The Pharmacist Activist

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Editorial

The TYLENOL Follies

Which of the following is the recommended maximum amount of acetaminophen that may be taken (in divided doses) by an adult during a 24-hour period?

a. 4,000 mg
b. 3,000 mg
c. 3,250 mg
d. 3,900 mg
e. It depends on the particular formulation
f. It depends on the company making the formulations
g. All of the above

And the answer is "g" – all of the above. We will come back to this question later after considering some background information.

Background

Acetaminophen is the most widely used medication in the United States. It is supplied as a single active ingredient in numerous products, and with one or more other active ingredients in hundreds of combination products. When used in the recommended dosage, it is one of the safest medications available. Because of its safety, as well as its effectiveness, I consider it to be the OTC analgesic of first choice for most situations associated with mild to moderate pain.

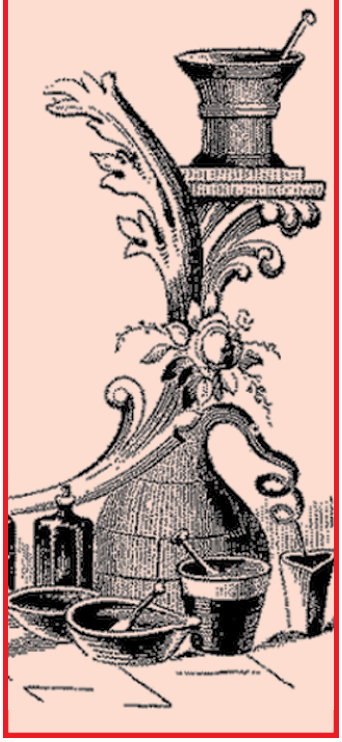
Very serious, and sometimes fatal, problems may result when acetaminophen is used in amounts that exceed the recommended maximum dosage. Acetaminophen overdosage is the most frequent cause of liver failure in the United States and approximately 100 people die each year from accidental overdoses (as distinct from intentional overdoses [i.e., suicide attempts]). Many of the accidental overdoses result from the concurrent use of two or more acetaminophen-containing products, and most of the deaths have involved the use of prescription combination products such as Percocet (acetaminophen and oxycodone) and Vicodin (acetaminophen and hydrocodone).

On June 29 and 30, 2009, 37 health professionals who serve on three FDA advisory committees were convened by the FDA for the purpose of recommending ways through which acetaminophen overdosages could be reduced. The most important of these recommendations are considered in my editorial in the July 2009 issue of *The Pharmacist Activist* (www.pharmacistactivist.com).

Recent actions

In early 2011 the FDA notified health professionals that it has asked manufacturers to limit the amount of acetaminophen in prescription drug products (primarily combinations of acetaminophen and opioids [e.g., Percocet, Vicodin]) to 325 mg per tablet, capsule, or other dosage unit, as a step to

Contents



reduce the risk of severe liver injury. This action is planned to be implemented over a three year period, and does not apply to OTC products. In the FDA communication, health professionals are reminded to advise patients not to exceed the acetaminophen maximum total daily dose, identified as 4 grams/day.

In May it was announced that the companies that make single-ingredient liquid acetaminophen pediatric products would now provide them in only one standard concentration (160 mg/5 mL) to help prevent dosing errors. The more concentrated solutions of acetaminophen intended for administration as drops will no longer be supplied. I agree with this action although I sympathize with the parents having the challenge of administering a larger amount of liquid to a young child.

The recalls

Over the last two years, Johnson & Johnson/McNeil Consumer have had to initiate recalls of dozens of lots of Tylenol and other OTC and prescription products for a variety of reasons primarily related to manufacturing, production, and storage issues. For a company that has enjoyed such an exceptional reputation for decades, due in large part to the confidence of consumers and health professionals in the quality of its products, the continuing series of recalls has been nothing short of shocking. Explanations have been incomplete and unconvincing, but that is another story.

