FDA Downgrades Efavirenz To Pregnancy Category D

BY JANE SALODOF MACNEIL
Southwest Bureau

The Food and Drug Administration has downgraded efavirenz to pregnancy category D, "Positive Evidence of Fetal Risk," and is urging women to avoid becoming pregnant while taking the antiretroviral drug.

The new package label stems from four retrospective reports of women who gave birth to infants with neural tube defects after first trimester exposure to efavirenz (Sustiva). Three infants were diagnosed with meningomyelocele and one with Dandy Walker syndrome.

Physicians are being asked to report pregnant patients exposed to efavirenz to the Antiretroviral Pregnancy Registry (800-258-4263), which was established to monitor fetal outcomes. The drug had previously been labeled category C: "Risk of Fetal Harm Cannot Be Ruled Out."

Bristol-Myers Squibb Co., Princeton, N.J., alerted health care providers to the label change in a letter dated March 2005 and made public in June. Signed by Freda C. Lewis-Hall, M.D., senior vice president for medical affairs, the letter urged pregnancy testing before women start on efavirenz.

"Though there are no adequate, well-controlled studies in pregnant women, Sustiva should be used during the first trimester of pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options," Dr. Lewis-Hall advised. "Barrier contraception should always be used in combination with other contraceptive methods."

Dr. Lewis-Hall described a prospective review of pregnancy outcomes for 206 women who carried 207 fetuses, while exposed to efavirenz. Five of 188 infants born after first-trimester exposure had birth defects; none were observed in 13 live births after second- or third-trimester exposures. Dr. Lewis-Hall did not describe the birth defects, except to say they were not neural tube defects, which, so far, have only been seen in retrospective reports.

"Although a causal relationship of these events to the use of Sustiva has not been established, similar defects have been observed in preclinical studies of efavirenz," she wrote. Her letter cited a preclinical animal study that reported malformations in 3 of 20 fetuses from cynomolgus monkeys treated with efavirenz throughout pregnancy.

Gerald G. Briggs, B. Pharm., told this newspaper that data from pregnancy registries and retrospective reports should be viewed as identifying possible signals and raising hypotheses. "Follow-up controlled studies are needed to determine if the association is causative," said Mr. Briggs, a pharmacist clinical specialist at Women's Pavilion at Miller Children's Hospital, Long Beach, Calif.

He did not rule out prescribing efavirenz for a pregnant woman who is positive for HIV. If she cannot take an alternative nonnucleoside reverse transcriptase inhibitor and has done well on efavirenz, he recommended continuing her on the drug.

"Taken in sum, the data suggest that there may be a small risk of neural tube defects and other defects, but no neural tube defects were observed in 188 prospective cases, so the risk must be low," he said.

As in all potential pregnancies, he added, the woman should be taking folic acid before conception. "It may not be preventive," Mr. Briggs said, "but based on the potential signal, I would recommend the same folic acid dose used for anticonvulsants known to cause neural tube defects and for women with a history of giving birth to an infant with a neural tube defect: 4 or 5 mg per day." ■

Pregnant Smokers: Cutting Back in Third Trimester Is Better Than Never

LOS ANGELES — A pregnant smoker who cuts back by just one cigarette a day in her third trimester can hope to increase her newborn's birth weight by 24 g, according to a prospective study reported at the annual meeting of the Society for Gynecologic Investigation.

The message is, "Don't stop trying to get women to reduce their smoking volume," said Ira M. Bernstein, M.D., who presented data on 160 women and their offspring.

The mothers were enrolled in a randomized, prospective trial of a voucher system designed to help pregnant women stop smoking or stay cigarette free. Dr. Bernstein of the University of Vermont, Burlington, said that a woman's smoking volume was assessed using self-reports as well as measurement of urinary cotinine and exhaled carbon monoxide levels.

Before pregnancy, the group averaged 18.2 cigarettes a day. They had already cut down to 6.7 cigarettes per day by the time they enrolled in the study, which was at 12 weeks' gestation on average. By 28 weeks, they were down to 4.8 cigarettes daily.

All had singleton pregnancies with a mean birth weight of 3,266 g. The mean gestational age at delivery was 38.6 weeks, with 17 babies born preterm.

Smoking in the third trimester accounted for 10% of variance in birthweight. Dr. Bernstein reported a linear relationship in which babies weighed 24 g less at birth for every cigarette their mothers smoked per day in the third trimester. The data support the idea that the third trimester is more important than the first, he said.

