Food and Drug Administration
Science Background

Safety Concerns Associated with Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use

January 22, 2004

This Science Paper is intended to raise the awareness of healthcare professionals about the important educational role that they can play in preventing unintentional acetaminophen induced hepatotoxicity and NSAID-related gastrointestinal bleeding and renal toxicity in their adult and pediatric patients. The FDA Nonprescription Advisory Committee (NDAC) reviewed safety data related to the use of these pain relievers on September 19-20, 2002, and made recommendations regarding ways to better educate patients and consumers in order to reduce the risk of these rare, but potentially serious adverse events.[1]

History

Acetaminophen has been marketed in the United States as an over-the-counter (OTC) antipyretic/analgesic agent since 1960. It is widely available in a variety of strengths and formulations for children and adults as a single-ingredient product, and can also be found in numerous combination OTC and prescription drug products.

Chemically acetaminophen is a para-aminophenol derivative that is also the active metabolite of the analgesic drug phenacetin.[2] Its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat center, while its analgesic efficacy is due to its ability to raise the pain threshold.[2]

Acetaminophen's ability to cause fulminant hepatic failure in acute intentional overdose situations or when used in combination with alcohol is well known. The latter resulted in the addition of an alcohol warning on all OTC acetaminophen-containing products since 1998. An internal review of post-marketing case reports collected by the FDA's Adverse Event Reporting System (AERS) identified 307 cases of hepatoxicity in both adults and children during the period from January 1998 to July 2001, where at least one acetaminophen containing product was considered to be a suspect drug. The agency review focused on cases of unintentional overdose (not related to a suicide attempt) of acetaminophen leading to hepatotoxicity. The agency also reviewed data from liver failure transplant lists and other information submitted to the agency. Many of these cases are consistent with published reports in the worldwide literature, and provided the basis for public discussion of the drug's safety profile at the September 2002 NDAC meeting.

NSAIDs include aspirin, which irreversibly acetylates cyclooxygenase (COX), and several other classes of organic acids, including propionic acid derivatives (ibuprofen, naproxen, etc.), acetic acid derivatives (indomethacin, etc.), and enolic acid acids (e.g., piroxicam), all of which are reversible competitors with arachidonic acid at the active site of cyclooxygenase [3]. There are two forms of cyclooxygenase, COX-1 found in blood vessels, stomach and kidney, and COX-2, which is induced in settings of inflammation by cytokines and inflammatory mediators. All currently available OTC NSAIDs are non-selective COX inhibitors. The antipyretic, analgesic, and antiinflammatory actions of NSAIDs are related to their ability to inhibit COX-2. Side effects such as gastrointestinal (GI) bleeding and renal toxicity are a result of the inhibition of COX-1 and are well-known complications of NSAID therapy [3,4,5].

Review of post-marketing case reports collected by the FDA's Adverse Event Reporting System (AERS) between 1998 and 2001 identified a total of 279 cases of GI bleeding associated with the OTC use of NSAIDs: 197 cases for ibuprofen, ketoprofen and naproxen, and 82 cases for aspirin. The cases were screened for the use of these analgesic products, or for mention of OTC use in the narrative of the report. These reports are consistent with published case studies from the worldwide literature.

Data supporting a nephrotoxic risk associated with use of OTC NSAIDs was compiled from adverse events reported to the FDA's AERS database and large population studies. Cases of acute renal failure with the use of OTC NSAIDs are rare. Individuals with conditions where renal perfusion is more dependent on prostaglandins (e.g. congestive heart failure, hepatic cirrhosis with ascitis, chronic renal disease, or hypovolemia such as occurs with dehydration) are at particular risk for acute renal failure.

Considering the wide spread use of OTC analgesic/antipyretic drug products, the FDA acknowledges that the serious adverse event rate is low. However, it is clear that many of the serious adverse events are preventable.

What are the factors that contribute to these cases?

