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REPORT

The Little-Known Dangers of Acetaminophen

Even when used as directed, acetaminophen can lead to liver toxicity or death. Here's how to use acetaminophen safely.

By Jay S. Cohen, MD, (Introduction by William Faloon)



What if a dietary supplement was proven to cause liver damage, liver failure and death? What if each year, this same supplement caused 100,000 calls to poison control centers, 56,000 emergency room visits, 26,000 hospitalizations, and more than 450 deaths from liver failure alone?

You know the answer. The FDA would immediately shut down the supplement company and seek to incarcerate the principals for life.

What if, on the other hand, a highly profitable drug caused this much disease and death? To no one's surprise, the FDA's response is to do the equivalent of nothing.

As we learned long ago, the FDA too often functions to protect the financial interests of pharmaceutical companies. The FDA's intentional inaction in this instance proves that this agency could care less about how many Americans suffer and die each year.

In his eye-opening article, Dr. Jay Cohen exposes a lethal hoax that has been perpetrated on infants, children, and adults by immoral drug companies and their conspirators within the FDA.

Many people assume that over-the-counter medications are safe when taken as directed. Yet even at recommended doses, aspirin can cause ulcers, antihistamines can cause sedation, and acetaminophen can cause serious liver damage.

You can read about some of these risks in the product information that accompanies over-the-counter medicines. For example, the acetaminophen package insert warns about taking the drug if you consume three or more alcoholic drinks a day. The link between acetaminophen, alcohol, and an increased risk of liver damage was identified in the 1980s. This research identified another factor that can increase the risks associated with acetaminophen: fasting. This can refer to fasting due to abdominal upset or pain, nausea, vomiting, loss of appetite, anorexia, or malnutrition. Consider this case published in 1992:

A 25-year-old, healthy Swedish man developed gastroenteritis while on holiday in Turkey. For a day and a half before flying home, the man experienced nausea and vomiting, and he was unable to keep food or liquid down. Noticeably ill during the flight, upon landing he was taken directly to a hospital. As his condition worsened, he was diagnosed with liver failure and transferred to await a liver transplant. Information from his brother, who had been with him in Turkey, indicated that the patient had taken 500 mg to 1,000 mg of acetaminophen two to three times each day, with a maximum total intake of 5,000-6,000 mg over two days. Unexpectedly, the patient's condition began to improve, liver transplantation was canceled, and he was discharged ten days later.¹

What had the Swedish man done wrong to develop liver failure? Nothing. His use of acetaminophen was within the recommended dosage range. The maximum recommended dosage of acetaminophen is 4,000 mg/day. The man took only 2,000 or 3,000 mg/day. He took acetaminophen merely to ease the pain of acute gastroenteritis, as do thousands of people each day. He followed the rules but nearly died.

The doctors presenting this case concluded that liver toxicity "can occur after low, repeated doses of acetaminophen." They added, "the drug should not be used under conditions of starvation, including acute gastroenteritis with nausea and vomiting."¹ Yet today, despite this report and many others, acetaminophen products do not list a warning against using the drug when unable to eat.



A POWERFUL LIVER TOXIN

Many drugs can cause liver damage, liver failure, and death. Yet, acetaminophen prompts the most calls to poison control centers—more than 100,000 per year. Each year, acetaminophen accounts for about 56,000 emergency room visits, 26,000 hospitalizations, and more than 450 deaths from liver failure.² Acetaminophen causes more cases of acute liver failure than all other medications combined.³

In comparison to the millions of people who take acetaminophen each day without harm, the occurrence of liver failure and death is relatively rare. Still, many experts believe the numbers are too high and must be reduced. Dr. William Lee, a highly respected expert on acetaminophen, wrote, “It still must be asked: Is this amount of injury and death really acceptable for an over-the-counter pain reliever?”⁴

