Vol. 31 No. 2 - Feb. 2002

drug therapy topics

ISSN 0882-6684

University of Washington Medical Center / Harborview Medical Center

SSRI Antidepressant Withdrawal Syndrome in Newborns

by Elizabeth Rudy, D.V.M., R.Ph.

Editor's Note: Adverse drug reactions experienced by UWMC or HMC patients and reported to the pharmacy are reviewed quarterly by the Pharmacy & Therapeutics Committee. Following the Committee's review, a summary is published in this newsletter (see page 9) along with a companion article regarding some aspect of adverse drug reactions. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, "No drug has only one action." By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you feel is experiencing an Adverse Drug Reaction, report it by calling the A.D.R. Phone Line, HMC: 731-3802; UWMC: 598-6837; SCCA: 288-6336.

The use of selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram) to treat depression during pregnancy has become increasingly popular, in part due to studies that indicate that these antidepressants are unlikely to be teratogenic at therapeutic doses.[1] However, case reports have appeared sporadically in the medical literature describing withdrawal symptoms in neonates whose mothers took these medications during pregnancy. The purpose of this Focus is to explore what potential adverse effects prenatal exposure to SSRI antidepressants may have on the newborn.

A variety of symptoms, most commonly involving the central nervous system and the gastrointestinal system, have been observed in neonates experiencing selective serotonin reuptake inhibitor (SSRI) antidepressant withdrawal.[2] Nordeng et al. described withdrawal symptoms in five infants exposed to SSRI antidepressants prenatally. [2] These neonates exhibited symptoms of irritability, constant crying, shivering, increased tonus, eating and sleeping difficulties, and seizures. Stiskal et al. described jitteriness, vomiting, irritability, hypoglycemia, and necrotizing enterocolitis in four infants exposed prenatally to paroxetine.[3] In adults, similar SSRI withdrawal symptoms have been observed.[3] In the above prenatal exposures, most of the pregnant women took the SSRI antidepressant throughout the pregnancy or started taking it in the second or third trimester and continued through term.

In their 1996 study on birth outcomes in pregnant women taking fluoxetine (Prozac^{R}), Chambers et al. reported that of the 73 infants exposed to the drug in the third trimester, 31.5% exhibited symptoms of "poor neonatal adaptation" that included respiratory difficulties, irritability, jitteriness, and cyanosis on feeding.[4] As of March 2001, there were a total of 13 reports to the Australian Drug Reaction Advisory Committee that were described as neonatal withdrawal syndrome in conjunction with maternal use of an SSRI antidepressant.[5] Additionally, there are scattered case reports in the medical literature describing neonatal withdrawal symptoms in infants exposed prenatally to SSRI antidepressants: 10 reports involved paroxetine, 2 reports involved sertraline, 1 report involved citalopram, and 3 reports involved fluoxetine.[2,3,6-12]

(Continued on page 8)

A University of Washington / Harborview Medical Center Drug Information Center publication
Distributed monthly by authority of the Pharmacy and Therapeutics Committee
Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.
Department of Pharmacy Services / School of Pharmacy

SSRI Antidepressant Withdrawal in Newborns (continued)

The use of selective serotonin reuptake inhibitors to treat depression during pregnancy has become increasingly popular, in part due to studies that indicate that these antidepressants are unlikely to be teratogenic at therapeutic doses.[1]

A variety of symptoms, most commonly involving the central nervous system and the gastrointestinal tract, have been observed in neonates experiencing SSRI antidepressant withdrawal.[2]

All cases involved symptoms that were transient and most resolved spontaneously. However, some neonates required costly monitoring or admission to special care nurseries.[2,4]

Although case reports cannot establish the prevalence of SSRI withdrawal syndrome in the prenatally exposed neonate population, the number of reports published to date may foreshadow a potentially significant trend.[2]

Isbister et al. debated whether these reports actually constitute a withdrawal syndrome (lack of serotonin effect or development of a hypo-serotonergic state) or are clinical features of serotonin toxicity (a hyper-serotonergic state).[13] They note that the symptoms seen in the cases involving infants are similar to those seen in adults with serotonin toxicity. Additionally, they point out that the time course of reactions are typical of serotonin excess and some of the exposed infants had elevated serum levels of the SSRI antidepressant. At this point, there is insufficient data to state that these cases are symptoms of serotonin toxicity.[14] There would seem to be a considerable amount of overlap between the two entities, making differentiation difficult without further information than the clinical assessments currently available for most cases can provide.[14] Regardless, the true cause needs to be delineated for clinical management options. A hypothetical concern might involve the ongoing use of an SSRI in the neonate to treat withdrawal symptoms potentially resulting in increased toxicity if the neonate's symptoms were actually due to a hyper-serotonergic state.[13] Another concern might be continued breastfeeding in mothers taking an SSRI in the postpartum period, if the cause of the neonate's symptoms was determined to be due to serotonin toxicity.[14]

