DRUG Watch

By Diane S. Aschenbrenner, MS, APRN,BC

A NEW TREATMENT FOR MODERATE-TO-SEVERE CROHN'S DISEASE

- The monoclonal antibody natalizumab (Tysabri), used to treat relapsing forms of multiple sclerosis, now is also approved for treating moderate-to-severe Crohn's disease in patients who cannot tolerate or have not responded to standard therapies.
- Because of the greater risks of progressive multifocal leukoencephalopathy and other serious events associated with use of the drug, patients must meet certain criteria and agree to comply with stringent monitoring requirements.

Formerly approved only for the treatment of relapsing forms of multiple sclerosis, the monoclonal antibody natalizumab (Tysabri) now is also approved for the treatment of moderate-to-severe Crohn's disease in patients evidencing inflammation who either respond inadequately to conventional therapy or cannot tolerate it. Natalizumab exerts an antiinflammatory therapeutic effect: it increases the number of circulating leukocytes by inhibiting their migration away from the vascular space. For both indications, the natalizumab product labeling bears a black box warning that use of the drug raises the risk of progressive multifocal leukoencephalopathy, an opportunistic viral infection of the brain that usually causes death or severe disability. Patients with Crohn's disease who are prescribed natalizumab must be enrolled in the Crohn's Disease–Tysabri Outreach Unified Commitment to Health (CD TOUCH), a special program that limits access to the drug to those who meet certain criteria (the absence of immune deficiency, for example) and who agree to comply with stringent monitoring requirements. Prescribers, pharmacies, and infusion centers at which natalizumab is administered must also enroll in the program, comply with its strict guidelines, and participate in a class on the drug's possible adverse effects and the serious risks associated with its use.

FDA approves Tysabri to treat moderate-to-severe Crohn's Disease [press release]. *FDA News* 2008 Jan 14. http://www.fda.gov/bbs/topics/NEWS/2008/NEW01775.html; Biogen Idec. *Prescribing information: Tysabri [natalizumab] injection for intravenous use*. 2008. http://www.tysabri.com/en_US/tysb/footer/TYSABRI-pi.pdf.

THE LABELING OF A TRANSDERMAL CONTRACEPTIVE IS REVISED AGAIN

- The labeling of the Ortho Evra contraceptive transdermal patch has been further revised to include study data indicating that women who use it have higher circulating levels of estrogen and are therefore at greater risk for venous thromboembolism than women who use oral contraception.

The labeling of the Ortho Evra contraceptive transdermal patch (norelgestromin–ethinyl estradiol transdermal system) has been revised to include findings of an epidemiologic study demonstrating that women who use that contraceptive are at greater risk for developing venous thromboembolism than those who use oral birth control. The labeling of the drug had been revised in September 2006 to indicate the findings of two earlier studies: one study revealed a greater risk of venous thromboembolism with use of the product, and the other demonstrated that the risk was not heightened. Because the transdermal absorption of estrogen results in higher circulating levels of the hormone, the contraceptive patch may not be an appropriate form of birth control for patients at high risk for venous thromboembolism. Such a patient should consult her health care provider about possibly more suitable methods of contraception.

FDA approves update to label on birth control patch [press release]. *FDA News* 2008 Jan 18. http://www.fda.gov/bbs/topics/NEWS/2008/NEW01781.html; Ortho-McNeil Pharmaceutical. Prescribing information: Ortho Evra [norelgestromin/ethinyl estradiol] transdermal system. 2008. http://www.orthoevra.com/orthoevra/shared/shared/pi/OrthoEvraPI.pdf.

BISPHOSPHONATES: ASSESSMENT FOR AN ADVERSE EFFECT

- Health care practitioners are failing to recognize that patients with severe musculoskeletal pain could be suffering an adverse effect of a bisphosphonate.
- The FDA has issued an alert to encourage physicians and nurses to monitor patients for the possible adverse effect of bisphosphonates.

