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


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

Remainder of exam was normal
Laboratory data

**ABG**
- pH: 7.24
- pCO2: < 20 mmHg
- pO2: 92 mmHg
- HCO3: 7
- CO2: 7

**Lactic Acid**: 1.0

**Anion Gap**: 31

Δ/Δ: 1.26

Baseline Creatinine: 1.30
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

**γ-Glutamyl Cysteine Synthetase (Step 1)**

```
H2N-\begin{array}{c}
\text{HO} \\
\text{CO} \\
\text{OH}
\end{array}
\begin{array}{c}
\text{HO} \\
\text{CO} \\
\text{OH}
\end{array}
\begin{array}{c}
\text{HO} \\
\text{CO} \\
\text{OH}
\end{array}
```

Glutamic Acid

```
\text{ATP} \quad \text{ADP} \quad \text{Pi}
```

```
\text{γ-Glutamyl Phosphate}
```

```
\begin{array}{c}
\text{HO} \\
\text{CO} \\
\text{OH}
\end{array}
```

```
\text{ATP Depleting 5-Oxoproline Futile Cycle}
```

```
\text{ATP} \quad \text{ADP} \quad \text{Pi}
```

```
\text{γ-Glutamyl Cysteine}
```

**γ-Glutamyl Cysteine Synthetase (Step 2)**

```
\text{H2N} \quad \text{HS} \\
\text{HO} \\
\text{CO}
```

Cysteine

```
\text{H2N} \quad \text{HO} \quad \text{OH}
```

5-Oxoproline

```
\text{H2N} \quad \text{HO} \quad \text{OH}
```

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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

- Admission
- 7 days later
- 14 days later
- 28 days later

Graph showing the Anion Gap over time with measurements taken at various intervals.
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


Thank You!