



EDUCATIONAL OBJECTIVE: Readers will advise patients to limit their acetaminophen dosage and specifically to avoid concurrently taking multiple acetaminophen-containing products

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Acetaminophen: Old drug, new warnings

ABSTRACT

The US Food and Drug Administration (FDA), concerned about the incidence of acute liver failure due to acetaminophen (Tylenol) overdose, has mandated new labeling on acetaminophen packaging. It is also considering (but has not enacted) reducing the maximum daily dose from 4 g (possibly to 3,250 mg), banning acetaminophen-narcotic combination products, and changing the current maximum single dose of 1 g to prescription status, making 650 mg the highest recommended nonprescription dose. We review the epidemiology, toxicology, and management of acetaminophen overdose and steps the FDA and physicians can take to prevent it.

KEY POINTS

Acetaminophen is the leading cause of acute liver failure in the United States, and nearly half of acetaminophen-associated cases are due to unintentional overdose.

In many cases of unintentional overdose, patients took more than one acetaminophen-containing product and did not know that both products contained this drug.

Prescribers need to inform all patients, especially vulnerable ones (eg, those taking enzyme-inducing drugs, those who chronically use alcohol, and those who are malnourished) of the risks associated with acetaminophen.

Although no consensus has been reached on what is a safe dose in patients with liver disease, 4 g/day is too much: a total daily dose of no more than 2 g is recommended to decrease the risk of toxicity in these patients.

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ACETAMINOPHEN (Tylenol, also known as paracetamol, N-acetyl-*p*-aminophenol, and APAP) is a popular antipyretic and analgesic found in many over-the-counter and prescription products, including cough-and-cold remedies and narcotic pain relievers (TABLE 1).¹

This drug is generally considered safe, but high doses can be toxic. The number of overdoses is worrisome. In 2006 alone, the American Association of Poison Control Centers implicated acetaminophen in nearly 140,000 poisoning cases, in which more than 100 patients died.² It is responsible for more emergency room visits than any other drug on the market.

According to a position statement from the American Association for the Study of Liver Diseases (AASLD),³ the incidence of acetaminophen-related liver toxicity has been steadily increasing over the past decade, and this drug is now the most common cause of acute liver failure.

MANY OVERDOSES ARE UNINTENTIONAL

Cases of acetaminophen-related liver toxicity can be categorized as either intentional (ie, due to a suicide attempt) or unintentional (ie, due to multiple therapeutic but excessive doses over a period of time, usually more than 3 days).

Up to 50% of cases are unintentional. Bower et al⁴ reviewed cases of acute liver failure that occurred in the Atlanta, GA, area between November 2000 and October 2004. Ac-

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TABLE 1

Selected products that contain acetaminophen

PRODUCT	ACETAMINOPHEN PER DOSAGE FORM (MG)
Over-the-counter products	
Tylenol Arthritis	650
Midol	500
Pamprin	500
Tylenol Extra-Strength	500
Benadryl Severe Allergy and Sinus Headache	325
Sudafed Sinus and Headache	325
Tylenol Allergy, Flu, PM	325
Goody's Fast Pain Relief	260
Excedrin	250
Prescription products	
Vicodin ES	750
Darvocet-N100	650
Lorcet 10/650	650
Lortab	500
Vicodin	500
Tylox	500
Percocet	325–650
Fioricet	325
Norco	325
Ultracet	325
Tylenol #3	300

Acetaminophen is responsible for more emergency room visits than any other drug

etaminophen was the most common cause in adult patients. Of greater concern is that 61% of the acetaminophen-related cases were due to unintentional overdose. According to the Institute for Safe Medication Practices,⁵ one hospital (not named) reported that an average of one patient per day was given more than the recommended maximum daily acetaminophen dose of 4 g while in the hospital.