The Food and Drug Administration (FDA) has issued an alert indicating that patients with severe bone, joint, or muscle (musculoskeletal) pain while taking a bisphosphonate, such as such as alendronate (Fosamax), ibandronate (Boniva), risedronate (Actonel), and zoledronic acid (Reclast, Zometa), could be experiencing an adverse effect of the drug. Because they increase bone density, the bisphosphonate drugs are often prescribed for the treat-

Understanding Pharmacokinetics:

Part 1: Drug Absorp tion

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

Pharmacokinetics (the processing of drugs in the body) involves four phases: absorption, distribution, metabolism, and elimination. Any variable that affects those processes can alter a drug's effectiveness. This column will examine each process, with emphasis on mechanisms that might alter it significantly—important nursing considerations in the administration of medication. This month's column examines *absorption.* To watch an animated illustration of drug absorption, go to http://links.lww.com/A417.

Several variables affect the rate and the completeness of drug absorption. Generally, a slowed rate of absorption presents less of a problem than the diminishment of total absorption; incomplete total absorption could lower the circulating level of the drug enough to cause significant loss in its therapeutic effect. A slower rate of absorption might not alter the serum drug level achieved, but it could delay full therapeutic effect.

The presence of food in the gastrointestinal (GI) tract commonly deters complete absorption of a drug dose taken orally. For example, penicillin V (Novo-Pen-VK, Veetids) should be taken on an empty stomach to facilitate its complete absorption. The patient might think, mistakenly, that she or he should take it on an empty stomach directly before a meal. Penicillin V should in fact be taken at least one hour before and at least two hours after a meal to be considered taken on an empty stomach. Because penicillin V is most often prescribed for use in the home, nurses should teach the patient about the timing of drug administration.

Because the absorption of phenytoin (Dilantin, Phenytek) is significantly decreased by many types of enteral feeding, the drug should be administered at least one hour before feeding. However, because food administered enterally is digested more quickly than solid food is, phenytoin can be administered as soon as one hour afterward. Continuous, hourly infusions of tube feeding must be suspended for at least one hour before and after the administration of phenytoin.

> *Incomplete total absorption could lower the circulating level of a drug enough to cause significant loss in its therapeutic effect.*

The presence or absence of a particular food group or fluid in the body can also alter drug absorption. For example, the protease inhibitor saquinavir (Invirase, Fortovase) must be taken within two hours after a meal to be fully absorbed. Meanwhile, the absorption and peak serum level of sildenafil (Viagra) have been found to be reduced when the erectile dysfunction drug is taken with a high-fat meal. Food or any beverage other than water decreases the absorption of alendronate (Fosamax) significantly when ingested less than 30 minutes after administration of the drug.

To mitigate complications presented by the myriad variations in the proper timing of the ingestion of food and fluid in relation to maximum drug absorption, the nurse should check the section designated "pharmacokinetics" in the drug labeling, which is usually divided into subsections pertaining to each phase. The

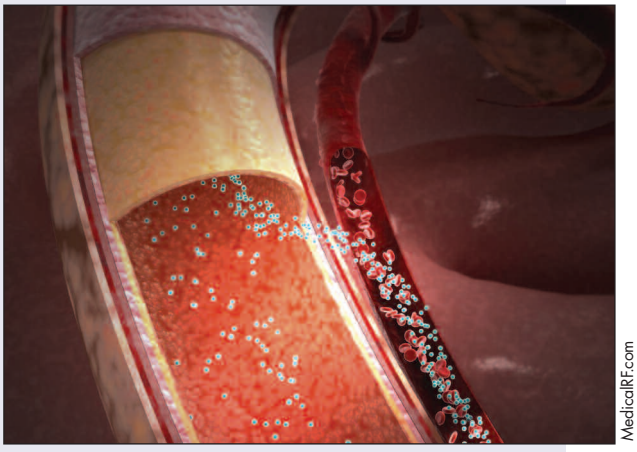
ment and prevention of osteoporosis in women who have reached menopause. Other indications are Paget's disease of bone and hypercalcemia of malignancy. Although severe musculoskeletal pain has always been listed as an adverse effect in the labeling of the drugs, nurses and physicians might overlook the association. Such a failure to identify a symptom as an adverse drug effect results in delayed diagnosis, prolonged pain, and unnecessary use of analgesics. The adverse effect can appear days, months, or years after the initiation of bisphosphonate use.

