Acetaminophen Toxicity: The Pharmacist's Role in Prevention and Treatment

**Event Type**
Live Online

**ACPE Expiration Date**
3/5/2016

**Credits**
1 Contact Hour

**Target Audience**
Nurses, Pharmacists, Pharmacy Technicians

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**Program Overview**
Acetaminophen toxicity is the leading cause of acute liver failure in the United States. The misuse of this common analgesic causes 56,000 emergency department visits, 26,000 hospital admissions, and 500 deaths each year. Pharmacists can play a vital role in preventing toxicity by educating patients about the safe use of acetaminophen. As members of the health care team, pharmacists should be knowledgeable of the indications and proper administration of acetylcysteine for the management of acetaminophen-induced hepatotoxicity.

**Nurse Educational Objectives**
- Describe reasons why acetaminophen overdoses occur
- Discuss the clinical presentation and treatment of acetaminophen overdoses
- List steps taken by the FDA and the pharmaceutical industry to prevent acetaminophen toxicity

**Pharmacist Educational Objectives**
- Describe reasons why acetaminophen overdoses occur
- Discuss the clinical presentation and treatment of acetaminophen overdoses
- List steps taken by the FDA and the pharmaceutical industry to prevent acetaminophen toxicity
- Identify strategies that pharmacists can apply to prevent acetaminophen overdoses

**Pharmacy Technician Educational Objectives**
- List symptoms of an acetaminophen overdose
**Activity Type**
Knowledge

**Accreditation**

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**Faculty**

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Toxicology Specialist, Maryland Poison Center

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Pharmaceutical Education Consultants, Inc.

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Acetaminophen Toxicity: The Pharmacist’s Role in Prevention and Treatment

Accreditation
Pharmacists: NABP-BUX-0798-0000-13130-L05-P
Pharmacy Technicians: NABP-BUX-0798-0000-13030-L05-T
Nurses: NABP-BUX-0820-0000-13010-L05-P

Faculty Disclosure
Dr. Booze has no actual or potential conflicts of interest in relation to this program.

Learning Objectives
• Describe reasons why acetaminophen overdoses occur
• Discuss the clinical presentation and treatment of acetaminophen overdoses
• List steps taken by the FDA and the pharmaceutical industry to prevent acetaminophen toxicity
• Identify strategies that pharmacists can apply to prevent acetaminophen overdoses

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Acetaminophen – each year...

• ~ 25 billion OTC doses
  – Pediatric tablets and liquids
  – Adult strength tablets, liquids
  – Cough and cold meds
  – Other combinations (ASA, diphenhydramine…)
• ~ 200 million acetaminophen-containing prescriptions
  – most in combination with an opioid

Acetaminophen – each year...

• >78,000 emergency room visits
• ~500 deaths
  – 69.8% self-directed violence
  – 16.7% therapeutic misadventures
  – 13.4% unintentional ingestions by children < 6

Acetaminophen Overdoses

- A 2 year old is found with an empty bottle of children’s acetaminophen and red liquid around her mouth
- A 4 year old is given acetaminophen-containing OTC products by Mom, Dad and babysitter
- A 16 year old boy ingested 50 acetaminophen extra-strength tablets in a suicide attempt
- A 62 year old man with worsening back pain has been taking Vicodin (8-10 tablets/day) and extra strength acetaminophen (12-16 tablets/day) for a few weeks

Acetaminophen-Induced Liver Failure

- 662 acute liver failure patients at 22 centers from 1998-2003
  - 42% due to acetaminophen
    - 1998: 28% due to APAP
    - 2003: 51% due to APAP
  - 48% of APAP cases were unintentional OD’s!
    - 63% were APAP/narcotic combinations
    - 38% took ≥ 2 APAP products

Acetaminophen-Induced Liver Failure (Acute Liver Failure Group)

- Acute liver failure patients at 23 transplant centers over 10 years
- ~50% due to acetaminophen
- 50% of acetaminophen cases were unintentional OD’s
  - 55% - only OTC’s taken
  - 29% - only acetaminophen/narcotic combinations
  - 15% took OTC + Rx products


- Acetaminophen/Opioid cases: 500% increase in severe injuries
- Acetaminophen alone: 134% increase in severe injuries
Reasons for Overdoses - Children

