

## Acetaminophen and NSAID Toxicity

Over-the-counter (OTC) drugs are a significant source of morbidity and mortality in the United States. Although the shelves of every major drug store and grocery store are heavily stocked with these common medications—and they are used millions of times every day—few people are aware of the dangers posed by common OTC medications, especially acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen. Acetaminophen and NSAIDs commonly cause serious liver and gastrointestinal side effects, yet most people have no idea how dangerous they can be.

Part of this ignorance is because these strong medications are available without prescriptions, and heavy television and magazine advertising has perhaps given the impression that cold medicines, pain killers, antihistamines, and other ubiquitous drugs are safe. In fact, OTC medications as a category are responsible for more than 150,000 hospitalizations every year, according to the Food and Drug Administration, and almost 1000 OTC medications have been linked to liver toxicity, which causes about 2000 deaths annually in the United States (Ford MD et al 2001).

A Harris Interactive consumer poll revealed some discouraging information about OTC use (Harris Interactive 2002):

- 51 percent of responding patients read the label when using an OTC for the first time.
- Only 34 percent read the label for the active ingredients.
- Only 19 percent read the label for usage instructions.
- Only 10 percent read the label for possible adverse effects or usage warnings.
- Only 34 percent who took an OTC medication for headache pain relief could correctly identify the active ingredient, which easily leads to widespread duplication of ingredients in different products.
- One out of three surveyed used more than the recommended dose of an OTC medication.
- 69 percent took more than the recommended dose at one time.
- 63 percent took the next dose sooner than directed on the label.
- 44 percent took more per day of the medication than the label directed.

Acetaminophen is especially dangerous because of its effect on the liver, which is responsible for metabolizing drugs. If toxic levels of acetaminophen occur in the liver, the natural antioxidant defenses of the body are overwhelmed, and the liver is damaged by the buildup of dangerous free radicals. It is therefore imperative that people who are taking acetaminophen also take sufficient quantities of antioxidants to help support healthy liver function.

### ACETAMINOPHEN

Found in more than 100 OTC preparations, including Sudafed®, Theraflu®, and Tylenol®, acetaminophen is used to reduce pain and fever. It has been available in the United States since 1960. Unlike NSAIDs, acetaminophen does not reduce inflammation or blood clotting or cause gastric complications (Roberts LJ et al 2001).

Nevertheless, acetaminophen overdose is one the most common causes of OTC drug poisoning in the United States and Britain. More than 30,000 cases per year of acetaminophen overdose are reported to the American Association of Poison Control Centers (Bartlett D 2004). It is a leading cause of liver failure in the Western world and the leading cause of drug-induced liver failure in the United States (Bartlett D 2004).

People who have liver disorders or who consume large amounts of alcohol are advised to avoid acetaminophen, which can damage both the kidneys and the liver, even at therapeutic doses (Bromer MQ et al 2003). People who use acetaminophen on a regular basis double their risk of kidney cancer (Kaye JA et al 2001; Gago-Dominguez M et al 1999; Derby LE et al 1996).

### Toxicity

Acetaminophen is extremely toxic to adults in single large doses of about 7000 mg (or 150 mg per kilogram of body weight). This large amount in one setting, however, is relatively rare. Instead, most cases of acetaminophen poisoning occur because people take smaller doses over a long period of time. In this setting, doses of 4000 mg daily can be toxic. In children, daily maximum oral dosing is not to exceed 90 mg per kilogram of body weight (O'Malley P 2005).

Acetaminophen poisoning affects the liver similarly to any other toxin, including alcohol. At higher doses, the drug can no longer be

metabolized by the liver, and the excess is oxidized into a toxic metabolite. This causes a rapid depletion of the internal antioxidants glutathione and S-adenosyl-L-methionine in the liver. When glutathione levels are reduced too far, liver cell death begins to occur.

### **Symptoms of Overdose**

Within 24 hours of a toxic dose of acetaminophen), nausea, vomiting, and abdominal tenderness may be present. Elevation of liver enzymes can occur from an acute dose as soon as 36 hours after ingestion (Ankeer A 2001). Within days, liver damage can result, followed by kidney damage. If liver failure occurs, mortality rates are relatively high (Oz HS et al 2004). Kidney function tests and liver enzyme measurements help assess adverse effects from acetaminophen (Wu E 1994; Brestel E 1994).

