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Update: Prozac (fluoxetine) and other selective serotonin re-uptake inhibitors (SSRIs)

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Inquiries regarding antidepressant medications, particularly the selective serotonin re-uptake inhibitors (SSRI's), are amongst the most common calls to the Illinois Teratogen Information Service. Estimates suggest that approximately 10% of women meet diagnostic criteria for clinical depression during pregnancy, with a higher percentage clinically depressed postpartum (Ohara, 1990). 1995 drug monitoring data suggest that Prozac (fluoxetine) is the 9th most commonly prescribed prescription medication, with Zoloft (sertraline) and Paxil (paroxetine) being 13th and 33rd, respectively (Leiken and Paloucek, 1998). It is appropriate, then, that concerns regarding inadvertent or planned exposures during pregnancy and/or lactation to such SSRIs are common in women of reproductive age. This newsletter will, therefore, review the most up-to-date information regarding common SSRIs. It should replace the information presented in the RISK//NEWSLETTER 4(3), 12/95.

Prozac (fluoxetine)

Over the past several years, fluoxetine has become one of the most well-studied prescription medications during pregnancy. It is commonly prescribed for depression, obesity, eating disorders, obsessive compulsive disorder, panic disorder, premenstrual syndrome and alcohol abuse (Gram, 1994). Clinically, fluoxetine produces fewer side effects than many other antidepressants, such as the tricyclic antidepressants, perhaps accounting for its frequent usage (Gram, 1994). Fluoxetine has a long half-life (averaging 2-3 days; norfluoxetine half-life, 7-9 days), and its metabolites are likely to remain in the body for several weeks after discontinuation; this is important to consider when counseling women about potential reproductive risks based on the time of exposure. Fluoxetine is known to cross the placenta and enter the breast milk. Animal studies have generally not found an increased risk for malformations, at up to 11 times the human dose, but a single study did note an increase in skin hematomas after in-utero exposure to fluoxetine (Stanford, 1993); this has not been noted in humans.

Human data on fluoxetine exposure in pregnancy is reviewed in the table below. From these studies, totaling over 530 retrospective reports and 1250 prospective reports, it appears that there is no significant increased risk for major malformations associated with first trimester exposure to fluoxetine, nor has a pattern been noted to the malformations that occurred. Chambers et al. (1996) noted an increase in 3 or more minor malformations; they suggested that the significance of this finding could predict an increased association of major malformations when multiple minor malformations were present. Other studies have not addressed this finding, however.

There is some controversy over whether fluoxetine exposure in the third trimester increases the rate of neonatal complications. Chambers et al. (1996) found a slight increase in NICU admissions (RR 2.6; 95% CI 2.2-6.9) and transient jitteriness, respiratory distress and feeding problems (RR 8.7; 95% CI

2.9-26.6) as compared to control infants. In response to the initial presentation of this in abstract form, Goldstein (1995) analyzed outcomes in 112 pregnancies exposed to fluoxetine in the third trimester. There was no increase in neonatal complications above that expected. Two case reports of neonatal toxicity have been published, detailing transient neonatal hypertonicity and jitteriness after maternal exposure to 20 mg and 60 mg/day, respectively (Spencer 1993; Mhanna et al., 1997). Since symptoms of jitteriness and hypertonicity were also reported with adult serotonin toxicity (Leiken and Paloucek, 1998), it is possible that they were related to in utero exposure. However, at this time, the magnitude of risk for exposed infants cannot be determined.

Zoloft (sertraline)

Initial animal studies on the reproductive toxicology of sertraline showed no increase in malformations at doses up to 20 times the human dose, but did show findings consistent with maternal toxicity (Roerig/Pfizer). Fifteen case reports of various abnormalities exist and were reported to the FDA; there was reportedly no pattern to these malformations (Rosa, 1994). Kulin et al. (1998) prospectively followed 150 women exposed to sertraline in the first trimester and found no increase in miscarriage, major malformations, stillbirth or prematurity. While this data is limited, when considered in combination with the information on fluoxetine, it appears that sertraline is unlikely to pose a significant risk for malformations when used in the first trimester. A single report describes neonatal toxicity after exposure to 200 mg sertraline daily in the third trimester (Kent and Laidlaw, 1995). A report of a woman on 150 mg sertraline daily without adverse neonatal effects suggests that these findings may occur only at the highest maternal doses (Ratan and Friedman, 1995).

