DRUG Watch

By Diane S. Aschenbrenner, MS, APRN,BC

A NEW WARNING FOR A PROTEASE INHIBITOR

- The product labeling of the protease inhibitor darunavir (Prezista) has been revised to include a warning of a possible association between use of the drug and development of hepatotoxicity.
- Liver function tests should be monitored carefully in patients taking the drug.

A new warning has been added to the labeling of the HIV-1 protease inhibitor darunavir (Prezista) indicating that use of the drug appears to be associated with hepatotoxicity. This revision was made after postmarketing case reports of adverse effects and clinical trial information were reviewed by the Food and Drug Administration and the manufacturer. It has not been established that darunavir itself, alone, causes hepatotoxicity. In fact, to ensure maximum bioavailability of the drug, it's often taken in combination with a low dose of ritonavir (Norvir), an inhibitor of the HIV-1 and HIV-2 proteases that has a known association with hepatotoxicity. Although most HIV antiretroviral drugs pose a risk of some degree of liver damage (as manifested in greatly elevated levels of liver enzymes), some of them, such as ritonavir, pose a comparatively greater risk. Nurses should be sure to discuss the risk of liver damage with patients who take the drug. Patients should report any symptoms to the prescriber that might indicate liver injury, such as nausea, abdominal pain, jaundice, dark urine, anorexia, and otherwise inexplicable fatigue. Nurses should monitor the results of liver function tests in patients taking darunavir and other HIV drugs and notify the prescriber when liver enzyme levels are higher than normal. Patients should also be informed of the importance of having follow-up blood work to monitor their liver function.

Center for Drug Evaluation and Research. *FDA alert: darunavir ethanolate (marketed as Prezista) information*. Rockville, MD: U.S. Food and Drug Administration; 2008 Mar 21. http://www.fda.gov/cder/drug/infopage/darunavir/default.htm.

A NEW DRUG FOR CROHN'S DISEASE

- Certolizumab pegol (Cimzia), newly approved for use in Crohn's disease, is initially administered subcutaneously every two weeks, and then every four weeks.
- There is a higher risk of serious infection in patients taking the drug.
- Postmarketing studies will be conducted to determine the long-term safety of the drug.

Certolizumab pegol (Cimzia), a PEGylated anti-tumor necrosis factor-α therapy, has been approved for use in adults to alleviate the signs and symptoms of Crohn's disease and to maintain a clinical response in moderate-to-severe disease that has not responded adequately to conventional therapy. Typically produced in inflammatory conditions, tumor necrosis factor-α is overproduced in autoimmune disorders; therefore, inhibition of its activity reduces inflammation. PEGylation is a chemical process that augments a drug molecule to increase its half-life, thereby delaying its elimination. The benefit of PEGylation in pharmacologic therapy is that the desired therapeutic level of a drug is maintained with less frequent dosing—for example, certolizumab pegol is administered subcutaneously every two weeks during induction (the first three injections), and then every four weeks as maintenance treatment in the presence of a clinical response.

In a clinical trial involving patients with moderate-to-severe Crohn's disease, a slightly greater improvement in symptoms was achieved with certolizumab pegol, compared with placebo (35% and 27%, respectively), after six weeks. In patients who responded favorably to induction therapy with certolizumab pegol in another clinical trial, sustained response and remission were more common in those taking the drug than in those taking placebo after 26 weeks (48% and 29%, respectively).

Because certolizumab pegol suppresses the immune system, patients taking the drug are at risk for developing serious, possibly fatal, infections, including tuberculosis and opportunistic infection. In patients who are chronic carriers of the hepatitis B virus, there can be a heightened risk of a possibly fatal reactivation of the virus. Other drugs that inhibit tumor necrosis factor activity are known to have the potential to cause lymphomas or other malignancies, none of which were reported in the clinical trials of certolizumab pegol; postmarketing research will be conducted to confirm the safety of long-term use of the drug. Nurses should instruct patients in the subcutaneous administration of certolizumab pegol and advise them to be vigilant for symptoms of infection. Patients should also be instructed to thoroughly read the medication guide dispensed with each prescription because

new information concerning the drug's safety will be included as it becomes available.