### **Treatment**

When a person with suspected acetaminophen poisoning is admitted to a hospital, the standard treatment is to administer a prescription drug called Mucosil as rapidly as possible. This drug inhibits the buildup of toxic by-products in the liver, thus limiting free radical damage and antioxidant depletion. The main ingredient in Mucosil is the nutrient N-acetylcysteine (NAC). In cases of acetaminophen poisoning, NAC should be administered within eight hours of ingestion of the acetaminophen. NAC stimulates synthesis of glutathione, which reduces free radical damage in the liver (Harris RA et al 2002). It also may act on the acetaminophen metabolite that directly depletes glutathione (Bartlett D 2004; Ankeer A 2001).

NAC is most effective when administered even before high acetaminophen levels are confirmed (Ankeer A 2001). Prior to NAC administration to improve liver function, a single dose of charcoal may be administered within the first four hours of acute ingestion to decontaminate acetaminophen not already absorbed in the gastrointestinal tract (Bartlett D 2004).

## **NSAIDS AND ASPIRIN**

**NSAIDs.** NSAIDs are common medications used to reduce pain and inflammation. They are available as both OTC medications (e.g., ibuprofen and naproxen, or Aleve®) and prescription drugs (e.g., cyclooxygenase enzymes, some of which are called COX-2 inhibitors). Because of the elevated risk of heart attack and stroke, several prescription COX-2 inhibitors, including Vioxx® and Bextra®, were removed from the market by their manufacturers in late 2004 and early 2005. Celebrex®, a prescription COX-2 inhibitor, remained on the market, but the Food and Drug Administration demanded that its manufacturer add a strong, prominent warning to the package detailing the elevated risks of heart attack and stroke.

OTC NSAIDs, however, were not implicated in these studies and so remain widely available. All told, more than 30 billion doses of NSAIDs are consumed annually in the United States alone. Ibuprofen, the most common OTC NSAID, can be found in scores of products or as a single-formulation drug. Even at nontoxic levels, NSAIDs damage tissue in the gastrointestinal tract, inhibit the function of platelets (blood cells that aid in coagulation and homeostasis), and alter kidney function.

NSAIDs work by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes, which convert arachidonic acid to pro-inflammatory prostaglandins (Schoenfeld P et al 1999). OTC NSAIDs are not selective inhibitors of COX enzymes; they inhibit both COX-1 and COX-2 (as opposed to prescription drugs such as Celebrex®, which is a selective COX-2 inhibitor) (Schoenfeld P et al 1999).

The gastrointestinal side effects caused by NSAIDs are due to their ability to inhibit COX-1. COX-1 is responsible for protecting the stomach through mucus production and immune cell defense, maintaining blood flow and kidney function, and processing sensations (Becker JC et al 2004). When these functions are compromised, the stomach lining is vulnerable to damage.

**Aspirin.** Aspirin is widely used for pain relief and has side effects and contraindications similar to those of NSAIDs. It is very important that people do not use aspirin and NSAIDs together unless directed by a physician. Like NSAIDs, aspirin can cause gastrointestinal upset.

Aspirin is used to relieve mild to moderate pain and to reduce fever, redness, and swelling. In low doses, it can be used to help prevent blood clotting. It is used to relieve discomfort caused by numerous medical problems, including headache, infections, and arthritis.

### **Incidence and Risk Factors for Overdose**

Regular use of NSAIDs increases the risk of kidney disorders. Acute deterioration of kidney function occurs in 0.5–1 percent of patients who regularly take NSAIDs (Whelton A et al 1991). The mortality rate from NSAID-related gastrointestinal toxicity, including toxicity from prescription NSAIDs, is 0.2 percent per year (Peura DA 2002).

The widespread intake of NSAIDs results in approximately 107,000 hospitalizations annually for gastrointestinal complications and

16,500 deaths for arthritis patients (Peura DA 2002). Some researchers have referred to NSAID toxicity as a “silent epidemic” that is little appreciated by the medical profession (Bandarage et al 2001). Corticosteroid use with NSAIDs increases risk of gastrointestinal complications and death, compared to NSAID use alone (Schoenfeld P et al 1999).