information may state that the drug's bioavailability is decreased by food or beverages. Again, the statement that food "may slow absorption" is not necessarily of serious concern as long as the bioavailability and ultimate therapeutic effect of the drug are not affected significantly. To find drug label information without the product package insert, the nurse should use a drug database or consult the Food and Drug Administration (FDA) Web site (http://www.fda.gov/cder/index.html; select the link "Drugs@FDA" and enter the drug name).

Because patients commonly administer drugs to themselves, nurses should include information on the timing of the consumption of food and beverages in their patient education. In addition to information on altered absorption, the patient education section of drug labeling usually contains information on food and beverage interactions.

Another important consideration regarding oral drug absorption is the integrity of the GI system. Because most drugs taken orally are absorbed mostly from the small intestine, the nurse should find out whether part of the intestine has been removed, which could impair the patient's ability to completely absorb medication. If part of the intestine is gone and the patient fails to demonstrate the desired therapeutic effect of a drug, the physician should be consulted to determine whether an adjustment of the dosage is indicated. If a route other than the oral one is available (the transdermal route, for example), that should be considered as a means of averting the problem of incomplete GI absorption of a drug.

Problems with drug absorption can also occur in administration by a route other than the oral one. For example, the absorption rate of a drug applied topically can be greatly increased if the drug is applied to broken skin or in the presence of a condition that promotes vasodilation. Recently, the FDA MedWatch program reported life-threatening respiratory effects of the fentanyl patch (Duragesic and others) when patients exposed the application site to a source of heat, causing faster absorption and higher serum levels of the drug. The agency has also received reports of life-threatening adverse effects (respiratory depression, for example) and death associated with the fentanyl patch when the patient either replaced it too frequently or applied more patches than prescribed, or when a defect in the product directly exposed the skin to the gel reservoir. These mishaps increased the rate of absorption of the drug to dangerous levels.



MedicalRF.com

Most drugs taken orally are absorbed primarily from the small intestine.

Generally, problems with drug absorption through the subcutaneous (SC) and intramuscular (IM) routes are attributable to improper needle selection. If the needle is too long (penetrating through the muscle into a blood vessel or through the subcutaneous tissue into the muscle), the route of administration changes (from IM to IV, and from SC to IM, respectively), which changes the rate of absorption.

Center for Drug Evaluation and Research. *FDA public health advisory: Important information for the safe use of fentanyl transdermal system (patch).* Rockville, MD: U.S. Food and Drug Administration; 2007 Dec 21. http://www.fda.gov/cder/drug/advisory/fentanyl_2007.htm; Food and Drug Administration. *Actavis recalls remaining fentanyl patches in the US as precaution.* Rockville, MD; 2008 Feb 17. http://www.fda.gov/oc/po/firmrecalls/actavis03_08.html.

The FDA alert serves as an important reminder. After obtaining a complete list of drugs that a patient is taking, the nurse should review all product labeling for the adverse effects identified. If it appears that the patient might be experiencing a serious adverse effect of a drug, the health care team should consider whether a modification in the therapy is warranted.

Center for Drug Evaluation and Research. *FDA alert: Information on bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa).* Rockville, MD: U.S. Food and Drug Administration; 2008 Jan 7. http://www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm.