One consequence of the recalls has been that some Tylenol and other OTC products have not been available for many months. When consumers can't find the products they are looking for, with whom do they speak? Although some may contact the company, the vast majority present their questions to pharmacists who then commit the time to explain why the product they are looking for is not available and to recommend another product. I hesitate to even estimate the number of discussions (and the amount of valuable time committed) that pharmacists have had with consumers resulting from the recalls of just the Tylenol products and/or dosage issues relevant to these products. I was interested in the comments of an executive with McNeil Consumer that the company had received more than 73,000 phone calls in 2008 and 2009 about infants' and children's Tylenol products. Based on this number of calls received by the company during a two year period, I have to think that the discussions between consumers and pharmacists regarding Tylenol products number in the many millions.

In my opinion, Johnson & Johnson/McNeil Consumer should be greatly indebted to the nation's pharmacists for the amount and value of time they have devoted to providing responses to questions about recalls and dosage issues regarding Tylenol products (and its other recalled products). However, I am not aware of any acknowledgement or expression of appreciation from the company or its executives for the service and time committed by pharmacists in explaining/clarifying problems the company caused.

Even more confusion ahead

As Johnson & Johnson/McNeil Consumer begins to bring recalled products back to the market, it is making changes in the dosage recommendations for some Tylenol products. In late July, it announced "plans for new dosing instructions lowering the maximum daily dose for single-ingredient Extra Strength Tylenol products sold in the U.S. from 8 pills per day (4,000 mg) to 6 pills per day (3,000 mg). The dosage is designed to help encourage appropriate acetaminophen use and reduce the risk of accidental overdose." These new dosing instructions will appear on packages of this product this fall.

The announcement also notes that the company "will also be lowering the maximum daily dose for Regular Strength Tylenol and other adult acetaminophen-containing products beginning in 2012." It is my understanding that the maximum daily dose that will be recommended for Regular Strength Tylenol will be 3,250 mg (10 tablets each containing 325 mg), and that the maximum daily dose for Extended-release Tylenol will remain at 3,900 mg (6 caplets each containing 650 mg). As a consequence, there will be Tylenol products for adult use that have maximum daily doses of 3,000 mg, 3,250 mg, and 3,900 mg. How do these changes reconcile with the request from the FDA earlier this year that health professionals advise patients to not exceed the maximum daily dose of 4,000 mg?

The dosage changes being implemented give every appearance of being some sort of marketing strategy rather than a plan to enable optimum pain relief and safety. If anything, the title of this editorial, The Tylenol Follies, is too weak of a description for this plan. If it is really important that the maximum daily dose of Extra Strength Tylenol be reduced to 3,000 mg, why should the maximum dose of Extended-release Tylenol not also be reduced in a similar manner?

Johnson & Johnson/McNeil Consumer has acted unilaterally in changing the dosage of certain Tylenol formulations. The FDA has not required these changes to be made. There is no reason to think that the other companies that make acetaminophen-containing products will decide that it is wise for them to change to the same multiple maximum doses being implemented for Tylenol products. Although the Johnson & Johnson/McNeil Consumer announcement notes that it "…is working closely with other manufacturers of acetaminophen products to help ensure consistency in dosing instructions," what incentive is there for other companies to do

(Continued on Page 4)

New Drug Review

Rivaroxaban (Xarelto – Janssen)

Anticoagulant

New Drug Comparison Rating (NDCR) = 4

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

Indication:

Prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

Comparable drug:

Enoxaparin (e.g., Lovenox).

Advantages:

- Is more effective in preventing venous thromboembolic events;
- Is administered orally (whereas enoxaparin is administered subcutaneously);
- Less risk of thrombocytopenia and hypersensitivity reactions.

Disadvantages:

- Interacts with more medications;
- Should not be used in patients with severe renal impairment or moderate or severe hepatic impairment;
- Labeled indications are more limited (labeled indications for enoxaparin also include DVT prophylaxis in abdominal surgery, DVT prophylaxis in medical patients at risk for thromboembolic complications due to severely restricted mobility, inpatient treatment of acute DVT, outpatient treatment of acute DVT without pulmonary embolism, unstable angina and non-Q-wave myocardial infarction, and acute ST-segment elevation myocardial infarction (STEMI);
- Antidote is not available (whereas protamine is an antidote for enoxaparin overdosage).