The risk of digestive upset, ulcers, and liver damage from NSAIDs may increase for people who drink regularly (Beers et al 2005). Increased risk associated with NSAID toxicity is also associated with the following factors (O’Malley P 2005):

- being older than age 65 (Peura DA 2002)
- being female (women are more common users)
- smoking
- having high body mass index
- having diabetes, cardiovascular disease, or hypertension

People who experience one gastrointestinal event from NSAIDs are at increased risk of a subsequent episode (Schoenfeld P et al 1999).

Other common risk factors for NSAID injury are infection with *Helicobacter pylori* (the organism associated with increased risk of ulcers), use of corticosteroids and anticoagulants, prior gastrointestinal complications, advanced age, and size of NSAID dose (Peura DA 2002). An association between *H. pylori* infection and NSAID-related ulcer disease is not clear (Schoenfeld P et al 1999).

### ***Toxicity***

Even at normal NSAID dosages, people with compromised kidney function can develop NSAID toxicity (Whelton A et al 1991). A standard CBC/Chemistry blood test that measures creatinine, blood urea nitrogen (BUN), and the BUN-to-creatinine ratio can help detect NSAID-induced kidney toxicity. If any of these blood markers of kidney damage is elevated, discontinuing NSAIDs and acetaminophen may result in a reversal of the kidney damage.

NSAIDs cause their gastric side effects by inhibiting the COX-1 enzyme. This causes mucus production to decrease in cells lining the gastrointestinal tract, leaving it vulnerable to gastric acid, bile, enzymes, and alcohol. Gastrointestinal injury ranges from heartburn, nausea, and abdominal pain to serious complications such as ulcers, hemorrhage, and tears in tissue (Schoenfeld P et al 1999). As you will read below, under “Nutritional and Supplemental Protection,” simple methods of reducing NSAID-induced gastric toxicity may enable those in chronic pain to continue using NSAIDs with minimal risk to the gastric mucosa.

### ***Symptoms of Overdose***

The most common symptoms of NSAID and aspirin overdose are heartburn, nausea, abdominal pain, ulcers, or even gastric perforation (Peura DA 2002). However, many people with gastrointestinal complications from NSAIDs exhibit no symptoms and may even have normal endoscopic exams (Schoenfeld P et al 1999). Although endoscopy is sometimes able to show NSAID gastric erosion within hours of acute ingestion, biopsy may be necessary to reveal the extent of injury and inflammation, especially with chronic ingestion. NSAID sensitivity can also be evaluated with spirometry measurements after administration of an oral NSAID dose (Brestel E 1994).

### ***Conventional Treatment***

Therapy for gastrointestinal complications from NSAID use includes proton-pump inhibitors such as Prilosec®, Prevacid®, or Nexium®. These drugs work by blocking the production of stomach acid. Some doctors prescribe the prostaglandin drug misoprostol, which was approved by the Food and Drug Administration for prevention of NSAID-induced ulcers. Misoprostol is an antisecretory agent that reduces stomach acid secretion (Peura DA 2002). It is the only agent to demonstrate success at preventing serious gastrointestinal complications (Schoenfeld P et al 1999).

Some studies show proton pump inhibitors to be more effective than misoprostol at healing and preventing ulcers among individuals who continuously use NSAIDs (Schoenfeld P et al 1999). Overall, proton pump inhibitors and misoprostol have shown more efficacy in healing ulcers than histamine-2 receptor antagonists such as Tagamet® and Zantac® (Schoenfeld P et al 1999).

Histamine-2 receptor antagonists, such as cimetidine (Tagamet®), ranitidine, and the stomach-coating agent sucralfate, can also heal ulcers if NSAID use continues (Schoenfeld P et al 1999).

### ***Nutritional and Supplemental Protection***

People who take acetaminophen and OTC NSAIDs regularly should be aware that these drugs can cause liver and kidney toxicity.

When you are taking these drugs, it is a good idea to provide antioxidant support to the liver and kidneys to protect them from the oxidant by-products caused by their metabolism.

Supplements that can be consumed in conjunction with acetaminophen include antioxidants such as selenium, vitamins E and C, alpha-lipoic acid, and nutrients such as S-adenosyl-L-methionine and NAC, which increase levels of glutathione. In addition, milk thistle extract has been shown to protect the liver and is widely used for degenerative liver diseases such as cirrhosis, which, like acetaminophen overdose, is associated with decreased levels of liver antioxidants.