A NEW DRUG TREATS HIV-1 RESISTANT TO NNRTIs

- Etravirine (Intelence), a new nonnucleoside reverse transcriptase inhibitor (NNRTI), has been approved to treat HIV-1 in adults who are not responding to other drug therapy.
- The drug is unique among NNRTIs because it has demonstrated efficacy in the presence of viral resistance to other NNRTIs.
- Etravirine should be administered as part of combination therapy.
- The most common adverse effects are rash and nausea, and as in other HIV drug therapy, adherence to the regimen is crucial.

Etravirine (Intelence), a new nonnucleoside reverse transcriptase inhibitor (NNRTI), has recently been approved for the treatment of HIV type 1 (HIV-1) in patients demonstrating virologic failure (manifested as an increase in the HIV viral load) while receiving other HIV drug therapy. In vitro studies of etravirine, which must be prescribed in combination with certain other antiretroviral drugs, have found it to be effective against HIV strains resistant to NNRTIs. This is unique because some mutations of HIV can produce resistance to all drugs in a class (especially the NNRTIs), rather than to only a specific drug.

The Food and Drug Administration's approval of etravirine, granted after a priority review, was prompted by 24-week data of two ongoing phase-3 clinical trials of identical design. (A drug receives a priority review if it is believed that its approval would represent "a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease.") Patients taking etravirine in combination with other HIV drugs in the clinical trials demonstrated a significant decrease in viral load and an increase in $CD4^+$ cell counts, compared with patients taking placebo and a background regimen.

The most common adverse effects of etravirine are rash (usually not serious) and nausea. Rarely, severe and possibly life-threatening skin reactions, such as erythema multiforme and Stevens–Johnson syndrome, have occurred in study subjects. Treatment should be discontinued if a severe rash develops. Because the drug received a priority review, the effects of its use for longer than 24 weeks are not known, and nurses should monitor patients closely for signs of any adverse events.

As many HIV drugs are, etravirine is metabolized by the cytochrome P-450 (CYP) isoenzyme system, primarily by CYP3A4, CYP2C9, and CYP2C19, the first of which it induces and the latter two of which it inhibits. Because of that, there is the possibility of interaction with other drugs that are also metabolized by any of those isoenzymes or that either induce or inhibit them; there is also the possibility of an alteration of the therapeutic effect and adverse reaction profile of etravirine or of any concurrently administered drug. Before the initiation of therapy with etravirine, nurses should consult a database for information on all other drugs the patient is taking (including HIV drugs) to determine whether such an interaction could occur.

Taking the full prescribed dose of etravirine at regular intervals is critical, as it is with other HIV drugs. The nurse should instruct the patient to take the drug twice daily after meals: the type of food eaten doesn't matter. (The absorption of some other HIV drugs can be diminished by a high-fat meal.) The patient should swallow the tablets whole, but if that is not possible, they can be dispersed in a glass of water. The patient should be instructed to stir the dispersion well and drink it immediately. The glass should be refilled several times with water, which the patient should drink so that the entire dose of etravirine is received, ensuring its full therapeutic effectiveness. The patient should also be told that when a dose is missed by less than six hours, it should be taken as soon as possible after a meal, and the regular dosing schedule should be followed thereafter. On the other hand, when a dose is missed by more than six hours, it should be omitted and only the next dose should be taken according to the schedule—that is, the "doubling up" of doses should be avoided. Finally, because interruption of the drug therapy increases the risk of drug resistance, the nurse should instruct the patient to refill the prescription well before taking the last dose.

FDA approves new HIV drug after priority review [press release]. *FDA News* 2008 Jan 18. http://www.fda.gov/bbs/topics/NEWS/2008/NEW01783.html; Tibotec Therapeutics. *Prescribing information: Intelence [etravirine]*. Ortho Biotech Products. 2008. http://www.fda.gov/cder/foi/label/2008/022187lbl.pdf; Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. *Guidance for industry. Standards for the prompt review of efficacy supplements, including priority efficacy supplements.* Rockville, MD: Food and Drug Administration; 1998 May. Procedural Guidance 4. http://www.fda.gov/cder/guidance/2423fnl.pdf. ▼

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.*