The Pharmacist Activist

Volume 4, No. 7 • July 2009

Editorial

The Acetaminophen Challenge (and Recommendations)

Acetaminophen is the most widely used medication in the United States, being used by approximately 100 million people. Often designated by its most popular brand name Tylenol or as APAP (the abbreviation for its chemical name), it is supplied as a single active ingredient in numerous products, and with one or more other active ingredients in hundreds of combination products. There are valid reasons for the extensive use of acetaminophen. It is effective in relieving mild to moderate pain and relieving fever, and, when used in the recommended dosage, is one of the safest, if not the safest, medications available. Its safety justifies its availability without a prescription.

The Problems

The maximum recommended adult dosage of acetaminophen is 4000 milligrams a day (in divided doses). When used in amounts that exceed this dosage, it may cause hepatic toxicity, and acetaminophen overdosage is the most frequent cause of liver failure in the U.S. Acetaminophen overdoses are responsible for an estimated 56,000 visits to emergency departments each year, and approximately 100 people die each year from accidental overdoses (as distinct from intentional overdoses [i.e., suicide attempts]). An estimated 60% of acetaminophen-related deaths have involved the use of prescription combination products such as Percocet (acetaminophen and oxycodone) and Vicodin (acetaminophen and hydrocodone). With these products, as well as with the nonprescription combination products used for conditions such as pain and colds, patients are often not aware that acetaminophen is one of the active ingredients. This is particularly true with the prescription opioid/acetaminophen combinations for which the primary attention and warnings focus on the more potent opioid component. Many of the accidental overdoses result from the use of two or more acetaminophen-containing products.

Failures to Reduce the Problems

The problems associated with acetaminophen overdosage have been recognized for many years. Warnings in the labeling and packages of the products have been strengthened, a public awareness campaign has been conducted, symposia have been held, and health professionals have been urged to be more diligent in monitoring for situations that could result in overdosage. However, hospitalizations for acetaminophen overdosage have not decreased. Although many patients have not demonstrated responsibility in knowing what medications they are taking and the precautions associated with their use, a large part of the responsibility for the failure to be more effective in preventing acetaminophen-associated problems rests with the companies marketing the products, health professionals, and the Food and Drug Administration (FDA). It was with this recognition that the FDA convened 37 health professionals who serve on three of its advisory committees (Drug Safety and Risk Management; Nonprescription Drugs; and Anesthetic and Life Support Drugs) to meet on June 29 and 30 for the purpose of recommending ways through which acetaminophen overdosages could be reduced.

Recommendations

Although the FDA is not required to accept the recommendations of its advisory committees, it usually does so. The joint advisory committee developed a number of recommendations at the end of its two-day meeting, although it is noteworthy that the vote on certain of the recommendations was very close. The most important of these recommendations are identified below, followed by my editorial comment/recommendation.

1. The committee recommended (by a vote of 21 to 16) that the FDA reduce the maximum daily dosage of acetaminophen from its current level of 4000 mg a day (for adults). A specific dosage to which

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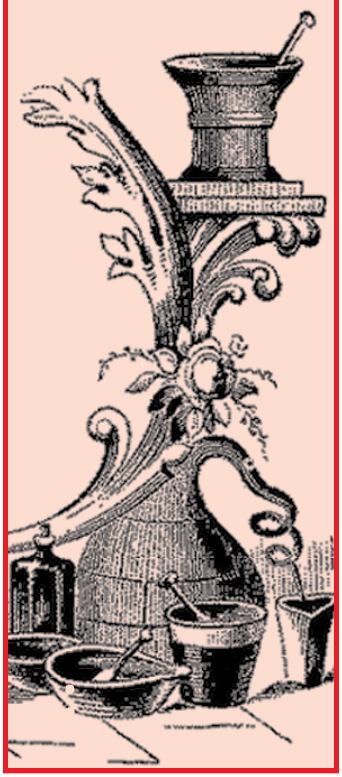

it should be reduced was not specified, although other committee recommendations suggest support for a maximum nonprescription dosage of 2600 mg a day (i.e., 650 mg four times a day).