Most important risks/adverse events:

Risk of epidural or spinal hematoma when used in patients receiving neuraxial (spinal/epidural) anesthesia or spinal puncture (boxed warning; an epidural catheter should not be removed earlier than 18 hours after the last administration of the drug and the next dose should not be administered sooner than six hours after the removal of the catheter); bleeding events including fatal bleeding, bleeding that requires re-operation, and extra-surgical site bleeding requiring transfusion; contraindicated in patients with active major bleeding; should not be used concurrently with another anticoagulant other than in a therapeutic transition period; concurrent use with clopidogrel (Plavix) or prasugrel (Effient) is best avoided, and caution should be exercised in patients who are also taking aspirin or a nonsteroidal anti-inflammatory drug; use should be avoided in patients with severe renal impairment or moderate or severe hepatic impairment; is a substrate of CYP3A4/5 and P-glycoprotein (P-gp), and concurrent use with medications that have combined P-gp and strong CYP3A4 inhibition (e.g., ketoconazole) should be avoided; action may be reduced by the concurrent use of medications that are combined P-gp and strong CYP3A4 inducers (e.g., rifampin).

Most common adverse events:

Bleeding events (6%).

Usual dosage:

10 mg once a day for 35 days in patients having hip replacement surgery, and for 12 days in patients having knee replacement surgery; initial dose should be taken at least six to 10 hours after surgery once hemostasis has been established; if it is not possible to avoid concurrent use with a drug that is a combined P-gp and strong CYP3A4 inducer (e.g., rifampin), an increase in dosage to 20 mg once a day should be considered; if the tablet is to be crushed for administration via a feeding tube, the gastric placement of the tube should be confirmed to attain optimum absorption.

Product:

Tablets – 10 mg.

(Continued on Page 4)

that? Indeed, the company that markets the new formulation of acetaminophen that is administered intravenously has specifically confirmed that the approved dosage recommendations remain at 4,000 mg/day for adults. The FDA should require Johnson & Johnson/McNeil Consumer to rescind its plans to change the dosage of Tylenol products until dosage regimens that provide the best balance of efficacy and safety considerations can be identified and adopted by all companies that supply acetaminophen-containing products.

The Johnson & Johnson Credo

Johnson & Johnson has what I consider to be an exceptional Credo (that may be accessed on its website), but it has one very important omission in the first sentence (noted below):

> "We believe our first responsibility is to the doctors, nurses, and patients, to mothers and fathers and all others who use our products and services."

The omission to which I refer is that pharmacists should be specifically identified as individuals to whom Johnson & Johnson has a responsibility. I have written to the current CEO and the previous CEO of Johnson & Johnson to specifically request this change. I received courteous responses from both individuals with the basic message (with my paraphrasing) that the company loves pharmacists but rarely changes its Credo.

Johnson & Johnson must no longer ignore the expertise, services, and time of pharmacists that have been of great value in the past success of its products and company. It should change the Credo now to include pharmacists. Our professional associations should take action to obtain this long-overdue recognition.

Daniel A. Hussar

New Drug Review (cont.)

Comments:

Rivaroxaban is the second new orally-administered anticoagulant to be marketed in a period of less than a year, following dabigatran (Pradaxa). Whereas dabigatran exhibits its anticoagulant action as a direct thrombin inhibitor and is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, rivaroxaban is a factor Xa inhibitor that has been initially approved for the prophylaxis of DVT which may lead to PE in patients undergoing knee or hip replacement surgery. Its effectiveness was demonstrated in studies in which it was compared with enoxaparin (40 mg once a day subcutaneously). Of the patients undergoing knee replacement surgery, 9.7% of those treated with rivaroxaban experienced venous thromboembolic events (VTE), compared with 18.8% of those treated with enoxaparin. In two studies in patients undergoing hip replacement surgery, 1.1% and 2% of the patients treated with rivaroxaban experienced VTE, compared with 3.9% and 8.4% of those receiving enoxaparin. The new drug was also more effective in preventing major VTE including nonfatal PE and VTE-related death.

As with other anticoagulants, bleeding complications are the most important concern with the use of rivaroxaban. Bleeding events were experienced by approximately 6% of the patients treated with rivaroxaban in the clinical studies, with major bleeding events (e.g., bleeding that required re-operation, extra-surgical site bleeding requiring transfusion, fatal bleeding) reported in less than 0.5% of patients. The frequency of all bleeding events and major bleeding events was similar in the patients treated with enoxaparin.

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