

Over-the-Counter Drugs: “Safe as Directed?”

Pharmacists should advise patients about potential hazards of OTCs

by Heidi Timmerman, RPh

PATIENT CASE

A 58-year old man presented to Rheumatology Clinic with severe right hip pain due to aseptic necrosis of the hip. He also had complaints of gastritis, loss of appetite and abdominal pain. He was taking Percocet (oxycodone 5 mg and acetaminophen 325 mg) two tablets every four hours for pain. He admitted to taking 10-12 tablets/day. Upon further review of his medication history, the patient admitted to taking an additional 4-8 grams of acetaminophen per day as over-the-counter medication, due to lack of response from the Percocet.

The patient presented with right upper quadrant tenderness. His liver was palpable five centimeters below the right costal margin. His liver function tests revealed an AST= 320 units/L (Normal: 5-29 units/L), LDH 400 units/L (Normal: 82-226 units/L), with a normal alkaline phosphatase and bilirubin. He denied a history of alcohol or other liver toxins.

The patient was diagnosed as having liver toxicity from an overdose of acetaminophen. All acetaminophen was discontinued and the patient's oxycodone dose was increased to achieve better pain control. He returned four weeks later with no gastrointestinal symptoms and normalization of his liver function tests.

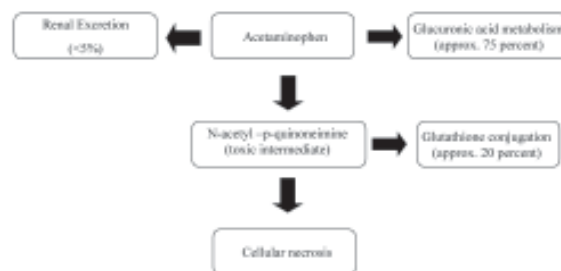
Over-the-counter drugs (OTCs) represent a significant portion of all therapeutic agents in this country. Non-prescription drugs account for about 60% of medications used in the United States.¹ Many of the components of OTCs are safe and effective for the conditions they are intended to treat when used as directed.² However, taking too much of a particular drug may lead to undesired toxicity. For example, acetaminophen, when taken in excess of four grams/day, can lead to serious liver damage.¹ In recent years, many compounds which were originally marketed as prescription medicines have become available as OTCs.¹ The consumer's role has thus changed from “passive patient” to “health manager.” Due to the increased availability of therapeutic agents as OTCs, patients rely on pharmacists as an important resource for assistance in their self-care.

Acetaminophen (APAP) is an example of an OTC that is frequently misused, either intentionally or unintentionally. APAP is used in a wide variety of combination products, from cough and cold preparations to sleep aids.¹ This can lead to unintentional overdosing when a patient ingests several OTC products containing APAP.² In addition, when taken in excessive quantities, or when combined with alcohol, APAP may cause death due to liver failure.²⁻⁵ Overdose of APAP is one of the most common causes of liver failure, as well as being the most common cause of drug-induced liver disease in the United States.^{4,5}

The mechanism by which liver toxicity occurs is metabolism of APAP to a reactive, electrophilic metabolite called n-acetyl-p-quinoneimine (NAPQI).⁴ NAPQI forms when the normal routes of hepatic elimination of APAP (glucuronidation and sulfation) are saturated.⁵ More metabolism is shifted to the cytochrome P450 enzymes, which generate NAPQI.^{4,5} NAPQI is highly reactive and overwhelms the stores of glutathione (a natural cellular antioxidant) in the liver.⁵ This process involves direct reaction with critical elements and resultant necrosis of the liver cell.⁵

A single dose of more than 150 mg/kg body weight of APAP is generally recognized as the hepatotoxic threshold.^{5,6} Patients who abuse alcohol or who have chronic liver disease may have a lower threshold for toxicity.^{2,4-6} Although chronic ingestion of alcoholic beverages (defined as >14 units/week for women, >21 units/week for men) decreases the threshold for toxicity, acute alcohol in-

OVERVIEW OF ACETAMINOPHEN METABOLISM



(Adapted from Bagheri SC, Beckley ML, Farish SE. Acute acetaminophen toxicity: report of a case. J Calif Dent Assoc. 2001; 29:687-690. Reprinted with permission.)

gestion reduces the toxicity of APAP.⁴ This is due to the inhibition by ethanol of the sub-enzyme of cytochrome P450 which produces NAPQI.⁴ Treatment of APAP overdose involves monitoring APAP serum concentrations and judging these concentrations against a standard nomogram developed by the manufacturer of Mucomyst®.^{6,7} Mucomyst® (acetylcysteine 20% solution, USP) is indicated for oral administration to patients who have overdosed on APAP.⁷ N-acetylcysteine is given as an initial dose of 140 mg/kg of patient body weight. This is followed by a regimen of 70 mg/kg of body weight every four hours. The nomogram in the package insert indicates

continuation of therapy until APAP levels have fallen below a threshold or 17 maintenance doses are given, whichever occurs sooner.⁷

