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Drugs in Pregnancy and Lactation: Literature and Resource Update

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A wide range of articles was published during the past year which add to our understanding of the effects of medication use during pregnancy and lactation on fetal and neonatal health. Among these are papers describing the pharmacokinetics and pharmacodynamics of common anti-infectives, antiepileptics, and analgesics. The use of antidepressants and other psychotropic medications was also addressed in several recent reviews and opinion papers. This issue of *Pediatric Pharmacotherapy* will review these papers, as well as describe upcoming changes by the Food and Drug Administration (FDA) in drug labeling information on use during pregnancy and lactation.

Neonatal Pharmacology Research

Neonatal pharmacology was the focus of the December issue of *Clinical Pharmacology and Therapeutics*. Among the articles were three thought-provoking opinion papers from leading investigators in the field on the future of pharmacology research in neonates.[1-3] In the first paper, Ward and Kern address the lack of clinical trials to support the use of drug therapy in neonates.[1] Their review of the impact of the FDA's incentive programs for pediatric research revealed that only 15 (4.7%) of the 321 drugs undergoing labeling changes to incorporate pediatric prescribing information included dosing for neonates. They also call attention to the impact of limited data on the accuracy of neonatal dosing in routine clinical practice, citing a recent pharmacokinetic study showing that current fluconazole dosing recommendations may produce subtherapeutic serum concentrations.

In the second paper, Zlotnik Shaul and Vitale discuss the impact of drug cost on treatment decisions in preterm infants, using the Canadian Charter of Rights and Freedoms as a framework for addressing allocation of limited resources.[2] The third paper, by Moran and colleagues, promotes the collaborative Children's Oncology Group as a model for creating a system to develop standards of care and improve consistency in clinical trial design among neonatal intensive care units.[3]

Developmental Pharmacogenetics

The same issue of *Clinical Pharmacology and Therapeutics* contained a concise review of the impact of developmental pharmacogenetics on neonatal pharmacology and toxicology.[4] The author uses two examples, gastroschisis following maternal acetaminophen use and neurologic impairment from bisphenol A, a chemical used in the manufacturing of plastics, to highlight the impact of developmental pharmacogenetics on outcome after exposure to teratogens. He proposes that knowledge of pharmacogenetic influences on the ontogeny of metabolic enzymes may explain, or even help to predict, the relative risk to the fetus after teratogen exposure and could be used to guide the development of neonatal clinical trials.

Psychotropic Medications

Much of the focus on medication use during pregnancy and breastfeeding has been on psychotropic agents.[5-8] It has been estimated that 3% of pregnant women take antidepressants. In spite of the frequency of their use, there is little information beyond case reports to evaluate their safety. Among the concerns over using these agents during pregnancy are the potential impact of altering serotonin concentrations on neurologic development and the risk for adverse pulmonary effects in exposed infants.

Venlafaxine, one of the most frequently prescribed antidepressants, has not been associated with teratogenic effects; however, there has been concern over adverse pulmonary effects after birth. Boucher and colleagues recently described the outcomes after venlafaxine exposure in seven infant-mother pairs.[9] The median maternal dose was 75 mg/day. Five of the seven infants exhibited tachypnea and respiratory distress after birth. The elimination half-life was evaluated in three infants, with a range of 12-15 hours for venlafaxine and 10-37 for the active *O*-desmethylvenlafaxine metabolite. The infant of

the mother receiving the highest dose (300 mg/day) was the most symptomatic. Symptoms worsened as serum concentrations declined, correlating with the drug's half-life and suggesting withdrawal after discontinuation.

The transfer of venlafaxine into breastmilk was studied by Newport and colleagues in 13 infant-mother pairs.[10] The mean milk:plasma ratio was 275.3%. The highest venlafaxine and desvenlafaxine concentrations in breastmilk occurred an average of 8 hours after a maternal dose. Infant plasma concentrations of venlafaxine/desvenlafaxine were 37.1% of the maternal plasma concentrations, with a theoretical infant dose of 0.208 mg/kg/day. No adverse effects were reported. The considerable transfer of drug into breastmilk suggests the need for confirmatory studies and caution when prescribing this drug in clinical practice.

