DRUG Watch

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This month we want to provide readers with a more in-depth treatment of the drugs and processes described below. Accordingly, you can find an expanded version of these pages online at http://links.lww.com/A457.

FDA SAFETY REVIEWS OF FIVE DRUGS

- In response to postmarketing case reports of adverse effects and ongoing clinical trial data, the FDA has begun safety reviews of five drugs:
  - **montelukast (Singulair)** and **tiotropium bromide inhalation powder (Spiriva),** used in chronic respiratory disorders
  - **abacavir (Ziagen)** and **didanosine (Videx),** two HIV drugs
  - **becaplermin (Regranex),** a topical drug used to treat ulcers in patients with diabetes
- Nurses should report any suspected adverse effects of these drugs to the FDA MedWatch program.

Postmarketing case reports of adverse effects of an approved drug and the findings of more recent clinical research can prompt the Food and Drug Administration (FDA) to perform a "safety review" of all such information received by the product manufacturer and the agency. Additionally, the FDA might ask the manufacturer to review all of its clinical trial data pertaining to a particular adverse effect of a drug.

A complete safety review can take as long as nine months, after which the FDA concludes either that there is no demonstrated association between the drug and a reported possible adverse effect or that there is such an association; in such cases revision of the product labeling—or withdrawal of the product from the market—might be required. Recently, the FDA issued an "early communication" stating that safety reviews of several drugs are under way.

The first drug of concern is **montelukast (Singulair),** a leukotriene-receptor antagonist used to treat asthma and allergic rhinitis. Postmarketing case reports indicating changes in behavior or mood, suicidality (suicidal ideation and behavior), and suicide possibly associated with the use of montelukast have been received by the manufacturer and the FDA. In 2007, prior to the recent call for a safety review, the manufacturer revised the drug's labeling, citing postmarketing reports of suicidality. Now the FDA is collaborating with the manufacturer to further evaluate the possible association between the use of the drug and the reported serious adverse effects. The FDA is also investigating other leukotriene-modifying agents. Although the incidence of the reported adverse effects would seem minimal, the best action for providers to take while the FDA completes the safety review would be to carefully monitor patients for changes in behavior or mood and suicidality. At present, the FDA isn't recommending that the drug no longer be prescribed; indeed, the FDA says that patients should not stop taking it without consulting their prescribers; any further recommendations concerning the use of montelukast would be made after completion of the safety review.

Another respiratory drug undergoing an ongoing FDA safety review is **tiotropium bromide inhalation powder (the Spiriva HandiHaler),** an anticholinergic bronchodilator used in the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). An analysis of pooled data conducted by the manufacturer revealed a higher risk of stroke with the use of Spiriva, preliminarily estimated at eight cases per 1,000 patients treated for one year, compared with six cases per 1,000 patients taking a placebo for one year. In addition, a large clinical trial conducted by the manufacturer to further assess the risk of stroke and other adverse effects associated with the use of Spiriva is in progress; results of that trial were expected to be submitted to the FDA in June (after we went to press). At present, the FDA doesn't recommend discontinuing treatment with Spiriva without consultation with the prescriber.

Another ongoing safety review announced by the FDA concerns the antiretroviral HIV drugs **abacavir (Ziagen)** and **didanosine** (also known as **ddI [Videx]**), both nucleoside reverse-transcriptase inhibitors. At the 15th Conference on Retroviruses and Opportunistic Infections, held in February, findings of the seven-year analyses of the Data Collection on Adverse Events of Anti-HIV Drugs study (D:A:D) were presented, revealing that the risk of myocardial infarction (MI) increased by 90% with the use of abacavir and by 49% with the use of didanosine, although the overall incidence of MI was slight (192 events in patients

Understanding Pharmacokinetics:
Part 3: Drug Metabolism

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

In the May and June issues, I described alterations in the first two of the four phases of pharmacokinetics (absorption, distribution, metabolism, and elimination). This month's discussion addresses the metabolism of drugs, the effects of drug route on metabolism, and alterations in metabolism related to genetic variation among patients.

Drug metabolism (sometimes referred to as "biotransformation") is the conversion of a drug into another substance (or other substances) for the purpose of excretion. The process takes place primarily in the liver, but occurs also in other tissues, principally those of the gastrointestinal tract, lungs, kidney, and skin. Metabolism, generally, is achieved predominantly through the action of specific microsomal enzymes constituting the cytochrome P-450 (CYP) system. The system is composed of specific enzymes, each one regarded as a distinct family, of which three—CYP1, CYP2, and CYP3—are involved in drug metabolism. The other enzymes in the CYP system metabolize naturally occurring substances, such as fatty acids. Specific members of each enzyme family have been identified and are designated by a number, a letter (representing the subgroup), and another number (indicating the specific *iso*enzyme) (CYP1A2, for example). CYP3A4 is the most common isoenzyme and the one responsible for the metabolism of most drugs. Isoenzymes are found predominantly in the liver but are also present in other organs, such as those of the gastrointestinal tract, where they're responsible for the drug metabolism that occurs at those sites. Research has demonstrated that the intestinal mucosa, for example, plays a major part in the metabolism of certain drugs.

Drugs taken orally move to the liver first. If a drug is highly metabolized in the liver, little of the dose enters the systemic circulation. Such drugs are considered to undergo a high "first-pass effect," necessitating a dose that's higher than one administered intravenously. (When drugs are administered intravenously, the entire drug dose enters the systemic circulation.) After a parenterally administered drug has traveled through the venous system and returns to the heart, only a portion of the dose is sent to the liver, which receives about 25% of the cardiac output. For example, cyclosporine (used to prevent rejection of transplanted organs) can be administered intravenously at first if the patient is to take nothing by mouth. But when the change to an oral preparation is made, the daily dosage of the drug must be tripled because of the high first-pass effect. If the patient takes cyclosporine orally at the same dosage that had been administered intravenously, the transplanted organ might be rejected. The dosage of morphine, too, needs to be three times as high as the parenteral dosage to achieve the same (analgesic) effect.

