Bioequivalence Studies of Drugs Prescribed Mainly for Women

Iain J. McGilveray
McGilveray Pharmacon Inc, Ottawa, Ontario, Canada

Outline

Disclaimer: Independent consultant to Pharma including Duchesnay Inc.

Clinically relevant pharmacokinetic changes in pregnancy
Few bioequivalence studies in pregnant women
Pharmacokinetics (PK), briefly
Alcohol, example
Bioavailability (BA) Bioequivalence (BE) sub-topic from PK
Regulatory guidances (mainly FDA)
Individual BE guidances
Examples
Concerns and conclusions

Semantics

We require a new word. I would use gender but a co-speaker, Dr. Soldin, defines it “Gender, a social construct, is expressed in terms of masculinity and femininity. It is defined by the way people perceive themselves and how they expect others to behave. Gender is largely determined by culture.”

- Sex is used in so many contexts, including, male-female definition that it is confusing and can cause misunderstandings. A neologism is needed!
- Most dictionaries note gender and sex as synonyms
Pharmacokinetics-gas prices complex models

Goodman & Gilman ADME schema

Regulatory

**Reports**
- Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosage and Labelling (draft).

**Overall participation by women and men was comparable—improved since prior report 1995-99. Under-representation of women in early phase trials and e.g., cardiovascular products continues to be an issue of concern.**

- For new drugs, reported in ICH CTD Clinical pharmacology summaries (2.7.2).
- Often pop PK studies in patients, but some analysis by gender. ICH E5 also notes.
More reports PK

Schwartz JB. The influence of sex on pharmacokinetics. Clin PK. 2003. Absorption is not significantly affected by sex, but rates may be slightly slower in women. BA, for CYP3A substrates in particular, may be somewhat higher in women compared to men. The role of sex on PK of genetics, age, disease, social habits, in the clinical setting is still being explored.

Beierle I, Meibohm B, Derendorf H. Gender differences in pharmacokinetics and pharmacodynamics. Int J Clin Pharmacol Ther. 1999. For the majority of investigated drugs in recent years, no or only very minor gender differences could be detected in PK and/or PD and their clinical significance seems very limited - rarely linked to treatment success or failure. Hence, it is undoubtedly necessary to include women in the clinical drug development process, but it seems questionable whether women of child-bearing capability should be exposed to potential risks in early phase I clinical trials.

Another report on PK in women

Soldin OP, Chung SH, Mattison DR. Sex differences in drug disposition. J Steroid Biochem Mol Biol. 2011. "Males and females may differ in specific drug pharmacokinetics and pharmacodynamics. It is, therefore, essential to understand those sex differences in drug disposition and response, as they may affect drug safety and effectiveness." - All, including regulators, agree that such studies are important, but at what stage? Except for drugs used only in women, such as for breast cancer, caution prevails and usually phase 3.

- Studies in pregnant women rarer but some in anti-virals and anti-malarials as concern is that fetal transfer might help protect the fetus.

Alcohol pharmacokinetics—a digression

Known since antiquity that women more susceptible than men to alcohol effects and fetal alcohol syndrome is a sad result of exposure, eloquently discussed by Dr. Brien Wednesday.
- Some effects due to body mass with higher blood levels. A small 1996 study "Dose-corrected values for AUC were on average 28% higher (p < 0.0001) in the women than in the men. But more complex.
- One 2001 report "The gender difference in alcohol levels is due mainly to a smaller gastric metabolism in females (because of a significantly lesser activity of chi-ADH), rather than to differences in gastric emptying or in hepatic oxidation of ethanol." Another review "Influences on alcohol elimination rate include gender, body composition and lean body mass, liver volume, food and food composition, ethnicity, and genetic polymorphisms in alcohol metabolizing enzymes. *Important determinant* allelic variants of the genes encoding the alcohol metabolizing enzymes, ADH and ALDH.
- Thus some women are less susceptible & even now why is not fully understood.
Simplified ADME

**BE intersect**
Formulation on absorption AUC
main exposure metric

**Clearance**
\[ C_l = \frac{\text{Dose}}{\text{AUC}} \]

Usually metabolism major influence on AUC studied by oral/IV

Absolute BA

**Oral product pre-absorption schema**

Solid dosage form prior to absorption (Wagner)
Simple absorption by diffusion, similar in men & women, but transporter mediated can be different (Goodman & Gilman)

**Some definitions**

*Bioavailability (BA)* is a PK attribute. "It is defined as the rate and extent of absorption of a drug into the systemic circulation." It is assessed by serial measurements of the drug in the systemic circulation, which provide a plasma concentration-time curve from which important PK parameters can be calculated, including the area-under-the curve (AUC), the maximum observed concentration (C_{max}) and the time when C_{max} is reached (t_{max}). AUC provides an estimate of the amount of drug absorbed in the systemic circulation while t_{max} reflects the rate of absorption. C_{max} is a more complex function, which, together with t_{max}, may reflect the rate of absorption." AUC-total exposure, C_{mean} rate of exposure.
Bioequivalence Canadian (mainly oral)
- Comparison of AUC values following oral vs. IV administration of the same active ingredient provides an estimate of **absolute BA**.
- Comparison of the test (T) and reference (R) product profiles of the drug provides an estimate of **comparative BA**. T and R are said to be bioequivalent (BE) when the profiles are similar according to statistical assessment and by meeting stated standards.
- Canada & US: the general standard for AUC is the 90% confidence interval of the geometric mean ratio (GMR) be within 80 and 125%. In the US this is the same standard for $C_{\text{max}}$. In Canada the GMR for $C_{\text{max}}$ should be within 80 to 125%, except critical dose drugs.

