DRUGS, PREGNANCY, AND LACTATION

Drugs Approved in 2009

In 2009, the Food and Drug Administration approved 19 new chemical entities, and, except for 1, human pregnancy experience is lacking.

The exception is vigabatrin, an antiepileptic drug (AED) that has been available for nearly 2 decades outside the United States.

These drugs can be categorized into 12 pharmacologic classes: 4 antineoplastic drugs, 2 immunomodulators, 2 antipsychotics, 2 hematologic agents, 2 antibiotics, 1 antiarrhythmic agent, 1 anticonvulsant, 1 antidepressant, 1 antigout drug, 1 antihistamine, 1 antihyperlipidemic agent, and 1 vasopressin antagonist.

As with any new drug, it is best to avoid prescribing these drugs for women of childbearing potential or during pregnancy and to use older agents with human pregnancy experience. But what if the new drug is a major breakthrough, or is the only or most efficacious drug to treat your patient's condition? How do you counsel the patient about the drug's risk to her embryo or fetus?

BY GERALD G. BRIGGS, B.PHARM., FCCP

Fortunately, as discussed in my August 2008 column, the package insert provides data for three of the four factors that can be used to estimate risk: drug class, potential to cross the placenta, and animal data. Then, when your patient asks, "What are the risks?" you don't have to say, "We just don't know."

The immunomodulators are canakinumab (Ilaris; pregnancy class C), indicated for cryopyrin-associated periodic syndrome, and golimumab (Simponi; B), indicated (with or without methotrexate) for ankylosing spondylitis, active psoriatic arthritis, or rheumatoid arthritis. The animal data for both agents suggest low risk. These two agents have long half-lives, 26 and 14 days, so fetal exposure is a potential complication. With the exception of thalidomide and lenalidomide, immunomodulators do not appear to represent a significant risk to the embryo or fetus. However, the combination of golimumab and methotrexate is contraindicated in pregnancy.

Dronedarone (Multaq, X) is an antiarrhythmic agent that is indicated for patients with atrial fibrillation or atrial flutter. The drug's properties suggest that it will cross the placenta. Major birth defects in rats and rabbits and embryo and fetal death in one species were observed at doses comparable to those used in humans. The effects of exposure after the first trimester are unknown.

Bepotastine (Bepreve; C), an antihistamine, and besifloxacin (Besivance; C), a quinolone antibiotic, are new ophthalmic products. Both have very low systemic bioavailability and low risk in animals, so they can be classified as low risk in pregnancy.

Telavancin (Vibativ; C), a synthetic derivative of vancomycin given intravenously, is indicated for complicated skin and skin structure infections resulting from gram-positive bacteria. The moderately high molecular weight will limit passage across the placenta, but the high fat solubility and long half-life may increase the fetal exposure. The manufacturer states that pregnancy must be excluded because of limb shortening and polydactyly in three animal species.

However, a presentation by Dr. Anthony Scialli of Tetra Tech Sciences at a public meeting of the FDA Advisory Committee on Antimicrobial Drugs in November 2008 did not support the recommendation. Among 654 rat and 156 rabbit fetuses, shortened limbs were observed in only 3 fetuses, 2 rats, and 1 rabbit. In minipigs, polydactyly was observed in controls and in all drug groups except the high-dose group, so inclusion of these results is questionable.

A better reason for not using this drug is that it does not appear to offer for the indication a clear advantage over other available antibiotics with pregnancy experience.

The animal data for vigabatrin (Sabril; C), an equal mixture of active and inactive enantiomers, suggest risk, as do the human data. However, in all of the reports, the agent was combined with first-generation antiepileptic drugs known to cause human birth defects. The contribution of vigabatrin to the toxicity cannot be determined until more data are available. In addition, the placental passage of the active enantiomer is slow with fetal levels less than maternal levels. For now, a more pressing concern is the vision loss, sometimes permanent, that occurs in a high percentage of those treated. For that reason alone, the drug should be avoided if possible.

Milnacipran (Savella; C), a selective serotonin-norepinephrine reuptake inhibitor (SNRI), is the fourth antidepressant in this class, but is indicated for fibromyalgia. The fetal risks from SNRIs are primarily in the second half of pregnancy and include low birth weight, prematurity, and neonatal serotonin or behavioral syndromes. Using the lowest possible dose may reduce these toxicities.

The antigout agent, febuxostat (Uloric; C), caused no developmental toxicity at exposures equal to or less than 10 times the human exposure, so it can be listed as low risk. It probably crosses the placenta. Pitavastatin (Livalo, X) is another statin and, as with the other six agents in this class, is contraindicated in pregnancy.

