ACETAMINOPHEN POISONING
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Dean Filandrinos, PharmD
Associate Director
PROSAR
Clinical Assistant Professor
Dept off Experimental and Clinical Pharmacology
College of Pharmacy, Univ of MN

I. INTRODUCTION

Severe and potentially lethal hepatotoxicity can result from acetaminophen poisoning. The key to prevention of hepatotoxicity is early recognition of the high risk patient and prompt treatment with acetylcysteine. In adults and adolescents, hepatotoxicity may occur following ingestion of greater than 7.5 to 10 gms.--24 to 30 regular strength or 15 to 20 extra-strength capsules or tablets (i.e. 150 mg/kg). Fatalities occur in less than 3% of untreated cases and are unlikely with overdoses of less than 15 gms. Serious toxicity or fatalities are extremely infrequent in children possibly due to differences in the way they metabolize acetaminophen.

An acetaminophen plasma level is the most important parameter used to determine the risk of hepatotoxicity and therefore the need for n-acetylcysteine therapy. The Rumack/Matthew nomogram predicts risk of hepatotoxicity based upon measured plasma or serum acetaminophen concentration at a specified time post ingestion. The graph applies only to plasma levels following a single acute overdose obtained 4-24 hours post ingestion; levels drawn before 4 hours may not represent peak levels and therefore are not recommended.

N-acetylcysteine (NAC) is a safe and extremely effective antidote for acetaminophen poisoning. By sparing hepatic glutathione, NAC prevents hepatocellular necrosis. It appears that NAC is almost completely protective if given within 8 hours of acetaminophen ingestion, partially protective between 8 and 15 hours, and has even shown to have some effectiveness at 15 and 24 hours.

II. PHARMACOLOGY

Acetaminophen (APAP) is normally metabolized by the liver with 90% being biotransformed to either sulfate or glucuronide metabolites. These are non-toxic and are excreted in the urine. Approximately 4% of a dose is metabolized by the cytochrome P450 system to an active metabolite, NAPQI. Normally, NAPQI is detoxified by conjugation with glutathione and excreted. However, as glutathione stores are depleted due to the large amounts of APAP introduced, NAPQI accumulates and binds to hepatocytes resulting in cell necrosis.
III. PHARMACOKINETICS

Normal peak concentrations are achieved in 1 hour. **In an overdose, absorption may not be complete for up to 4 hours due to concretions or coingestants.**

IV. RANGE OF TOXICITY

Acute

- Ingestions of ≥150 mg/kg or 7.5 grams can potentially result in hepatic damage.
- Children may tolerate higher levels (up to 200 mcg/ml)
- High risk patients (e.g. chronic alcoholics, anorexics, patients on enzyme inducing drugs) may tolerate less although there is no data to predict at what dose these subgroups may become toxic.

Chronic

- Ingestions of several high therapeutic doses (e.g. 7.5-10 grams/day by an adult) for 1-2 days may lead to hepatic damage especially in the above mentioned high risk groups.
- Chronic supratherapeutic dosing can lead to hepatotoxicity especially in children with an already present illness

V. CLINICAL EFFECTS

There are 4 stages of APAP poisoning:

Stage 1 (0 - 24 hrs)

- Nausea, vomiting, pallor, lethargy
- Labs: LFTs, PT should appear normal. Abnormalities seen at this time would indicate an underlying pathophysiologic state or a later presentation. Serious overdoses can manifest LFT changes within 15 hours (e.g. transaminase elevations 2-3 times upper limit of normal). These cases typically present with very high acetaminophen levels (500 mg/l or greater) May also see mild elevations in PT.

