PharmaNote®

VOLUME 25, ISSUE 1 OCTOBER 2009

25TH ANNIVERSARY OF THE PHARMANOTE®

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PHARMACOKINETIC VARIABILITY IN PREGNANCY AND PROPOSED LABELING CHANGES

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The issue of drug use in pregnancy continues to be a perplexing topic for many practitioners. The safe use of drugs in pregnant patients is a dilemma because of the limited clinical trial data involving these patients and the pharmacokinetic and pharmacodynamic changes during pregnancy. This issue is compounded by the increasing number of women on chronic medications who are becoming pregnant. This article will review pharmacokinetic changes in pregnancy. It will also discuss the current pregnancy categories and the new labeling changes proposed by the Food and Drug Administration (FDA).

EPIDEMIOLOGY

Prescription drug use in pregnancy is growing in the United States. As the average age of pregnant women increases, practitioners are faced with more pregnant patients who require treatment for chronic medical conditions. These medical conditions must be addressed throughout their pregnancy. The main problem with prescription drug use in pregnant patients is the potential teratogenic effects on the fetus. Studies estimate that 10-15% of congenital anomalies originate from maternal teratogen exposure.[1] Practitioners must be aware of the potential risks of drug exposure to the fetus and weigh these against the potential benefits to the mother.

PHARMACOKINETIC CHANGES IN PREGNANCY

Understanding the pharmacokinetic changes that take place during pregnancy provides practitioners insight into the treatment of these women. Current pharmacokinetic data, primarily from small observational studies, is summarized in Table 1.

Several important pharmacokinetic parameters are altered in pregnancy. The first parameter is ab-

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Table 1. Pharmacokinetic changes in pregnancy.[2]

PHARMACOKINETIC PARAMETER	PHYSIOLOGICAL PARAMETER	EFFECT	EXAMPLES
Absorption	↑ Gastric emptying time ↑ Gastric acid pH ↓ GI motility	↑ or ↓ Systemic absorption of medications	Ampicillin (theoretical) Cefazolin (theoretical)
Distribution	↑ Plasma volume ↑ Adipose tissue volume ↑ Cardiac output	↑ Volume of distribution ↓ Plasma drug concentration	Phenytoin, valproic acid
Excretion	↑ GFR and renal blood flow	↑ Clearance of drugs that are cleared through the kidney	Digoxin, atenolol
Protein Binding	↓ Albumin concentration	↑ Free drug concentrations of highly protein bound drugs	Phenytoin, valproic acid

sorption. The interaction between absorption and certain antibiotics is theoretical since no studies have proven that this interaction leads to clinically significant changes. The second parameter is distribution. The combined effects of an increase in cardiac output and a decrease in plasma albumin concentrations can have a measurable effect on highly protein bound medications. This effect occurs in pregnant women on anti-seizure medications such as phenytoin and valproic acid.[3] The third parameter is an increase in the clearance of medications. The increase in glomerular filtration rate (GFR) and renal blood flow can have an effect on drugs that are cleared extensively by the kidneys. An increase in the elimination of these drugs can lead to sub-therapeutic drug concentrations in pregnant patients. For example, the clearance of certain B-lactam antibiotics can be increased in pregnancy.[4] A pooled analysis of several studies showed that the elimination of intravenous cefazolin in pregnant patients was twice that of corresponding non-pregnant patients.[5] These pharmacokinetic changes should be considered when a practitioner is prescribing medications for pregnant patients.

Many drugs used in pregnancy are metabolized via the hepatic cytochrome p450 (CYP) system. The various CYP isoenzymes are altered to different extents in pregnant patients. Consequently, altered metabolic rates can result in substantial changes to drug concentrations. The changes to these metabolizing enzymes can lead to a change in the clearance and steady state concentration of drugs in patients. The pharmacokinetic changes in metabolizing enzymes are summarized in Table 2.