Many patients take more than one acetaminophen product

Unintentional overdoses or “therapeutic misadventures” are most often due to taking multiple products that contain acetaminophen, taking acetaminophen-narcotic combinations, and impulsive behavior involving a lack of understanding of possible injury in consuming multiple acetaminophen-containing products.³

In the US Food and Drug Administration (FDA) Medwatch Database, in 307 cases of

unintentional acetaminophen overdose between 1998 and 2001, 25% of patients had been taking more than one acetaminophen-containing product.⁵

Larson et al⁶ found that one-third of patients who had had an unintentional acetaminophen overdose were taking an acetaminophen-narcotic combination in addition to another acetaminophen-containing product.

Many consumers don't know they are taking acetaminophen

Many consumers don't know that some of the drugs they take contain acetaminophen. This may be because many drug labels contain abbreviations for acetaminophen such as “APAP” or have inconsistent formatting that makes it difficult to determine if the product contains acetaminophen.

Others may not be aware of the total maximum recommended daily dose or may not be able to calculate the total daily intake from the information on the label. The problem is not only with over-the-counter products. For example, if a physician prescribes one or two tablets of hydrocodone/acetaminophen (Vicodin) 5 mg/500 mg every 4 to 6 hours, a patient could easily exceed the recommended maximum daily dose of 4 g of acetaminophen.

Toxicity can occur even at therapeutic doses

Acetaminophen hepatotoxicity can also occur even with therapeutic doses in certain conditions. Risk factors:

- Chronic alcohol use (ie, more than three drinks per day)
- Malnutrition
- Concurrent use of drugs that induce cytochrome P450 (CYP450) enzymes (more on this below).⁶

FIRST USED IN 1893

Acetaminophen was first used in medicine in 1893, and it became widely used after 1949, when it was found to be a less-toxic metabolite of two parent compounds, acetanilide and phenacetin.¹

Acetaminophen is an effective antipyretic and analgesic, but its anti-inflammatory properties are minimal, especially compared with nonsteroidal anti-inflammatory drugs

