

DRUGS INDICATED FOR USE DURING PREGNANCY

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ABSTRACT

The Society of Obstetricians and Gynaecologists of Canada (SOGC) advocates that drugs used during pregnancy be tested exclusively in women. The SOGC holds the opinion that drugs to be used exclusively in men *or* in women should not be tested in a small number of men *and* women.

The SOGC, always cautious with the choice of pharmacological treatments recommended for use during pregnancy, welcomes the increased options resulting from the introduction of generic formulations of drugs shown to be bioequivalent to currently available brand name products. These formulations provide less expensive options to Canadian women in need of drug therapy. However, the Society does not believe that drugs should be substituted without the patient and the physician both agreeing to such a change. Generic substitutions of some products may mean a potentially clinically significant difference in drug dose, possibly resulting in a changed patient effect. Furthermore, substituting a product on the basis of price alone is not acceptable.

The SOGC, as an organization with the role of advising its members on clinical practice, calls on Health Canada to review its guideline on testing of drugs for vulnerable populations, especially pregnant women.

Key Words: *Bioequivalence, intrasubject variability, sex-related differences, pregnancy, Society of Obstetricians and Gynaecologists of Canada (SOGC)*

Introduction

This presentation will introduce the discussions that have been underway at the Society of Obstetricians and Gynaecologists of Canada (SOGC) as regards the use of drugs in pregnancy. The Society's objectives on this topic include discussion of appropriate testing of drugs for use in men and women in Canada, and to advocate for testing of drugs used during pregnancy exclusively in women.

The SOGC is always cautious with the choice of pharmacological treatments recommended for use during pregnancy. The Society welcomes the increased choice of products resulting from the introduction of generic formulations of drugs that have been shown to be bioequivalent to currently available brand name products. These formulations provide less expensive options to Canadian women in need of

drug therapy. According to Health Canada, 'bioequivalence' implies that the drug product has the same systemic exposure and effects, both therapeutic and adverse, as a reference product when administered to patients under conditions specified in the labelling. When testing bioequivalence, "An important objective in the selection of subjects is to reduce the intrasubject variability in pharmacokinetics that may be attributable to certain characteristics of the subject. Subjects should be assigned in such a way that the study design is balanced for any factors that are suspected to contribute to variability."¹

Bioequivalence of Generic Drugs

Both Health Canada and the U.S. Food and Drug Administration (FDA) recognize that bioequivalence studies demonstrate significant variability between men and women. More than

30% of studies reviewed for bioequivalence would not have passed the required criteria for one sex when they did for the other, according to a review of trials by Chen et al.² Table 1 shows

the intrasubject variability in men vs. women for 6 drugs, where not only are there differences within individuals' results, but the differences between the sexes range from about two- to six-fold.

TABLE 1 Intrasubject Variability in Men vs. Women in Bioequivalence Trials^a

DRUG	MEN	WOMEN
Alprazolam	4.9%	29.4%
Cimetidine	15.8%	9.9%
Erythromycin	18.1%	25.7%
Naproxen (at low dose)	5.0%	9.1%
Nitroglycerine	21.3%	39.5%
NAPA (N-Acetylprocainamide) - Class III antiarrhythmic agent)	9.0%	4.4%

^aAdapted from Chen M-L, et al. Clin Pharmacol Ther. 2000;68(5):510-521.²

In addition, the SOGC would like to advocate for testing of drugs within the appropriate test groups, so that drugs intended for use by women should only be tested in women. Presently in Canada, there is no regulation for preferring female over male subjects when studying drugs intended only for women. This could lead to serious errors when interpreting bioequivalence studies performed in men, or in combinations of male and female subjects. Hence, a generic formulation may be approved by Health Canada, based on an inadequate assumption that variability in the sexes is similar; and there is marked concern with the small patient numbers used for such testing. A recent SOGC survey showed that members believe that the introduction of a generic product has been tested in a few hundred to a thousand subjects. However, clinicians are very concerned when they learn that in some cases as few as 14 subjects are used to show bioequivalence. Furthermore, there is concern about the adequacy of results where the majority of subjects is male (e.g., of 20 subjects, only 4 are female), yet average results are used and then applied to the population as a whole. Also, although Health Canada requires that a generic formulation be bioequivalent to the innovator formula, where a drug is intended for treatment of pregnant women, the test population

may include both men and women and the average results used. If a sex:formulation interaction occurs, the safety and efficacy of the generic formulation could not necessarily be considered equivalent to the reference formulation. These difficulties are even more evident for bioequivalence studies in pregnant women, which are almost non-existent.

There are currently no specific requirements for the approval of drugs intended for vulnerable populations, such as pregnant women. In addition, there are no requirements to disclose the exact population used for the determination of bioequivalence, which is a real concern for clinicians across Canada.

SOGC Opinions

The SOGC holds the opinion that drugs to be used exclusively in men *or* in women should not be tested in a small number of men *and* women. Drugs should be tested in an adequate number of men only or women only, depending on the demographic in which the drug is intended to be used. The SOGC also asks for higher subject numbers to be used in bioequivalence testing.

The SOGC does not believe that drugs should be substituted without the patient and the physician both agreeing to such a change. Generic substitutions of some products, e.g., very low dose

estrogen contraceptives, may mean a potentially clinically significant difference in drug dose, possibly resulting in a changed patient effect. Furthermore, substituting a product on the basis of price alone is not acceptable, especially for drugs that have been tested in very few subjects—sometimes as few as 15-20 patients and most often in both males and females.

CONCLUSIONS

The SOGC, as an organization with the role of advising its members on clinical practice, calls on Health Canada to review its guideline on testing of drugs for vulnerable populations, especially pregnant women, and would like to see a policy change established.

We recommend that testing standards be set at a minimum of 100 patients in order to detect intrasubject variability and to eliminate errors that can happen when transposing tests between males and females, especially for diseases or conditions that affect exclusively one sex or the other.

Call to Action

Healthcare professionals and women's groups are called to advocate that the Government of Canada establish an *ad hoc* committee to develop recommendations to change the way drugs intended for exclusive use in women, and particularly for use in pregnant women, are tested.

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