AN UNUSUAL CASE OF ACUTE LIVER FAILURE SECONDARY TO ACETAMINOPHEN TOXICITY

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OUTLINE

- Introduction
- Acetaminophen Metabolism
- Clinical Case
- Hospital Course
- Management
- Discussion
- Conclusion
INTRODUCTION

- Acetaminophen (APAP) is one of the most common OTC drugs
- Recommended maximum dose in adults: 4 g/day
- Recommended dose in patients with increased hepatotoxicity: 2 g/day
- 56,000 ED visits, 2,600 hospitalizations, and 450 deaths due to acute liver failure annually
ACETAMINOPHEN METABOLISM

2% excrete unchanged in urine

Glucuronidation
Sulfation

90%

5-9%

CYP 2E1

Excessive intake
Single overdose
Repeated overdoses

Excessive CYP activity
Fasting state
Drugs (CYP inducers)
Chronic alcohol ingestion
Genetic polymorphisms

NAPQI

NAPQI-protein adducts
Mitochondrial dysfunction
Oxidative stress
Sterile inflammation

GSH-dependent pathway

Naproxen and cysteine conjugates
(non-toxic metabolites)

Hepatocyte necrosis

Decreased capacity
for glucuronidation
or sulfation
Gilbert's disease

Glucuronide and Sulfate metabolites
(non-toxic metabolites)

GSH depletion
Chronic liver disease
Chronic alcohol ingestion
Malnutrition
CLINICAL CASE

• **CC:** Abdominal pain, N/V/D, generalized weakness, chest tightness

• **HPI:** 48 YOM PMH significant for alcohol abuse and opiate abuse, who presented to the ED with a 4 day duration of loss of appetite, abdominal pain, N/V/D, generalized weakness, and chest tightness.
  - Recent hospitalization at another facility requiring dialysis secondary to “taking too many pain pills and drinking too much alcohol”
CLINICAL CASE

• **PMH:** opiate abuse, alcohol abuse, anxiety

• **PSH:** None

• **Meds:** Xanax 1 mg PO BID

• **Allergies:** NKDA

• **FH:** No history of cancers, MIs, DVTs, or PTEs

• **SH:** 30 pack year tobacco history. Quit drinking 2 months ago. Heavy drinker and opiate abuse in the past
• **Physical exam:**
  - VS: T 99 °F, HR 108 bpm, BP 135/70, RR 26 bpm, O2 sat 97% on room air
  - General: AO x 3 with slurred speech and increased somnolence, no tremor
  - HEENT: Anti-icteric, normal conjunctiva, no signs of jaundice
  - Respiratory: CTAB, no increased work of breathing
  - CV: Tachycardic but regular rhythm
  - Abdomen: soft, nontender, nondistended, no signs of hepatomegaly or ascites
CLINICAL CASE CONT’D

- **Labs:**

  - UDS: + benzos
  - Urine alcohol level: 20 mg/dL
  - Acetaminophen level: 9.4 µg/mL
  - D-dimer: 2.03 mg/dL

- **CTA Chest:** pulmonary embolism in the right lower lobe

- **Ca:** 8.9 mg/dL
- **AST:** 20 u/L
- **ALT:** 28 u/L
- **Alk phos:** 86 u/L
- **T bili:** 0.2 mg/dL
<table>
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<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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<td><strong>ALT</strong></td>
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<td><strong>12,124</strong></td>
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<td><strong>APAP level</strong></td>
<td>9.4</td>
<td>30.1</td>
<td>7.8</td>
<td>5.4</td>
<td></td>
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Tylenol 325 mg tablet

NAC

NAC
MANAGEMENT

- Rumack-Matthew nomogram
- “200 line” or “probable toxicity line” – risk for developing severe hepatotoxicity
- “150 line” or “treatment line” – arbitrary 25% safety margin
Patient’s serum APAP level is plotted against the time interval from ingestion.
DISCUSSION

• Factors that influence APAP toxicity
  – Chronic alcohol ingestion
  – Medications that induce CYP2E1 (e.g., INH, rifampicin, phenobarbital, and St. John’s wort)
  – Medications that compete with hepatic glucorunidation (e.g., zidovudine and trimethoprim-sulfamethoxazole)
  – Gilbert Syndrome
  – Malnutrition
  – Fasting State
  – Chronic Liver Disease
  – Advanced Age
DISCUSSION

• NAC replenishes glutathione stores in APAP toxicity
  – Improves cerebral edema and hepatic clearance
  – Most effective within 8-24 hours

• Liver transplant still the cornerstone of ALF

• Challenges: reliability of the patient’s history
  – Patient repeatedly denied history of alcohol abuse
  – Unable to obtain outside hospital medical records
  – Difficult to determine what meds and how much patient used at home
CONCLUSION

• Obtaining an accurate history can present as a challenge at times

• Important to be aware of all risk factors for APAP toxicity, which include not only chronic alcohol abuse but also malnutrition, fasting state, and underlying liver disease
REFERENCES


QUESTIONS?