Metabolism and hepatotoxicity of acetaminophen

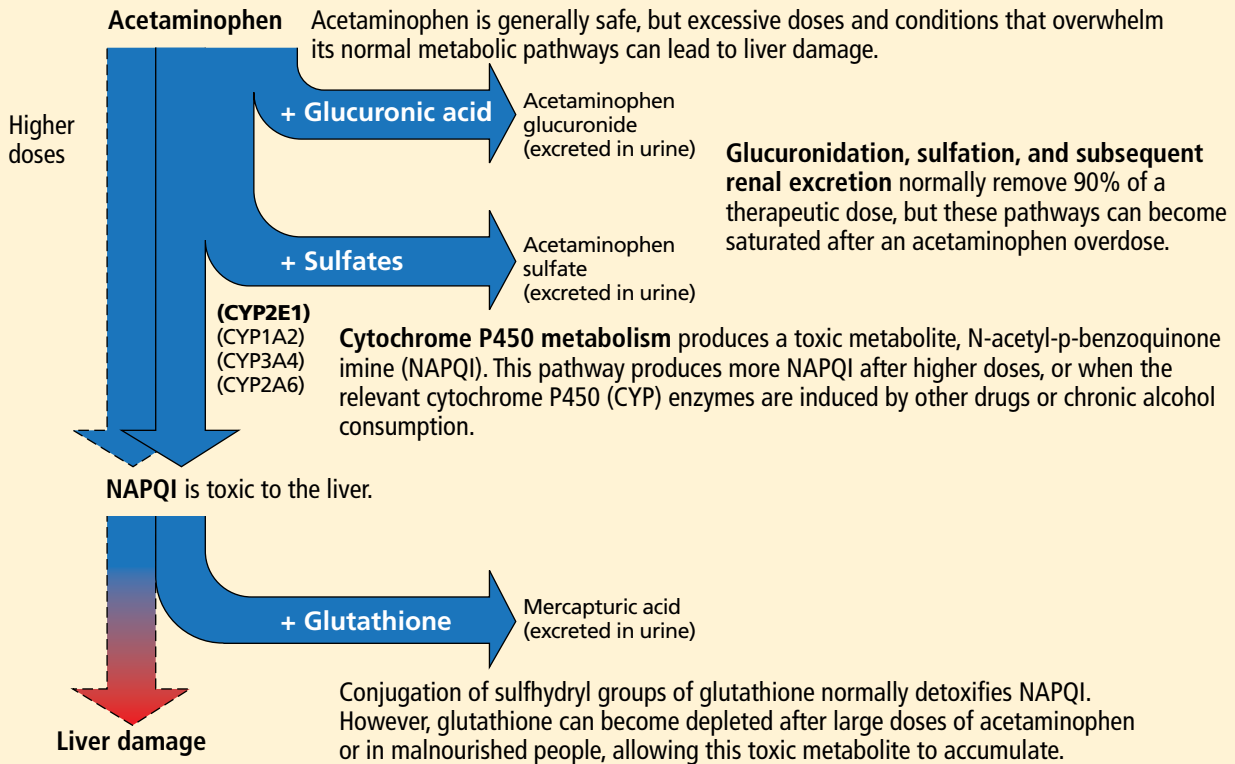


FIGURE 1

(NSAIDs). Nevertheless, acetaminophen is preferred over NSAIDs in some patients because it carries a lower risk of gastrointestinal toxicity (eg, ulceration, bleeding) and so may be better tolerated.¹

INDICATIONS AND DOSAGE

Acetaminophen is indicated for mild to moderate pain or fever, including the pain of osteoarthritis. It is not recommended for chronic inflammatory conditions such as rheumatoid arthritis, since it lacks anti-inflammatory properties.

In adults and in children over age 12, the usual dosage is 325 to 650 mg orally or rectally every 4 to 6 hours, or 1,000 mg three to four times daily.

The current package label recommends that the total daily dose not exceed 4 g in most adults. Lower maximum daily doses (eg, 2 g) are recommended in patients who may be at higher risk of hepatotoxicity, such as those

who drink heavily, are malnourished, or take enzyme-inducing drugs. Tylenol products currently include an alcohol warning, advising those who consume three or more alcoholic drinks a day to ask their doctor if they should take acetaminophen.

In children up to 12 years of age, the recommended dosage is 10 to 15 mg/kg orally or rectally every 4 to 6 hours. The maximum dosing for children in this age group should not exceed five doses (or 50 to 75 mg/kg) in 24 hours.⁷ In children under age 2 or weighing less than 11 kg, acetaminophen should only be used under the direction of a physician.

MOST ACETAMINOPHEN IS CONJUGATED AND THEN EXCRETED IN THE URINE

Acetaminophen usually has excellent bioavailability (up to 98%), but the exact amount absorbed varies, depending on the dosage form and concomitant use of other drugs.⁸

At therapeutic doses, the elimination half-life is about 2 hours. Peak plasma concentrations are reached 30 to 60 minutes after the dose is taken,¹ but taking acetaminophen with opioids, anticholinergic drugs, or even food may delay the time to peak concentration by delaying gastric emptying.⁸

NAPQI is a toxic metabolite

Most of the acetaminophen in the blood undergoes conjugation in the liver with glucuronic acid (40%–67%) and sulfates (20%–46%).⁹ The conjugated metabolites, as well as small amounts that have been hydroxylated and deacetylated, are excreted in the urine (FIGURE 1).

Under normal circumstances, a small amount of acetaminophen undergoes hepatic metabolism by a different pathway, ie, by CYP450 enzymes, primarily CYP2E1 and to a lesser extent CYP1A2, CYP2A6, and CYP3A4, forming a toxic metabolite, N-acetyl-*p*-benzoquinone imine (NAPQI). Then, the sulfhydryl groups of glutathione convert NAPQI into harmless metabolites that are excreted in the urine.^{1,7}

Well tolerated and relatively safe

At recommended doses, acetaminophen is well tolerated, and it is considered relatively safe when used according to labeling instructions.