The four antineoplastics are everolimus (Afinitor; D), a protein-tyrosine kinase inhibitor for advanced renal cell carcinoma; ofatumumab (Arzerra; C), a monoclonal antibody for chronic lymphocytic leukemia; pazopanib (Votrient; D), a tyrosine kinase inhibitor for advanced renal cell carcinoma; and romidepsin (Istodax; D), a histone deacetylase inhibitor for cutaneous T-cell lymphoma.

Although there is a potential risk to the fetus with any antineoplastic agent, the maternal benefits from the first three drugs appear to outweigh the risks.

However, romidepsin competes with estradiol for estrogen receptors and, because estrogen is required to maintain pregnancy throughout gestation, should be avoided in pregnancy.

The package insert provides data for estimating risk during pregnancy, so 'when your patient asks, "What are the risks?" you don't have to say, "We just don't know." '

Asenapine (Saphris, C) and iloperidone (Fanapt, C) are atypical antipsychotics (i.e., they have a reduced ability or an inability to cause extrapyramidal syndrome). Both drugs will probably cross the placenta, but there is no evidence that other atypicals cause embryo or fetal harm. Although the American College of Obstetricians and Gynecologists does not recommend routine use of atypicals, a risk-benefit assessment may indicate that such use is appropriate (Obstet. Gynecol. 2008;111:1001-19).

The hematologic agents are ecallantide (Kalbitor, C) for acute attacks of hereditary angioedema, a rare genetic disorder, and prasugrel (Effient, B) to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention. The animal data for ecallantide suggest low risk, but the doses used were less than 10 times the human dose. A dose slightly above 10 times in one of the species caused embryo death. However, the drug's properties (high molecular weight and a short half-life) suggest that exposure of the fetus will be low, if it occurs at all. A major concern, though, is the nearly 4% risk of anaphylaxis that has occurred in patients. The prodrug prasugrel is an irreversible inhibitor of platelet activation and aggregation. The manufacturer recommends taking aspirin with it. The prodrug is not detected in plasma, but the active and inactive metabolites are and may cross the placenta. Nevertheless, the maternal benefit appears to outweigh any embryo or fetal risks.

Tolvaptan (Samsca, C) is a selective vasopressin receptor antagonist that is used to treat nonurgent, resistant symptomatic hyponatremia. There are no human pregnancy data for the other agent (conivaptan) in this class. Tolvaptan probably crosses the placenta, but the animal data suggest low risk.

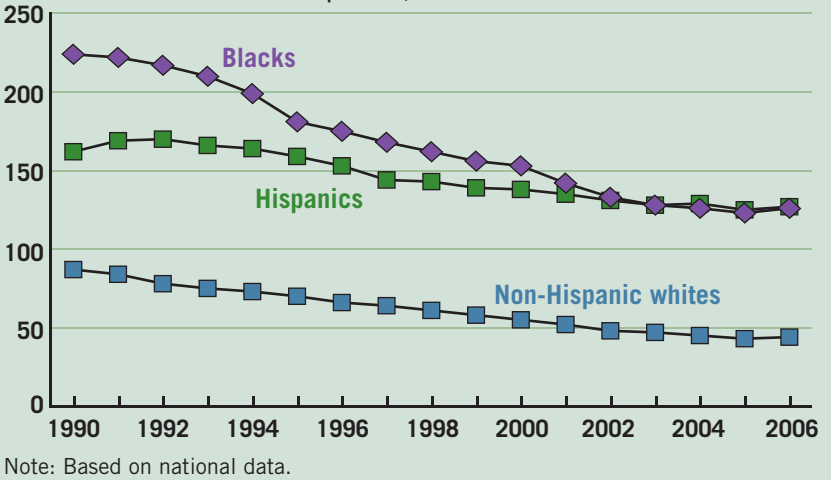
Bepotastine, besifloxacin, ecallantide, golimumab, ofatumumab, prasugrel, telavancin, and vigabatrin appear to be compatible with breastfeeding, but there are human data only for vigabatrin. Everolimus, golimumab combined with methotrexate, pazopanib, and pitavastatin, should be classified as contraindicated.

There is potential toxicity for a nursing infant from the other agents, but human data are needed to quantify the risks. ■

MR. BRIGGS is a pharmacist clinical specialist in Perinatal Support Services at Miller Children's Hospital, Long Beach, Calif.; clinical professor of pharmacy at the University of California, San Francisco; and adjunct professor of pharmacy at the University of Southern California, Los Angeles. He is also a fellow of the American College of Clinical Pharmacy and coauthor of "Drugs, Pregnancy, and Lactation." He has no disclosures related to the content of this column. E-mail him at obnews@elsevier.com.

DATA WATCH

Pregnancy Rates for Girls Aged 15-19 Years
(per 1,000)



Note: Based on national data.
Source: Guttmacher Institute