Commentary

Liver Toxicity At Normal Doses Of Acetaminophen

By
Donald Harvey Marks, M.D., Ph.D.

[Dr. Marks (DHMarks@NNCS.net), is a board-certified internal medicine physician, with an active hospital-based clinical practice. He the former Associate Director and Director of Clinical Research at several international pharmaceutical and vaccine manufacturers, and consults on pharmaceutical toxicity issues. Copyright 2006 by the author. Replies to this commentary welcome.]

What Acetaminophen Is

Acetaminophen is an analgesic (pain reliever) and anti-pyretic (controls fever) medication that is sold over-the-counter — without a prescription. More than 200 pain relievers and cold remedies under various trade names, including Tylenol, contain acetaminophen.

Two other classes of medication are also both analgesic and anti-pyretic, and in addition are also anti-inflammatory (they reduce inflammation):

- NSAID — Non-Steroidal Anti-Inflammatory Drugs. NSAIDs include aspirin, ibuprofen and naproxen.

- COX-2 inhibitor — a drug that counters an enxyme in the human body (Cyclo-oxygenase) invloved in biochemical reactions that cause pain). COX-2 inhibitors include Vioxx, Celebrex, and Bextra.

How Acetaminophen Is Different From NSAIDs And COX-2 Inhibitors

Acetaminophen differs from NSAIDs and COX-2 inhibitors in that it is not anti-inflammatory. Although considered relatively non-toxic and taken by as many as 100 million Americans each year, a number of acetaminophen-related liver injuries and deaths are reported every year to poison control centers. These include cases of accidental overdose, but also cases of what we call "adverse effects."

We discuss below the initial symptoms of toxic dose ingestion. These can at first seem minimally serious, and can occur at normal doses, but they can be quite deceiving and after several days can progress to irrevocable liver failure and death.

How Acetaminophen Works And How It Can Poison

The liver converts most acetaminophen to inactive compounds by conjugation (joining) it with sulfate and glucuronide. Only a small portion of acetaminophen is usually not modified, and this is metabolized in what's called the cytochrome P-450 enzyme system. The cytochrome P-450 system oxidizes acetaminophen to produce a highly reactive, intermediary metabolite called N-acetyl-p-benzo-quinone imine (NAPQI). Under normal conditions, the liver detoxifies NAPQI by conjugation with glutathione.

If more acetaminophen is ingested than the body can detoxify, the sulfate and glucuronide pathways become *saturated*. When this happens, more acetaminophen is shunted to the cytochrome P-450 system, producing more of the toxic NAPQI. If hepatocellular supplies of glutathione run out, the toxic NAPQI is left free to react with molecules in the liver cell membrane. This can result in in widespread hepatocyte (liver cell) damage and may lead to acute hepatic necrosis (liver death).

[Animal studies have shown that 70% of hepatic glutathione must be depleted before hepatotoxicity occurs.]

We commonly use the Rumack, Matthew (1984) nomogram to access the risk of liver injury from acetaminophen toxicity. This takes into account the time that has passed since the last acetaminophen ingestion and the current plasma level of acetaminophen. The clinical course after a toxic ingestion typically follows four stages.

- **Stage 1** occurs 12-24 hours after ingestion. Symptoms can include nausea, vomiting, diaphoresis, and anorexia. Children frequently have episodes of vomiting, even without toxic levels. Those patients with plasma levels of acetaminophen in the toxic range have a mean onset of symptoms by six hours, with 100% showing symptoms by 14 hours. Laboratory studies (liver enzyme elevation as a measure of liver inflammation, clotting time as a measure of hepatic synthetic capacity) are typically normal during Stage 1.

- **Stage 2** occurs 24-48 hours post ingestion. By that time, symptoms may have decreased but laboratory abnormalities indicative of liver injury begin to appear, with a rise of liver enzymes (AST and ALT), bilirubin, and prothrombin time.

- **Stage 3** occurs between 48-96 hours post-ingestion and is when the peak abnormalities are seen, with AST levels as high as 30,000. An AST level in excess of 1,000 is generally thought to be a marker of acetaminophen hepatotoxicity. Fortunately, less than 1% of patients in Stage 3 will develop fulminant hepatotoxicity.

- **Stage 4** occurs during the first week after ingestion, with hepatic abnormalities returning to near normal by 7 or 8 days.

Early therapeutic intervention for acetaminophen toxicity is crucial for survival, but because the symptoms and liver damage lag ingestion time, a number of unfortunate persons do not have their symptoms immediately recognized, and do not receive appropriate therapy for a number of days.

Problems With Labeling

Acetaminophen is hepatotoxic if taken in overdoses, and for adults, more than 7.5 - 10g/d are considered an overdose (2002 FDA Advisory Meeting). The currently recommended maximal therapeutic dose is 4 g/d; however, instructions for use are often confusing. One product states that up to two 500 mg extra strength tablets can be taken every 4-6 h as required, but not more than 4 g/d. If the condition for which acetaminophen is taken extends over more than 18 hr, even with the longer (every 6 hr) interval, there is a chance to go over the recommended daily dose even by following the dosing recommendations. One gram (two 500 mg tablets) at the start of the therapy, 1g at 6 hr, 1g at 12 hr, 1g at 18 hr and finally a dose at 24 hr, equals a total of 5 g in a 24 hr period. If taken every 4 hours, the total if taken according to directions, but not limiting to a max dose per day, can total up to 7 g/d. This by itself would not necessarily become a clinical problem if toxicity would really start at a total 24 hour ingestion of 7.5 – 10g. However, there have been several reports where doses between 4 – 7.5g/d have been associated with hepatoxicity and fulminant hepatitis.