Why does acetaminophen affect the liver? Acetaminophen is a dose-dependent liver toxin. Even at standard doses, the metabolism of acetaminophen in humans releases small amounts of a toxic substance, N-acetyl-benzoquinoneimine (or NAPQI).⁵ With excessive doses, a much larger amount of this toxin is formed. There is a fine line between a safe dose of acetaminophen and one that is dangerous, which means that doses even slightly above the maximum recommended dose of 4 g/day can cause liver damage. “Just doubling the maximum adult dosage for a few days can be toxic, even deadly,” warns Consumer Reports.⁶ Dr. T.M. MacDonald adds, “Used incorrectly and taken in excessive dose either accidentally or intentionally, acetaminophen is a very toxic drug.”⁷

Fasting reduces the body’s store of glutathione, which is needed to metabolize acetaminophen safely. Decreased levels of glutathione lead to an increased risk of acetaminophen toxicity. Liver damage may occur at recommended doses, as seen with the Swedish man, or in people who unintentionally overmedicate with acetaminophen.

UNINTENTIONAL OVERDOSES TAKE A HEAVY TOLL

Another daunting statistic about acetaminophen is that nearly half of all overdoses are unintentional.⁸ These people do not intentionally take excessive amounts of acetaminophen; instead, they lose track of the amount they are taking and inadvertently take more than recommended.

Other individuals intentionally take 5,000-8,000 mg/day of acetaminophen because their pain is not relieved by the recommended doses. These people are not trying to harm themselves, but merely seeking relief from pain and are not aware that doses even slightly above the maximum therapeutic dose of 4,000 mg/day can be toxic.

Another type of accidental overdose occurs when people take multiple remedies, for example, for the flu, cough and cold, headache, and fever, without realizing that each contains acetaminophen. Accidental overdoses can also occur in those who take prescription medications containing acetaminophen, such as Vicodin® or Percocet®, since they may not be aware of the medications’ acetaminophen content. Unknowingly, they can overmedicate with acetaminophen when they reach for an over-the-counter product containing this drug at the onset of flu, a cold, or fever. It is all too easy to make this mistake. A 2003 study found that when doctors prescribed narcotic-acetaminophen combination pain medications to 108 patients, not one was warned that the medications contained acetaminophen and that they should reduce or discontinue the use of other acetaminophen-containing products, including over-the-counter remedies.⁹

Unintentional overdoses of acetaminophen are often more toxic and difficult to treat than intentional overdoses.¹⁰ Doctors often see people who take intentional overdoses within a few hours of ingestion. In these cases (usually attempted suicide), the amount taken is usually known and liver damage is not yet extensive. The acutely high blood levels of acetaminophen seen in these cases help doctors make a quick diagnosis and start treatment.

In contrast, unintentional overdose cases usually occur after people have been taking acetaminophen over several days and the exact amount ingested may not be known. Blood levels of acetaminophen are often deceptively low, yet liver damage may already be extensive and critical time may be lost while doctors struggle to make a diagnosis.

REQUESTS FOR BETTER WARNINGS IGNORED

In addition to its alcohol warning, over-the-counter acetaminophen packaging also warns against use “with any other product containing acetaminophen.”¹¹ Unfortunately, this weak warning does not convey the serious risks of acetaminophen overmedication, even at slightly elevated doses. Overuse can cause liver injury, liver failure, and death, but you would never know it by reading the information provided with acetaminophen products.

You would also never know about the risks of taking acetaminophen while fasting. Current product information does not mention it at all. Meanwhile, cases continue to be reported as highlighted below:

A 45-year-old man developed severe liver toxicity while taking 4,000 mg/day of acetaminophen for four days. He had several risk factors, including malnutrition and illness-induced starvation.¹²

A 54-year-old woman developed liver failure after unintentionally overmedicating with 5,000-6,000 mg/day of acetaminophen for six to eight weeks. She had taken 3,000 to 4,000 mg/day of over-the-counter acetaminophen and was unaware that her prescription pain medication (Lortab®) also contained acetaminophen.¹³ Her history provided no risk factors except for a gastric bypass, which can lead to malabsorption of micronutrients needed to synthesize glutathione.¹⁴