The National Institutes of Health and a General Clinical Research Center grant supported the study.

—Jane Salodof MacNeil

DRUGS, PREGNANCY, AND LACTATION

Migraine Drugs

Migraine symptoms improve in up to 70% of women during pregnancy, usually during the second and third trimesters. But in 4%-8% of women, migraines worsen, and as many as 16% of all migraine cases during pregnancy may be new onset.

A 2002 review identified drugs or drug classes used for preventing migraine attacks (N. Engl. J. Med. 2002;346:257-70), including four drugs available in the United States that were considered well-accepted treatments or had proved to be effective: metoprolol, propranolol, amitriptyline, and valproate. Verapamil (Calan, Isoptin) and selective serotonin-reuptake inhibitors (SSRIs) also were widely used, but the reviewers concluded that there was poor evidence of benefit. Gabapentin (Neurontin) and topiramate (Topamax), were considered promising for migraine prophylaxis.

BY GERALD G. BRIGGS, B. PHARM.

Only amitriptyline, verapamil, and low-dose propranolol (30-40 mg/day) have sufficient data to be classified as low risk throughout pregnancy. But higher doses of propranolol may cause intrauterine growth retardation (IUGR) and other fetal/neonatal toxicity. Based on the drug class (antihistamine and calcium channel blocker), flunarizine is probably compatible with pregnancy. Gabapentin and topiramate should be avoided in the first trimester because of inadequate human data to assess their risk. Valproate is known to cause neural tube defects and other structural anomalies if used in the first trimester, and use of metoprolol during the second and third trimesters is associated with an increased risk of IUGR. Use of the SSRIs in the third trimester may cause newborn toxicity, and methysergide and other ergot alkaloids are contraindicated in pregnancy.

Many other drugs have been used in treating migraines, including: acetaminophen (alone, or in combination with caffeine and butalbital, aspirin and caffeine, or isometheptene and dichloralphenazone); NSAIDs, including aspirin; chlorpromazine (Thorazine); dimenhydrinate (Dramamine); diphenhydramine (Benadryl); morphine; meperidine; intranasal butorphanol (Stadol); and corticosteroids.

Combination products with butalbital are not recommended because in studies, the butalbital component did not increase efficacy. Acetaminophen, caffeine, dimenhydrinate, diphenhydramine, narcotic analgesics, lidocaine, and butorphanol are compatible (i.e., very low risk) in pregnancy. However, frequent, prolonged use of narcotic analgesics may result in maternal and fetal addiction.

NSAIDs, including aspirin, have been associated with miscarriage when used around the time of conception, and exposure in the third trimester is associated with premature closure of the ductus arteriosus with the risk of persistent pulmonary hypertension of the newborn.

Since aspirin causes irreversible inhibition of platelet function and other clotting disorders, its use near term may enhance maternal blood loss at delivery and increase the incidence of intracranial hemorrhage in premature infants. Use of corticosteroids in the first trimester is associated with a low risk of oral clefts. Ergot alkaloid preparations are contraindicated in pregnancy because of dose-related developmental toxicity and oxytocic properties.

In the United States, seven triptans indicated for the short-term treatment of migraine with or without aura are available: sumatriptan (Imitrex), almotriptan (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), rizatriptan (Maxalt), and zolmitriptan (Zomig). Triptans do not appear to be major teratogens in humans, but more data are needed to adequately assess this risk.

In animal studies at doses or systemic exposures 10 times the human dose, triptans caused developmental toxicity. Human data, primarily from pregnancy registries, are available only for naratriptan, sumatriptan, and rizatriptan. As of early 2004, about 500 women had been prospectively enrolled, about 90% with first-trimester exposure. Except for a small cluster of five ventricular septal defects, a common heart condition, there was no consistent pattern of defects to suggest a common cause.

Other than ergot drugs (contraindicated) and amitriptyline (concern for long-term neurotoxicity), all antimigraine agents appear to be compatible with breast-feeding. However, there are few or no data available for gabapentin and topiramate. Ergot alkaloids may inhibit lactation, and high doses have been associated with toxicity in nursing infants. The effect of triptans on a nursing infant is unknown, but the small amount of drug found in milk does not appear to represent a risk and it is probable that they are all compatible with breast-feeding.

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