Maternal Citalopram Tied To Various Adverse Events

BY SHARON WORCESTER
Southeast Bureau

ST. PETE BEACH, FLA. — A total of 228 adverse events associated with the use of citalopram (Celexa) during pregnancy has been reported to the Food and Drug Administration's Adverse Event Reporting System since the drug's approval in 1998, J. Edward Fisher, Jr., Ph.D., reported at the annual meeting of the Teratology Society.

Of these reports, 120 involved adverse developmental events, including 38 during the peri- or postnatal period. Of the 38 cases, 31 occurred during the first week of life, and 18 of these involved neonatal withdrawal symptoms, including jitteriness, rigidity, tremor, and confusion associated with citalopram exposure in either the 3rd trimester or throughout pregnancy.

The doses used ranged from 20-40 mg/day, said Dr. Fisher, a pharmacologist with the FDA Center for Drug Evaluation and Research, Rockville, Md.

Reports of symptoms consistent with neonatal withdrawal syndrome and associated with maternal use of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) prompted the FDA last year to require labeling changes warning of the risk associated with their use during pregnancy.

Possible cases of neonatal withdrawal syndrome have been reported with all SSRIs, but paroxetine was most frequently involved in one study of 93 cases: 64 were associated with paroxetine, 14 with fluoxetine, 9 with sertraline, and 7 with citalopram, marketed as Celexa by Forest Laboratories. (One patient received both paroxetine and fluoxetine.) In another large study, the association between paroxetine and neonatal symptoms was no greater than that of other SSRIs.

The citalopram reports noted by Dr. Fisher and the other reports involving various SSRIs and SNRIs; their association with neonatal withdrawal symptoms suggest a class effect. But the data cannot verify significant differences among individual drugs in this class, he told this newspaper.

As a rule, "the use of this agent has to be balanced with respect to the benefit to the mother if she is depressed. There is a general consensus that SSRIs and SNRIs are preferable to tricyclics in terms of safety and efficacy," said Jeffrey Jonas, M.D., senior vice president of Forest Research Institute, a division of Forest Labs.

Experts urge clinicians to weigh the risks and benefits of SSRI and SNRI use in pregnancy and to consider the increased risk of maternal morbidity associated with untreated maternal depression. ■

Antidepressants Raise Concern About Neonatal Withdrawal

BY NANCY A. MELVILLE
Contributing Writer

TUCSON, ARIZ. — Recent research linking use of selective serotonin reuptake inhibitors in pregnancy with neonatal withdrawal symptoms heightened concerns about treating depression during pregnancy, but depression in mothers-to-be carries its own serious risks, Marlene Freeman, M.D., said at a psychopharmacology conference sponsored by the University of Arizona.

The study in question received extensive media coverage about a "neonatal withdrawal syndrome" in the first days of life that is linked to SSRI use, especially to SSRI use later in pregnancy (Lancet 2005;365:482-7).

The findings came from a World Health Organization database of adverse drug reactions. Researchers reported 93 suspected cases of the withdrawal syndrome, but the study is fraught with complications, and it "raises more questions than it answers," Dr. Freeman said.

The lack of a control group makes it impossible to determine if depression and anxiety disorders played a role. Also, there was no clear denominator, so it's not clear how many people were exposed to the medications and did not have the problems, said Dr. Freeman, director of the women's mental health program at the university.

Other small studies looking at antidepressants in pregnancy have shown possible transient side effects after use of antidepressants late in pregnancy, but the few long-term studies that have looked at the topic did not find any lasting consequences of antidepressant exposure during pregnancy, she said.

But there is substantial evidence of the impact of depression during pregnancy on both women and children, including negative effects on maternal weight gain and the child's birth weight as well as an increased risk of prematurity.

That consideration has not been lost on the U.S. Food and Drug Administration. With its own letter rating system considered by many—including the agency's own officials, according to Dr. Freeman—to be highly unreliable, the agency is talking about addressing the concerns of antidepressants in pregnancy with a paragraph on labels that would describe not only what is known about the drug in pregnancy from studies thus far but also the risks of untreated maternal depression, she said.

"Discuss the risks and benefits of antidepressant treatment and seek advice from other clinicians," Dr. Freeman advised at the meeting.