A 16-year-old boy underwent surgery for severe scoliosis. Fever developed postoperatively, and a low dose of 1,200 mg/day of acetaminophen was given for three days. The boy was malnourished, and he was fasting during the postoperative period with only limited intravenous support. A few days later, the boy developed acute liver failure, and he died soon after. Autopsy revealed liver injury consistent with acetaminophen toxicity. The doctors commented, "This case may illustrate that acetaminophen may cause liver injury even in therapeutic doses, if certain risk factors are present. Such factors are malnutrition and starvation."¹⁵

A 58-day-old infant girl was seen in an emergency room after two days of fever, decreased appetite, lethargy, and irritability. As instructed, the parents had given acetaminophen every four hours to the infant. Tests revealed highly elevated liver enzymes and an elevated acetaminophen level. Tests for other liver disorders were negative. The girl improved quickly with treatment. The authors noted that children who have fever, vomiting, or diarrhea often have inadequate oral intake, and that a fasting state could increase the toxicity of acetaminophen.¹⁶

Two children developed severe liver and kidney damage after receiving repeated doses of acetaminophen for illness and fever. The authors commented that when low doses of acetaminophen are used at frequent intervals for a number of days, the drug puts children who are vomiting or have sharply reduced caloric intakes at increased risk for liver and/or kidney toxicity.¹⁷

In this last case, the authors added that there was a need for increased caution and awareness among health care professionals about the toxic effects of acetaminophen. This increased awareness required "appropriate package-label warnings,"¹⁷ and is one of many calls for more informative warnings on acetaminophen products.

DANGERS OF ACETAMINOPHEN: WHAT YOU NEED TO KNOW

- The widely used pain and fever reliever acetaminophen is a leading cause of acute liver failure, even at doses that are within the recommended range.
- Acetaminophen accounts for tens of thousands of calls to poison control centers and hospital admissions each year, as well as hundreds of deaths.
- Both alcohol consumption and fasting (due to illness, anorexia, or malnutrition) greatly increase the risk of liver injury due to acetaminophen. Fasting decreases levels of glutathione, an antioxidant that helps the liver detoxify acetaminophen.
- Nearly half of people who overdose on acetaminophen do so unintentionally, due to unrelieved pain or combining medications (over-the-counter or prescription) that contain acetaminophen.
- Despite calls for increased safety measures and education campaigns, the FDA has failed to take decisive action to protect the public from the health risks posed by acetaminophen.
- You can protect yourself by avoiding alcohol and fasting while using the drug, and by using one acetaminophen product at a time. Consider targeted nutritional therapies to help protect your body against the dangers of acetaminophen toxicity.



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THE FDA FAILS TO ACT

Despite calls for better warnings, nothing has changed. Over the years, the FDA has intermittently voiced a desire to reduce the number of cases of acetaminophen toxicity. In 2004, the agency launched an educational campaign on the safe use of over-the-counter medications.¹⁸ This initiative appears to have had no impact on acetaminophen statistics. Since then, a large study has been published demonstrating that therapeutic doses of acetaminophen cause liver injuries in a substantial number of users,¹⁹ and has raised serious questions about the safety of therapeutic doses of acetaminophen.

In 2007, an FDA medical officer revealed that the staff of the FDA's Office of Surveillance and Epidemiology (formerly Office of Drug Safety) had recommended initiating measures similar to those adopted in Great Britain to reduce acetaminophen toxicity. These measures include limiting the number of acetaminophen pills in a package and packing the pills individually in foil packs. This recommendation never reached the FDA's Nonprescription Drugs Advisory Committee, where it could have been considered and approved.²⁰



Recently, in response to a scathing report by the Institute of Medicine, the FDA has made a lot of noise about enhancing its efforts to promote drug safety. Until proven otherwise, the FDA's promises are hollow. The tilt of the FDA will continue to be in favor of the drug industry. For years, the FDA has understaffed and underfunded its safety divisions. It has not been unusual for high-ranking FDA officials to approve new drugs despite serious concerns of FDA medical officers about the drugs' safety. Indeed, just recently another article critical of the FDA was published in the *New England Journal of Medicine* (September 6, 2007), in which Dr. Sheila Weiss Smith concluded that the FDA's actions once again underscored "the low priority it assigns to its responsibility for arbitrating drug safety."²¹