- Unintentional ingestions
- Therapeutic errors
  - 40% of parents & caregivers determined the correct weight-based dose of acetaminophen
  - 65% of parents said they gave "Tylenol" to a child but only 8% said they used "acetaminophen"
  - Turn to adult products if pediatric products are not available in the home

Reasons for Overdoses/Toxicity - Adults

- Intentional overdose
- Prescription drug abuse
- Intentional excessive dosing for pain
- Therapeutic errors
  - 500 interviewed: 23.8% would take more than 4 g/day; 45.6% would take 2 products containing acetaminophen

Acetaminophen: Metabolism

- Glucuronide
- Sulfate
- Glutathione
- NAPQI
- Hepatocyte

Toxic Doses

- Acute Ingestion
  - ≥ 200 mg/kg or 10g (whichever is less)

- Chronic Ingestion
  - For 24 hours: ≥ 10 g or 200 mg/kg, whichever is less
  - For > 48 hours: ≥ 6 g/day or 150 mg/kg/day, whichever is less
  - If risk factors: ≥ 4 g/day or 100 mg/kg/day, whichever is less

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Risk Factors for Toxicity

- pre-existing liver disease
- chronic alcoholism
- malnutrition
- starvation (prolonged fasting)
- chronic use of CYP2E1 inducing drugs
  - e.g. phenobarbital, isoniazid, rifampin, carbamazepine

APAP Toxicity: Clinical Course

**Phase 1 (0-24 hours)**
- No hepatic injury yet
- Nausea, vomiting, anorexia
- Diaphoresis, lethargy, malaise
- Normal AST, ALT, bili, INR

**Phase 2 (24-72 hours)**
- Onset of hepatic injury
- Improvement of GI SXS
- RUQ pain & tenderness
- Increased AST, ALT, bili, INR

**Phase 3 (3-5 days)**
- Jaundice, coagulopathies, coma, encephalopathy
- Metabolic acidosis
- Renal failure
- Peak AST, ALT, bili, INR

**Phase 4 (5 days to 2 wks)**
- Resolution of hepatic injury
- Recovery phase

Acute Acetaminophen Overdose Nomogram

- ≥ 4 hours post ingestion
- Repeat 4 hours later
- Treat if either is above treatment line
- Units: mcg/mL
- Only used for acute overdoses; must know time of ingestion

Chronic Acetaminophen Overdose

- A 28 year old male, with a history of hepatitis C and alcohol abuse, presents to the ED with RUQ pain and vomiting for 2 days
- He has been taking 6 grams of acetaminophen/day for 2 weeks
- His AST and ALT are 360 u/L and 489 u/L respectively
- APAP level is 35 mcg/mL
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### Acetylcysteine

- Glutathione precursor and substitute
- Provides sulphydryl groups for sulfate conjugation
- Antioxidant
- Indicated if toxic acetaminophen level, history of ingestion, acetaminophen-induced hepatotoxicity, or unexplained elevated AST/ALT
- Delay in administration decreases effectiveness

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### Oral Acetylcysteine

- 140 mg/kg po load; 70 mg/kg po q4h X 17 doses
  - 1330 mg/kg over 72 hours
- Shorter course might be OK for some patients
- Dilute to 5% solution
- Adverse effects: nausea, vomiting
  - Repeat dose and give antiemetics if patient vomits within one hour

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### Discontinuing Acetylcysteine Too Soon

- 78 yo ingested 96 x 500 mg acetaminophen tablets. Concentration at 2.25 hours was 264 mcg/mL
- IV acetylcysteine started at 5 hours post ingestion, continued for 21 hours then discontinued despite an acetaminophen concentration of 116 mcg/mL
- Hepatotoxicity, coagulopathy, renal injury
- Acetylcysteine restarted 24 hours after it was discontinued; recovered and discharged on day 12

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### Intravenous Acetylcysteine

- 300 mg/kg over 21 hours
  - Loading dose: 150 mg/kg IV over 1 hour
  - 1st maintenance dose: 50 mg/kg IV over 4 hrs
  - 2nd maintenance dose: 100 mg/kg IV over 16 hrs
- Adverse effects: flushing, urticaria, angioedema, respiratory distress, hypotension
- >21 hours of therapy sometimes needed
  - Continue if + acetaminophen level or liver function tests not improving

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**IV Acetylcysteine Errors**

- 66 patients in UK
  - <40% had acetylcysteine concentrations within 10% of intended concentration
  - Concentrations from 0%-305% of intended concentration
  - 9% varied by >50% of intended concentration
- 221 patients receiving IV acetylcysteine
  - 33% administration errors (delays in hanging bags, calculation errors, inappropriate use...)