"It's definitely important to use the lowest effective doses, but we also don't want to undertreat people," she added. ■

DRUGS, PREGNANCY, AND LACTATION

Rheumatoid Arthritis Drugs

The autoimmune disorder rheumatoid arthritis occurs in about 1%-2% of the population. The disease is more prevalent in women than men by about a 3:1 ratio, but in the reproductive years, the ratio may be as high as 6:1. During pregnancy, the incidence is about 1 in 1,000.

RA is characterized by production of cytokines, including tumor necrosis factor–α (TNF-α) and interleukin-1 in the synovial cavity, and irreversible damage to soft tissues and bones. Drug therapy of RA involves using disease-modifying antirheumatic drugs (DMARDs) to prevent or lessen this damage. The therapy can be categorized as biologic DMARDs, synthetic DMARDs, and anti-inflammatory agents.

BY GERALD G. BRIGGS, B.PHARM.

Biologic DMARDs include three agents that inhibit TNF-α —adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade)—and one interleukin-1 receptor antagonist, anakinra (Kineret). Although the human pregnancy data for these four drugs are lacking, animal reproduction data suggest they pose a low risk for developmental toxicity (growth retardation, structural defects, functional/behavioral defects, or death).

The safest course is to avoid these agents during the first trimester, but with their long elimination half-lives, inadvertent exposures during organogenesis of unplanned pregnancies is likely.

Synthetic DMARDs include azathioprine (Imuran), cyclosporine (Sandimmune, Neoral), gold compounds, hydroxychloroquine (Plaquenil), leflunomide (Arava), methotrexate, penicillamine, and sulfasalazine (Azulfidine).

The two immunosuppressants, azathioprine and cyclosporine, do not appear to cause congenital defects, but they may be associated with growth retardation. There is limited human pregnancy experience with the gold compounds—auranofin (Ridaura), aurothioglucose (Solganal), and gold sodium thiomalate (Aurolate)—but the animal data suggest the risk for developmental toxicity is low.

Hydroxychloroquine is probably compatible in pregnancy, but there is limited pregnancy experience with the high doses commonly used in RA. The drug has a very long elimination half-life from maternal tissues (weeks to months), so stopping the drug when pregnancy is confirmed will not prevent embryo/fetal exposure.

Leflunomide, a pyrimidine synthesis inhibitor, causes dose-related teratogenicity and toxicity in animals at doses much lower than those used in humans. Human pregnancy experience is too limited to determine the risk to the embryo or fetus, and the drug is contraindicated in pregnancy. Exposure of unplanned pregnancies will probably occur because the drug and its active metabolite may take up to 2 years to reach nondetectable plasma levels.

The folic acid antagonist methotrexate is contraindicated during pregnancy. The drug is associated with spontaneous abortions and a spectrum of congenital defects collectively termed methotrexate embryopathy. The critical exposure period for structural defects is 8-10 weeks after the first day of the last menstrual period. Exposure after this period is associated with fetal toxicity and mortality. The critical dose is thought to be 10 mg or more per week.

Another folate antagonist, sulfasalazine, does not seem to cause developmental toxicity, but supplemental folic acid (1 mg/day) should be used if there is a risk of unplanned pregnancy or if pregnancy occurs. The drug has caused bloody diarrhea in a nursing infant, so breast-feeding should be done with caution. Penicillamine, a chelating agent associated with a risk of fetal connective tissue defects (cutis laxa), should be avoided during pregnancy.

The NSAIDs, which include aspirin, have considerable potential for embryo/fetal toxicity: spontaneous abortions when used around the time of conception, fetal renal toxicity, and premature closure of the ductus arteriosus in the third trimester. Aspirin use near term may increase the risk of bleeding in the mother and the infant. The use of prednisone during organogenesis carries a low risk for oral clefts and prolonged use in pregnancy has been associated with growth retardation.

The biologic DMARDs, gold compounds, hydroxychloroquine, NSAIDs (except high-dose aspirin), and prednisone are probably compatible with breast-feeding. The other agents are either contraindicated (methotrexate) or should be avoided because of potential toxicity. High-dose aspirin and sulfasalazine have been associated with toxicity in nursing infants.

The Organization of Teratology Information Services is conducting a study of pregnancy exposure to rheumatoid arthritis drugs. Health care professionals can call the toll-free number (877-311-8972) for information about enrolling patients in this study.

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