Genetic variation in isoenzymes also accounts for differences in the rates of metabolism and clearance in patients undergoing drug therapy. The CYP2D6 isoenzyme, while accounting for only 2% to 5% of all hepatic CYP isoenzymes, metabolizes about a quarter of all medications used clinically. Those genetic variations—or polymorphisms—result in poor, intermediate, extensive, or "ultrarapid" metabolism of drugs. Because the CYP2D6 phenotype that produces extensive metabolism is the one expressed by most people, it is considered the norm; approximately 8% of American whites have the "poor metabolizer" phenotype, and about 4% have the "ultrarapid metabolizer" phenotype. In comparison, the incidence of poor metabolism in black patients ranges from nearly 2%

taking abacavir and 124 in those taking didanosine, out of more than 33,000 total subjects). The greatest risk was in patients at high risk for cardiovascular disease at the beginning of the trial. The heightened risk of MI was not seen in patients who had discontinued therapy with either abacavir or didanosine for at least six months. In analyses of their own clinical trial data, the manufacturers of abacavir and didanosine didn't find that use of the products increased the risk of MI, findings that the FDA considers inconclusive. At this time, the FDA also considers the analyses of the D:A:D study data incomplete.

It is recommended that patients consult their prescribers to determine whether modification of their HIV drug regimen is appropriate. To help patients lower their risk of MI, nurses should emphasize the importance of quitting smoking, decreasing the intake of fats and cholesterol, and controlling diabetes and hypertension.

to approximately 7%, according to ancestry, and nearly 5% are ultrarapid metabolizers. Among Asian populations there generally are extremely slight incidences of the genetic variations in CYP2D6 that determine poor metabolism and ultrarapid metabolism—particularly among Thai, Chinese, and Japanese subjects, in whom the incidence is 1.2% or lower (data pertaining to Asian Americans, specifically, are not available).

Patients who are poor metabolizers of a certain drug have higher circulating levels of it than would normally be expected, which can produce greater therapeutic effects—and greater adverse effects. In contrast, patients who are ultrarapid metabolizers of a drug have lower circulating levels of it than would normally be anticipated and might not achieve the desired therapeutic response from a dose. For example, the tricyclic antidepressant desipramine (Norpramin) is metabolized by the CYP2D6 isoenzyme, and patients who are poor metabolizers need to take lower doses of the drug than most other patients do. Also, a drug can increase or decrease the amount of an isoenzyme in the liver, changing the rate of metabolism of drugs metabolized by that isoenzyme. For example, if the selective serotonin reuptake inhibitor paroxetine (Paxil), which slows the oxidation reactions catalyzed by CYP2D6, is taken concurrently with desipramine by a patient who is an extensive metabolizer, there is a fivefold decrease in the rates of desipramine metabolism and clearance. In other words, the first drug (paroxetine) changes the patient from an extensive metabolizer of the second drug (desipramine) to a poor metabolizer of it, resulting in both a substantially higher circulating level of desipramine than was expected and a greater likelihood that the desipramine will produce adverse effects. In contrast, if the same combination of drugs was taken by a patient who is a poor metabolizer, she or he would experience only a slight delay in the metabolism and clearance of desipramine and the risk of adverse effects wouldn't be higher.

Information on the effects of the CYP system on drug metabolism and clearance is vast and complex, but many hospitals and nursing schools provide access to helpful electronic references such as MicroMedex, Lexi-Comp, and Facts and Comparisons.

Aschenbrenner DS, Venable SJ. *Drug therapy in nursing*. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams and Wilkins 2009; Bernard S, et al. *Oncologist* 2006;11(2):126-35; American College of Physicians. *Clinical exercises*. Exercise 2. 2004. http://www.acponline.org/clinical_information/journals_publications/acp_internist/dec04/pain/clinical.htm.

Finally, another drug undergoing an ongoing FDA safety review is **becaplermin (Regranex),** a topical medication used in patients with diabetes to promote the healing of ulcers in the lower extremities that extend into the subcutaneous tissue or deeper, in the presence of sufficient blood supply. Because becaplermin promotes rapid cell division, the manufacturer continued to monitor ongoing clinical studies (begun before approval of the drug in 1997) for evidence of a greater incidence of cancer in patients using the drug, and the product labeling indicates that the drug shouldn't be used if there is neoplasm at the site(s) of application.

Recently, the FDA received information indicating that there were more deaths attributable to cancer among study patients who'd been given three or more prescriptions for becaplermin than among those who didn't use the drug. No single type of cancer was identified, nor did the research yield information sufficient to determine whether the use of becaplermin increased the incidence of new cases of cancer.

In patients with diabetes, untreated leg and foot ulcers pose a number of serious risks, including infection and the need for amputation. The quality of the lives of such patients is also adversely affected. Therefore, in each case any risk that might be incurred in the use of becaplermin must be weighed against the expected benefits. Prior to the initiation of treatment with becaplermin, nurses should confirm the absence of any type of cancer at the site of the ulcer; they should also teach patients how to use the drug properly, according to the manufacturer's detailed instructions. Further, a patient's need for more than one course of becaplermin therapy should be discussed by the health care team to determine whether the expected benefits outweigh any risks that might be incurred.

Nurses and other health care providers can report serious suspected adverse effects of all of the drugs discussed above, as well as of any other drug, to the FDA's MedWatch program at www.fda.gov/medwatch. For additional safety information released by the MedWatch program, see www.fda.gov/medwatch/ safety/2008/ safety08. htm (the site is updated continually). ▼

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