Rarely, patients experience an erythematous or urticarial rash or other allergic complications.¹

However, acetaminophen is a dose-dependent hepatotoxin, and excessive doses (intentional or unintentional) may lead to acute liver failure. In addition, even in therapeutic doses, acetaminophen may still cause transient liver enzyme elevations and possibly hepatotoxicity, particularly in people who are malnourished or alcoholic or are taking certain CYP450-inducing drugs.^{3,6,10}

HOW ACETAMINOPHEN CAN INJURE THE LIVER

Glucuronidation and sulfation, the major metabolic pathways, become saturated after an acetaminophen overdose.⁷ When this happens, more of the toxic metabolite NAPQI is formed by CYP450-mediated N-hydroxylation. When glutathione is depleted after large

doses of acetaminophen or in malnourished people, the toxic metabolite accumulates, resulting in liver damage (FIGURE 1).⁶

The liver is damaged by two mechanisms. In one, NAPQI binds to hepatic cell macromolecules, causing dysfunction of the enzymatic systems, structural and metabolic disarray, and eventually necrotic cell death. The other mechanism is oxidative stress due to depletion of glutathione.

In children, single acetaminophen doses of 120 to 150 mg/kg of body weight have been associated with hepatotoxicity,¹¹ as have single doses of more than 150 mg/kg or a total dose of greater than 7.5 g in adults. However, the minimal dose associated with liver injury has ranged from 4 to 10 g, and in healthy volunteers even therapeutic doses of 1 g orally every 6 hours resulted in mild liver injury.¹²

Patients who are malnourished or fasting are thought to be at greater risk of acetaminophen hepatotoxicity because they may be deficient in glutathione at baseline. In addition, even at lower-than-therapeutic doses, induction of CYP450 enzymes by drugs or chronic alcohol consumption may lead to an increase in the formation of NAPQI, increasing the risk of hepatotoxicity. Examples of drugs that induce CYP450 enzymes to produce more NAPQI include the anticonvulsants phenytoin (Dilantin) and phenobarbital.

CLINICAL PRESENTATION OF ACETAMINOPHEN OVERDOSE

The diagnosis of acetaminophen overdose is often established by a thorough history. The pertinent information may be difficult to obtain, however, because the patient may be confused or stuporous at presentation, may not know that the over-the-counter products he or she has been taking contain acetaminophen, or may be embarrassed about taking too much acetaminophen.¹³

In acute intentional overdose, signs may not be apparent immediately

The symptoms of toxicity may not be apparent immediately after ingestion of an acute overdose of acetaminophen, but early recognition and treatment can prevent more severe liver damage, decreasing morbidity and the risk of death.⁹

Altered mental status may make it difficult to obtain a history

Phase 1 of an acetaminophen overdose begins shortly after ingestion and can last for 12 to 24 hours. Patients may have signs of gastrointestinal upset, nausea, vomiting, anorexia, diaphoresis, and pallor. Although the signs and symptoms show a consistent pattern and are more pronounced after larger acute overdoses, they are not diagnostic or specific.

Phase 2 (up to 48 hours after ingestion). Patients may begin to feel better during this phase. However, the hepatic enzyme levels, the prothrombin time (PT), and the international normalized ratio (INR) may continue to rise, and right upper quadrant pain may develop. Additionally, other laboratory results may be abnormal, and renal insufficiency can occur due to acetaminophen-induced renal tubular necrosis.⁶ Most patients receive the antidote, acetylcysteine (Mycomyst, Acetadote) before or during this phase, and consequently, liver function gradually returns to normal.

Phase 3, if reached, may be marked by severe hepatic necrosis, typically 3 to 5 days after ingestion. Symptoms during this phase range from less severe (eg, nausea and general malaise) to more severe (eg, confusion and stupor). Also, at this time, liver enzyme levels can be as high as 10,000 IU/L or even higher, and lactic acidosis and coagulopathy may worsen. If death should occur, it is most likely from complications associated with fulminant hepatic failure, including cerebral edema, multiorgan-system failure, or sepsis.⁶

Phase 4. Patients who recover generally have complete recovery of liver function with no long-term sequelae.