I do not agree with this recommendation. There has been extensive experience with the current dosage recommendation and the safety record of the drug when used within these dosage parameters has been exceptionally good. The potential disadvantage of using acetaminophen in a lower dosage is that patients will not experience adequate/complete relief of pain. In view of the experience of the vast majority of patients who have used acetaminophen that the drug is both effective and safe in its currently recommended dosage, I anticipate that a recommendation to use a lower dosage will be widely ignored.

2. The committee recommended (by a vote of 24 to 13) that the single, nonprescription adult dose be reduced to 650 mg (from 1000 mg).

I do not agree with this recommendation. Many individuals do not use acetaminophen on a continuing basis but, rather, use one or two doses for the treatment of conditions such as headache. Although some will suggest that a dose of 650 mg will be sufficient to relieve pain, experience and reason suggest that a dose of 1000 mg will be more effective in relieving pain. The committee's recommendation also has the potential to invite the development of an immediate-release tablet formulation that contains 650 mg of acetaminophen. Such a formulation might be confused with the controlled-release formulation of the same potency that is currently available.

Although I disagree with the committee's recommendation, I do support the initial use of a dose of 500 mg (rather than 1000 mg that is recommended for some products) that may be subsequently increased to 1000 mg if the relief of pain is not adequate.

3. The committee recommended (by a vote of 26 to 11) that the current maximum single dose of 1000 mg (2 x 500 mg) be available only on prescription.

I do not agree with this recommendation. This recommendation recognizes the validity of single doses of 1000 mg of acetaminophen (as addressed in my comment in #2 above), but would limit such a dose to prescription use. A quantity of 1000 mg of any medication would result in a tablet formulation that is large in size and possibly difficult to swallow, particularly for the elderly. Therefore, this dose would most likely be provided by taking two tablets of a 500 mg-potency. This situation could create confusion for patients as to why they must have a prescription for 500 mg tablets when the recommended single dose for nonprescription use is 650 mg. It is also difficult to imagine that patients will be pleased with a prescription for acetaminophen as an outcome of a physician visit when they could have purchased the medication without a prescription. If the 500 mg tablets are no longer available on a nonprescription basis, a dose of 1000 mg can be approximated with the use of three 325 mg tablets.

4. The committee recommended (by a vote of 36 to 1) that there be only one concentration of nonprescription acetaminophen liquids for pediatric patients. However, some committee members thought that the one concentration should be the more concentrated formulation for infants, whereas others thought that it should be the less concentrated formulation for older children.

I agree with this recommendation. Confusion regarding the two concentrations of the liquid formulations that are currently available has resulted in the administration of overdoses to children. I recommend that the single concentration be the less concentrated formulation, although I sympathize with the parents having the challenge of administering a larger amount of liquid to a young child.

5. The committee recommended (by a vote of 20 to 17) that the FDA eliminate prescription acetaminophen combination products (e.g., Percocet, Vicodin).

I do not agree with this recommendation. Products that contain acetaminophen in combination with hydrocodone or oxycodone are extensively prescribed for the relief of moderate to moderately severe pain. Notwithstanding the problems associated with the misuse/abuse of these products, there is a sound rationale for their use in combination in that acetaminophen and the opioid (narcotic) analgesic relieve pain by different mechanisms of action, and that the inclusion of acetaminophen may permit the use of a lower dosage of the opioid analgesic. In my opinion, the elimination of these products will create more confusion and problems than it will resolve. I do not believe that the interests of patients experiencing significant pain are best served by prescribing only the opioid analgesic or the two analgesics separately.

6. The committee recommended against (by a vote of 13 to 24) eliminating nonprescription acetaminophen combination products from the market.