Antiepileptics

The teratogenic effects of many of the older antiepileptics, including carbamazepine, phenytoin, and valproic acid, have led to the increasing use of newer antiepileptics during pregnancy. As the number of women being treated increases, there has been a slow, but steady, increase in the publications describing the effects of these drugs in their offspring. Fotopoulou and colleagues conducted a prospective study of lamotrigine in nine women during pregnancy, delivery, and lactation.[11] The authors found that clearance increased by an average of 197% during the first trimester, 236% in the second trimester, and 248% in the third trimester. All patients in the study required dosage adjustment to maintain desired serum concentrations. Clearance decreased to initial values within 3 weeks of delivery. The authors proposed, as have other investigators, that the change in clearance may reflect induction of N-2-glucuronidation during pregnancy. The median lamotrigine concentration ratio of the cord blood to maternal serum was 1.01, while the ratio of lamotrigine in breastmilk to maternal serum was 0.59. Breastfeeding newborns in the study had a median serum concentration approximately 26% of the maternal value. There were no adverse effects in the infants, but the authors recommended close monitoring due to the presence of significant amounts of lamotrigine in breastmilk.

In contrast, Nordmo and colleagues describe an otherwise healthy, term infant with severe apnea after exposure to lamotrigine in breastmilk.[12] The 16-day old infant had several mild apneic episodes, followed by a major episode requiring resuscitation. The patient's mother received lamotrigine monotherapy throughout gestation, and the infant had a serum lamotrigine level of 7.71 mcg/mL on the first day of life. At the time of admission for the apneic episode, his level was 4.87 mcg/mL. Breastfeeding was discontinued, and the infant recovered without sequelae. The authors proposed that the apnea was related to the relatively high serum concentration observed in the infant, reflecting both the higher than typical maternal dose following delivery and the reduced capacity of newborns to metabolize lamotrigine.

A single case report of topiramate use during pregnancy and breastfeeding was also published in 2009.[13] The mother had been on topiramate monotherapy (300 mg/day) for nearly a year prior to conception. She was also receiving folic acid supplementation. A healthy infant was delivered at 38 weeks gestation, weighing 3.54 kg. The infant was breastfed exclusively, without signs of adverse effects. The lack of teratogenic effects or adverse effects during breastfeeding in this case confirms similar findings in previous reports. While potential risk from topiramate cannot be ruled out based on the small number of infant-mother pairs studied to date, the results are reassuring.

Codeine

In 2007, the FDA notified health care providers of the risk to breastfeeding infants from maternal use of acetaminophen with codeine. The advisory came as the result of the death of a healthy newborn the previous year. Further investigation revealed that both mother and baby were cytochrome P450 2D6 ultrarapid metabolizers, converting codeine to much higher levels of morphine than observed in typical patients. Last year, Willmann and colleagues created a pharmacokinetic/pharmacodynamic model to describe the quantitative risk for opioid toxicity in infants exposed to codeine through breastmilk.[14] The model demonstrated a 60-fold variation in peak morphine concentrations depending on CYP2D6 genotype and morphine clearance rates. Based on the results of multiple simulations, the authors concluded that mothers and infants who are ultrarapid or extensive metabolizers are at high risk for opioid toxicity. Since genotyping for CYP2D6 activity is not routinely performed, the ability to assess risk for an individual infant-mother pair cannot be determined. As a result, codeine should be prescribed with caution during breastfeeding, with close attention to dose and duration.

Antimicrobials

While antimicrobials remain some of the most widely studied drugs in pregnancy and lactation, there are gaps in our knowledge of the efficacy and safety of newer therapies and those used for uncommon infections. In an article for *Clinical Pharmacology and Therapeutics*, Theiler highlights the need for a systematic method to capture and assess clinical experience with antimicrobials not often used during pregnancy.[15] He cites the off-label use of ribavirin during the severe acute respiratory syndrome (SARS) epidemic as an example of a situation in which the lack of data degrading teratogenic effects hampered decision-making in the treatment of critically ill pregnant women.

There are also limits to our understanding of the passage of many antimicrobials into breastmilk. Mitrano and colleagues recently published a brief review of the excretion of drugs used to treat methicillin-resistant *Staph. aureus* (MRSA) into breastmilk.[16] The article focuses on 11 drugs used in treating MRSA, including clindamycin, daptomycin, doxycycline, linezolid, minocycline, quinupristin-dalfopristin, rifampin, tetracycline, tigecycline, trimethoprim-sulfamethoxazole, and vancomycin. The authors provide a useful table with factors affecting transfer into breastmilk (molecular weight, protein binding, and half-life), as well as the relative dose to the breastfeeding infant (as a percentage of the maternal dose) and recommendations from the AAP and the World Health Organization.