Paxil (paroxetine)

Animal studies of paroxetine have not shown an increase in malformations at up to 50 times the usual human dose (Baldwin et al. 1989; Smithkline Beecham, 1996.). Human studies consist of a case series of three exposed infants (McElhatton et al., 1996), postmarketing data following 63 women exposed in the first trimester (Inman et al., 1993), and a prospective cohort study examining outcomes in 98 women exposed in the first trimester (Kulin et al., 1998). None of these studies showed an increase in malformations, nor were miscarriage, stillbirth or prematurity increased in the Kulin et al. report (1998). While this data is limited, when considered in combination with the information on fluoxetine, it appears that paroxetine is unlikely to pose a significant risk for malformations when used in the first trimester. A single report of transient neonatal toxicity (jitteriness and hypertonia) was reported in an infant whose mother consumed 30 mg paroxetine from six months of pregnancy (Dahl et al., 1997).

Luvox (fluvoxamine)

There is little information available on the reproductive effects of fluvoxamine in animals or humans. Animal studies at twice the human dose did not show adverse effects, but the manufacturer states that at doses 4 times the human dose, mortality and growth were affected. McElhatton et al. (1996) reported 2 out of 66 exposed pregnancies resulted in malformations; both of these mothers reported other medication exposures. Kulin et al. (1998) prospectively monitored 26 women exposed to fluvoxamine, and found no increase in malformations, miscarriage, stillbirth or prematurity. While this data is limited, when considered in combination with the information on fluoxetine, it appears that fluvoxamine is unlikely to pose a significant risk for malformations when used in the first trimester.

Neurobehavioral data

Studies have only recently begun to address the long-term effects of exposure to psychotropic agents in utero. As all psychotropic medications affect maternal neurotransmitters, there remains the theoretical possibility of similar effects on a developing fetal brain, which in turn might result in subtle behavioral or learning deficiencies. Animal studies on rats have shown that in utero exposure to fluoxetine resulted

in auto-radiographically visible alterations in the biochemical systems of the brain, particularly the serotonin systems (summarized in Carrera-Vera and Battaglia, 1998). Two other studies did not detect alterations in the behavior of prenatally exposed rats, however (Hoyt, 1989; Vorhees, 1994). The implications of such findings on human exposure and neurodevelopment remain unclear.

Human studies are limited to a single study which assessed the developmental parameters of 55 children exposed to fluoxetine as compared to 80 exposed to tricyclic antidepressants and 84 control infants. At a mean age of three years old (range 18-86 months), no significant differences were noted between global IQ or language scores in the groups (Nulman et al., 1997). While this suggests there is not a significant risk for severe neurological impairment, the more subtle developmental issues have not been well addressed. Compounding issues, e.g., the potential role of maternal depression on neurodevelopment and difficulty in obtaining long-term follow up, will likely make this a complex question to answer in the future (Loebstein and Koren, 1997).

Breastfeeding data

Several studies document the presence of fluoxetine (Isenberg 1990; Burch and Wells, 1992; Taddio et al., 1996), sertraline (Altshuler et al., 1995; Stowe et al., 1997), paroxetine (Spigset et al., 1996) and fluvoxamine (Wright et al., 1991) in human breast-milk. Outside of a single abstract finding decreased weight gain after breastmilk exposure to fluoxetine (Chambers et al., 1998), no data exists providing short or long-term follow up after exposure in breastmilk. As with any medication used while breastfeeding, the physiologic and psychologic benefits of breast-feeding must be weighed against the benefits of treatment for the mother and potential risks to a newborn exposed to the medication. The American Academy of Pediatrics considers the effects of all antidepressants to be “unknown but of possible concern (1994).”

Summary

Fluoxetine is well studied in humans and does not appear to increase the risk for malformations when used in the first trimester of pregnancy. Less data is available on other SSRIs, but it does not suggest a significant increase in malformations with these other medications. Based on a single study and a handful of case reports, controversy exists about whether fluoxetine and other SSRIs increase the chance of neonatal complications, specifically those similar to serotonin overdose (jitteriness, hypertonicity) when used in the third trimester. Virtually no human research has addressed the long-term effects of exposure to psychotropic medications in utero, and therefore the potential for neurobehavioral effects remains undetermined but theoretically possible. As with any medication it is important that patients work with their health care providers to weigh the benefits of medication use versus the likely low risks of exposure in pregnancy or lactation.

Resources: Contact ITIS for a copy of a patient-oriented FACT SHEET on Fluoxetine, or at <http://orpheus.ucsd.edu/otis/index.html>

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