

FDA Advisory Committee Considers New Warnings and Proposed Changes to Acetaminophen Products

On June 29-30 2009 the FDA convened a Joint Meeting of the Drug Safety and Risk Management Advisory Committee to address the continuing public health problem of liver injury related to the misuse of acetaminophen in both over-the-counter (OTC) and prescription (RX) products. The convening of this advisory committee to study this important issue is only the latest in a long list of past efforts starting in the late 1990s to try and alert the public and medical personnel of the dangers of liver injury due to excessive doses of acetaminophen.

Acetaminophen is one of the most commonly used drugs in the United States with a reported 28 billion acetaminophen containing products purchased by consumers in 2005. When utilized appropriately, acetaminophen is considered a safe medication, especially because it lacks the gastrointestinal, renal and bleeding adverse effects seen with non-steroidal anti-inflammatory agents. Unfortunately, acetaminophen's reputation for safety may be one of the very factors that contribute to its misuse by patient and provider alike. It can also lead many patients to delay seeking medical advice when the signs of overdose first occur.

Acetaminophen is hepatically metabolized with 90% of the acetaminophen dose changed into water soluble conjugates that are eliminated in the urine. However, a small amount is metabolized into a hepatotoxic metabolite (NAPQI) which requires binding to glutathione for safe elimination. In cases of misuse or overdose glutathione stores are rapidly depleted and NAPQI is not detoxified. In these situations NAPQI binds to hepatocytes causing hepatotoxicity. Glutathione stores can be replaced from dietary sources (e.g. fruits and vegetables) or from drugs, such as the antidote for acetaminophen poisoning, n-acetylcysteine.

There are a number of risk factors for acetaminophen-induced hepatotoxicity. These result from a reduction in glutathione body stores and include malnutrition due to prolonged fasting, gastroenteritis, chronic alcoholism, or HIV disease. In addition, a number of medications (e.g. ethanol, isoniazid, rifampin, phenytoin, barbiturates and carbamazepine) can actually increase the production of NAPQI and therefore increase the risk of hepatocellular injury. **Acetaminophen is the most common cause of acute liver failure in the United States** with a reported 56,000 emergency room visits, 26,000 hospitalization, and **458 deaths** as a result of acetaminophen overdoses from 1990 to 1998.

The majority of acetaminophen overdoses is unintentional and occurs for a number of reasons:

- **Some individuals may be especially sensitive to liver injury from acetaminophen** and therefore the maximum safe dose may not be the same for all individuals. For example, those persons with existing liver disease or who consume excessive amounts of alcohol may have decreased tolerability to the toxic effects of the NAPQI metabolite.
- There is a **wide array of both OTC and prescription products containing acetaminophen**, in different dosage forms, for a variety of medical indications. For example, it is possible for a patient to take acetaminophen in the form of a prescription pain reliever, night time sleep aid, and allergy medication all at the same time.
- Compounding acetaminophen's identity crisis is the fact that it can sometimes be **difficult to identify acetaminophen as an ingredient**. Prescription pain relievers frequently contain acetaminophen in addition to a more potent opioid agent and label acetaminophen as 'APAP'. Many patients are still unaware of that abbreviation and may accidentally consume additional acetaminophen containing OTC products.
- **Multiple products exist for children containing different strengths**. For example, liquid acetaminophen formulations intended for use in infants are typically more concentrated to allow for proper dosing in a small volume. Failure to distinguish between the two strengths of liquid can result in an accidental overdose when utilized in older children.
- The **association between acetaminophen and liver injury is not common knowledge**. Consumers are not sufficiently aware that acetaminophen can cause serious liver injury and their perceptions may be influenced by the marketing of the products and the current labeling on OTC products is often overlooked.

