Zolpidem Doesn't Seem to Affect Pregnancy Outcomes

BY KERRI WACHTER
Senior Writer

WASHINGTON — Even though the sleeping aid zolpidem crosses the placenta, use of the drug during pregnancy does not appear to significantly affect outcomes, a study of 45 women shows.

The study, presented as a poster at the annual meeting of the American Psychiatric Association, included pregnant women who were enrolled in a prospective study of the pharmacokinetics of psychotropic drugs during pregnancy and who were treated with zolpidem (Ambien) during pregnancy. Maternal diagnoses were determined using the Structured Clinical Interview for DSM-IV (SCID). Maternal and cord blood were obtained at delivery when possible.

The placental passage rate was calculated as the ratio of medication concentration in the umbilical cord plasma to that in maternal plasma. When umbilical cord concentrations were below the limit of detection (less than 4.0 ng/mL), this value was used for data analysis. This approach was thought to be conservative, erring toward overestimation of fetal exposure to zolpidem. When both maternal and umbilical plasma concentrations were less than the detection limit, the pair was excluded from the analysis.

Obstetrical and neonatal outcomes in women who had given birth to a live infant after taking zolpidem during pregnancy were compared with outcomes in a group of 45 women who were matched for age, race, level of education, SCID diagnosis, and pregnancy exposure to the same classes of nonzolpidem psychotropic medications.

For women who took zolpidem during pregnancy, exposure by trimester included 38% in the first trimester, 56% in the second trimester, and 38% in the third trimester. The average zolpidem exposure during pregnancy was 14 weeks, and the average dose was 9 mg.

There were no statistically significant differences between the two groups in terms of obstetrical and neonatal outcomes. However, there was a trend toward preterm delivery and low-birth-weight infants in women on zolpidem during pregnancy. In that group, 27% of the women had a preterm delivery and 16% had low-birth-weight infants, compared with 16% and 8%, respectively, for the nonzolpidem group.

"It is unclear if these outcomes were driven by zolpidem exposure and/or sleep disturbance or other pharmacological intervention in pregnancy," wrote Sandra Juric and colleagues at Emory University's Women's Mental Health Program, Atlanta.

Women who reported longer zolpidem use during pregnancy (10 weeks or longer) did not have a greater rate of complications. There also appeared to be no difference between drug use in a particular trimester versus use throughout the pregnancy in terms of complications. Ms. Juric reported no conflicts of interest. ■

Metformin Appears to Enhance Antitumor Effect in Breast Ca

BY FRAN LOWRY
Orlando Bureau

CHICAGO — The diabetes drug metformin may have an antitumor effect, according to data from a retrospective study of more than 2,500 breast cancer patients, including 155 women with diabetes.

Patients on metformin for diabetes had a threefold higher pathologic complete response (pCR) rate after neoadjuvant chemotherapy, compared with those who had diabetes but were not on metformin (24% vs. 8%), Dr. Sao Jiralerspong of the University of Texas M.D. Anderson Cancer Center in Houston said in a poster at the annual meeting of the American Society of Clinical Oncology.

The rate of pCR, defined as no residual disease in the breast or lymph nodes, also was higher in the cohort of patients taking metformin than in those without diabetes, who had a pCR rate of 16% after neoadjuvant chemotherapy.

Recent data suggest metformin may reduce the incidence of cancer and cancer-related mortality in diabetic patients. It activates adenosine monophosphate-activated protein (AMP) kinase, inhibits the mammalian target of rapamycin (mTOR) pathway, and has been shown to inhibit the growth of breast cancer cell lines in preclinical studies, said Dr. Jiralerspong.

He and his colleagues reviewed the charts in the M.D. Anderson Breast Medical oncology database of 2,529 patients who received neoadjuvant systemic therapy for early-stage breast cancer. Of those, 2,374 patients did not have diabetes; 68 had diabetes and were treated with metformin, and 87 had diabetes but were not treated with metformin. The median age was 49 years, most tumors were hormone receptor–positive; 25% were HER2-positive. Patients' baseline characteristics were similar, but diabetic patients tended to be older and more obese. Metformin use was independently predictive of pCR after adjustment for diabetes, body mass index, age, stage, grade, estrogen/progesterone receptor status, and neoadjuvant taxane use.

