

## DRUGS USED IN PREGNANCY: THE REGULATORY PROCESS

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Most drugs are not studied during pregnancy before being marketed. In my over 30 years' experience in the pharmaceutical industry, I have never seen a drug studied during pregnancy before being marketed. Information on teratogenic potential is picked up in post marketing surveillance. It took almost four years of marketing before the link between thalidomide and the adverse effects it was producing, i.e., phocomelia, was recognized. Malformations with warfarin took over 20 years to identify. Reproductive tract abnormalities with DES also took many years to identify. These were all picked up in post marketing surveillance and took many years to be understood.

In terms of the standard requirements for marketing a drug in Canada, the United States or any country in the world, there are usually two steps: filing of a Clinical Trial Application (CTA) or an Investigational New Drug (IND) submission for studies in humans, later followed by a New Drug Submission (NDS) or a New Drug Application (NDA) to get the product marketed. Usually the drug is filed and approved for use in adults, with information regarding pregnancy obtained during the post marketing phase. There is a requirement for doing animal reproductive toxicology in order to estimate potential risks of exposure in pregnancy; however, the positive and negative predictive values of such studies for humans are uncertain. For example, there are false positives, e.g., hydrocortisone and clefts in mice, where problems occurring in animals are not carried over to humans. There are also false negatives where strong signals are not obtained from animal testing, e.g., thalidomide and no teratogenesis in rats. If there are positive findings in more than one species, there is greater predictive value of effects in humans. Overall, animal studies give us a basis to predict outcomes,

but they are uncertain and it is difficult to know how much reliance can be placed on them.

At present, Canada does not have regulatory guidelines for how to develop products indicated for use during pregnancy. Guidance is usually obtained on a case by case basis by Health Canada. This guidance is highly product specific and can vary from one department to another. Health Canada does not have guidelines for surveillance programs or registries, nor are there guidelines on how to conduct pharmacokinetic or pharmacodynamic studies involving pregnant women. For the most part we then look to other countries to see what guidance they recommend in this vulnerable population.

In general, Health Canada advises drug products should always be used only when absolutely necessary, that the quantity should be as small as possible, and that exposure should be as short as possible during pregnancy. These are "motherhood" statements with which most of us would agree. The Policy Bureau, the group within Health Canada establishing policies for drugs and their registration, recognizes that there is a need to address this issue. It has identified the need for guidance that hopefully will be available in a year; however, there does not seem to be any indication that action is occurring at the moment.

In 1997, a guideline was issued on the inclusion of women in clinical trials.<sup>1</sup> It states that a drug should be studied in the full range of patients likely to receive it once marketed. However, pregnancy is generally excluded. When women are enrolled in clinical trials, they are usually required to be using a well recognized method of contraception. Conducting a clinical trial on pregnant women would be out of the norm from the perspective of Health Canada.

New regulations and guidelines have come into play from Health Canada regarding labelling

and product monographs where pregnant women are considered a special population. This is handled within the Warnings and Precautions section of the product monograph.<sup>2</sup>

The guidelines state that the type of data that is available should be briefly stated (human or animal) and the recommendation (e.g., avoid in a particular trimester, avoid altogether) for prescribing the drug should be given. Non-teratogenic effects should be included (e.g., withdrawal symptoms, hypoglycemia).

If there is clinical data, there need to be indications regarding the extent of exposure:

- Wide: >1000 pregnancies,
- Limited: <1000 pregnancies,
- Very Limited: Individual cases only,
- No Experience.

I would like to talk for a moment about policy at Health Canada. We have spoken a little this morning about how we have been a little more successful with development of dosing for paediatric drugs than with drugs in pregnant women. This can be aligned with the issue of orphan drugs in Canada. An orphan drug is generally recognized as one with little marketing potential and therefore a pharmaceutical firm is not very interested in developing it. In the United States, there is a definition for orphan drugs: those drugs that have a patient population of less than 200,000 in the country. Europe also has orphan drug legislation.

In Canada, we have no legal definition of an orphan drug and no legal recognition of such drugs. We also have no legislation to encourage the development of those drugs. With the past federal government, there was legislation coming forward to encourage the development of paediatric research; however, it was not finalized and it is unknown whether the current government will pass it. In several other countries, incentives have been in place for the development of dosage forms, dosing regimens and labelling instruction for paediatric populations. The issue of drugs use in pregnancy is probably similar to that in paediatrics. This is probably a pertinent time to begin the discussion regarding drugs in pregnancy.