CURRENT CLASSIFICATION SYSTEM

In 1979, the FDA issued a classification system for drugs that serves as a guide to physicians in the selection of drugs for use in pregnancy.[8] The current classification system is summarized in Table 3. Some of these classes are based on the potential risk of harm to the fetus, while others are a risk versus benefit comparison. However, because this system

Table 2. Pharmacokinetic changes in metabolizing enzymes through the trimesters.[6, 7]

ENZYME	1ST TRIMESTER (%)	2ND TRIMESTER (%)	3RD TRIMESTER (%)	SUBSTRATES
CYP 1A2	↓ 33	↓ 50	↓ 65	Theophylline, Clozapine, Olanzapine
CYP 2A6	No Data	↑ 54	↑ 54	Nicotine
CYP 2C9	No Change	No Change	↑ 20	Phenytoin, Losartan, Celecoxib
CYP 2C19	No Data	↓ 50	↓ 50	Omeprazole. Pantoprazole, Lansoprazole
CYP 2D6	No Data	No Data	↑ 50	Metoprolol, Fluoxetine, Nortriptyline
CYP 3A4	No Data	No Data	↑ 50-100	Cortisol, Nifedipine, Ritonavir
CYP UGT 1A1	↑ 200	↑ 200	↑ 300	Lamotrigine

has caused significant confusion, a more evidence-based model for classifying the risks and benefits of medication use in pregnancy is needed.

Several deficits exist in the current system. First, many practitioners and patients think that the risk increases as you proceed from A to X; however, this is not the case. Classifications A and B are only based on the risk of harm to the fetus, while classifications C and D also consider the benefit of drug therapy to the mother. This method of classifying drugs differently in different categories contributes to the confusion. There is no linear comparison between classifications A and B and classifications C and D. In class C and D, the medicine is a risk to the fetus, but the effects of the disease state on the fetus and the mother are also considered. Finally, the vast majority of drugs fall into category C. Since most of these drugs have not been studied in pregnant women or animals, the class C designation does not help physicians determine the risk versus benefit of the drug. If data became available for a class C drug, it could move to any of the other classes. Class C drugs are not necessarily any better than class D or X drugs, or any worse than class A or B drugs. This contributes to provider and patient confusion regarding the safety of these medications. These deficits in the current labeling of medications have prompted the FDA to re-evaluate the current system. Last year, a new system was proposed that will hopefully aid clinicians and patients to better understand the risks and benefits of medication use in pregnancy and lactation.

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Table 3. Pregnancy categories for prescription drugs.[8]

CATEGORY	DESCRIPTION
A	• Drugs in this category have controlled studies in pregnant women that have failed to demonstrate harm to the fetus in the first trimester and have no evidence of further risk in later trimesters • *Examples:* folic acid and vitamin B_{12}
B	• Presumed safety is based on animal studies, but there are no controlled studies in pregnant women; OR animal studies have shown a risk, but controlled trials in pregnant women have not shown a risk. • *Examples:* acetaminophen, insulin aspart, metformin, and famotidine
C	• Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women; OR no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. • *Examples:* pseudoephedrine, fluconazole, ciprofloxacin, fexofenadine, escitalopram, fluoxetine, and bupropion
D	• Adequate well-controlled or observational studies have been done in pregnant women that have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk. • *Examples:* phenytoin, diazepam, and alprazolam
X	• Adequate, well-controlled or observational studies have been done in pregnant women or in animals and have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant. • *Examples:* warfarin, medroxyprogesterone, estrogens, methotrexate, and simvastatin

help physicians determine the risk versus benefit of the drug. If data became available for a class C drug, it could move to any of the other classes. Class C drugs are not necessarily any better than class D or X drugs, or any worse than class A or B drugs. This contributes to provider and patient confusion regarding the safety of these medications. These deficits in the current labeling of medications have prompted the FDA to re-evaluate the current system. Last year, a new system was proposed that will hopefully aid clinicians and patients to better understand the risks and benefits of medication use in pregnancy and lactation.

PROPOSED NEW LABELING

The proposed system would discontinue the A, B, C, D, and X categories. The new format for the pregnancy product labeling would include a summary of information on fetal risk, clinical considerations, and a summary of the available study data.[9,10] Other sections on lactation would provide a risk summary, clinical consideration, and any available lactation data. Since the American Academy of Pediatrics (AAP) recommends breastfeeding for at least the first six months after birth, information on the effects of medications on breastfeeding is needed now more than ever.[11] The proposed labeling changes for pregnancy and lactation are summarized in the following sections and Figure 1.

Pregnancy

Fetal Risk Summary:

The fetal risk section would discuss the relationship between drug use and the risk of developmental abnormalities in humans. The four types of developmental abnormalities that would be addressed include structural anomalies, fetal and infant mortality, impaired physiologic function, and alterations in growth. Any available data would also be differentiated between animal and human data.[12]

Clinical Considerations:

Clinical considerations would address five main topics. First, a statement would be made regarding the potential risk in the event of an accidental exposure. The manufacturer would also disclose the known risks of both the drug and the disease. Information about dosing adjustments in pregnancy and any known adverse reactions that are unique to pregnant patients would be addressed. This statement would also discuss potential complications and the appropriate management if these complications arise. A final statement would provide information on indications for use during the delivery process and the drug effects during labor.