Acetaminophen Hepatotoxicty

The acetaminophen safety review update identified four factors, which have resulted in potentially fatal or life threatening unintentional overdoses in the adults:

- failure by consumers to recognize the ingredients contained in OTC drug products and/or the potential for harm due to exceeding the recommended dose
- the wide variety and availability of both OTC and prescription drug products that contain acetaminophen (e.g., single ingredient, combinations, and multiple formulations)
- the lack of consumer awareness for the potential to develop serious adverse events from taking two or more different products containing acetaminophen concomitantly
- the failure of prescription container labels to list acetaminophen as an ingredient

Four situations were identified which resulted in unintentional overdoses in children:

- administering the **wrong** pediatric acetaminophen formulation [i.e., substituting the concentrated infant drops (80mg/0.8ml) for the less concentrated children's suspension (160 mg/5 ml)]
- administering the adult instead of the age-appropriate children's formulation
- incorrectly calculating the weight-appropriate dose of acetaminophen
- using the wrong dosing device (e.g., tablespoon instead of teaspoon, dropper versus syringe)

NSAIDs Gastrointestinal Bleeding and Renal Toxicity
The NSAID safety data review identified the following risk factors for GI bleeding for OTC and prescription NSAIDs:

- use of concomitant medications such as anticoagulants and/or corticosteroids
- concomitant use of low dose aspirin and other NSAIDs
- increasing age ($\geq$ 60 years)
- increasing dose
- previous history of GI bleeding
- concomitant use of alcohol

The following at-risk populations for NSAID-induced nephrotoxicity were identified:

- patients with volume depletion
- underlying kidney disease
- congestive heart failure
- elderly ($\geq$ 65 years)
- hypertension
- diabetes

Discussion
The unintentional acetaminophen overdoses resulting in liver failure, and the cases of GI bleeding and renal toxicity attributable to the use of OTC NSAIDs underscore the need for better consumer education about which products contain acetaminophen or an NSAID and conditions for safe product use. Many of these adverse events are preventable. Consumers need to recognize that serious health consequences can result from unsafe use of over-the-counter analgesics.

Recommendations
Health care providers should prescribe adequate pain medication regimens for patients and provide instructions regarding the use of other pain medications, including appropriate warnings about use of multiple and combination products containing the same active ingredient. The FDA encourages healthcare providers to help prevent the morbidity and mortality of acetaminophen-induced hepatotoxicity and NSAID-related GI and renal effects by educating their patients about the following:

- that **any OTC analgesic** is a drug and appropriate safety precautions need to be taken when using or storing it

- the wide variety of different strengths, formulations, and combinations of acetaminophen- and NSAID-containing products that are available OTC and by prescription
- the correct dosing frequency for each of the acetaminophen or the NSAID formulations
- the correct weight-based dose for each child
- the use of the correct measuring device for liquid formulations
- drinking more than 3 alcoholic drinks every day is not compatible with safe acetaminophen or NSAID use
- risks of taking OTC analgesics with other prescription or non-prescription medications
- signs and symptoms of self-recognizable side effects
- the potential problems associated with using more than one pain reliever product simultaneously

The FDA is also recommending that all U.S. Boards of Pharmacy implement changes to the container labeling for all prescription drugs containing acetaminophen or NSAIDs so that all active ingredients (such as acetaminophen or NSAID), their strengths, recommended single and daily dose, and warnings appear on the prescription label.

Most importantly health care professionals should remind their patients to always read their OTC and prescription medication labels and carefully follow the directions.

References

[1] Nonprescription Drug Advisory Committee Meeting, September 2002 transcripts located at www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T1.htm

[2] Woodbury DM, Fingl E: Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout. *In* Hardman JG, Gilman AG, Limbird LE (eds): Goodman's &Gilman's The Pharmaceutical Basis of Therapeutics, 5th ed. New York, Mcgraw-Hill, 1970: 325-58

[3] Insel P: Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout. *In* Hardman JG, Gilman AG, Limbird LE (eds): Goodman's &Gilman's The Pharmaceutical Basis of Therapeutics, 5th ed. New York, Mcgraw-Hill, 1996: 617-43

[4] Lanza FL, et al: A guideline for treatment and prevention of NSAID-induced ulcers. Am J Gastroenterol 1998; 93(11):2037-46

[5] Altman RD, et al: Recommendations for the medical management of osteoarthritis of the hip and knee; 2000 update. Arthritis Rheum 2000; 43(9): 1905-15