

# Is it Appropriate to Study the Pharmacokinetics of Drugs Aimed at Pregnant Women in Men?

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Before a medication can receive regulatory approval, its pharmacokinetic profile must be accurately described in terms of absorption, distribution, and elimination from the body. This is commonly done by giving a group of healthy volunteers the typical dose to be marketed and measuring levels in samples of their blood over time.

For many years these studies had been conducted entirely in males, until the United States Federal Drug Administration published new guidelines in 1993, endorsing the inclusion of women in these studies.<sup>1</sup> Since then, various bioequivalence studies have included mixed data containing both sexes.

Consider the following: a pharmaceutical company hoping to market a medication indicated only for pregnancy-induced biliary cholestasis submits data on the bioequivalence of the drug to the regulatory agency. They present data showing drug levels over time after giving the medication to 20 male volunteers. They reason that it was much easier to recruit male volunteers and that the results should not show significant sex differences in drug levels over time. Are these assumptions valid?

The concentrations of drugs in blood as a function of time after taking an oral dose depend on three processes: absorption, distribution, and elimination. Absorption through the gut is characterized by its rate (i.e., how quickly or slowly it is occurring) and extent (the percentage of molecules absorbed out of the total swallowed). Distribution of a drug depends on its binding affinities to different tissue compartments and organs. As an example, an agent that remains mostly in the blood (e.g., immunoglobulins) will have a very small distribution volume compared with an agent that binds extensively to muscles (e.g., digoxin).

Elimination of a drug is typically achieved by the renal route or metabolism by the liver and excretion of the metabolites by either the bile system or the kidney. The assumption that bioequivalence of drugs in men and women is similar must

therefore be based on the assumption that the processes of drug absorption, distribution, and elimination are similar in both sexes. But are they?

Chen and colleagues<sup>2</sup> reviewed 26 bioequivalence studies involving both sexes submitted to the American Food and Drug Administration. They studied a large variety of agents, including benzodiazepines, H<sub>2</sub> blockers, non-steroidal anti-inflammatory drugs, antiepileptics, and antiarrhythmics. The authors established a 20% difference between sexes as clinically significant and found that there were differences between sexes in the area under the concentration-time curve in 13% of studies, and in peak concentrations in 35% of studies. Mean sex-related differences greater than 20% in pharmacokinetic parameters were observed in 39% of all data sets. In 28% of data sets, these differences were statistically significant. The frequency was 15% after correcting for body weight.

Review of the pharmacological literature corroborates the results of the systematic review by Chen et al., showing common sex differences in cytochrome P4503A drugs, as well as many other agents. The following are examples of important sex differences.

- Cytochrome P4503A drugs have a significantly faster clearance rate in women for both IV and oral administration.<sup>3</sup>
- Sufentanil has a faster clearance rate in men.<sup>4</sup>
- Clozapine has a faster clearance rate after oral administration in males.<sup>5</sup>
- There is a modest increase in plasma concentrations in women of the antiretrovirals saquinavir, ritonavir, efavirenz, and nevirapine, compared with the increase in men.<sup>6</sup>
- Ofloxacin has a higher area under the curve and maximum concentration in young women than in young men.<sup>7</sup>
- Torasemide has reduced elimination in women.<sup>8</sup>
- Chlordiazepoxide has reduced oral clearance in elderly men, but not in elderly women.<sup>9</sup>

Given these data, the idea of mixing men and women in the same study seems unreasonable, as different sex proportions may skew the results of any study.

Recently, the US Government Accountability Office reported that while women's participation in National Institutes of Health-funded trials has increased, data are often not analyzed separately on the basis of sex. Such analysis is critical to differentiate therapeutic and adverse effects in men and women.<sup>10</sup>

Thus, the common practice of studying the pharmacokinetics of drugs aimed at women (in our example, biliary cholestasis) in men or mixed populations is illogical and should be abandoned, as it may lead to erroneous dosing recommendations. Regulatory agencies and clinicians should insist on basing dosing schedules for women on data collected in women.