Stage 2 (24 - 48 hrs)

- Signs and symptoms are less pronounced; may see RUQ pain
- Labs: can begin to see more pronounced increases in LFTs (transaminases > 1000) and PT at this time

Stage 3 (48 - 96 hrs)

- See peak abnormalities at this time including nausea, confusion, coma, jaundice, coagulopathies
- Labs: LFTs, PT usually peak at this time. AST can peak as high as 30,000 IU. Prothrombin times exceeding 25 seconds may be an indicator of impending encephalopathy.
Stage 4 (4 days - 2 weeks)
• The overwhelming majority of patients will recover fully and LFTs/PT will begin to decrease over this time and return to normal.
• Less than 1 % of patients go on to develop fulminant hepatic failure and death.

Other potential sequelae
• **Oliguric renal failure** can develop without concomitant liver failure. However, if liver failure does develop, renal failure will develop in about 70% cases.
• **Metabolic acidosis** occurring within 15 hours is a result of APAP effect on hepatic uptake of lactic acid. Acidosis developing after this is a result of decrease hepatic clearance of lactate and tissue hypoxia.
• **Hypoglycemia** can develop secondary to impaired gluconeogenesis, increased circulating insulin and inability to mobilize glucose stores.
• **Hypophosphatemia** may be secondary to renal losses
• Hemorrhagic pancreatitis, DIC, thrombocytopenia, myocardial necrosis

VI. DECONTAMINATION

Group 1 **Patients presenting within one hour of ingestion.**

1. Induce emesis with syrup of ipecac or perform gastric lavage.
2. Give activated charcoal with a cathartic.
3. Draw blood for a stat acetaminophen level at four hours following ingestion.
4. Initiate acetylcysteine therapy for any level on or above the lower line on the nomogram
5. Continue acetylcysteine treatment for any level on or above the lower line on the nomogram

Group 2 **Patients presenting one to four hours after ingestion.**

1. Do not evacuate the stomach unless other potentially toxic substances were ingested and delayed absorption is suspected.
2. Give activated charcoal with a cathartic.
3. Draw blood for a stat acetaminophen level at four hours following ingestion.
4. Initiate acetylcysteine therapy for any level on or above the lower line on the nomogram (see attached).
5. Continue acetylcysteine treatment for any level on or above the lower line on the nomogram (see attached).
Group 3  Patients presenting four or more hours after ingestion.

1. Do not evacuate the stomach or give activated charcoal unless other potentially toxic substances were ingested and delayed absorption is suspected.
2. Give the loading dose of acetylcysteine. If the time of ingestion is unknown, if more than 8 hours has passed since the ingestion occurred, or if a level cannot be obtained by 8 hours post ingestion.
3. Draw blood for a stat acetaminophen level.
4. Continue acetylcysteine treatment for any level on or above the lower line on the nomogram (see attached).

Pediatric Ingestions

1. Ingestions of >150 mg/kg presenting ≤ 30 minutes post ingestion should be given ipecac if no contraindications exist.
2. Ingestions of ≥150 mg/kg presenting >30 minutes post ingestion should be given activated charcoal if no contraindications exist and a 4 hour acetaminophen level drawn.

Chronic Ingestions

With ingestions of greater than 4 g/day chronically treatment with NAC should be considered if either:
1. The AST is elevated, or
2. There is any detectable APAP level and the patient is considered high risk for developing hepatotoxicity (e.g. chronic alcoholics, patients chronically on enzyme inducers). Starvation or fasting prior to chronic ingestion may increase the risk of hepatotoxicity (see Section IX below).

VI. TREATMENT

A. Serum APAP level

A single acetaminophen level drawn at least four hours post ingestion is sufficient for patient management. At least two additional acetaminophen levels drawn four hours apart for half-life determination may be useful in some patients especially when time of ingestion is uncertain. A half-life equal to or greater than four hours suggests potential for hepatotoxicity and therefore need for acetylcysteine treatment. In any case where the time of ingestion is unknown, a level should be attained. If there is a delay in obtaining a level of more than 8 hours after the ingestion or if the time is unknown, antidote therapy should be started. Rapid turn-around time is important.
Extended Relief Tylenol
With normal dosing the extended release preparations experience similar kinetics to the regular release forms with a peak occurring at less than 4 hour and with a lower maximal drug concentration. One study indicated that the pharmacokinetics do not change when a supratherapeutic dose of an extended relief formulation of APAP is ingested compared to regular APAP formulations. However, it is unknown what would happen when the dose ingested is more in line with the typical toxic ingestion. Given the potential for a differences in the kinetics in an overdose situation, obtaining 2 levels 4-6 hours apart post ingestion seems prudent. Either level on or above the dotted line of the nomogram should be treated and treatment recommendations listed below remain the same.

