# Clinical Pharmacology & Toxicology Pearl of the Week

## ~ Acetaminophen-Related Pyroglutamic Acidosis ~ (5-oxoprolinemia)

**Case**

- A 75-year-old woman has been admitted to hospital for one month after a ground level fall with orthopedic injuries. She has been treated with acetaminophen 1000 mg scheduled every 6 hours and hydromorphone 1 mg PO every 3 hours as needed for four weeks.
- The patient developed URTI symptoms and was noted to be tachypneic with a respiratory rate of 28. Therefore, bloodwork including an ABG was performed which revealed a pH 7.23, pCO2 14, HCO3 6, Anion Gap 23, and Lactate 1.6.
- Creatinine was mildly elevated at 144 (baseline 73). Salicylate level was negative, urine ketones were negative, and toxic alcohol testing was negative.
- During her hospital admission, the patient had poor oral intake and had lost 7 kg of weight over the course of 4 weeks. Her new weight was 44 kg with a BMI of 19 $kg/m^2$.
- Given the patient's longstanding acetaminophen use and lack of alternative diagnosis for her anion gap metabolic acidosis, she was started on empiric treatment for pyroglutamic acidosis with n-acetylcysteine. Urine organic acid results eventually reveal a pyroglutamic acid to creatinine ratio of >2633 mmol/mol (Reference < 170 mmol/mol) confirming the diagnosis of pyroglutamic acidosis.

**Physiology & Toxicology**

- Glutathione is produced through the combination of glutamic acid, cysteine, and glycine. The first step of this process is the linkage of glutamic acid and cysteine by the enzyme Gamma-Glutamyl Cysteine Synthetase. Under normal conditions, adequate glutathione stores inhibit this enzyme to prevent further glutathione production.
- Acetaminophen reacts with sulfur-containing amino acids and glutathione via sulfation reactions with acetaminophen and conjugation of NAPQI. When chronic acetaminophen use is combined with protein malnutrition, cysteine and glutathione depletion may develop.
- With glutathione depletion, Gamma-Glutamyl Cysteine Synthetase activity is increased. This enzyme performs a two-step reaction in which γ-glutamyl phosphate is formed and then combines with cysteine. However, when cysteine is not available the reaction cannot proceed and the γ-glutamyl phosphate degrades into 5-oxoproline also known as pyroglutamic acid (Figure 1). 5-oxoproline can accumulate and cause a metabolic acidosis.

**Clinical Features**

- Risk factors for acetaminophen-related pyroglutamic acidosis include:
    - Elderly
    - Female
    - Low Body Weight
    - Malnutrition
    - Cirrhosis
    - Chronic Kidney Disease
    - Acute Illness

- Patients have often been on acetaminophen regularly for several weeks at the higher end of the therapeutic dosing range (i.e., 3000 to 4000 mg per day).
- Most patients with pyroglutamic acidosis are found to have an anion gap metabolic acidosis incidentally, without specific symptoms. However, symptoms related to the acidosis may be present including dyspnea, tachypnea, and malaise.

