An Under-Recognized Cause of Metabolic Acidosis

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CC: Back Pain & Altered Mental Status

- 72 year old female with a history of
- CKD stage III
- Chronic back pain/sciatica
- Ran out of pain medications

Daughter was worried her mother appeared confused, somnolent, and had a decreased appetite

Presentation

Pertinent medications:

- Hydrocodone/acetaminophen
- Codeine/acetaminophen
- Acetaminophen

Patient was taking at least 4000 mg of acetaminophen daily from 3 different sources for one year

Physical exam

Vitals: Temp: 99.3˚ , Pulse: 85, RR: 24, BP: 136/61, SpO_2: 100%

HEENT: NCAT, PERRL, EOMI, anicteric sclera, mucous membranes appear dry

Remainder of exam was normal

Laboratory data

137	94	38
4.2	9	1.63

106

Baseline Creatinine 1.30

	15.6	
11.3		307
	47	

Lactic Acid: 1.0

Anion Gap: 31

Δ/Δ : 1.26

ABG

pH: 7.24

pCO2: < 20 mmHg

pO2: 92 mmHg

HCO3: 7

CO2: 7

Laboratory data

Serum Drug Screen

-ASA: Negative

-APAP: Negative

-Benzo: Negative

-TCAs Negative

-Ethanol: Negative

-Methanol: Negative

Volatile Drug Screen

- Methanol: Negative
- Ethanol: Negative
- Acetone: Negative
- Isopropanol: negative

GOLDMARK

Glycols (Ethylene and Propylene)

Oxoproline

L-Lactate

D-Lactate

Methanol

Aspirin

Renal Failure

Ketoacidosis

Proposed by Ankit Mehta in the Lancet
GOLD MARK: an anion Gap mnemonic for the 21st century
Volume 372, No. 9642, p892, 13 September 2008

Hospital course

Urine was sent out for urine organic acid screen, results came back 5 days later:

- Urine organic acid analysis revealed a large elevation of 5-oxoproline (pyroglutamate)
- Tylenol metabolites were observed in this specimen.

Oxoprolinemia

- First seen in children with in-born errors of metabolism
- Acquired form was first described in 1989, and it’s relationship to Acetaminophen use in 1990
- Thought to be due to glutathione depletion

Oxoprolinemia

Who is at Risk

- Chronic Tylenol Use
- Women
- People with Chronic Kidney Disease
- Malnourished
- Vegetarians
- Pregnant Women
- People with Sepsis