Moving to the situation in the United States, there are recent US FDA guidelines available:

1. Risks of drug exposure in human pregnancies (2005)<sup>3</sup> - Provides guidance on how to evaluate human data on the effects of in utero drug exposure on the developing fetus, i.e., how to go about determining whether or not there has been causality with a specific effect;
2. Lactation studies in women (2005)<sup>4</sup> - Draft guidance that provides framework for designing, conducting and analyzing clinical lactation studies;
3. Determining the appropriate dose of a drug for pregnant women (2004)<sup>5</sup> - Draft guidance that provides the framework for designing, conducting and analyzing pharmacokinetic and pharmacodynamic studies in pregnant women, i.e., usually after the clinical efficacy has already been established in the adult population;
4. Pregnancy exposure registries (2002)<sup>6</sup> - Provides guidance on how to establish registries that prospectively monitor the outcomes of pregnancies in women exposed to a drug.

When a company receives approval to market a drug in the United States, there are frequently US FDA Post Marketing Commitments associated with the approval. There are specific codes associated with various types of post marketing commitments, identified in the CDER Data Standards Manual. Code 030 is one such code: A human study designed to capture and evaluate birth outcomes in women exposed to marketed drugs during pregnancy.<sup>7</sup> Health Canada does not currently have the ability to require post marketing commitments, with the exception of an approval process called Notice of Compliance with Conditions (NOC/c). There are about two to three drugs a year approved with a conditional NOC. This is again a policy issue and perhaps we should put a process in place in Canada to enable some post marketing commitments to be required.

In the United States, there are Pregnancy Categories<sup>8</sup>:

- 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 are positive OR not done
- D: Human data show risk, benefit may outweigh risk
- X: Animal or human data positive.

Most drugs are labelled with a Pregnancy Category of “C” in the United States. The FDA has had a Pregnancy Labelling Task Force organized to review pregnancy labelling and to explore how the category information could be presented in the most effective manner. A long term goal was to determine how animal toxicology information contributes to clinically meaningful information. Because most drugs are Category C, the Task Force was also assessing the meaning of this category, whether it really intends that these drugs should not be used, and should there be other words to convey information to physicians on how to use these drugs in pregnancy.

There is the erroneous impression that there are very few drugs which can be safely given to women of childbearing potential. The following are examples of drugs that are generally recognized as being appropriate in pregnancy: electrolytes (e.g., potassium chloride), doxylamine (e.g., in Diclectin®, although not sold in the US, it is listed as a Category A drug in publications), several thyroid agents (e.g., levothyroxine), and vitamins at the RDA (recommended daily allowance) levels are listed as Category A (Drugs in Pregnancy and Lactation, Seventh Edition).

The pregnancy section of US drug labels was first addressed in regulations in 1979. The intent was to assist physicians prescribing for pregnant women. Letter categories were assigned. What has happened is that since most products only have animal data, almost all products are labelled with a Category C, e.g., “Use only if necessary”. In addition, these pregnancy warnings are rarely changed or updated by the pharmaceutical company, for both litigation reasons and because the data is not available. This “Warning” is perceived as optimal by the regulatory body, the manufacturer, and even the broader clinical

community, as the best way to go forward. Today we are suggesting that perhaps this situation is not right and that we should begin the process of change.

Sources of information for labelling of drugs in pregnancy are primarily obtained post marketing. These include occasional case reports and ad hoc descriptions of incidents that have occurred; some retrospective or prospective epidemiological studies, including cohort studies and pregnancy exposure registries; and retrospective studies, including birth defect registries and case control studies.

The draft guidance from the US for conducting pharmacokinetic and pharmacodynamic studies in pregnancy first discusses the physiological changes during pregnancy, i.e., changes in total body weight and body fat, delayed gastric emptying and prolonged GI transit, increase in extra cellular fluid and total body water, increased cardiac output, increased stroke volume and elevated maternal heart rate, decreased albumin concentration with reduced protein binding, increased blood flow to the various organs (e.g., kidneys, uterus), increased glomerular filtration rate, and changed hepatic enzyme activity. Because of these physiologic changes that occur during pregnancy, there is a need to conduct such studies to gather pharmacokinetic and pharmacodynamic information in this condition. Flagyl (metronidazole) is an example of a drug that was first marketed for use in adults and when found to be used extensively in pregnant women, the company then conducted pharmacokinetic studies to define the kinetics of the drug in this condition.