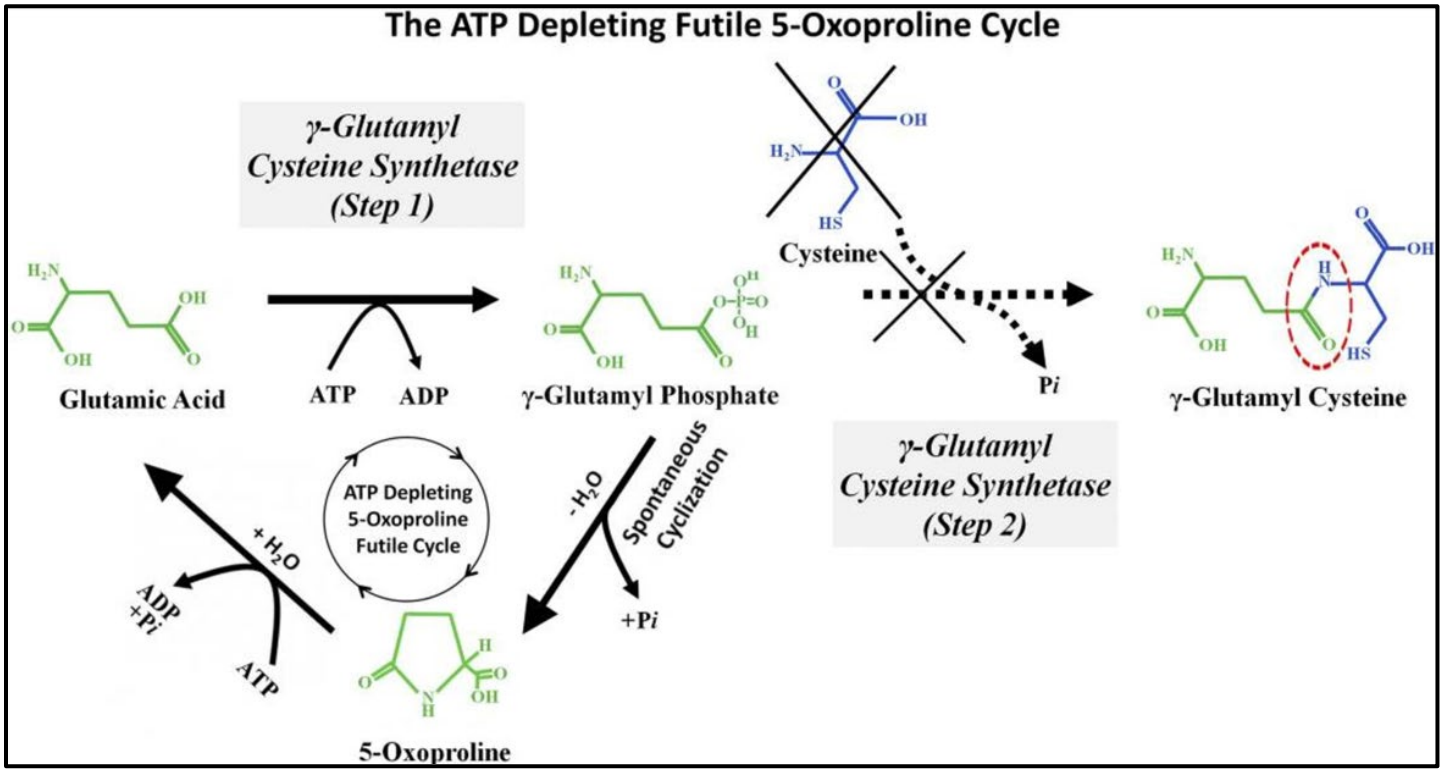


Figure 1: Generation of 5-oxoproline in Cysteine Deficiency (Emmett, 2013)

**Diagnostic Testing**

- Bloodwork will show a metabolic acidosis with high anion gap.
- Alternative etiologies should be investigated and ruled out.
- Rapid testing for pyroglutamic acid is not available. Therefore, any patient with a significant acidosis thought to be caused by pyroglutamic acidosis should be treated empirically.
- The diagnosis of pyroglutamic acidosis can be confirmed by testing for urine organic acids.
    - Alberta Precision Labs offers a **Urine Organic Acids, Semi-Quantitative** panel which provides an organic acid: creatinine ratio for an array of metabolites including pyroglutamic acid.
    - Turnaround time for testing averages 1 to 2 weeks and therefore management should not be delayed while awaiting results. Results can help to retrospectively confirm the diagnosis.
    - Given the broad panel of organic acids assessed, providing relevant clinical information with testing orders is important for result interpretation.

## Management

- Management consists of stopping acetaminophen exposure, addressing malnutrition, and treating glutathione/cysteine deficiency with n-acetylcysteine (NAC).
- NAC is converted to cysteine and glutathione. Adequate cysteine concentrations allow Step 2 of the Gamma-Glutamyl Cysteine Synthetase reaction to proceed and prevents accumulation of pyroglutamic acid.
    - There is no universally excepted NAC dosing regimen. Most reported cases utilize an accepted NAC protocol for treatment of acute acetaminophen toxicity.
    - To maintain consistency and reduce the risk of medication errors, it is recommended to follow the PADIS 2-Step IV NAC regimen of 150 mg/kg over 1 hour followed by a NAC infusion of 15 mg/kg/hour.
    - Traditional NAC endpoints for acetaminophen are **not applicable** for patients with pyroglutamic acidosis. The NAC infusion should continue until resolution of the anion gap acidosis.

## Summary

- Pyroglutamic acidosis is a rare cause of a metabolic acidosis with high anion gap associated with therapeutic acetaminophen use and malnutrition.
- Pyroglutamic acidosis is most seen in elderly women with low body weight and malnutrition who are using acetaminophen regularly for a prolonged period.
- Management consists of holding acetaminophen, increasing protein intake, and treatment with n-acetylcysteine.
- Duration of n-acetylcysteine treatment is not well defined, but resolution of the anion gap metabolic acidosis is a reasonable endpoint.

## References


1. Banks MF, Stipanuk MH. The utilization of n-acetylcysteine and 2-oxothiazolidine-4-carboxylate by rat hepatocytes is limited by their rate of uptake and conversion to cysteine. J Nutr. 1994 Mar;124(3):378-87.
2. 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. 2013 Nov;9(1):191-200.
3. Hunter RW, Lawson C, Galitsiou E, Gifford F, Neary JJ. Pyroglutamic acidosis in association with therapeutic paracetamol use. Clin Med (Lond). 2016 Dec;16(6):524-29.


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