In preparation for the advisory committee meeting in June 2009, the FDA developed a number of **potential options** to address the issue of acetaminophen toxicity. These options include:

- **Reduce the current dose recommendations for maximum adult daily dose and single adult dose.** Due to acetaminophen's narrow therapeutic range it has been proposed that maximum single dose should be lowered to 650mg (rather than 1,000mg) and the maximum daily adult dose would be 3,250mg (instead of the current 4,000mg). For this option, currently available products would have to be reformulated to a maximum dose of 325mg per tablet or liquid dosage form.
- **Clarify dosing for alcohol users.** It is proposed that acetaminophen labeling also include a statement that people who consume three or more alcoholic beverages daily should use less than the maximum daily dose unless a specific dose is recommended by their healthcare provider.
- **Establish package size limits for OTC acetaminophen products.** To make it more difficult to obtain a large number of doses at one time, it has been proposed that each OTC package contain a smaller number of doses and limit the amount of acetaminophen that can be purchased by a consumer in a single visit.
- **Require prescription products to be packaged in units of use.** Unit of use packaging would contain standardized information including warnings and the word 'acetaminophen', (instead of the abbreviation 'APAP') in addition to a Medication Guide attached to each package.
- **Expand the warning information on acetaminophen-containing prescription products.** Acetaminophen-containing products would include the highlighted or bolded ingredient name 'acetaminophen' and a specific warning about hepatotoxicity on the carton or outer container. It is proposed that similar warnings be included for prescription acetaminophen-containing products as well.
- **Eliminate OTC and possibly prescription acetaminophen-containing combination products.** Due to the fact that consumers are not always aware of acetaminophen content in combination products purchased without a prescription, it has been proposed that OTC acetaminophen be available only as a single ingredient.
- **Limit dose formulations for OTC liquid preparations.** It has been proposed that OTC acetaminophen be marketed in a single strength. Other proposed safety measures would require pediatric dosing instructions for children younger than two years of age and would require each package of acetaminophen to contain a properly calibrated measuring spoon or container which is marked for correct product dosing.

Acetaminophen related liver toxicity continues to represent a significant healthcare safety issue despite ongoing efforts by the FDA and other healthcare quality improvement organizations. Medical providers can play an important role in educating their patients to the dangers and appropriate use of this ubiquitous medication. Some of the more important issues to discuss with your patients include:

- First of all, **patients need to be made aware of the dangers of acetaminophen overdose.**
- **Remind patients that acetaminophen comes in many forms** and are used in combination preparations for treatment of a variety of different complaints so they should always review the package labeling carefully before use.
- Describe how **early symptoms of acetaminophen overdose can mimic a 'flu-like illness'** and that if acetaminophen toxicity is suspected the nearest poison center should be contacted to determine if medical treatment is needed.
- **Calculate the possible total daily dose of acetaminophen from a prescription pain reliever.**
- **Parents of small children should be instructed to utilize proper measuring devices for liquid acetaminophen-containing products** and to be aware of the differing concentrations of these products.

Medical providers are asked to monitor their patients carefully for unusual signs and symptoms while taking acetaminophen containing products and to report all suspected adverse drug reactions to the **FDA's MedWatch Program** by phone at 800.FDA.1088, by fax at 800.FDA.0178, by mail at MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, M.D. 20852-9787, or on the MedWatch Web site at www.fda.gov/medwatch.

References:

1. U.S. Food and Drug Administration. June 29-30, 2009: Joint meeting of the Drug Safety and Risk Management Advisory Committee with the Anesthetic and Life Support Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee: Meeting Announcement May 2009, Accessed on 8/25/2009 at: <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm143083.htm>
2. U.S. Food and Drug Administration. FDA Requires Additional Labeling for Over-the-Counter Pain Relievers and Fever Reducers to Help Consumers Use Products Safely. 4/28/2009, Accessed on 8/25/09 at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149573.htm>
3. U.S. Food and drug Administration. Questions and Answers on the Final Rule for Labeling Changes to Over-the Counter Pain Relievers. 5/1/09. Accessed on 8/25/09 at: <http://www.fda.gov/Drugs/NewsEvents/ucm144068.htm>
4. O'Mara, Neeta Bahal. New Warnings and proposed Changes to Acetaminophen products. July 2009. Accessed on 8/25/09 at <http://www.pharmacistsletter.com>
5. Foxhall, Kathryn. WebMD. FDA may restrict Acetaminophen. 7/1/09. Accessed on 8/25/09 at: <http://webmd.com/pain-management/news/>.