In unintentional overdoses, patients may have low drug levels

Many patients who present with unintentional acetaminophen toxicity have been taking the drug or products that contain the drug over several days to treat an acute or chronic medical condition. They often have low or undetectable serum acetaminophen levels after 2 to 3 days of nonspecific symptoms.¹²

MANAGING ACETAMINOPHEN OVERDOSE

Measuring serum acetaminophen levels may be useful in cases of single, acute overdoses if the time since ingestion is known. The Rumack-

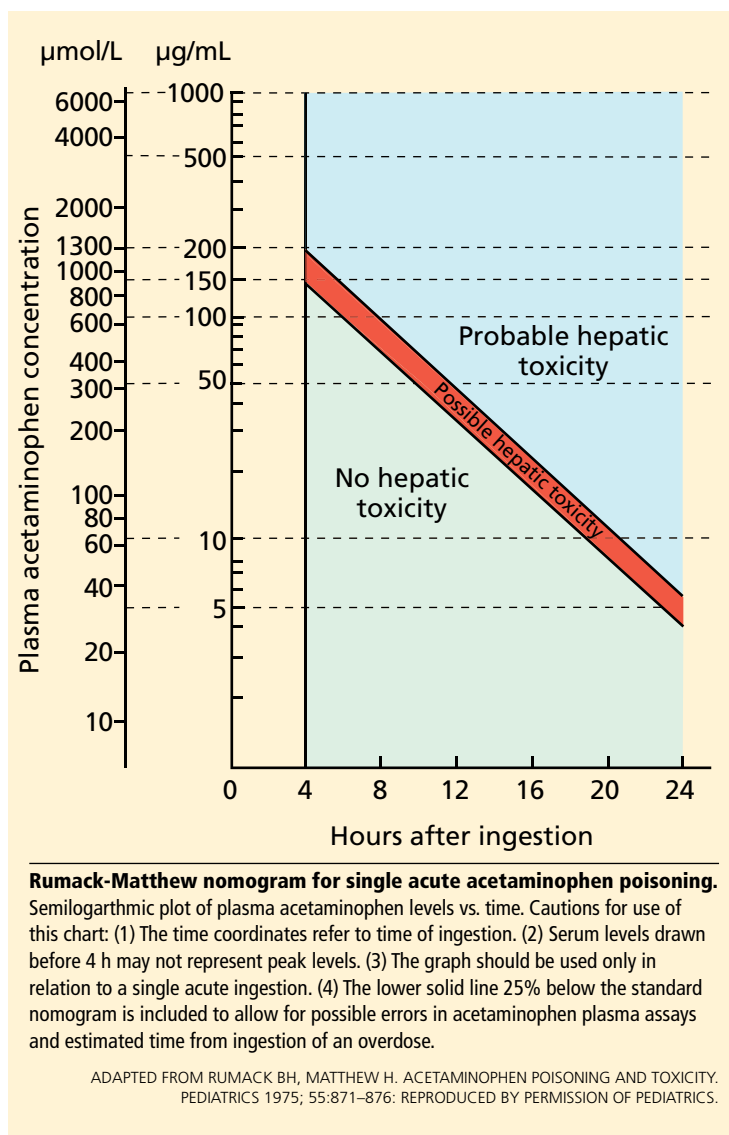


FIGURE 2

Matthew nomogram (FIGURE 2), used in cases of acute acetaminophen overdose, predicts the probability of hepatotoxicity on the basis of plasma levels and time after ingestion.¹³⁻¹⁵

Unintentional overdoses occur over a more prolonged period, and therefore the nomogram is not useful in this situation.