For a drug with a narrow dosing margin of safety, an overdose could be considered simply not much more than the recommended dose. By labeling liver toxicity at minimally elevated doses of acetaminophen as due to an "overdose," the impression is created that the toxicity is the predictable effect of an overdose rather than the more problematic consequence of high-normal acetaminophen doses.

It is more reasonable, from a medication safety standpoint, to conclude that the therapeutic window for acetaminophen may be much smaller than claimed.

Watkins, et al (2006) studied 145 healthy volunteers at two U.S. medical centers. They were given a placebo, Extra Strength Tylenol and prescription painkillers that contain acetaminophen, such as Percocet (acetaminophen plus oxycodone). Patients took the medication or placebo every six hours for 14 days. The liver enzyme AST was measured daily for eight days and at regular intervals after that. All patients were on the same diet. Out of 106 patients, 41 patients (39%) who took acetaminophen alone or in combination with another drug had their liver enzymes increase to more than three times the upper limit of normal.

Twenty-seven patients had enzyme levels exceeding five times normal, and eight patients had eight times the normal enzyme amount. Of the 39 patients given placebo, only one had enzymes that exceeded twice the normal level.

Is the drug acetaminophen, especially with its current labeling, really safe for OTC use? One point of consideration for OTC use is that consumers must be able to correctly judge the dose of a drug.

It's doubtful that even the most savvy of clinical-product consumers can easily manage milligram conversions and safe, total daily dose computation. The mere pursuit of locating, reading, and understanding tiny-print descriptions and cautions on the boxes of several different products at once can be daunting even to those with 20-20 vision — with or without glasses.

If acetaminophen's therapeutic window of safety is smaller than commonly understood, we can expect a subpopulation of normal users to be quite susceptible to adverse effects, even when they are consuming what they understand are "safe" therapeutic doses. We emphasize this because we know that economic strata, education levels, and biologic conditions are diverse.

Influence Of Fasting On Acetaminophen Toxicity

An important patient variable that influences potential acetaminophen toxicity is the nutritional state (Whitecombe 1994) — whether a patient has been eating a normal diet or fasting. Several reports have implicated fasting as a factor that enhances the prospect of hepatoxicity associated with therapeutic doses of acetaminophen. Yet, it is reasonable to expect that an individual who takes acetaminophen for symptoms of a cold, for example, or for other minor illness may not be hungry. That person's decreased food and fluid intake could potentially exacerbate acetaminophen toxicity.

Consider also that nausea is one of the early symptoms of acetaminophen-induced toxicity. Patients who feel nauseated logically stop eating and drinking — further enhancing the very symptom that made them stop eating and drinking: acetaminophen toxicity. And then — the acetaminophen toxicity increases.

Best Safety Labeling For Products Containing Acetaminophen

In the interests of safe and reliable use, all products containing acetaminophen should display labeling with the following additional precautions:

- Add comparative dose information, so that if a particular product has more (double strength) or less acetaminophen than might be expected, that caution can be raised,
- How many milligrams, and percentage of maximum daily intake, will occur with maximum daily recommended dose,
- Caution consumers to not concurrently take multiple products containing acetaminophen, and to provide a list of common products containing acetaminophen, irrespective of the manufacturer,
- Caution consumers that signs and symptoms of liver toxicity (list them) may not appear for several days after acetaminophen was last used, and ask consumers to consider the development of liver toxicity as an alternate explanation to persistent cold symptoms.
- Caution consumers not to use alcohol with acetaminophen, and to maintain adequate food and fluid intake.

Conclusions

Although commonly used and thought of as relatively harmless, acetaminophen can be quite toxic, even at recommended dosing intervals. Health care providers need to communicate these facts to their patients who may be using acetaminophen.

References

Brunton L, Lazo J, Parker K. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th Ed. New York: McGraw-Hill; 2006.

Meredith TJ, Vale JA. Non- narcotic analgesics. Problems of overdosage. *Drugs*. 1986;32[Suppl 4]:177-205.

Rumack BH. Acetaminophen overdose in children and adolescents. *Pediatr Clin North Am*. 1986 Jun;33(3):691-701.

Riggs BS, Kulig K, Rumack BH. Current status of aspirin and acetaminophen intoxication. *Pediatr Ann*. 1987 Nov;16(11):886-98.

Rumack BH. Acetaminophen overdose in young children. Treatment and effects of alcohol and other additional ingestants in 417 cases. *Am J Dis Child*. 1984 May;138(5):428-33.

Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA. 2006 Jul 5;296(1):87-93.

Whitecombe DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA*. 1994;272:1845-50. ■