FDA IGNORES ITS OWN GUIDELINES

With acetaminophen, FDA officials have long ignored their own regulations. FDA guidelines require drug companies to list adverse drug events if: 1) they are serious; 2) they occur in close proximity to using the drug; and 3) they are consistent with a drug's known effects.²² Acetaminophen fits all of these requirements. In addition, animal studies provide ample evidence of a link between fasting, acetaminophen use, and liver failure.²³

Moreover, a recent report demonstrated the link between acetaminophen, fasting, and liver toxicity. Doctors were at first puzzled why a nine-month-old child had developed liver toxicity after only two days of therapeutic doses of acetaminophen. Laboratory analysis revealed that the child had a genetically determined glutathione deficiency, causing her glutathione activity to be only 5% of normal. Without adequate glutathione, standard doses of acetaminophen were toxic in this child.²⁴ The case provides human evidence that markedly decreased glutathione activity, which can also be caused by fasting, increases the risk of acetaminophen liver toxicity in humans.

FDA guidelines also state that rare, serious adverse events should be listed in product information "even if there are only one or two reported events."²² The first cases linking acetaminophen, fasting, and liver toxicity were reported in the 1980s. More than 20 years have passed, during which time many more cases have been published. Where is the warning? Where are the meaningful measures to improve acetaminophen safety?

Perhaps the FDA's inaction is related to resistance by the largest producer of acetaminophen products (McNeil Consumer Health, Tylenol® products) to implement a fasting warning and other safety measures. Acetaminophen is a widely used drug that generates more than two billion dollars per year in sales in the US. Additional warnings might undo acetaminophen's reputation as the safest over-the-counter pain and fever remedy, and safety packaging might depress sales.



Some argue that it has not been fully proven that fasting increases the risk of liver toxicity from acetaminophen. This is a specious argument. Experts know that absolute proof will be difficult to obtain. Liver toxicity from acetaminophen and fasting is a rare event. If it occurs in one in 100,000 users, a study demonstrating this would require at least 300,000 patients, and it would take years to accomplish. This is why FDA guidelines do not require absolute proof of causality. The FDA simply requires a close, plausible association between a drug and an adverse event. This is certainly the case with acetaminophen and fasting.

Over the years, more and more physicians have accepted fasting as a legitimate risk factor for acetaminophen toxicity. In 2001, the Harvard Health Letter stated flatly: "It is dangerous to take acetaminophen after you've been fasting."²⁵ Three years later, in response to articles debating fasting and other risk factors with acetaminophen, Dr. Timothy Davern noted that in the gastroenterology division at the University of California, San Francisco, "fasting due to intercurrent illness [e.g. flu] appears to be a common predisposing factor" for acetaminophen toxicity.²⁶

THINGS YOU CAN DO

Given the potential risks of overusing acetaminophen, it is wise to use it sparingly, if at all. Those who have to take acetaminophen need to be aware of the factors that can increase the risks. These include taking acetaminophen while having three or more alcohol drinks a day, using multiple acetaminophen-containing products, or taking acetaminophen when you are unable to eat because of nausea, vomiting, loss of appetite, anorexia, malnutrition, or other causes of reduced nutrition. If your doctor prescribes a medication for pain, headache, or muscle tension, be sure to ask whether the drug contains acetaminophen. If you forget to ask your doctor, ask your pharmacist.

Be sure to read the label of any over-the-counter medication. If you are taking more than one medication, make sure that only one contains acetaminophen. Read the warnings. Stay within the recommended doses of acetaminophen. Overmedicating by even small amounts raises acetaminophen's risks.