**IV Acetylcysteine Overdoses**

- mL/kg instead of mg/kg
  - Hypotension, hemolysis, hemolytic uremic syndrome
- 50 mg/kg/hr instead of over 4 hrs; 100 mg/kg/hr instead of over 16 hours
  - Delirium, cerebral edema, seizures, brain injury

**FDA Actions**

- 1998: required all OTC acetaminophen products to include an alcohol warning.
- 2002: Committee recommended liver toxicity warning on labels and consumer education
- 2004: public education campaign launched
- 2004: letters to state boards of pharmacy to consider requiring “acetaminophen” instead of “APAP”; avoid concurrent use of other drugs with acetaminophen...
- 2006: proposed regulations to clearly identify acetaminophen as an ingredient

**FDA Advisory Committee Recommendations - June 2009**

- Single dose: 650 mg max
- 500 mg tablets: Rx only
- Decrease max daily dose from 4000 mg
- Rx combination products eliminated or black box warning
- Unit dose packaging for Rx products
- One OTC liquid concentration
FDA Actions

- **2009**: “acetaminophen” on front of OTC packages
- **January 13, 2011**: FDA limits Rx products to 325mg
  - Boxed warning
  - 3 years to comply
- **May 2011**: FDA advisory panel; Pediatric products
  - Label infant acetaminophen products for fever only
  - Weight-based dosing for children >6 months
  - Packaging changes to prevent unintentional ingestions
  - Clearly labeled measuring device
  - Solid dosage forms in one concentration

Other Actions

- **May 2011**: Manufacturers agree to limit liquid pediatric acetaminophen products to 160 mg/5 mL, eliminating infant drops (80 mg/mL)
- **July 2011**: McNeil lowers maximum daily dose of 500 mg Tylenol to 6 tablets (3000 mg)
  - Max daily dose of 325 mg tablets = 3250 mg
  - Max daily dose of 650 mg tablets = 3900 mg

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Other Actions

- **July 15, 2010**: National Association of Boards of Pharmacy recommends that state boards of pharmacy prohibit the use of “APAP” on labels
- **2011**: National Council for Prescription Drug Programs (NCPDP) recommends to spell out all active ingredients on acetaminophen-containing Rx labels
  - Also: adopt a standard concomitant use and liver warning label
- **Jan 2013**: NCPDP reports that at least 45% of U.S. retail market have implemented; soon to be 75%

Why Not Make 500 mg Tablets Rx Only?

- Little evidence that it would reduce the number of cases of liver toxicity
- Might take 3 or more 325 mg tablets instead
- Would more toxic meds be used instead?

*Why Not Limit the Size of Extra Strength Packages?*

- UK: packages of 16 (non-pharmacy) or 32 (pharmacy)
- Little or no reduction in liver failure cases
- Inconvenient and costly
What Can Pharmacists Do?

- Do not use “APAP” or “ACET” on labels
- Use warning labels for concomitant use and liver
- Check patient profiles for multiple sources of acetaminophen – alert patients and alert physicians
- Look for potential interactions with drugs that induce CYP450
- Watch for opioid tolerance and increased usage of Rx combination products
- Warn about acetaminophen toxicity if chronic alcohol intake or liver dysfunction
- In-store signs, flyers, etc

What Can Pharmacists Do?

Educate Patients!

- Carefully read all drug labels to see if they contain acetaminophen (cough and cold meds too!)
- Never give or take more than one OTC medicine containing acetaminophen
- Avoid OTC acetaminophen products if taking Rx meds with acetaminophen
- Do not take more than is recommended; an acetaminophen overdose is a medical emergency that can result in liver damage or death

Resources

- KnowYourDose.org
  – Acetaminophen Awareness Coalition
- FDA.gov
- GetReliefResponsibly.com
  – McNeil
- Talkaboutrx.org & MustForSeniors.org
  – National Council on Patient Information & Education
- OTCSafety.org
  – Consumer Healthcare Products Association
- NCPDP.org
  – National Council for Prescription Drug Programs

What Can Pharmacists Do?

Educate Patients!

- Give the proper dose for the child’s weight and age
- Measure liquids accurately; use the given dosing device
- Store safely away from small children
- Advise parents to discard infant drops

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