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"CLINICALLY RELEVANT PHARMACOKINETIC CHANGES IN PREGNANCY"

MAY 27, 2011
MONTREAL, QUEBEC

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SPEAKERS AND PRESENTATIONS

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"SAFETY AND EFFICACY OF DRUGS IN PREGNANCY"
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"PREDICTION OF PLACENTAL DRUG TRANSFER USING THE HUMAN PLACENTAL PERFUSION MODEL"
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SAFETY AND EFFICACY OF DRUGS IN PREGNANCY

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ABSTRACT

Although most drugs are used to treat chronic or pregnancy-induced conditions during pregnancy and lactation, very few are studied in pregnant or breastfeeding women. The information we have on drugs taken during pregnancy and lactation is usually obtained after market approval through published case reports or case series and from pregnancy exposure or retrospective birth defect registries. Furthermore, generic drugs approved for use in this vulnerable population may be approved based on results from a male trial population. This disregards the changes that can occur during pregnancy which can affect the pharmacokinetics of drugs. In an effort to improve the information provided to prescribers, in 2008 the United States Food and Drug Administration proposed a change in product labelling where information from pregnancy exposure registries would be required. As of 2009, European Medicines Agency requires additional statements on use during pregnancy within drug labelling information. In Canada, it is anticipated that the efficacy and safety of drugs in pregnancy will be included under the Drug Safety and Effectiveness Network initiative, and that this will offer a unified approach for such assessments. Pregmedic, a non-profit organization for the advancement of safe and effective use of drugs in pregnancy, has presented a number of proposals and draft guidelines to Health Canada on the inclusion of pregnant women in pharmacokinetic studies and the establishment of registries for women who take drugs during pregnancy. Pregmedic advocates for ensuring that drugs indicated for women are studied in women.

Key Words: *Pregnancy, lactation, pharmacokinetics, registries, women, Pregmedic, advocacy*

Introduction

Pregmedic is a non-profit organization for the advancement of safe use of drugs in pregnancy. The mission of Pregmedic is to advocate for the safe and effective use of medications in pregnancy and lactation. Our goals are to increase awareness of pregnancy issues at the government level through Health Canada; to require standard labelling of medicines for use in pregnancy and lactation; to provide practitioners and patients access to current and reliable information for decision-making during pregnancy and lactation; and to advocate for the development of patient registries or surveillance programs for medications used during pregnancy and breastfeeding.

Changes during Pregnancy

A number of physical changes occur during pregnancy, which in turn affect the pharmacokinetics of drugs.

These include:

- changes in total body weight and body fat;
- delayed gastric emptying and prolonged gastrointestinal transit time, which can affect the bioavailability of drugs;
- increased extracellular fluid and total body water, which can affect water-soluble drug kinetics, e.g., aminoglycosides;
- increased cardiac output as a result of increased stroke volume and maternal heart rate;

- increased blood flow to the organs, e.g., liver and kidney, thus drug clearance can be increased;
- decreased albumin concentration with decreased protein binding, affecting drugs that are highly protein bound; and
- altered hepatic enzyme activity, which can alter drug metabolism and interactions.

Odd Facts about Drugs in Pregnancy

Most drugs *are* used in pregnancy and lactation in order to treat chronic or pregnancy-induced conditions, such as high blood pressure, increased blood sugar, and infections; and most are used 'off label'. Very few drugs are studied for use during pregnancy or lactation, providing little guidance to physicians, pharmacists, and patients. Product monographs generally advise that drugs *should not* be used when women are pregnant and breastfeeding; as well, for reasons related to litigation, most pharmaceutical companies do not address the use of drugs during pregnancy. The information we do have is usually obtained after market approval through published case reports or case series and from pregnancy exposure or retrospective birth defect registries. Such reports are limited, representing only a fraction of the circumstances where drugs are used in pregnancy or lactation.

There is a significant difference in pharmacokinetics of drugs between men and women, and especially between men or non-pregnant women and women who are pregnant or lactating; yet bioequivalence studies include both men and women and report on the average findings from both genders. There is currently no requirement to disclose the exact population used in bioequivalence trials. Generic drugs approved for use in a vulnerable population, such as pregnant women, may be approved based on results from a male trial population. This disregards any of the changes that can occur during pregnancy (noted above), which can affect the pharmacokinetics of drugs.

The consequence of all these facts is that healthcare professionals are left with the burden of evaluating the risk or the benefit of using a medication during pregnancy or lactation.

Other Countries

What is happening in other countries? In the United States, the Food and Drug Administration (FDA) currently requires labelling according to preset categories for drug use in pregnancy (Table 1).[1] A few drugs are in categories A or B; some are clearly contraindicated during pregnancy; but most drugs are categorized under "C": Human data is lacking and animal studies have either not been conducted or have shown an adverse effect on the fetus.

TABLE 1 FDA Pregnancy Categories Summarized

Pregnancy Category	Description
A	Controlled studies in humans
B	Human data is reassuring (animal positive) or animal studies show no risk
C	**Human data is lacking - animal studies positive or not done**
D	Human data show risk; benefit may outweigh risk
X	Animal or human data positive

In 2008, an FDA proposal was made to amend the labelling regulations for drug use in pregnancy. Pregnancy information would move from the "Contraindications" section of the product monograph to the section "Use in Specific Populations".[2] Prescription drug labelling would then require information from pregnancy exposure registries, if applicable, a general statement about the background risk of fetal developmental abnormalities, clinical considerations, and a data component. Thus more information would be available to help the prescriber in decision-making.

On December 30, 2009, the FDA announced collaboration with researchers on the “Medication Exposure in Pregnancy Risk Evaluation Program”, where data will be used from 11 U.S. health plan-affiliated research sites.[3]

In Europe, the European Medicines Agency (EMA) has a Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data.[4] Furthermore, the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling,[5] which came into effect in January 2009, requires additional labelling information.

Examples of acceptable statements for use in the "Pregnancy" section of a product monograph, which provide more guidance for clinicians, are:

- Based on human experience (specify), Drug X is suspected to cause congenital malformation (specify) when administered during pregnancy.
- Drug X should not be used during pregnancy (specify trimester) unless the clinical condition of the woman requires treatment with Drug X.
- A moderate amount of data on pregnant women (between 300-1000 pregnancy outcome) indicate no malformative or feto/neonatal toxicity for Drug X.
- No effects during pregnancy are anticipated, since systemic exposure to Drug X is negligible.

Canada

In Canada, the Drug Safety and Effectiveness Network (DSEN) has been established as a program through the partnership of the Canadian Institutes of Health Research (CIHR) and Health Canada. "New evidence generated via the DSEN will provide Health Canada with an important additional source of information for use in the ongoing assessments of drug products' safety risks relative to their therapeutic benefits. This evidence will also support decision-making on public reimbursement, and the safe and optimal prescribing and use of drugs within the Canadian health care system."[6] Certainly the efficacy and safety of drugs in pregnancy will be included under this initiative and will offer a unified approach across Canada for such assessments.

The priority actions undertaken by Pregmedic in Canada include the Draft Guideline for Inclusion of Pregnant Women in Pharmacokinetic Studies, which was presented to Health Canada in June 2009. Pregmedic also advocates for the adoption by Health Canada of the European Labelling Requirements for Pregnancy and Lactation; requests creation of registries for women who need to take drugs during pregnancy and for post-market surveillance studies; and advocates for ensuring that drugs indicated for women are studied in women.

So, although progress is being made in our country, there remains much work to be done, and action to be taken, in the field of drug safety in pregnancy.

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