B. Plot level on the Rummack-Matthew nomogram

This is a semilogarithmic plot of the serum acetaminophen level over time (between 4 and 24 hours post ingestion). It contains two lines. It is estimated that approximately 60% of patients with levels on or above the solid line will develop elevated liver transaminases above 1000 IU/L. The second line was introduced after the initial nomogram was developed as a "safety net" that would take into account lab error, error in the time of ingestions, etc. There is no clinical research to date evaluating the need to treat patients in this "possible" toxicity range. Only 0.4% of patients whose level falls below the bottom line will develop toxicity although no fatalities have been reported.

- Treatment is to be initiated if the level is on or above this dotted line.

It should be noted that this nomogram's applicability to children is unproven as the test subjects used in development were all adults. Even its validity after 15 hours is uncertain. It was developed based on data from 30 adult cases, 10 of whom had ingested other agents and 4 of whom had alcohol as a coingestant.

C. Use of N-acetylcysteine (NAC) - (trade name - Mucomyst)

1. Mechanism of action
   a. NAC is converted to cysteine which is converted to glutathione
   b. NAC can substitute directly for glutathione and decrease NAPQI
   c. NAC can supply substrate for sulfation

2. Indications
   a. APAP level on or above the bottom dotted line of the nomogram, OR
   b. No level can be obtained in a reasonable time period and the potential for a toxic ingestion exists
   c. Presentation after 24 hours and symptomatic

3. Dosing NAC
   Loading dose: 140 mg/kg PO
   Maintenance dose: 70 mg/kg q 4 hours for 17 total doses
LOADING DOSE:

<table>
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<th>Body Weight (kg)</th>
<th>20% Mucomyst(ml)</th>
<th>Diluent(ml)</th>
<th>5% Solution (total ml)</th>
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<td>225</td>
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MAINTENANCE DOSE: one half amount used for loading dose (70 mg/kg).

**Use of NAC with Activated Charcoal**

NAC is adsorbed by AC but only to a minor degree. It is almost certain that the amount of NAC administered greatly exceeds that which is necessary to prevent hepatotoxicity. Because of this any small decrease in the bioavailability of NAC secondary to use of AC would be insignificant. Furthermore, since NAC is rapidly absorbed from the proximal bowel and the stomach, administering the NAC even an hour after administering AC would minimize any interaction.

**Late presenting ingestions (> 24 hours)**

Past studies have shown that the efficacy of NAC decreases as the time it is started post ingestion increases. After 24 hours it was thought that NAC had little role in therapy. Newer data would seem to indicate that NAC may be of benefit in ingestions presenting late who are symptomatic, and its use is now considered standard of practice in the patient with a history of a large ingestion and signs/symptoms. Possible mechanisms of action include increasing oxygen delivery via correction of a deficiency in endothelium derived relaxing factor and decreasing neutrophil accumulation in the liver.

**If the patient vomits the NAC dose,** the following may be attempted:

- Make sure product is diluted to 5%
- Use a nasogastric tube
  - NAC can be dripped in over an hour and/or the NG can be passed into the duodenum.
- Use an antiemetic:
  - Reglan (metoclopramide) - can administer up to 1 mg/kg slow IV over 1-2 minutes,
  - Zofran (ondansetron) - 0.15 mg/kg IV over 15 minutes, 30 minutes before NAC dose
- IV NAC

**There is no FDA approved IV product.** However, the oral product has been given IV in the past with success (this also is an unapproved use). There is the potential for adverse effects, e.g. anaphylactoid reaction. Premedicating with antihistamines and increasing the duration of the initial infusion time may help minimize problem in sensitive individuals. These reactions typically occur within the first hour of administration.
Note: Doses vomited within 1 hour of administration should be repeated.

