



Medical Assistance Division Medicaid Drug Utilization Review Newsletter

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HUMAN
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Acetaminophen Toxicity Felice R. Slaughter RPh.

Introduction

One of the most commonly used analgesic/antipyretic medicines in the United States is acetaminophen. IMS data reveals that nearly 25 billion doses of acetaminophen are sold in the United States every year.¹ In addition, an excess of 200 million prescriptions containing acetaminophen are dispensed annually. Acetaminophen is a favorable choice with providers because of its low side effect profile, low cost and over-the-counter convenience. The safety and efficacy is well documented when used according to label directions. There has been some overdose toxicity that has led to acute liver failure. This injury to the liver from acetaminophen overdose has become a serious public health problem. Regulatory and educational efforts have increased to improve the safe use of medicines that contain acetaminophen.

Pathophysiology of Acetaminophen Toxicity:

When acetaminophen is ingested in therapeutic amounts, approximately 90% of the parent compound undergoes a combination of sulfate and glucuronide conjugation.⁴⁻⁷ These conjugates are eliminated as nontoxic metabolites. The remaining is excreted in urine. A small amount of acetaminophen is metabolized by the cytochrome P450 system, primarily by the enzyme CYP2E1, resulting in the highly toxic metabolite, N-acetyl-p-benzoquinone imine. Endogenous glutathione in the liver serves as a substrate for the toxic metabolite, and this combination produces a nontoxic metabolite called mercapturic acid. This metabolite is excreted in the urine.

Overdose occurs when the normal metabolic pathways become saturated and more acetaminophen is pushed through the P450 system. This results in more N-acetyl-p-benzoquinone imine production and the depletion of glutathione. The increase in N-acetyl-p-benzoquinone imine binds to hepatocytes causing cellular toxicity. This results in hepatic necrosis.

Liver disease is considered any disturbance of liver function that causes illness. The critical functions within the body managed by the liver will cause significant damage to the body if liver disease occurs. Liver disease can be life-threatening and demands urgent medical care. Most often, liver failure occurs gradually over time. Examples of acute liver failure include acetaminophen (Tylenol[®]) overdose, viruses like hepatitis A, B and C, reactions to certain prescription medications, and ingestion of poisonous mushrooms.

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Inside This Issue

• Acetaminophen Toxicity

Clinical Symptoms/Diagnosis:

Acetaminophen overdose occurs when someone takes more than the normal or recommended amount of this medication. The American Association of Poison Control Centers reports that acetaminophen overdose has become one of the most common pharmaceutical poisonings in the last 8 years.²

Acetaminophen is often considered very safe, but if taken in large doses may be deadly. The daily dose of acetaminophen should not be more than 4,000mg a day.

The symptoms of acetaminophen overdose are abdominal pain, appetite loss, coma, convulsions, diarrhea, irritability, jaundice, nausea, sweating, upset stomach and vomiting. The symptoms may not occur until 12 or more hours after the acetaminophen is swallowed.

Overdose Definitions:

Overdose of acetaminophen is classified as 1) acute acetaminophen overdose and 2) chronic acetaminophen overdose⁹. Acute acetaminophen overdose is ingestion of a toxic amount of acetaminophen within a period of time of 8 hours or less. A toxic amount of acetaminophen would be 7.5 grams to 10 grams (24 regular-strength tablets or 15 extra-strength tablets). A chronic overdose is the repeated ingestion of a toxic amount of acetaminophen over more than 8 hours.

A management approach is needed to achieve optimal outcomes following an acetaminophen overdose. Medical providers should evaluate any person that has ingested a toxic dose of acetaminophen, including estimation of the quantity and dosage form ingested along with any other substances ingested. There should also be consideration to use the FDA-approved treatment of acetylcysteine (Acetadote[®], Mucomyst[®], Mucosil[®]). Any person presenting with an unknown amount of acetaminophen ingested should have a serum acetaminophen level drawn and should be treated with acetylcysteine³.

Concurrent Use of Other Acetaminophen-Containing Products:

There are hundreds of prescription and nonprescription medications which contain acetaminophen. Patients can unknowingly overdose on acetaminophen when nonprescription pain relief products, cough and cold products and prescription medications are taken concurrently. A list of these medications can be found at KnowYourDose.org or <http://www.knowyourdose.org/common-medications>.

Prevention and Education:

Medical providers and pharmacists must take an active role in education of patients about acetaminophen. Although acetaminophen can be purchased without medical supervision, consumers are not aware of the risk associated with acetaminophen use. It is important to be proactive with education about acetaminophen and the more than 600 different products that contain it. This makes reading labels of nonprescription and prescription medications important. Consumers should understand that acetaminophen is a safe and effective medication when used properly, but that any ingestion beyond the maximum daily dose could result in a grave condition.

McNeil Laboratories, the manufacture of Tylenol, provides free pediatric and adult patient education handouts on the proper use of acetaminophen. The topics of discussion are proper uses in the following areas:

- Pediatric Dosage and Proper Use · Fever · Otitis Media · Pediatric Cold and Flu
- Infant Crying and Gas · Teething · Sport Injuries · Skin Care · Cold and Flu
- OA Management · Pain · Sleeplessness

The handouts are available in different languages. Providers can create an account and register to order consumer handouts on a quarterly basis at this website:

<https://www.tylenolprofessional.com/user/signin.html>.

Conclusion:

Acetaminophen is a commonly used analgesic and fever reducer, but can lead to serious liver toxicity with improper use. There has been an increase in life-threatening liver injury from the over use of acetaminophen. The FDA has provided literature to limit exposure to high-dose acetaminophen. Consumer education should remain a priority in this matter due to the number of over-the-counter medications containing acetaminophen. Consumers should be able to identify products that contain acetaminophen with labels that are easier to read, and patients need to avoid taking multiple medicines containing acetaminophen.

The Safe Use Initiative continues to work with the Acetaminophen Best Practices Task Group to encourage adoption and adherence to their recommendations. These groups recommend the following:

1. Complete spelling of acetaminophen on pharmacy labels.
2. Eliminate use of abbreviations or other shortened versions of active ingredients.
3. Add a liver warning label to pharmacy containers.

Initiatives will continue to remain active to help decrease the overdose of acetaminophen-containing medicines.

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To report medical fraud, contact the Medicaid Quality Assurance Bureau. NMMedicaidFraud@state.nm.us or (505) 827-3100. We appreciate your continued support of our efforts to encourage quality care for our Medicaid clients.

Questions and/or comments about this newsletter may be directed to Diana Moya, R.Ph. at (505) 827-3174 or DianaJ.Moya@state.nm.us. DUR newsletters are posted on the New Mexico Human Services Department website: <http://www.hsd.state.nm.us/providers/utilization-review.aspx>.



Acetaminophen Toxicity Prescriber Response Form

We would greatly appreciate if you would answer the following questions and return it fax to: 804-644-4241. Thank you for your professional consideration.

1. What is your area of practice?

A. General Family Practice

B. Pediatrician

C. Psychiatrist

D. Specialty Please specify: _____

2. Did you find this newsletter to be informative?

A. Yes

B. No

3. Did the information affect the way you practice?

A. Yes

B. No

Please share any drug topics suggestions you would like to address by a newsletter.