It should also be remembered that alternative medications such as ibuprofen, naproxen, or other anti-inflammatory drugs have their own risks (e.g. stomach ulceration and cardiovascular complications).^{27,28}

For those who need to take these over-the-counter medications, consider taking antioxidants and other supplements at the same time to mitigate any adverse effects on the liver, kidney, and stomach.²⁹ These nutrients provide antioxidant support to counteract the harmful build-up of oxidant by-products caused by taking acetaminophen. They also preserve the liver's supply of glutathione, an antioxidant that is essential for the body's detoxification of a number of drugs and toxins, and which is depleted by the metabolism of acetaminophen. Furthermore, glutathione levels fall with aging, thus increasing the risk of acetaminophen-induced liver damage, so it is even more important to maintain healthy liver function in the elderly.³⁰

Nutritional supplements that may be used in conjunction with acetaminophen include N-acetylcysteine (NAC),³¹ vitamins C and E,^{32,33} S-adenosylmethionine (SAME),³⁴ whey protein,³⁵⁻⁷ milk thistle extracts (silymarin and silibinin),^{38,39} and polyenylphosphatidylcholine.⁴⁰

N-acetylcysteine is part of the body's natural antioxidant system and helps maintain stores of glutathione in the liver.³¹ This nutrient is also used intravenously in conventional therapy as a primary treatment for liver toxicity triggered by acetaminophen overdose. Life Extension recommends taking 600 mg of N-acetylcysteine with at least 1 g of vitamin C per dose of acetaminophen, which will provide significant protection for the liver. Alternatively, whey protein, 20 g/day, mixed with cereal or a liquid, contains a high concentration of cysteine, which acts a key precursor to restoring glutathione levels in the liver.^{36,37}



A lack of vitamin C or glutathione also causes vitamin E levels to fall. Supplementing with vitamin E, 400 IU per day (along with at least 200 mg of gamma tocopherol) can protect the liver while taking acetaminophen.³³

For those who must take acetaminophen chronically, the herb milk thistle, which contains the active ingredients, silymarin and silibinin, restores the body's supplies of glutathione, while reducing free radical production and lipid peroxidation in the liver.^{38,39} The recommended dose is 250 mg of milk thistle extract two or three times a day in patients taking long-term acetaminophen therapy.

In cases where liver function has already become compromised by analgesics or other toxins, S-adenosylmethionine (SAME) may help repair the liver and prevent further damage.³⁴

Polyenylphosphatidylcholine (PPC) is a soy extract that also protects the liver against injury from fibrosis, oxidative stress, and toxicity due to acetaminophen use.⁴⁰ Life Extension recommends taking 1800 mg/day of PPC to protect the liver from noxious

substances. Polyenylphosphatidyl-choline also offers powerful protection for the gastric mucosa, which is vulnerable to irritation and ulceration from high-dose analgesics such as aspirin, ibuprofen, or prescription anti-inflammatory drugs.⁴¹

It should be noted that any dietary supplementation regime should not be launched without the supervision of a physician or a qualified health care practitioner, who will be able to create a program that is appropriate for you.

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professor of family and preventive medicine and psychiatry at the University of California, San Diego. Dr. Cohen is a nationally recognized expert on medications and their side effects. He has published books and medical journal articles and has spoken at major conferences and at the US Food and Drug Administration regarding the need for improved drug safety. Dr. Cohen also provides expert analyses and opinions in cases involving medication-induced injuries. His most recent book, *What You Must Know About Statin Drugs and Their Natural Alternatives* (Square One Publishers, 2006), explains who needs to reduce cholesterol or other risk factors for heart disease, and how they can do so safely. For more information, visit Dr. Cohen's website at www.MedicationSense.com.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.



PRESCRIPTION DRUGS CONTAINING ACETAMINOPHEN

Here are some frequently prescribed medications that contain acetaminophen. This list is not exhaustive; there are many other prescription drugs and scores of over-the-counter remedies that contain acetaminophen. If your doctor prescribes a drug for pain, headache, or muscle tension, ask your doctor or pharmacist whether it contains acetaminophen.

- Tylenol® No.2, Tylenol® No.3, Tylenol® No.4: acetaminophen and codeine
- Vicodin®, Lorcet®, Lortab®, Maxidone®, Zydone®: acetaminophen and hydrocodone
- Percocet®, Roxicet®: acetaminophen and oxycodone
- Fioricet®: acetaminophen, butalbital, and caffeine
- Darvocet-N®, Wygesic®: acetaminophen and propoxyphene

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