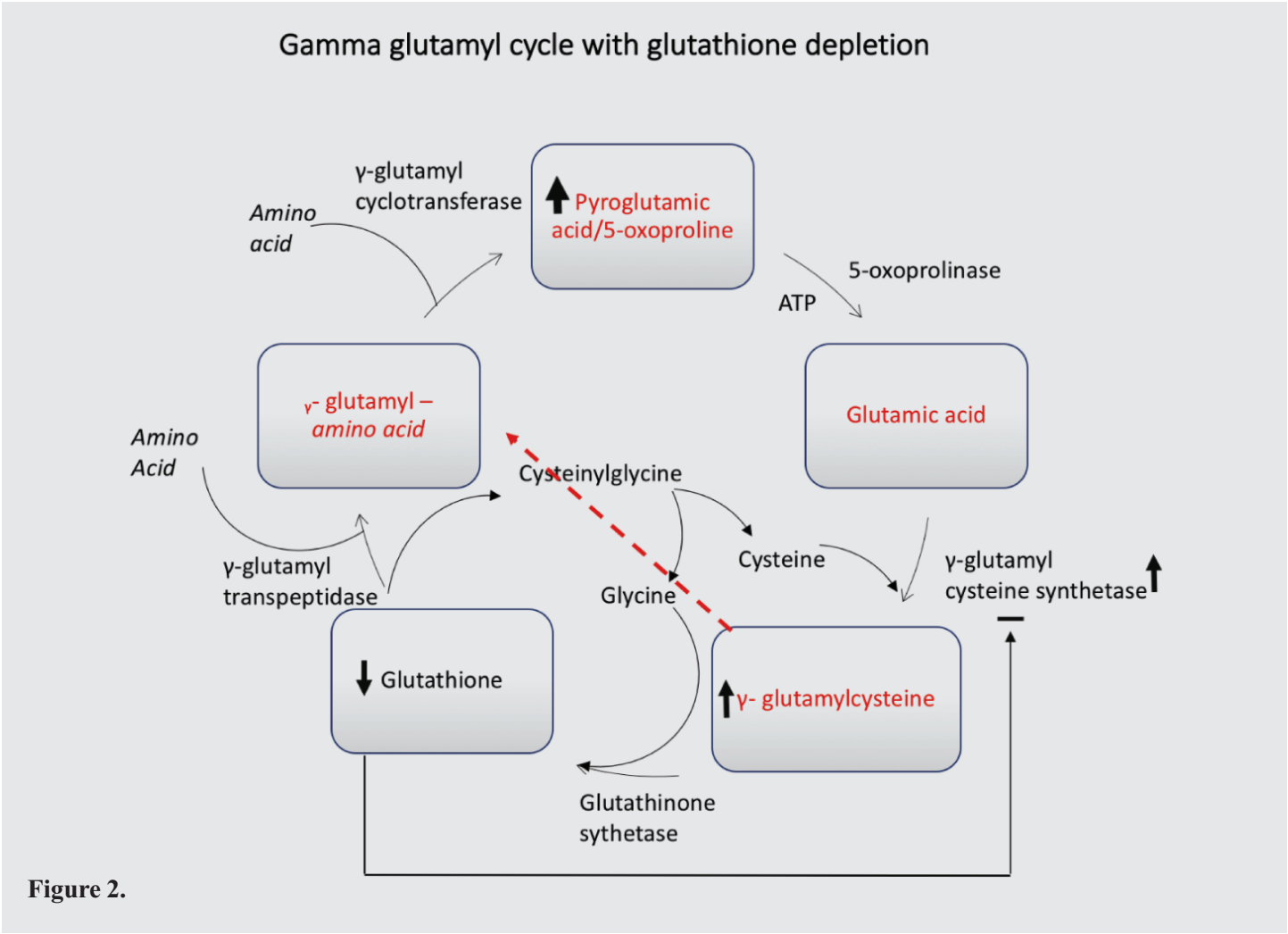
Gamma glutamyl cycle with glutathione depletion
γ-glutamyl
cyclotransferase
Amino
acid
Pyroglutamic
acid/5-oxoproline
5-oxoprolinase
ATP
γ- glutamyl –
amino acid
Glutamic acid
Amino
Acid
Cysteinylglycine
γ-glutamyl
transpeptidase
Cysteine
γ-glutamyl
cysteine synthetase
Glycine
Glutathione
γ- glutamylcysteine
Glutathinone
sythetase

Figure 2.

Table 3. Case reports and clinical findings

Case	Sex	Age	Acetaminophen concentration	Arterial pH/ s-bicarbonate	Anion gap
Presented with altered mental status while in jail; had no reported medical history[12]	M	28	Serum level: 616 μg/mL at 16 h post ingestion	6.97/7mEq/L	34mEq/L
Presented with a prosthesis infection after a trochanteric fracture; had a history of CKD with a sCr: 2.0, DM, HTN, DLP, and CHF[13]	M	75	40g over a 10 day period	7.18/5mmol/L	25mmol/L
Presented with diarrhea and failure to thrive; had a history of Crohn's disease, a. fib, and malnutrition[14]	F	80	650mg Q6h	n/a-11.3mEq/L	25mEq/L
Presented with altered mental status and coma in the setting of a frail older woman[15]	F	77	Serum: 1078 μg/mL	7.19/8mmol/L	25mmol/L
Presented with nausea, vomiting, and history of chronic abdominal pain[16]	F	27	5-oxoproline: 35.8 mmol/L	7.12/7mEq/L	22mEq/L
Presented with altered mental status and history of alcohol abuse[17]	F	40	Serum: 430 μg/mL	n/a -15mmol/L	18mmol/L
Presented with a traumatic fracture of the humerus and had a history of DM and HTN[18]	F	84	n/a	7.18/4mmol/L	25mmol/L
Malnourished woman presented with altered mental status; had a history of hepatitis B and breast cancer[19]	F	72	Serum: 2 μg/mL 5-oxoproline: 205 mmol/L	7.33/10mmol/L	22mEq/L
Presented with altered mental status and failure to thrive; had a history of alcoholism and eating disorder[20]	F	58	Serum: 49 μg/mL	7.02/5mEq/L	31mEq/L
Presented with malaise and altered mental status; had a history of anorexia[21]	M	48	n/a	6.98/3mEq/L	32mEq/L