Sandborn WJ, et al. *N Engl J Med* 2007; 357(3):228-38; Schreiber S, et al. *N Engl J Med* 2007;357(3):239-50; FDA approves Cimzia to treat Crohn's Disease. *FDA News* 2008 Apr 22. http://www.fda.gov/bbs/topics/news/2008/new01821.html.

IMPROPER USE OF AN ANTITUSSIVE

- Tussionex Pennkinetic Extended-Release Suspension has been reported to cause severe, sometimes fatal, respiratory depression in patients who either have taken too much of the drug or are too young to take it at all.
- Prescribers are reminded to follow the product label indication specifying drug administration every 12 hours and to observe its contraindication in children younger than six years of age.

The Food and Drug Administration (FDA) has issued an alert to health care professionals concerning the safe and proper use of Tussionex Pennkinetic Extended-Release Suspension, a combination of hydrocodone polistirex and chlorpheniramine polistirex. The FDA released the alert after receiving case reports of severe and sometimes fatal respiratory depression resulting from improper use of the long-acting cough suppressant. The narcotic hydrocodone is a semisynthetic derivative of codeine that also suppresses cough (presumably by directly inhibiting the cough center) and depresses the respiratory drive—high doses of it can produce significant respiratory depression. Chlorpheniramine, an antihistamine that also has sedative properties, reduces edema in the respiratory mucosa.

Two problems are apparent in the case reports—first, as an extended-release product, Tussionex Pennkinetic Extended-Release Suspension is designed to be taken no more than once every 12 hours. Patients who suffered adverse effects either were given a prescription for its use at more frequent intervals or they themselves had chosen to take the drug more often. (There have also been reports of physicians prescribing higher doses or patients taking higher doses of their own accord.) Second, Tussionex Pennkinetic Extended-Release Suspension is not indicated for use in children younger than six years of age, yet some of the reported adverse effects have occurred in young children. Both misusages have resulted in life-threatening respiratory effects and death, sometimes in children younger than six.

Nurses should be sure to instruct patients not to take Tussionex Pennkinetic Extended-

Understanding Pharmacokinetics:

Part 4: Drug Elimination

The last in a four-part series from the coordinator of Drug Watch.

This month's column concerns alterations in the last of the four phases of pharmacokinetics (absorption, distribution, metabolism, and elimination) that can affect drug therapy. To watch an animated video demonstrating the process of drug elimination in the body, go to http://links.lww.com/A471.

Elimination is the process by which a drug or its metabolites are removed from the body. (Actually, elimination refers to a combination of the processes of drug metabolism and excretion of the drug from the body. While technically different, the terms "excretion" and "elimination" are commonly used interchangeably, and most practitioners use the latter term, as I have in this four-part series. For the purposes of this discussion, *elimination* refers to drug excretion.) Drugs are most commonly eliminated through urine, bile in the gastrointestinal tract, expired air, breast milk, sweat, and saliva (although sweat and saliva aren't clinically significant routes). Metabolism changes the structure of lipophilic drugs so they become hydrophilic and can be excreted in urine. Drug molecules that are still lipophilic when they reach the kidneys are reabsorbed into the bloodstream. The time it takes to eliminate half the blood concentration of a drug is considered its "half-life," and this period of time varies according to pharmacologic properties and metabolism and elimination rates; some drugs' half-lives last minutes whereas others' last days. (It's important to understand that in one half-life a specific *percentage* of drug molecules is eliminated from the blood, not an absolute *number* of molecules.)

