Acetaminophen is an analgesic (pain reliever) and anti-pyretic (controls fever) medication which is sold without prescription in over **200 types of pain relievers and cold remedies** under many trade names, including Tylenol. NSAID (such as ibuprofen and naproxen) and COX-2 inhibitors (Vioxx, Celebrex, Bextra) are also analgesic and anti-pyretic, and in addition are anti-inflammatory. Acetamionphen differs from NSAID and COX-2 inhibitors in that it is not anti-inflammatory. Although thought of as relatively non-toxic, and taken by as many as 100 million Americans each year, there are a number of acetaminophen-related liver injuries and deaths reported every year to poison control centers, including those from accidental overdose. The initial symptoms from ingesting a toxic dose, as pointed out below, can be falsely disalarming, but can after several days progress to irrevocable liver failure and death.

**Mechanism of action**

Acetaminophen is mostly converted in the liver to inactive compounds by conjugation with sulfate and glucuronide, with a small portion being metabolized via the cytochrome P-450 enzyme system. The cytochrome P-450 system oxidizes acetaminophen to produce a highly reactive intermediary metabolite: N-acetyl-p-benzo-quinone imine (NAPQI). Under normal conditions, NAPQI is detoxified in the liver by conjugation with glutathione. In cases of acetaminophen toxicity, the sulfate and glucuronide pathways become saturated, and more acetaminophen is shunted to the cytochrome P-450 system to produce NAPQI. If hepatocellular supplies of glutathione become exhausted, NAPQI is free to react with cellular membrane molecules, resulting in widespread hepatocyte (liver cell) damage and death, clinically leading to acute hepatic necrosis. In animal studies, 70% of hepatic glutathione must be depleted before hepatotoxicity occurs.

Commonly, the Rumack (1984,1986,1987) Matthew nomogram is used to access risk of liver injury from acetaminophen toxicity, and is based on time passed since ingestion of the acetaminophen and the current plasma level of acetaminophen. The clinical course after a toxic ingestion follows four stages.

- **Stage 1** occurs 12-24 hours post ingestion. Symptoms can include nausea, vomiting, diaphoresis, and anorexia. Children frequently have episodes of vomiting even without toxic levels. Those patients with plasma levels 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 this time.
- **Stage 2** occurs 24-48 hours post ingestion. By that time, symptoms may have decreased but laboratory abnormalities 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, under 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, 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 h, even with the longer (every 6 hr) interval, there is a chance to go over the recommended daily dose. One gram at the start of the therapy, 1g at 6 h, 1g at 12h, 1g at 18h and finally a dose at 24 h, equals a total of 5 g in a 24 h 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 7.5 – 10g/d. 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 toxicity is a not-unexpected effect of the overdose rather than liver toxicity at high normal 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, or 39 percent, taking acetaminophen alone or in combination with another drug saw 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 amount of enzyme. Of the 39 patients on a placebo, only one had enzymes that exceeded twice the normal level.

Is the drug acetaminophen, especially with it's current labeling, really safe for OCT use? One point that has to be considered for OCT use is that consumers must be able to correctly dose a drug. I remain of low confidence that consumers can manage milligram conversions, totaling doses, and locating acetaminophen in small print on the sides of several different products at once. If the therapeutic window is smaller than commonly appreciated, it can be expected that a subpopulation of normal users, because of biologic diversity and individual conditions, may actually be more susceptible to adverse effects with therapeutic doses.

**Influence of Fasting on Acetaminophen Toxicity**
One of the patient variables that influences the toxicity of acetaminophen is fasting

(Whitecombe 1994). There have been several reports implicating fasting as a factor in hepatoxicity by therapeutic doses of acetaminophen. Yet, it is reasonable to expect that an individual who takes acetaminophen for symptoms of a cold, for example, may not be hungry, and have a decreased food and fluid intake, which potentially could exacerbate acetaminophen toxicity. Another point to consider is that nausea is one of the early symptoms of acetaminophen-induced toxicity. Patients who feel nauseated will stop eating and drinking, therefore further enhancing the toxic effect of acetaminophen.

**Labeling for Products Containing Acetaminophen**

In the interests of safe and clear use, it would be advisable for all products which contain acetaminophen to display the following additional labeling:

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

**Conclusions:**

Although commonly used and thought of as relatively harmless, it is becoming clear that acetaminophen can be quite toxic, even at recommended dosing intervals. Providers need to communicate these facts to their patients who may be using acetaminophen.

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