Acetylcysteine is the antidote

Acetylcysteine is the antidote for acetaminophen toxicity and should be given within 8 hours of ingestion for maximal protection against hepatic injury in patients whose serum acetaminophen levels are above the "possible" toxicity line on the nomogram.¹⁵ If acetamino-

TABLE 2

**King's College criteria
for poor prognosis in acute liver failure**

In acetaminophen-induced acute liver failure

Arterial pH < 7.3

Or all of the following:

Grade III or IV encephalopathy

Prothrombin time > 100 seconds

Serum creatinine > 3.4 mg/dL

In acute liver failure from other causes

Prothrombin time > 100 seconds

Or three of the following:

Age < 10 years or > 40 years

Non-A, non-B hepatitis, halothane-induced hepatitis,
idiosyncratic drug reactions

More than 7 days of jaundice before the onset of encephalopathy

Prothrombin time > 50 seconds

Serum bilirubin > 18 mg/dL

BASED ON O'GRADY JG, ALEXANDER GJ, HAYLLAR KM, WILLIAMS R. EARLY INDICATORS OF PROGNOSIS IN FULMINANT HEPATIC FAILURE. GASTROENTEROLOGY 1989; 97:439-445. COPYRIGHT ELSEVIER 1989.

**Acetylcysteine
should be given
within 8 hours
of ingestion
for maximal
protection**

phen overdose is suspected but the time elapsed since ingestion cannot be determined, acetylcysteine should be given immediately regardless of the quantity of acetaminophen ingested.¹⁶ In cases of unintentional overdose, it is often given at the discretion of the physician.

Acetylcysteine limits the toxicity of acetaminophen by increasing glutathione stores, binding with NAPQI as a substitute for glutathione, and enhancing sulfate conjugation.⁶ It may further limit acetaminophen toxicity by nonspecific mechanisms including anti-inflammatory, antioxidant, inotropic, and vasodilating effects.⁶ In addition, it may prevent further hepatic damage in any patient thought to have acetaminophen-related liver toxicity even beyond the first 12 hours of an overdose.¹

Acetylcysteine is available in an oral (Mucumyst) and an intravenous (Acetadote) formulation, which are similar in efficacy. Because many patients find the taste of the oral solution unpleasant and difficult to tolerate, it should be diluted in a 1:3 ratio with cola, orange juice, or other drink to mask its flavor. This mixture should be used within 1 hour of preparation.

Anaphylactoid reactions have occurred in patients receiving intravenous acetylcysteine for acetaminophen overdose soon after the infusion

was started, most commonly during the loading dose. The frequency of infusion-related reactions has been reported to be 0.2% to 20.8%.¹⁵

The recommended dosage for intravenous acetylcysteine is a loading dose of 150 mg/kg given over 60 minutes, followed by a second dose of 50 mg/kg given over 4 hours, and finally a third dose of 100 mg/kg given over 16 hours.¹⁵ For oral acetylcysteine, the loading dose is 140 mg/kg followed by 70 mg/kg every 4 hours for 17 additional doses.¹⁷

Other measures

Activated charcoal can be used if the patient presents within 1 to 2 hours after taking acetaminophen. However, the rapid gastrointestinal absorption of acetaminophen makes this treatment ineffective in most cases.⁹

Liver transplantation. In patients with acute liver failure and a poor prognosis, early referral to a liver transplant center is essential. The King's College criteria (TABLE 2),¹⁸ a widely used prognostic model in patients with acute liver failure, are used to predict the need for liver transplantation. They are based on the arterial pH, the PT and INR, the severity of encephalopathy, and the serum creatinine concentration.

FINDINGS FROM LARGE REGISTRIES

Findings in adults

Ostapowicz et al,¹⁹ as part of the Acute Liver Failure Study Group, in 2002 prospectively characterized the short-term outcomes of acute liver failure in a large number of patients at 17 tertiary care centers in the United States over approximately 41 months. All centers except one performed liver transplants. Eligible patients had to meet criteria for acute liver failure, including an INR higher than 1.5, evidence of hepatic encephalopathy, and presentation within 26 weeks of illness onset without apparent chronic liver disease.