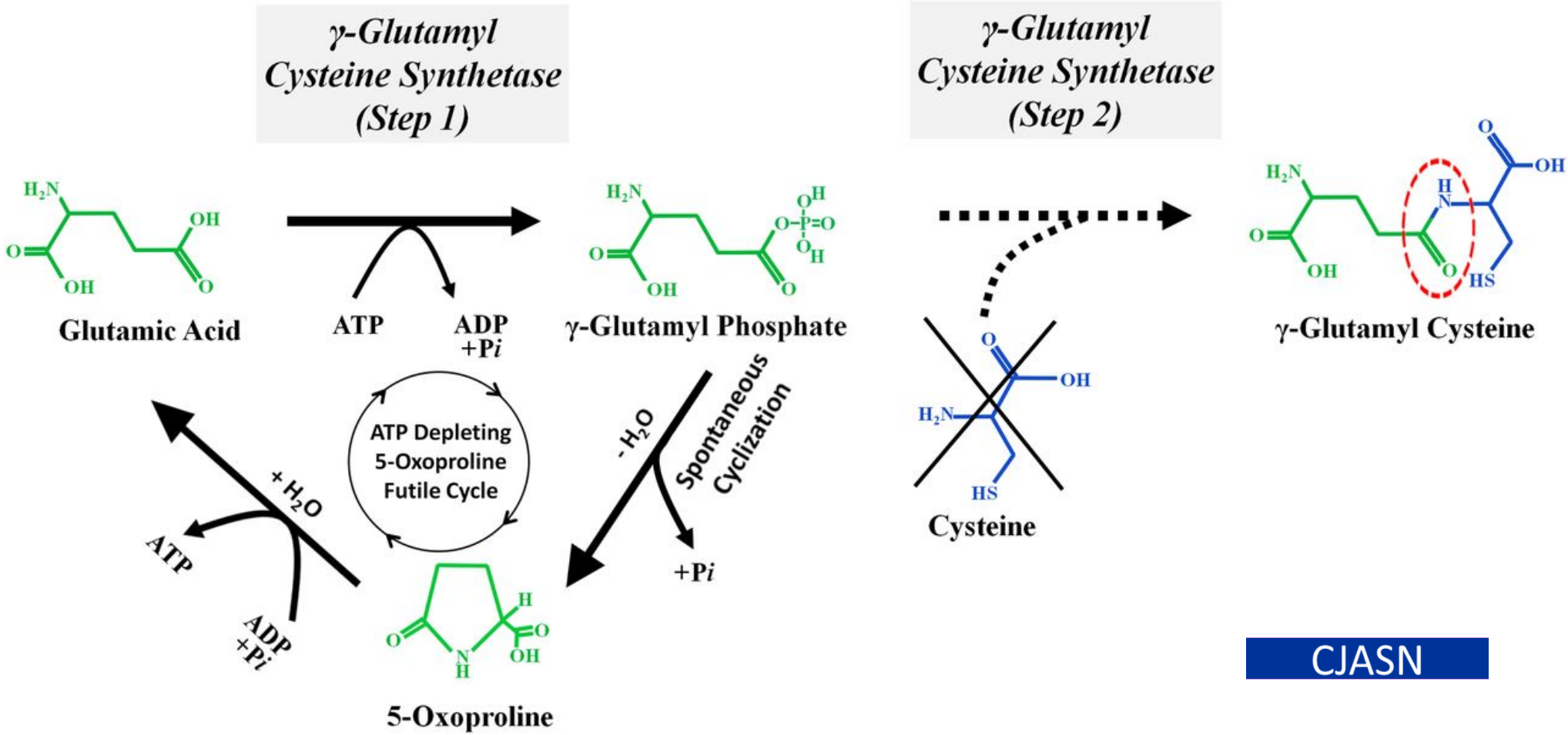
Oxoprolinemia

Women metabolize acetaminophen with sulfated amino acids like cysteine

- Cysteine is an essential amino acid in the production of glutathione

Oxoproline exclusively undergoes renal excretion

The ATP Depleting Futile 5-Oxoproline Cycle



CJASN

Michael Emmett CJASN 2014;9:191-200

Treatment

No defined treatment regimen

- Only clear treatment is cessation of acetaminophen
- N-Acetylcysteine is often used given the physiology of glutathione depletion
  - No proven benefit in humans, though mouse models have shown benefit
- Sodium bicarbonate is often given with no clear benefit

Our patient

- Acetaminophen was stopped
- Sodium bicarbonate for first 2 days
- N-acetylcysteine for first 4 days
- Anion gap remained elevated in the mid 20’s, though clinically she improved and was discharged after 10 days in the hospital


Anion Gap
35
30
25
20
15
10
5
0
Admission
7 days later
14 days later
28 days later

Take Home Points

1. Many cases of oxoprolinemia may go unrecognized due to limited availability of screening and lack of awareness
2. Consider oxoprolinemia in patients with unexplained anion gaps with CKD and chronic acetaminophen use
3. GOLDMARK

- A new mnemonic for High Anion Gap

References

GOLD MARK: an anion gap mnemonic for the 21st century. Ankit N. Mehta, Joshua B. Emmett, Michael Emmett Lancet. 2008 September 13; 372(9642): 892

Duewall JL, Fenves AZ, Richey DS, Tran LD, Emmett M. 5-Oxoproline (pyroglutamic) acidosis associated with chronic acetaminophen use. *Proceedings (Baylor University Medical Center)*. 2010;23(1):19-20.

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. *Clinical Journal of the American Society of Nephrology : CJASN*. 2014;9(1):191-200. doi:10.2215/CJN.07730713.

Thank You!