## REFERENCES

1. US Department of Health and Human Services. Food and Drug Administration. Guideline for the study and evaluation of gender differences in clinical evaluation of drugs. Federal Register, July 22, 1993;58(139):39406–16.
2. Chen ML, Lee SC, Ng MJ, Schuirmann DJ, Lawrence JL, Williams RL. Pharmacokinetic analysis of bioequivalence trials: implication for sex-related issues in clinical pharmacology and biopharmaceutics. *Clin Pharm Ther* 2000;68:5.
3. Greenblatt DJ, von Moltke LL. Gender has a small but statistically significant effect on clearance of CYP3A substrate drugs. *J Clin Pharmacol* 2008;48:1350–5.
4. Zhao Y, Wu XM, Duan JL, Sheng XY, Liu W, Lu W, et al. Pharmacokinetics of sufentanil administered by target-controlled infusion in Chinese surgical patients. *Chin Med J (Engl)* 2009; 122:291–5.
5. Ng W, Uchida H, Ismail Z, Mamo DC, Rajji TK, Remington G, et al. Clozapine exposure and the impact of smoking and gender: a population pharmacokinetic study. *Ther Drug Monit* 2009;31:360–6.
6. Best BM, Capparelli EV. Implications of gender and pregnancy for antiretroviral drug dosing. *Curr Opin HIV AIDS* 2008;3:277–82.
7. Zulfiqar-ul-Hassan, Riffat S, Naseer R. Gender differences on bioavailability of ofloxacin. *J Ayub Med Coll Abbottabad* 2008;20:114–7.
8. Werner U, Werner D, Heinbuchner S, Graf B, Ince H, Kische S, et al. Gender is an important determinant of the disposition of the loop diuretic torasemide. *J Clin Pharmacol* 2010;50:160–8.
9. Greenblatt DJ, Divoll MK, Abernethy DR, Ochs HR, Harmatz JS, Shader RI. Age and gender effects on chlordiazepoxide kinetics: relation to antipyrine disposition. *Pharmacology* 1989;38:327–34.
10. Fang J. Sex bias blights drug studies. *Nature* 2010;464:332–3.

## Errata

**Abstracts of Papers and Posters to be Presented at the SOGC 66<sup>th</sup> Annual Clinical Meeting / Résumé des exposés et des affiches qui seront présentées à la 66<sup>e</sup> assemblée Clinique annuelle. J Obstet Gynaecol Can 2010;32(6 Suppl 1):S1-S80.**

The abstract below was not published in the supplement.

### P-OBS-MD-002

#### PNEUMOCEPHALUS COMPLICATING LABOR EPIDURAL: A CASE REPORT

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**Objective:** To present a case of pneumocephalus in a parturient following labor epidural analgesia.

**Study Methods:** Regional anesthesia with epidural is a popular technique for pain management during labor and delivery.

Pneumocephalus, the introduction of air into the cranial cavity, is a rare and potentially severe complication of epidural placement when the loss of resistance to air technique is used to identify the epidural space.

**Result:** The Case: A 39 y/o primigravida undergoing epidural placement reported sudden onset of headache with associated neurological symptoms and nuchal rigidity. Postpartum, the headache persisted with increasing severity unresponsive to intravenous fluids, analgesia and thecal blood patch. Emergent CT showed pneumocephalus. Her symptoms resolved with conservative management. Repeat CT demonstrated complete interval resolution of the air collection.

**Conclusion:** Pneumocephalus is an uncommon complication of epidural placement. Eleven (11) obstetric cases have been reported. Iatrogenic pneumocephalus typically presents with acute onset of headache following epidural placement and may be associated with neurologic signs and symptoms. Prompt evaluation is necessary. Conservative management is the standard of care with symptomologic and radiologic resolution within one (1) week for most cases.

As well, abstract **P-OBS-MFM-MD-008 MATERNAL OBESITY IS ASSOCIATED WITH PLACENTOMEGALY AND REDUCTION OF FETAL OXYGEN MARGINE OF SAFETY** was listed with the authors *R. Gagnon, T. Fadvy, R. Gratton, O DaSilva*. The authors should have been listed as:

*F. Tabir, R. Gagnon, R. Gratton, O. DaSilva.*

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The Journal of Obstetrics and Gynaecology Canada regrets the errors and any inconvenience they may have caused.