After a median follow-up of 39 months, the recurrence-free survival was similar in the three groups. Overall survival was significantly better, in the nondiabetic cohort (86%), compared with 81% for diabetic patients on metformin and 78% for diabetic patients not on metformin.

Dr. Jiralerspong said further studies are warranted to evaluate the potential of metformin as an antitumor agent. He said he had no conflicts of interest to declare. ■

DRUGS, PREGNANCY, AND LACTATION

Neonatal Withdrawal Symptoms

Poor adaptation syndrome in newborns exposed in late pregnancy to a selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI)—with symptoms such as jitteriness, being inconsolable, and difficulty in feeding—were first described several years ago.

The most unusual feature of this syndrome that has not been described in babies experiencing opioid or benzodiazepine withdrawal is respiratory distress, which often needs respiratory support. These symptoms were present in about 20% of newborns exposed to an SSRI or SNRI late in pregnancy in a series of cases we studied. The good news is that those symptoms resolved, usually within several days; most of the babies were treated with sedation, after which they did well.

BY GIDEON KOREN, M.D.

We reviewed all published reports of neonatal discontinuation syndrome after exposure to anti-depressants in late pregnancy and estimated that between 10% and 30% of babies exposed in utero to an SSRI or SNRI in that stage experienced some signs of withdrawal (Can. Med. Assoc. J. 2005;172:1457-9). Adults who stop these drugs abruptly can experience typical withdrawal symptoms, such as nervousness, unrest, tremors, insomnia, and even seizures, so it makes biologic sense that a newborn may develop withdrawal symptoms after exposure in utero.

It is often assumed that these symptoms are manifestations of withdrawal, but in some cases, they could be the signs of toxicity of these drugs—serotonergic syndrome—which in neonates are indistinguishable from those described in withdrawal.

Given what we know about the pharmacokinetics of the SSRIs and SNRIs and measured drug levels in newborns exposed in late pregnancy, it is highly likely that most observed cases represent genuine withdrawal.

Differentiating between toxicity and withdrawal may therefore be important. Based on the same pharmacologic rationale behind the treatment of newborns in opiate withdrawal with small doses of narcotics, it would make sense to treat the baby with antidepressant withdrawal symptoms with small amounts of the antidepressant. But if there is a chance that some cases are a result of toxic drug levels, one has to be careful with this approach.

The only way to determine if a baby is experiencing withdrawal or toxicity is with therapeutic drug monitoring, which currently is not practiced in newborns anywhere.

A European report of a baby exposed to the SNRI venlafaxine (Effexor) in late pregnancy, whose symptoms resolved after receiving a small dose of the drug, strengthened the concept that this might be a beneficial approach to treating neonatal withdrawal symptoms.

The Food and Drug Administration and Canadian authorities responded to reports of neonatal withdrawal syndrome with suggestions that physicians may consider tapering these antidepressants during the third trimester, which is included in the U.S. labels of these drugs.

This is unfortunate, since the best predictor of postpartum depression is depression in late pregnancy. Up to 20% of women may be diagnosed with depression in pregnancy and may need treatment with an antidepressant. Many experts concur that stopping treatment late in pregnancy is not necessarily the ideal approach and that women with depression responsive to SSRIs or SNRIs should be properly treated, especially since the neonatal withdrawal syndrome is self-limited.

Exposure to an SSRI or SNRI late in pregnancy should be considered a possible cause in newborns with symptoms consistent with withdrawal. When symptoms of respiratory distress are present, hyaline membrane disease, aspiration, infections, cardiac malformations, and other possible causes of the symptoms need to be ruled out.

My colleagues and I believe that if a new mother is treated with an SSRI or SNRI for depression, discharging her and her newborn within the regular 24 hours is not ideal. Babies whose mothers were treated with antidepressants should be monitored closely for more than 24-48 hours after birth, and we are working to develop practice guidelines on discharge recommendations for women and for their babies who were exposed in utero to antidepressants.

There are no current official protocols on how to manage babies with these withdrawal symptoms, and neonates are most commonly managed with phenobarbital, which, after many years of use in this age group, has a strong safety record. In future studies, we hope to define the role of therapeutic drug monitoring in this situation, and whether treatment with low doses of the SSRI or SNRI would be safe and effective in severe cases.

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