Of the 308 cases of acute liver failure, 120 (39%) were from acetaminophen overdose, making this drug the most common cause of acute liver failure. Forty-four (37%) of the patients with acetaminophen-related acute liver failure were trying to commit suicide, 57% of cases were accidental, and the remaining reasons for acetaminophen overdose were

unknown. The median amount ingested was 13.2 g/day (range 2.6–75 g), and 99 (83%) of the 120 patients took more than 4 g/day.

The patients with acetaminophen-related acute liver toxicity differed from those with other causes of acute liver failure such as idiosyncratic drug reactions or indeterminate causes. The acetaminophen group had a shorter duration of disease and higher serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine than those with acute liver failure from other causes. They also had lower bilirubin levels and a lower arterial pH.

Rates of liver transplantation were 6% in the acetaminophen group, 53% in the group with other drug-induced liver toxicity, 51% in the indeterminate group, and 36% in the remaining groups. Of the acetaminophen group, 47% met the criteria for transplantation, but only 57% of those eligible were listed for transplantation. Those excluded from the transplant list had medical contraindications or were excluded for psychosocial reasons. The short-term transplant-free survival rate was 68% in the acetaminophen group.

Overall, 11% of the patients died, including 28% of the acetaminophen group. The authors concluded that most cases of liver injury in the United States are due to medications and may be preventable.

Larson et al,²⁰ as part of the Acute Liver Failure Study Group, examined the incidence, risk factors, and outcomes of acetaminophen-induced acute liver failure at 22 tertiary care centers in the United States over a 6-year period. Of the 662 patients in the study, 302 had acetaminophen-related toxicity and 275 were included in the final analysis; some of them had been included in the study by Ostapowicz et al.¹⁹ During the study period, the number of cases of acute liver toxicity related to acetaminophen increased from 28% to 51%.

Of the patients enrolled in the study, 56% met the criteria for potentially toxic acetaminophen ingestion. Of those who met the criteria, 77% had detectable acetaminophen levels in their serum, and 91% had ALT levels higher than 1,000 IU/L. The time between ingestion and symptom onset ranged from 1 to 32 days, and the median dose was 24 g (range 1.2–180 g).

Of the overdose cases, 48% were unintentional, 44% were intentional, and the remaining 8% had no definable reason. Of the patients in the unintentional-overdose group, 38% were using more than one acetaminophen-containing product and 63% were taking combination products containing narcotics. Overall, 44% of patients reported using narcotic-acetaminophen combination products. The unintentional-overdose group had lower serum acetaminophen levels than the intentional-overdose group, but they were more likely to present with severe hepatic encephalopathy.

The number of patients with an unintentional overdose was worrisome. Furthermore, one-third of the patients who were receiving an acetaminophen-narcotic combination product were taking an additional acetaminophen-containing product. The authors concluded that unintentional overdose is the leading cause of acetaminophen-related hepatotoxicity, and efforts to limit the over-the-counter package size and to restrict prescriptions of acetaminophen-narcotic combinations may be necessary to decrease the incidence of this preventable cause of acute liver failure.

Findings in children

Squires et al²¹ and the Pediatric Acute Liver Failure Study Group examined the pathogenesis, treatment, and outcome of acute liver failure in children (any age from birth to 18 years) with no previous evidence of chronic liver disease, evidence of acute liver injury, or hepatic-based coagulopathy. From December 1999 to December 2004, 348 patients were enrolled.

Fourteen percent of the cases were due to acetaminophen. The median dose of acetaminophen ingested was 183 mg/kg. Most of these patients were white and female, and 96% were over age 3. Hepatic encephalopathy was more common in the non-acetaminophen groups than in the acetaminophen group, although this is often difficult to assess in infants and children. Children with acetaminophen toxicity had the highest rate of spontaneous recovery: 45 (94%) of 48 recovered.