APAP is perhaps one of the most widely known agents involved in accidental poisoning and overdose; however, other OTC agents can be just as deadly. A three-month retrospective evaluation attempted to determine the overall percentage of OTC medicine-related overdoses, both alone and in combination with prescription-only medication (POM).⁸ During the study, four emergency rooms received a total of 392 patients who had overdosed on a pharmaceutical agent. More than 40% (n=169) of the overdose cases were OTC drug-related, of which 18.1% (n=71) were OTC-only overdoses. APAP was involved in 36.7% of all overdose cases, while OTC aspirin and ibuprofen were implicated in 8.9% and 3.2% of all cases, respectively.

Demographic information indicated that those individuals most likely to overdose were single females between 25 and 40 years of age. Those who were single were more likely to overdose with an OTC agent only compared with a mixed overdose (13.8% vs. 8.8%, p<0.05).

Even when OTCs are taken according to the directions on the package label, they aren't guaranteed to be safe for every patient who takes them.⁷ In a presentation given to the APhA, Dr. Timothy R. Covington urged pharmacists to become more proactive in their dealings with patients who purchase OTCs.⁹ He made several recommendations for strategies that pharmacists can utilize to help patients.⁹ One particular method would be to put banners above the OTC shelves, indicating the pharmacist as an expert resource on nonprescription medicines.⁹ Patients should be encouraged to ask questions about medications, especially those available from non-pharmacy outlets.¹⁰ Pharmacists should also utilize a structured questionnaire approach when advising patients about self-care.¹⁰ An easy acronym for such a questionnaire is WWHAM.¹⁰ The acronym represents five questions:

- Who is the patient?
- What are the symptoms?
- How long have the symptoms been present?
- Action being taken?
- Medication recommendation? (if prescribed by the pharmacist)

The last question establishes whether the patient is on any regular medication. In addition, the pharmacist should determine whether the patient has already used any products to alleviate the symptoms.¹⁰

Ease of access to OTCs is central to the philosophy of self-treatment.¹⁰ The good news for consumers is the increased availability of OTC pharmaceuticals through non-pharmacy vendors. For example, in 1970, 65% of OTC products were purchased in pharmacies; in 2001, the number had decreased to 39%.⁹ The self care ethos promotes choice and empowerment for the patient; however, patients need to be educated accordingly in order to make the right decisions regarding self-medication.¹⁰

In conclusion, the pharmacist can take advantage of the positive changes involved with increased numbers of OTCs. A wide selection of OTCs allows patients to conveniently and effectively treat a number of minor ailments without generating the additional cost of a patient visit. However, many dangers coexist with the benefits of self-medication with OTCs. Pharmacists can help prevent the adverse reactions and drug misadventures that can occur due to patient confusion and unrealized overdose. Through patient education and training, the lack of knowledge of the lay public, with respect to self-treatment, will decrease. ●

FDA Issues and Concerns Regarding OTC Analgesics

The FDA recently issued a statement to health care professionals regarding the role they play in providing information to the public about unintentional acetaminophen-induced liver damage and NSAID-related GI bleeding and kidney damage. This statement arose from a review by the FDA Nonprescription Advisory Committee.

This statement describes the history of OTC acetaminophen use in this country. The statement also warns of the heightened danger of consuming acetaminophen with alcohol. Between January 1998 and July 2001, 307 cases of acetaminophen-related hepatotoxicity were reported to the FDA's Adverse Event Reporting System. Factors contributing to these cases included the following:

- Failure by consumers to recognize the presence of acetaminophen in OTC products
- The wide variety and availability of OTC products containing acetaminophen
- The lack of consumer awareness of the potential for harm by consuming multiple acetaminophen-containing products simultaneously
- The failure of prescription container labels to list acetaminophen as an ingredient


Four cases of unintentional overdose in children occurred as the result of administering the wrong pediatric formulation, incorrect calculation of weight-appropriate dose, and using the wrong dosing device to prepare the dose.

The FDA outlined a series of recommendations for health care providers to address this public health problem and to assist consumers in recognizing the potential problems of acetaminophen ingestion.

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 THE FULL FDA STATEMENT IS AVAILABLE AT
WWW.FDA.GOV/CDER/DRUG/ANALGESICS/SCIENCEPAPER.PDF