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References

1. Tan EM, Kalimullah E, Sohail MR, Ramar K. Diagnostic challenge in a patient with severe anion gap metabolic acidosis. *Case Rep Crit Care.* 2015;2015:272914.
2. Mehta AN, Emmett JB, Emmett M. GOLD MARK: an anion gap mnemonic for the 21st century. *Lancet.* 2008; 372(9642):892.
3. Kamran H, Ram N. Chronic acetaminophen use associated with anion-gap metabolic acidosis. *Am J Med.* 2016;129(8):e127-128.
4. Zein JG, Wallace DJ, Kinasewitz G, Toubia N, Kakoulas C. Early anion gap metabolic acidosis in acetaminophen overdose. *Am J Emerg Med.* 2010;28(7):798-802.
5. Fenves AZ, Kirkpatrick HM, Patel VV, Sweetman L, Emmett M. Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. *Clin J Am Soc Nephrol.* 2006;1(3):441-447.
6. Creer MH, Lau BW, Jones JD, Chan KM. Pyroglutamic acidemia in an adult patient. *Clin Chem.* 1989;35(4):684-686.
7. Mizock BA, Belyaev S, Mecher C. Unexplained metabolic acidosis in critically ill patients: the role of pyroglutamic acid. *Intensive Care Med.* 2004;30(3):502-505.
8. Verma R, Polsani KR, Wilt J, Loehrke ME. 5-Oxoprolinuria as a cause of high anion gap metabolic acidosis. *Br J Clin Pharmacol.* 2012;73(3):489-491.
9. Duewall JL, Fenves AZ, Richey DS, Tran LD, Emmett M. 5-Oxoproline (pyroglutamic) acidosis associated with chronic acetaminophen use. *Proc (Bayl Univ Med Cent).* 2010;23(1):19-20.
10. Emmett M. Acetaminophen toxicity and 5-oxoproline (pyroglutamic acid): a tale of two cycles, one an ATP-depleting futile cycle and the other a useful cycle. *Clin J Am Soc Nephrol.* 2014;9(1):191-200.
11. Liss DB, Paden MS, Schwarz ES, Mullins ME. What is the clinical significance of 5-oxoproline (pyroglutamic acid) in high anion gap metabolic acidosis following paracetamol (acetaminophen) exposure? *Clin Toxicol (Phila).* 2013; 51(9):817-827.
12. Villano JH, O'Connell CW, Ly BT, Schneir A. Case files from the University of California San Diego Health System Fellowship coma and severe acidosis: remember to consider acetaminophen. *J Med Toxicol.* 2015;11(3):368-376.
13. Abkur TM, Mohammed W, Ali M, Casserly L. Acetaminophen-induced anion gap metabolic acidosis secondary to 5-oxoproline: a case report. *J Med Case Rep.* 2014;8:409.
14. Vichot AA, Rastegar A. Use of anion gap in the evaluation of a patient with metabolic acidosis. *Am J Kidney Dis.* 2014;64(4):653-657.
15. Kanji HD, Mithani S, Boucher P, Dias VC, Yarema MC. Coma, metabolic acidosis, and methemoglobinemia in a patient with acetaminophen toxicity. *J Popul Ther Clin Pharmacol.* 2013;20(3):e207-211.
16. Armenian P, Gerona RR, Blanc PD, Wu AH, Mookherjee S. 5-oxoprolinemia causing elevated anion gap metabolic acidosis in the setting of acetaminophen use. *J Emerg Med.* 2012;43(1):54-57.
17. Lawrence DT, Bechtel LK, Charlton NP, Holstege CP. 5-oxoproline-induced anion gap metabolic acidosis after an acute acetaminophen overdose. *J Am Osteopath Assoc.* 2010;110(9):545-551.
18. Holman M, ter Maaten JC. [Severe metabolic acidosis as a result of 5-oxoproline in acetaminophen use]. *Ned Tijdschr Geneeskd.* 2010;154:A1838.
19. Rolleman EJ, Hoorn EJ, Didden P, Zietse R. Guilty as charged: unmeasured urinary anions in a case of pyroglutamic acidosis. *Neth J Med.* 2008;66(8):351-353.
20. Hodgman MJ, Horn JF, Stork CM, et al. Profound metabolic acidosis and oxoprolinuria in an adult. *J Med Toxicol.* 2007;3(3):119-124.
21. Tailor P, Raman T, Garganta CL, et al. Recurrent high anion gap metabolic acidosis secondary to 5-oxoproline (pyroglutamic acid). *Am J Kidney Dis.* 2005;46(1):e4-10.