I agree with the committee's recommendation. These combination products provide a convenient and less expensive way in which patients may use multiple medications to relieve multiple symptoms. However, my support for this recommendation is coupled with my further recommendation that these combination products be available only behind the counter in pharmacies from a pharmacist (products that contain only acetaminophen as the single active ingredient would continue to be available as they are now). This recommendation places the pharmacist in a position to be aware of all combination products that contain acetaminophen that a patient has been prescribed or is requesting on a nonprescription (behind-the-counter) basis. When a patient presents a prescription for a product such as Vicodin, or requests a nonprescription acetaminophen combination product, the pharmacist should determine whether the patient is taking any other acetaminophen-containing products. With this information, the pharmacist is in a position to counsel the patient and/or initiate any intervention that may be necessary. This recommendation has an added benefit in that it permits the pharmacist to assess whether the combination product the patient has requested is an appropriate choice to provide relief for the symptoms identified. For example, a patient with allergy symptoms (e.g., sneezing, runny nose) and nasal congestion would be best treated with a product that contained an antihistamine and decongestant, and would not need acetaminophen.

The committee also made several other recommendations but space does not permit their consideration here. To my knowledge, the committee did not consider several other issues that are also pertinent. As one example, in my opinion the use of the abbreviation APAP should be strongly discouraged because some patients do not know that it refers to acetaminophen.

A potential consequence of the deliberations and recommendations that looms larger than any other is the following. What if restrictions are imposed on the availability and use of acetaminophen that result in more extensive use of aspirin and other nonsteroidal anti-inflammatory drugs with their risks of gastrointestinal hemorrhage and resultant deaths? Some would contend that, at the present time, this is a greater risk for more people than acetaminophen overdosage. We can do much more in enhancing the safety of using acetaminophen but these steps must be taken in a manner that does not limit its substantial value.

Daniel A. Hussar

New Drug Review

Lacosamide (vimpat – UCB)

Antiepileptic Drug

New Drug Comparison Rating (NDCR) = 4

(significant advantages) in a scale of 1 to 5, with 5 being the highest rating

Indication:

Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older; injection for intravenous use may be used when oral administration is temporarily not feasible.

Comparable drugs:

Carbamazepine (e.g., Tegretol), oxcarbazepine (Trileptal), lamotrigine (e.g., Lamictal), levetiracetam (e.g., Keppra).

Advantages:

- Has reduced seizure frequency in some patients in whom previous treatment did not provide adequate seizure control;
- Has a unique mechanism of action;
- Less likely to cause serious adverse events (compared with carbamazepine that has a boxed warning regarding serious dermatological reactions, aplastic anemia, and agranulocytosis, lamotrigine that has a boxed warning regarding serious rashes, and oxcarbazepine that may cause serious dermatological reactions and anaphylaxis/angioedema);
- Less likely to interact with other drugs (compared with carbamazepine);
- Less risk if used during pregnancy (is in Pregnancy Category C compared with carbamazepine that is in Category D);
- Available in a formulation for intravenous use when oral administration is not feasible (compared with carbamazepine, oxcarbazepine, and lamotrigine).

Disadvantages:

- Is not indicated for use as monotherapy (compared with carbamazepine, oxcarbazepine, and lamotrigine);
- Is not indicated for use in patients less than 17 years of age (levetiracetam is indicated for use in children as young as 4 years of age, lamotrigine and oxcarbazepine in children as young as 2 years of age, and there has been extensive experience with carbamazepine in pediatric patients);
- Labeled indications are more limited (compared with carbamazepine that is also indicated for generalized tonic-clonic seizures, mixed seizure patterns, bipolar disorder, and trigeminal neuralgia, lamotrigine that is also indicated for tonic-clonic seizures, Lennox-Gastaut syndrome, and bipolar disorder, and levetiracetam that is also indicated for tonic-clonic seizures and myoclonic seizures);
- Is a controlled substance (Schedule V);
- May prolong the PR interval of the electrocardiogram;
- Is administered twice a day (compared with formulations of levetiracetam [Keppra XR] and lamotrigine [Lamictal XR] that are administered once a day).