**IV Protocol:**

**20 hour European Protocol**

150 mg/kg IV over 15 min, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours

D. Extracorporeal Methods

- At this time there is no evidence that forced diuresis, hemodialysis or hemoperfusion are of much benefit in early stages of the poisoning. However, in late stages (> 18-24 hours), hemodialysis or hemoperfusion may be an adjunct therapy worth consideration.

**VIII. MONITORING**

For patients at risk for hepatotoxicity, the following laboratory tests should be obtained on admission and at least daily for three days: CBC, platelets, prothrombin time, INR, glucose, electrolytes, SGOT, LDH, bilirubin, BUN, creatinine. Urinalysis should be done at the time of admission. In cases of severe hepatotoxicity, amylase should also be monitored.

**Prognostic factors in patients developing severe hepatic damage**

1. Prothrombin time (PT):
   - Patients in one study in which peak PT was less than 90 seconds survived in 80% of the cases. Only 8% survived when the peak PT was 180 seconds or greater.
   - In another study, an increase in the PT on day 4 was also a predictor of severe hepatic injury
2. Acid Base disturbances
   - In patients with a pH of less than 7.30 more than 24 hours after overdose, only 15% survived.
3. Plasma Creatinine
   - In 125 patients with fulminant hepatic failure developing plasma creatinine greater than 300 mmol/L, only 23% survived vs 65% survival if it was less than 100 mmol/L
4. Age of patient
   - Younger patients with fulminant hepatic failure have a higher chance of survival. Those aged 15-30 years had survival rate of 37% vs 24% for those age 50 or older.
IX. SPECIAL ISSUES

APAP and pregnancy
• Animal data would indicate that fetal hepatocytes are capable of oxidizing drugs fairly early in pregnancy. Because of this, toxic metabolites may be formed in an APAP ingestion. NAC does not appear to cause teratogenicity, and therefore it should be used in patients who are pregnant and present with toxic APAP concentrations. NAC does pass the placental barrier.

APAP and alcohol use
• Concurrent use of alcohol with an APAP ingestion has been shown to inhibit the function of the P450 enzyme system which may actually be beneficial to the patient. In patients with a history of chronic alcohol use however, the reverse holds true since in these patients, enzyme activity may be accelerated thus producing more of the NAPQI.

APAP and the use of other enzyme inducing drugs
• Enzyme inducers such as phenobarbital and phenytoin may increase NAPQI production in the same way chronic alcohol does. When presented with a patient who is also currently taking such medications, the nomogram may underestimate toxicity since these patients may be producing sufficient NAPQI to result in toxicity even at "non-toxic" serum APAP levels. Use of NAC even at concentrations below the bottom diagonal on the nomogram should be considered.

Chronic APAP Ingestions
• There is little information on what dosage or duration of administration would be considered toxic. Patients taking anticonvulsants and children with acute febrile illness seem to be at most risk. Use of NAC in these patients should be considered even at levels below the nomogram line although an exact range has not been established. There are almost no cases of chronic alcoholics developing hepatotoxicity when taking the recommended 4 g/24 hours of APAP. However in this subgroup they are more likely to take more of the drug as well as have poor diets (see "Fasting" below).

Fasting and APAP toxicity
• Fasting has been shown to be associated with the development of hepatotoxicity when chronic dosing of greater than 4g/day occurred. This may be due to the body shunting metabolism from glucuronidation to microsomal oxidation thus increasing the product of NAPQI. Chronic alcoholism could potentiate this effect due to induction of microsomal enzymes.
References