Although there are fewer acetaminophen-related cases of acute liver failure in children than in adults, the use of acetaminophen in

**Needed:
education
of patients
and physicians
about
acetaminophen
products**

TABLE 3

Updated labeling requirements for over-the-counter products containing acetaminophen

Alcohol warning is included as part of the liver warning, instead of the separate alcohol warning previously required.

Warning included information on the potential for severe liver damage associated with exceeding the maximum daily dose or consuming three or more alcohol-containing drinks per day while taking acetaminophen.

The liver warning is required directly on the container labels in addition to the carton or outer container.

The ingredient name (ie, acetaminophen) is highlighted or in bold type and in a prominent print size on the package's principal display panel.

The statement "See new warning information" is highlighted or in bold type and in a prominent print size on the principal display panel.

The label must contain a warning to avoid concomitant use of other acetaminophen-containing products and instructions to speak with a physician before taking acetaminophen if the user has liver disease or is using warfarin.

FOOD AND DRUG ADMINISTRATION. QUESTIONS AND ANSWERS ON FINAL RULE FOR LABELING CHANGES TO OVER-THE-COUNTER PAIN RELIEVERS. WWW.FDA.GOV/DRUGS/NEWSEVENTS/UCM144068.HTM. ACCESSED OCTOBER 30, 2009.

children is still worrisome. The authors concluded that if they do not have hepatic encephalopathy, children with acetaminophen-induced liver toxicity have an excellent prognosis.

■ THE FDA LOOKS AT THE PROBLEM

Why overdoses occur

A recent FDA report²² cited the following reasons for acetaminophen overdose:

- Some patients may experience liver injury at doses only slightly above the recommended 4-g daily limit.
- Some patients may be more prone to liver injury from acetaminophen.
- The symptoms associated with liver injury due to acetaminophen can be nonspecific and tend to evolve over several days.
- Many acetaminophen-containing products are available, including over-the-counter and prescription drugs with many different

strengths and indications.

- Consumers are unaware of the risk of liver toxicity with acetaminophen.
- Prescription products are not always clearly labeled with acetaminophen as an ingredient.
- Pediatric dosage forms are available in many different concentrations.

New package labeling

In view of this information, the FDA has mandated new labeling for acetaminophen-containing products (TABLE 3).²²

Recommendations from an advisory panel

In addition, an FDA advisory panel recommended decreasing the maximum recommended daily dose (possibly to 3,250 mg/day in adults, although this is not final) to help prevent overdoses, and reducing the maximum amount in a single nonprescription dose of the drug to 650 mg.²³ The panel also voted (by a narrow margin) to ban all acetaminophen-narcotic combination products.

As of this writing, the FDA has not adopted these recommendations. (Although the FDA is not obliged to follow the advice of its advisory panels, in most cases it does.) The recommendations about acetaminophen could take years to implement fully.

■ THE UNITED KINGDOM ACTED IN 1998

In response to a rising number of analgesic-related deaths, the United Kingdom enacted legislation in 1998 to limit the package size available to consumers.²⁴ Packages sold in general stores can contain no more than 16 capsules, while those sold in pharmacies can contain 24. Blister packs were also introduced to make it harder for people to impulsively take handfuls of tablets.²⁵

Two studies since then both found that the number of deaths related to paracetamol (as acetaminophen is known in the United Kingdom) had fallen since the legislation was implemented.^{24,26} Greene et al²⁷ found that patients who ingested potentially toxic doses of paracetamol had obtained the drug "in a manner contravening the 1998 legislation."²⁷ In other words, shops in London were not obeying the law.

SUMMARY

The new labeling and the proposed changes are sensible and draw needed attention to the problem of acetaminophen toxicity. To pre-

vent unintentional acetaminophen overdoses, education of patients and health care professionals is urgently needed so that the dangers of consuming excess acetaminophen daily are understood.

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