Antiretrovirals

The use of highly active antiretroviral therapy (HAART) has become the established method of reducing viral load in patients with human immunodeficiency virus (HIV). Administration of HAART during pregnancy has been shown to significantly reduce the risk of HIV transmission. While effective, there have been concerns that fetal exposure to the drugs utilized in HAART, particularly protease inhibitors, may adversely affect growth and prompt premature delivery. In December 2009, Carceller and colleagues published a retrospective cohort study of the effects of fetal exposure to protease inhibitors on prematurity, birthweight, and growth.[17] The authors evaluated 206 infant-mother pairs who received HAART between 1997 and 2005 and 206 matched controls. The HAART group included 176 pairs who received a protease inhibitor, including the nucleoside reverse transcriptase inhibitors indinavir, lopinavir-ritonavir, nelfinavir, ritonavir, and saquinavir, and the non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz. There was no significant difference in the rate of premature delivery (10.6% with all HAART patients and 11.1% in the sub-group who received a protease inhibitor, compared to 7.8% in the controls). The percentage of babies who were small for gestational age was also similar (9.8% with HAART, 10.3% of the protease inhibitor sub-group, and 5.3% in the controls). Birthweight, length, and head circumference were also similar in the treated and control infants. The authors concluded that there were no significant increases in premature birth or growth impairment in infants whose mothers received protease inhibitors.

FDA Labeling Changes

On May 29, 2008, the FDA released information on a new proposal for consistent pregnancy and lactation labeling requirements on all prescription drugs and biological products.[18] The proposal is focused on making information more useful for prescribers and will eliminate the current A, B, C, D, or X classification (representing lowest to highest risk) and replace it with a narrative text describing relevant human and animal data. Once finalized, all prescribing information would contain standardized subsections for pregnancy and lactation, divided into a summary, specific clinical considerations (such as methods for reducing drug exposure or dosage adjustments), and an overview of the supporting clinical data. The pregnancy section would also include information about pregnancy exposure registries for health care providers or patients to submit information on pregnancy outcomes. The proposed change is available at www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 (accessed 11/19/09).

Resources

Keeping up with the medical literature in this area can often seem overwhelming. Health care providers should have both basic references for routine questions and a means of searching the literature for recent updates. Review articles, such as the two-part series on medications in pregnancy and lactation published last year in *Obstetrics and Gynecology*, are an excellent resource for background information.[19,20] The first part of this series focuses on known teratogens, while the second part covers drugs that have not been found to produce fetal or neonatal harm. There are also several well-known texts that provide detailed information on drug administration in the prenatal and perinatal period, including Briggs' *Drugs in Pregnancy and Lactation*, available at http://www.lww.com/product/?978-0-7817-

7876-3 (accessed 11/18/09) and Hale's *Medications and Mothers' Milk*, available at http://www.hale-publishing.com/ (accessed 11/18/09). Both texts were updated in 2008.

For clinicians needing a quick, easy-to-use resource on drug administration during breastfeeding, LactMed is available on-line without charge at www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT (accessed 11/18/09). This searchable database is provided by the United States National Library of Medicine. The information is peer-reviewed prior to posting and is fully referenced. Each monograph contains the date of the last revision and, like both of the texts listed previously, includes recommendations from the American Academy of Pediatrics.

Summary

Recent publications have provided valuable new information on the safety and efficacy of medications prescribed in pregnant and lactating women. In addition to these reports, the availability of updated resources and more detailed prescribing information will help clinicians select therapies that provide optimal treatment of the mother and baby.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 12/18/09:

1. Recombinant antithrombin (ATryn®) was added to the Inpatient Formulary.
2. Romiplostim (Nplate™), a thrombopoetin mimetic, and clofarabine (Clolar®), a purine nucleoside analog used in patients with relapsed or refractory ALL, were added to the Inpatient Formulary and for use in the infusion center.
3. Intravenous methyldopa and certolizumab were removed due to lack of use.

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