An after-marketing study using a database of spontaneous SSRI adverse drug reaction reports showed that the reporting rate of withdrawal reactions in adult patients was 10 times higher with paroxetine (0.3 per thousand) than with sertraline and fluvoxamine (0.03 per thousand), and 100 times higher than with fluoxetine (0.002 per thousand).[15] Based on the extremely limited number of cases of neonatal SSRI antidepressant withdrawal syndrome reported in the literature, it might be plausible to hypothesize that maternal paroxetine use may also result most frequently in withdrawal symptoms in the SSRI exposed newborn population. One author states that the drug's short elimination half-life (17 hours) may be an important contributing factor.[3] Theoretically, a medication with a longer half-life might reduce the risk of withdrawal symptoms because the drug would be more gradually tapered-off in the infant.[2]

In the cases described in the literature, withdrawal symptoms were present in the exposed infant during the first days and lasted up to one month after birth.[2] In those case reports where neonate SSRI serum levels were determined, most exposed infants had detectable levels of the medication their mothers were taking.[3,6,10] All cases involved symptoms that were transient and most resolved spontaneously. However, some neonates required costly monitoring, treatment with medications such as chlorpromazine, or admission to special care nurseries.[2,4] Although not described specifically as a neonatal withdrawal syndrome, 23% of infants whose mothers took fluoxetine during the third trimester in the Chambers et al. study required admission to special-care nurseries versus only 9.5% of the neonates exposed to the drug in the first and second trimesters, and 6.3% of the control neonates.[4] Additionally, some of the symptoms described in the reports could be considered life threatening if left untreated. The two cases of necrotizing enterocolitis in paroxetine exposed infants are of particular concern, although the authors of this report noted that other maternal medications may have contributed to the clinical pictures in the affected infants.[3]

In many cases, pregnant patients suffering from significant depression will require an antidepressant in order to continue to function during pregnancy and in the postpartum period. The prescribing of antidepressants for the pregnant patient needs to be approached on a case-by-case basis. The potentially significant benefits of medication therapy for the mother need to be weighed carefully against any harmful effects to the neonate. Descriptions in the medical literature of symptoms that probably constitute cases of neonatal withdrawal syndrome, but not identified as such in the published

(Continued on page 9)

In many cases, pregnant patients suffering from significant depression will require an antidepressant in order to continue to function during pregnancy and in the postpartum period. Health care professionals caring for pregnant patients need to be aware of the existence and prevalence of this syndrome and need to be educated about symptoms that may occur in an infant exposed to these agents prenatally.

Note: The editor gratefully acknowledges the assistance of Janine Polifka, Ph.D., and Sarah Limesand, Pharm.D. candidate, in reviewing this article.

report, suggest a general lack of knowledge concerning this phenomenon in the medical community.[2] Health care professionals caring for pregnant patients need to be made aware of the existence and prevalence of this syndrome and need to be educated about symptoms that may occur in an infant exposed to these agents prenatally. Because of the long half-life of antidepressants in infants, symptoms of withdrawal may not be present and hence not identified at discharge, or, may alternatively, be incorrectly diagnosed and treated.[2] Additionally, it is very important for the pregnant patient to be educated about the existence of an SSRI withdrawal syndrome in neonates when she makes a decision in conjunction with her physician about initiating antidepressant therapy. A mother knowledgeable about this syndrome could be on the look out for withdrawal symptoms if they occurred in her newborn.

Although case reports cannot establish the prevalence of SSRI withdrawal syndrome in the prenatally exposed neonate population, the number of reports published to date may foreshadow a potentially significant trend.[2] Future studies need to focus on which SSRI antidepressants may be most appropriate for the pregnant patient. Such studies need to identify those agents which will provide the best therapy for the mother and at the same time be least likely to cause adverse reactions, such as withdrawal symptoms, in the exposed newborn.

References

1. Friedman JM, Polifka JE: The TERIS and Shepard Catalog Database. Seattle, WA.: 2002.
2. Nordeng H, et al. Neonatal withdrawal syndrome after *in utero* exposure to selective serotonin reuptake inhibitors. Acta Paediatr 2001;90:288-291.
3. Stiskal JA, et al. Neonatal paroxetine withdrawal syndrome. Arch Dis Child Fetal Neonatal Ed 2001;84:F134-F135.

(Continued on page 10)

UWMC/HMC ADVERSE DRUG REACTION SUMMARY
Fiscal Year 2001/2002
1st Quarter (July 2001-September 2001)

University of Washington Medical Center

- A total of 189 adverse drug reactions were reported at UWMC this quarter.
- These ADRs were reported by physicians, nurses, and pharmacists.
- One hundred and fifty-six inpatients and 33 outpatients experienced an ADR this quarter.
- The drug class for which the largest numbers of ADR reports were filed was antibiotics- 38.
- The ADR reaction types† reported were: augmented- 94, hypersensitivity- 28, false alarm- 1, and idiosyncratic- 66.
- Adverse drug reaction severity ratings‡ included: unknown- 4, insignificant- 8, mild- 119, moderate- 39, and severe- 19.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "highly probable" in 7 reports, "probable" in 78 reports, "possible" in 102 reports, and "doubtful" in 2 reports.
- Three ADR reports were submitted to the FDA this quarter.