*Data***:**

In the data section, the manufacturer would disclose pertinent aspects of the data that was used for the approval process. First, the company would elaborate on the study type, exposure levels, identified fetal abnormalities, and adverse events reported during the trials. Secondly, human trial information would include positive and negative outcomes, the number of patients studied, and the duration of the study. Additionally, animal trials would reflect which species were included as the model, the doses given to the animals, and the equivalent human doses. If no data was available a statement would be made to that effect.

Lactation

Risk Summary:

The lactation risk summary section would address the potential effect the drug may have on maternal milk production. Furthermore, it would disclose the presence or absence of the drug in maternal milk. If the drug is present in breast milk, then both the quantity present and the concentration would be reported. If the drug is not present in breast milk, then a disclosure of the limits of the assay would be reported. A third statement would include the potential effects of the drug on the nursing child, including the likelihood and seriousness of the effects.

Clinical Considerations:

In the clinical considerations section, practitioners would be provided with options that minimize the exposure of the child to the drug, including information about the timing of breast feeding or pumping to coincide with troughs in the concentration of the drug. Dosing adjustments appropriate for breastfeeding mothers would also be included. Additionally, this section would highlight the potential effects of the drug on the breastfed child. This would include recommendations for practitioners regarding the monitoring of the child as well as possible responses to the effects of the drug if they manifest in the child.

Fig 1. Fictitious example of revised pregnancy labeling.[13]

All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes ALPHATHON's potential to increase the risk of developmental abnormalities above the background risk.

Fetal Risk Summary
Based on animal data, the likelihood that ALPHATHON increases the risk of developmental abnormalities is predicted to be high (see Data).

Clinical Considerations
Asthma complicates approximately 1% of all pregnancies resulting in higher perinatal mortality, low birth weight infants, preterm births, and pregnancy-induced hypertension compared to outcomes for nonasthmatic women. Because of the risks of even mild maternal hypoxia to the developing fetus, asthma should be clinically well-controlled during pregnancy. There are no human studies evaluating ALPHATHON use in pregnant women. The time of gestation at which risk may be greatest is unknown; therefore, risks of inadvertent exposure in early gestation cannot be evaluated. Animal data suggest that ALPHATHON exposure may result in early fetal loss and anomalies of major organ systems. There are no data regarding dose adjustment needs in pregnancy. Given the lack of human data and the risks suggested by animal data, prescribers should consider alternative treatments for asthma for pregnant women when possible (especially during the first trimester) and women planning pregnancy.

Data
Human data:
- There are no data on human pregnancies exposed to ALPHATHON.

Animal Data:
- Reproductive studies performed during early pregnancy in rats at oral doses 0.75 to 1.0 times the recommended human dose (adjusted for body surface area) showed implantation loss, fetal resorptions, and major congenital anomalies of the cardiac, skeletal and renal systems without signs of maternal toxicity.
- Reproductive studies performed in early pregnancy in rabbits at doses approximately 0.33 to 1.0 times the recommended human dose (adjusted for body surface area) showed increased post-implantation loss. Studies at 3 times the human dose showed significant fetal loss without signs of maternal toxicity.
- The effects of ALPHATHON on fetal growth, labor, or post-natal complications were not evaluated in the animal studies.

Data:
The data section would provide an overview of the studies that were used to support the labeling of the medication. The addition of this section would provide clinicians with the information that was used to draw conclusions regarding medication use in lactating patients. This would also state how relevant the data presented is to lactating patients.

CONCLUSION

The topic of prescription drug use in pregnancy continues to be a dilemma. Knowing the pharmacokinetic changes in pregnancy can help physicians more effectively treat their patients; however it is clear that more information about prescription drug effects in pregnancy is needed. The current method of classifying medications does not provide enough information for health care providers to make informed decisions about prescribing medications to this subset of the population. A better classification system is needed in an attempt to provide more accurate information in an easily accessible format. If the proposed labeling changes are accepted, the new labels will provide clinicians and patients with more of the information they need to better understand the risks and benefits of prescription drug use in pregnancy.

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The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research
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