Most important risks/adverse events:

Suicidal ideation and behavior (patients should be monitored for the emergence or worsening of depression, suicidal thoughts, and/or unusual changes in mood or behavior); central nervous system (CNS) effects (e.g., dizziness, fatigue, ataxia; patients should be advised not to engage in potentially hazardous activities until they have assessed whether the drug adversely affects their mental and/or motor performance, and cautioned about the added risk if other CNS depressants, including alcoholic beverages, are used concurrently); syncope; prolongation of PR interval (caution is advised in patients with cardiac conduction problems, severe cardiac disease [e.g., myocardial ischemia, heart failure], or who are taking other drugs that prolong the PR interval [e.g., calcium channel blockers]); multiorgan hypersensitivity reactions (e.g., nephritis, hepatitis).

Most common adverse events:

Dizziness (30%), headache (14%), nausea (11%), vomiting (9%), diplopia (11%), blurred vision (9%), somnolence (8%), ataxia (7%), fatigue (7%).

Usual dosage:

50 mg twice a day initially; dosage can be increased at weekly intervals by 100 mg/day given as two divided doses up to the recommended maintenance dosage of 100 to 200 mg twice a day; a dosage of 300 mg/day should not be exceeded in patients with severe renal impairment or mild to moderate hepatic impairment; use in patients with severe hepatic impairment is not recommended; formulations for oral use and intravenous infusion (over a period of 30 to 60 minutes) may be used in the same dosage; if treatment is to be discontinued, should be withdrawn gradually over a period of at least one week.

Products:

Tablets – 50 mg, 100 mg, 150 mg, 200 mg; vials – 200 mg in 20 mL of solution; parenteral formulation may be used without dilution or may be mixed with a diluent (Sodium Chloride Injection 0.9%, Dextrose Injection 5%, Lactated Ringer's Injection).

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New Drug Review (cont.)

Comments:

Partial-onset seizures are usually treated with a combination of antiepileptic drugs (AEDs), and carbamazepine, lamotrigine, levetiracetam, and oxcarbazepine are often considered to be among the first-line treatment options. However, numerous other AEDs have also been used effectively in these seizure disorders. Lacosamide is a functionalized amino acid that is thought to selectively enhance slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes. In addition, it binds to collapsin response mediator protein-2, although whether this binding contributes to a reduction in seizures is not known.

The effectiveness of lacosamide was demonstrated in three 12-week, placebo-controlled studies in patients who were not adequately controlled with 1 to 3 concomitant AEDs. Of the patients treated with lacosamide (400 mg/day), 40% experienced a 50% or greater reduction in seizure frequency, compared to 23% of the patients receiving placebo with concomitant AEDs.

Like other AEDs, lacosamide may increase the risk of suicidal thoughts or behavior, and patients should be closely monitored. CNS effects are common and patients should be cautioned about the pertinent risks. Dose-dependent prolongations in the PR interval of the electrocardiogram have been observed, and asymptomatic first-degree atrioventricular block was reported in 0.4% of patients receiving lacosamide but in none of the patients receiving placebo. In patients at risk, an electrocardiogram should be obtained before starting treatment and after the dosage is titrated to a steady-state.

Higher doses of lacosamide have produced euphoria-type responses similar to those associated with alprazolam (e.g., Xanax). The incidence of euphoria reported as an adverse event in the clinical studies is less than 1%. However, as with pregabalin (Lyrica), lacosamide has been classified in Schedule V under the provisions of the Controlled Substances Act.

Lacosamide is a substrate for the CYP2C19 metabolic pathway but more than 40% of a dose is eliminated in unchanged form. Interactions via pharmacokinetic mechanisms appear unlikely to occur.

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