FDA Warns Against Efavirenz During Pregnancy

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 who have been 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, she added."

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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, Miller Children's Hospital, Long Beach, Calif., and coauthor of the reference book "Drugs in Pregnancy and Lactation" (Philadelphia: Lippincott Williams & Wilkins, 2005).

Mr. Briggs 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," Mr. Briggs said.

As in all potential pregnancies, he added, the woman should be taking folic acid before conception.

"It may not be preventive, 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," the pharmacist clinical specialist said. ■

Interactions Potent Between HIV Agents, Opiates

BY DAMIAN MCNAMARA
Miami Bureau

SAN JUAN, P.R. — Better understanding of interactions between opioids and antiretroviral agents can improve clinical care and patient outcomes, said Elinore McCance-Katz, M.D.

"It may be that methadone is not the best opiate therapy for everyone with HIV who is opioid dependent," Dr. McCance-Katz said at the annual meeting of the American Academy of Addiction Psychiatry. "These drug interactions are so potent, it is important to know if there are optimal combinations of opiate therapies and HIV medications."

Through the cytochrome P-450 system, many antiretroviral agents interact with opioids, including methadone (see box), levomethadyl acetate (LAAM), and buprenorphine. HIV drugs that induce metabolism of methadone can cause symptoms of opiate withdrawal between doses; HIV drugs that inhibit such metabolism can cause opiate toxicity.

Such interactions can lead to nonadherence to antiretroviral regimens, viral resistance, and illicit drug use "in an attempt to self-medicate some of these noxious drug interactions that often go unrecognized," said Dr. McCance-Katz, chair of the division of addiction psychiatry, Virginia Commonwealth University, Richmond.

Antiretroviral Agents Reported to Interact With Methadone

Abacavir
Combivir
Delavirdine
Didanosine
Efavirenz
Lopinavir
Nelfinavir
Nevirapine
Ritonavir
Saquinavir
Stavudine
Zidovudine

SOURCE: Dr. McCance-Katz

Drug toxicities that are additive can be a significant risk to patients. Because of the clinically significant interactions, the Food and Drug Administration now requires methadone interaction data before approval of a new antiretroviral agent.

Researchers are assessing alternatives to methadone for HIV patients. Buprenorphine, for example, may not have the same liabilities as methadone in combination with antiretroviral therapy, she said. "I'm still looking at the data, but we don't see the toxicities with buprenorphine and LAAM that we see with methadone."

Methadone-maintained patients who use efavirenz as part of highly active antiretroviral therapy require a 50% increase in methadone concentration, from 80 mg/dL at baseline to 120 mg/dL, according to research by Dr. McCance-Katz. With buprenorphine, the mean 17.2-mg/dL dosage did not change when efavirenz was added. "We did not have to increase the opiate dose for anyone, and we did not have to restabilize people as a result."

Not all of methadone's effects on HIV drugs are via cytochrome P-450 metabolism. For example, didanosine and stavudine concentrations drop to subtherapeutic levels when these drugs are taken with methadone. Methadone decreases gastrointestinal motility, and didanosine and stavudine are particularly sensitive to stomach acid.

Dr. McCance-Katz highlighted some specific interactions between methadone and agents that combat HIV:

- Delavirdine mesylate inhibits cytochrome P-450, leading to a significant increase in methadone concentrations—the half-life is extended by almost 50%. "We would worry about accumulation," she said. "With LAAM, we see even more dramatic effects and LAAM metabolites, which have implications for cardiac toxicity."
- Nevirapine is similar to delavirdine, causing a decrease of about 50% in methadone area-under-the-curve concentrations. Withdrawal symptoms can occur if methadone dosages are not increased.
- Nelfinavir mesylate shows a "dramatic drop" in 7-day plasma levels when given with methadone. "Interestingly, we did not see withdrawal in these patients. We think that is because nelfinavir is a very good competitor for protein binding—so there was more free methadone available to protect them from opiate withdrawal," she said.
- Kaletra, a combination of lopinavir and ritonavir, causes methadone levels to become subtherapeutic. Dr. McCance-Katz observed withdrawal symptoms in these patients. "But we did not know if it was an effect of lopinavir, ritonavir, or both." When ritonavir was studied alone, the nonsignificant increase in methadone level implicated lopinavir as the component interacting with methadone. ■

Condom Use Can Reduce Duration Of HPV Infection

LOS ANGELES — Condom use does matter in human papillomavirus infections, because it is associated with a shorter persistence of infection in females, according to a study of 57 sexually active female adolescents.

The study followed the adolescents for an average 2.2 years and included periods during which the subjects collected vaginal swabs weekly. The study found that those who reported the least-frequent condom use had a mean duration HPV infection of 251 days, vs. 138 days for those reporting the most, Marcia L. Shew, M.D., said at the annual meeting of the Society for Adolescent Medicine.

Noting that a recent National Institutes of Health report concluded that previous studies have not provided good enough evidence to know if condom use prevents or influences HPV infection and transmission, she said, "We were so excited when we found out that condoms had a role, and it makes sense because condom use has clearly been shown to be associated with more frequent regression in cervical intraepithelial neoplasia."

The study, which, in addition to the weekly vaginal swabs collected by the subjects themselves, looked at cervical swabs collected by the investigators every 3 months, found that 49 of the 57 subjects got at least one infection during the average 2.2 years, for a cumulative incidence of 86%, said Dr. Shew of Indiana University, Indianapolis.

There were 241 infections, or an average of about 5 per individual. Of the infections, 168 were of a high-risk, oncogenic type of papillomavirus, and 73 were of a low-risk type. The types most frequently detected were 52 and 16, high-risk types, and 66, a low-risk type.

—Timothy F. Kirn