Renal disease, conditions that cause a decrease in the flow of blood to the kidneys, and changes that normally accompany

the aging process all decrease the effectiveness of the kidneys in drug excretion. Drugs with long half-lives can produce adverse effects in older adults that are similar to those produced in patients with renal disease. The Beers criteria for potentially inappropriate medication use in older adults describe certain difficulties presented in that population. (First published in 1991, the Beers criteria is a consensus-based list of drugs that are thought to pose more risk than benefit in people older than age 65.) For example, the half-lives of long-acting benzodiazepines (used to treat anxiety) are increased in elderly patients—the half-life of diazepam (Valium) increases from about one to two days to as long as seven days, the half-life of the principal active metabolite of chlorazepate (Tranxene) increases from 46 hours to as long as 120 hours in older men (interestingly, it does not increase significantly in older women), and the half-life of the second active metabolite of quazepam (Doral) increases from 84 hours to more than twice that duration in older adults. Fick and colleagues note that in the Beers criteria, the very long half-lives of long-acting benzodiazepines produce in elderly adults "prolonged sedation . . . increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required."

Diminished liver function also increases the half-life of a drug because metabolism is prolonged, and therefore the drug or its metabolites cannot be excreted in the interval expected. The normally four-to-16-day half-life of the active metabolite of fluoxetine (Prozac), for example, is lengthened by diminished liver function, and as a result little excretion of the unmetabolized drug occurs. In the normal course of aging, liver function is diminished, and the Beers criteria note that daily use of fluoxetine increases the risks of excessive central nervous system stimulation, sleep disturbance, and agitation in older adults.

Another possible alteration in drug excretion is the reabsorption of active drug into the bloodstream from the renal tubules. An example is seen in the use of lithium (Eskalith, Lithobid) in treating mania in manic–depressive illness (bipolar disorder). Lithium, as an ion, is processed in the body in the same manner in which sodium ions are. When the sodium level is low, the body compensates by reabsorbing sodium ions into the bloodstream from the kidney. When a patient takes lithium in the presence of a low sodium level, the kidney reabsorbs lithium ions from the urine, sensing them to be sodium ions. Therefore, conditions that deplete the sodium level (such as excessive sweating, prolonged diarrhea, diuretic therapy, and sodium-restrictive diets) or that decrease perfusion to the kidney, thereby promoting greater retention of sodium and water (such as dehydration, inadequate fluid intake, or heart failure) cause the kidneys to mistakenly reabsorb lithium at a rate greater than normal, possibly causing lithium toxicity.

> Drugs are most commonly eliminated through urine, bile in the gastrointestinal tract, expired air, and breast milk.

Nurses should assess patients for possibly altered drug elimination—according to the patients' condition, certain drugs might be inappropriate. Close monitoring is warranted in patients who need to take a particular drug despite being at risk for its adverse effects because of such possible alterations in elimination. Further, changes in a patient's health can increase the risk of adverse effects attributable to changes in drug elimination.

Aschenbrenner DS, Venable SJ. *Drug therapy in nursing*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams and Wilkins; 2009; Fick DM, et al. *Arch Intern Med* 2003;163(22):2716-24.

Release Suspension more often than once every 12 hours and, to prevent overdosage, to accurately measure doses with a dosing spoon, medication cup, or syringe, not with a household teaspoon or tablespoon. Patients and their families should also be instructed to watch for any labored, irregular, or periodic breathing; very slow breathing; very slow heart rate; severe sleepiness; or cold, clammy skin. If patients experience (or their families notice) any of these symptoms, the drug should be discontinued and the prescriber notified at once. Nurses who note that a child younger than six years of age has a prescription for this antitussive should consult the prescriber.

FDA issues alert on Tussionex, a long-acting prescription cough medicine containing hydrocodone. Agency gives new safety information on proper use of Tussionex as a cough suppressant. *FDA News* 2008 Mar 11. http://www.fda.gov/bbs/topics/NEWS/2008/NEW01805.html. ▼

Diane S. Aschenbrenner is the course coordinator for undergraduate pharmacology at Johns Hopkins University School of Nursing in Baltimore, MD. She also coordinates Drug Watch: *dianea@son.jhmi.edu.*