Should a company in Canada wish to conduct a clinical study in pregnant women, all regulations must be met (CTA/IND filing and, conduct of the trial under Good Clinical Practice (GCP) standards, etc). There must be an Investigational Review Board (IRB) review and informed consent. Preclinical studies, including teratology, would have to be performed. Generally, clinical studies in non-pregnant women would be expected to have been conducted to provide data to assess human risk. The risk to the fetus would not be expected to be greater than minimal. And the purpose of the research would be the development of important biomedical knowledge which cannot be obtained by any other means.

It is usually expected that clinical studies in pregnant women would be conducted post marketing, i.e., not pre-marketing or in phase III, and in women for whom the drug would be prescribed anyway, at least in guidelines that are currently available. When should pharmacokinetic studies be done? The US guideline describes the following situations where studies of some nature would be appropriate. When the drug is known to be prescribed in or used by pregnant women, especially in the second and third trimesters. For a new drug, if use in pregnancy is anticipated, studies in pregnant women should be conducted. When use is expected to be rare, but the consequences of uninformed dosages are great (e.g., narrow therapeutic range drugs, cancer chemotherapy), studies in pregnant women should be conducted. If it is expected that pregnancy is likely to significantly alter the pharmacokinetics of the drug (e.g., renally excreted drug) and it will likely be used in pregnancy or if its rare use may have great consequences in pregnancy, it is important to gather clinical data.

In terms of pregnancy registries, the US guideline defines that a pregnancy exposure registry is a prospective observation study that collects information on exposure during pregnancy and the associated pregnancy outcome. Patients are enrolled before the outcome of the pregnancy is known. The study is done under a protocol with specific inclusion/exclusion criteria and sample size calculation. There is active patient enrolment and there is a comparison group.

In looking back, there are few drugs that are developed for use during pregnancy. Some have been developed for the induction of labour or for cervical ripening, but there is usually no exposure of the developing fetus to the drug. Others have been developed for treatment of menstrual disorders and fertility, but the drug is discontinued if pregnancy occurs (short term treatment regimens). Still others have been developed post approval, e.g., asthma drugs, antihypertensives and antidepressants, but even then are not supported or labelled by the manufacturer for use during pregnancy. Flagyl was utilized in pregnancy to such an extent that at the request of the FDA, the company (Searle) ran a pharmacokinetic/pharmacodynamic study in pregnant women. Vitamin/mineral preparations,

including prenatal/postpartum preparations are generally regarded as dietary supplements in the US and are not subject to approval. In Canada, these products would be subject to minimal approval as “old” drugs. Pharmacokinetic (PK) and absorption profiles are not required to determine how well the products are delivering their contents, even though critical vitamins, such as folic acid, have been clearly shown to reduce the risk of fetal neural tube defects (NTDs).

My recommendations to a pharmaceutical company are:

1. If developing a drug for use during pregnancy only, have early and frequent communication with the agency.
2. If investigating the effect of a drug that is currently used in adults and during pregnancy, do development for pregnancy post marketing.
3. Conduct kinetic studies in pregnant women on the critical components of vitamin/mineral supplements intended for use in this population.
4. Update labelling as frequently as possible.

If conducting studies in pregnant women:

1. Ensure that the study is publicly registered;
2. Ensure that the Investigator Brochure has the most updated information on risks in pregnancy;
3. Ensure the Informed Consent is as clear as possible and as complete as possible in terms of identifying risks and possible benefits; and
4. Utilize an independent Safety Monitoring Board or Committee of Experts regarding drug use in this population.

It would behoove us to establish Canadian guidelines, similar to those in the US or to acknowledge that we will adapt their guidelines for deciding risk, the need for a pregnancy registry, and the need for pharmacokinetic and pharmacodynamic studies. It would be wise of us to look at our policies regarding orphan drugs, paediatric drugs and drugs during pregnancy. Furthermore, we should also consider establishing

a process to require some post marketing requirements, such as making pregnancy registries or post marketing surveillance programs mandatory throughout the lifecycle of drugs used during pregnancy. Currently, it is not possible to require post marketing conditions in Canada without a Notice of Compliance with Conditions.

Until such a process is in place, drugs approved for use in pregnancy should be limited to a Notice of Compliance with Conditions on the basis that the safety of drugs for use in pregnancy are dependent on post marketing surveillance studies and ongoing clinical evidence.

## REFERENCES

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