Harborview Medical Center

- A total of 53 adverse drug reactions were reported at HMC this quarter.
- These ADRs were reported by physicians, pharmacists, nurses, and CT technicians.
- Forty-four inpatients and 9 outpatients experienced an ADR this quarter.
- The drug class for which the largest numbers of ADR reports were filed was antibiotic drugs- 19.
- The ADR reaction types† reported were: augmented- 24, hypersensitivity- 20, and idiosyncratic- 9.
- Adverse drug reaction severity ratings‡ included: mild- 31, moderate- 12, and severe- 10.
- According to the Naranjo Algorithm, the likelihood that the administered drug was responsible for the reported ADR was "probable" in 25 reports, and "possible" in 28 reports.
- Nine ADR reports were submitted to the FDA this quarter.

† ADR reaction type definitions- **Augmented**: reactions consistent with the pharmacology of the drug; **Idiosyncratic**: unusual reaction independent of the pharmacology of the drug; **Hypersensitivity**: newly identified allergy or one previously identified; **False Alarm**: reaction deemed not related to drug therapy.

‡ ADR reaction severity rating definitions- **Insignificant**: requires no change in therapy; **Mild**: requires therapeutic intervention but no change in length of hospital stay; **Moderate**: requires intervention and increased length of hospital stay by at least one day; **Severe**: life threatening contributes to death or permanent disability, or recovery takes greater than 2 weeks.

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost ‡	Therapeutic Classification	Use	Usual Adult Starting Dose*
Argatroban (Acova)	Injection: 100mg/mL(2.5mL)-$502.07	Thrombin inhibitor	Anticoagulant in heparin-induced thrombocytopenia	2mcg/kg/minute
Methylphenidate (Concerta)	Tablet, extended-release: 18mg-$1.45; 36mg-$1.53; 54mg-$1.61	CNS Stimulant	Attention deficit disorder	Individualized
Octreotide (Sandostatin-LAR)	Injection, depot: 10mg-$962.22; 20mg-$983.56; 30mg-$1461.73	Somatostatin analog	Acromegaly; VIPomas	Individualized
Tenofivir (Viread)	Tablet: 300mg-$9.43	Nucleotide Analog Reverse Transcriptase Inhibitor	HIV infection	300mg PO Q day taken with a meal
Zoledronic acid (Zometa)	Injection: 4mg-$ 574.98	Bisphosphonate	Hypercalcemia of malignancy	Individualized

* Refer to product labeling for full prescribing information. ‡ Costs represent UWMC/HMC outpatient acquisition costs and do not include pharmacy dispensing fees.

References (continued)

4. Chambers CD, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010-1015.
5. Australian Adverse Drug Reactions Advisory Committee. SSRIs and neonatal disorders: withdrawal reactions, breast milk transfer. Austral Adverse Drug Reactions Bull Nov 1997;16(4):14.
6. Dahl ML, et al. Paroxetine withdrawal syndrome in a neonate [letter]. Br J Psychiatry 1997;171:391-392.
7. Nijhuis JM, et al. Withdrawal reactions of a premature neonate after maternal use of paroxetine [letter]. Arch Dis Child Fetal Neonatal Ed 2001;84:F77.
8. Gerola O, et al. Antidepressant therapy in pregnancy: a review from the literature and report of a suspected paroxetine withdrawal syndrome in a newborn. Rivista Italiana di Pediatria 1999;25:216-218.
9. Kent LSW, et al. Suspected congenital sertraline dependence. Brit J Psychiatry 1995;167:
10. Oca MJ, et al. Association of maternal sertraline (zoloft) therapy and transient neonatal nystagmus. J Perinat 1999;19(6):460-461.
11. Spencer MJ. Fluoxetine hydrochloride (prozac) toxicity in a neonate. Pediatrics1993;92:721-722.
12. Mhamma MJ, et al. Potential fluoxetine chloride (prozac) toxicity in a newborn. Pediatrics 1997;100:158-159.
13. Isbister GK, et al. Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? [letter]. Arch Dis Child Fetal Neonatal Ed 2001;85(2):F147-F148.
14. Stiskal JA, et al. Authors' response [letter]. Arch Dis Child Fetal Neonatal Ed 2001;85(2):F147-F148.
15. Price JS, et al. A comparison of the post-marketing safety of the four selective serotonin reuptake inhibitors including the investigation of symptoms occurring on withdrawal. Br J Clin Pharmacol 1996;42:757-763.

IN THIS ISSUE:

VOL. 31, NO. 2

Supplement: Contemporary Issues in Drug Therapy

UNIVERSITY OF WASHINGTON
DRUG INFORMATION CENTER
Box 356015
Seattle, WA 98195-6015

drug therapy topics