**NAC.** NAC, an amino acid derivative, is part of the body's natural antioxidant system. It is the established conventional treatment for acetaminophen overdose because it can protect glutathione supplies in the case of a toxic acetaminophen event. When converted to cysteine, NAC is the key precursor to biosynthesis of glutathione (Faintuch J et al 1999).

**Vitamin E.** Like the other antioxidants, vitamin E (tocopherol) becomes deficient due to lack of glutathione or vitamin C (Marcus R et al 2001). Infusions of vitamin E become necessary when glutathione levels drop (Faintuch J et al 1999). To treat acetaminophen toxicity, pretreatment with vitamin E (30 mg/kg) combined with melatonin (10 mg/kg) was just as effective at fighting free radicals and reducing oxidative damage to the liver as NAC (150 mg/kg) (Sener G et al 2003). Vitamin E, along with vitamin C, also helps prevent NSAID-induced gastric injury by counteracting lipid peroxidation in the gastrointestinal tract.

**Vitamin C.** Like vitamin E, vitamin C becomes deficient once glutathione levels are reduced. Infusions of vitamin C are also necessary to combat lowered glutathione levels occurring from toxic substances that affect liver function, such as acetaminophen (Faintuch J et al 1999).

Vitamin C also induces a protective stomach enzyme (heme-oxygenase-1, or HO-1) that declines after toxic exposure to NSAIDs. HO-1, a vasodilating agent with anti-inflammatory and antioxidant effects, counteracts poor circulation and NSAID-induced gastric injury associated with release of free radicals (Becker JC et al 2004).

**Polyenylphosphatidylcholine (PPC).** PPC is a soy extract and has been shown to protect the liver against toxicity from acetaminophen. PPC also offers a powerful protective effect to the mucosa, or stomach lining. NSAIDs are known to decrease the protective mucosa, which makes the stomach lining vulnerable to injury and ulceration (Anand BS et al 1999). PPC has been shown to improve the gastric tolerance of ibuprofen by protecting the stomach wall (Leyck S et al 1985).

**Whey.** Whey, a serum protein representing 20 percent of milk, has a high concentration of the amino acid cysteine, enabling it to act as a potent antioxidant in the liver and a key rate-limiting precursor to glutathione levels.

**Milk thistle.** *Silybum marianum*, commonly known as milk thistle, has been a treatment for liver diseases for more than 2000 years (Flora K et al 1998). As an antioxidant, silymarin (milk thistle's active constituents) reduces free radical production and lipid peroxidation in the liver and slows glutathione depletion (Basaga H et al 1997). In laboratory rats, silymarin significantly reduced hepatic necrosis caused by toxic doses of acetaminophen and protected liver cell membranes exposed to an array of hepatotoxins (Muriel P et al 1992; Davila JC et al 1989; Shear NH et al 1995).

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Considering the dangers associated with acetaminophen and OTC NSAIDs, it is a good idea to use these drugs sparingly, if at all. To help protect the liver, kidney, and stomach, consider mitigating the ill effects of OTC medications by taking nutrients such as the following:

- **NAC**—600 to 1800 milligrams (mg) daily. If NAC is taken with acetaminophen, Life Extension recommends NAC dosages of 600 mg with at least 1 gram (g) vitamin C per dose of acetaminophen.
- **Vitamin E**—400 international units (IU) daily (along with at least 200 mg of gamma tocopherol)
- **Vitamin C**—around 2000 mg daily. Precaution: A buffered vitamin C may be desired by those with stomach lining irritation.
- **PPC**—900 mg with each NSAID dose to help protect the stomach lining and guard against liver toxicity
- **Whey protein**—20 g daily, mixed with cereal or a liquid
- **Milk thistle extract**—250 mg two or three times daily in cases of chronic acetaminophen use

## OTC DRUG TOXICITY SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

## **Milk Thistle**

- Consult your doctor before taking milk thistle with tranquilizers such as Haldol, Serentil, Stelazine, and Thorazine. Milk thistle combats the effect of tranquilizers.
- Do not combine milk thistle with the blood pressure medication Regitine. Milk thistle combats the effect of Regitine.

## **NAC**

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

## **Phosphatidylcholine**

- Phosphatidylcholine can cause increased salivation, a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.

## **Vitamin C**

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

## **Vitamin E**

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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