Bioequivalence (BE) projection
BE implies that the drug product can be expected to have the same systemic effects (both therapeutic and adverse) as the reference product when administered to patients under the conditions specified on the label. For > 30 years, the premise was & is that healthy volunteer studies can support this assumption.
- HC: “Drugs with uncomplicated characteristics can usually be tested in normal, healthy volunteers. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study.”
- FDA: “We recommend that if the drug product is intended for use in both sexes, the sponsor attempt to include similar proportions of males and females in the study.”

BE Metrics & some statistics
Importance of within subject (ws) CV
- Highly variable drugs ws CV > 30%
- ws CV<15% use of 15 to 20 subjects.
- 30% perhaps 60-100 to meet standard

AUC extent of exposure metric
Cmax rate of exposure metric
Some BE results

3 way cross over of 2 new formulations vs original. Fail AUC standard.

Different formulations inequivalent n=24; AUC 60-113%; Cmax 61-142%

Meyer et al, Pharm Res. 1992; 9(12):1612-6

Plasma glibenclamide profiles innovator 3.5mg (new) and 5mg (old) tablets. Blume et al, 1993.

FDA background for women in BE studies

“The sample sizes for these studies were not chosen to examine the sex-related effects considered”

- 26 BE studies 1977-95, n < 20 per study AUC > in women 71% of the time Cmax > 87% of the time. > 20% stat higher for reference in 28% of data sets. The frequency of statistically significant differences was lower when body weight was included in the statistical model.

- Women tend to have higher variability. “The results of this study support recommendations of the 1993 FDA gender guideline that women not be excluded from BE.” It seemed that the crossover study was considered efficient to detect bio-inequivalence.
Individual drug BE guidances
The FDA website (2011) has 805 draft and 153 final guidances. Most recommend that subjects be "Healthy males and non-pregnant females, general population." [There are some inconsistencies: the instructions for pregnancy & lactation tests need standardization.]

About 15% do not mention pregnancy checks. Phenytoin is surprising as it has been associated with birth defects. Breast cancer drugs, e.g., anastrozole, vaginal preparations and oral contraceptives (norethindrone, etc) have women only subjects and some hormones, exemestane- post-menopausal women: drugs for prostate cancer and erectile dysfunction require men only. Progesterone healthy males and post-menopausal females are suggested (androgen interference in pre-menopausal problem?). Tamoxifen has both men & women as it is used in both sexes.

In general the subject inclusion "recommendations" are reasonable.

- It would be useful since now FDA has more data to examine, if BE in men vs women subjects always provide similar results.

New and Old Drugs - Gender PK
- Since the mid 1990’s more women have been included in clinical trials, including PK of new drugs - an advance.
- However, prior to that time, less between gender PK was studied and one example is Diclectin® (doxylamine succinate & pyridoxine HCI, Vit B6).
- Bendectin® had a difficult history: voluntarily removed it from US market (1993) as a result of a populist uprising, fueled by tabloid accusations of deforming babies; scientifically, never proven to cause more birth defects than in general population.
- Duchesnay Inc. has provided me access to new data, which included improvements in assay methods.

Diclectin® 10/10 mg Multiple dose study in women
16 non-pregnant women subjects were administered a single oral dose of Diclectin®, as 2 x 10 mg/10 mg delayed-release tablets at 10 pm on Days 1 and 2, and then multiple oral doses from Days 3 through 18, according to the following schedule: 1 x 10 mg/10 mg delayed-release tablet at 9 am & 4 pm, and 2 x 10 mg/10 mg delayed-release tablets at 10 pm, under fasted conditions (at least 2 hours after eating). This is the maximum recommended daily dose of 40 mg (Diclectin® Product Monograph).

$\text{Comparison of the first dose AUC with the final } \text{AUC}_{\text{day}18} \text{ on day 18 provided an accumulation index } AI = \frac{\text{AUC}_{\text{day}18}}{\text{AUC}_{\text{day}1}}$
**Single - multiple dose Diclectin® and doxylamine**

This new study obtained the PK parameters when doxylamine/pyridoxine 10/10 mg (Diclectin®) was administered to 18 healthy non-pregnant women in the recommended TID maximum dose regimen (40 mg/day) cf. single 10/10 mg dose. The accumulation index (AI) as defined by AUC_{0-24}(day 18) / AUC_{0-24}(day 1) suggests an ~ 3-fold accumulation of doxylamine after multiple doses.

![Graph showing accumulation](image)

**Single multiple dose: pyridoxine (Pyr)**

The prodrug, Pyridoxine, as an endogenous substance, is more difficult to research with complex metabolism. The assay was improved and many more metabolites were profiled: primarily metabolized in the liver following phosphorylation. Its main active metabolite is pyridoxal 5'-phosphate (PLP). Other metabolites measured were pyridoxal (PYL), pyridoxal 5'-phosphate (PLP), pyridoxamine (PYM), pyridoxamine 5-phosphate (PMP).

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>t_{1/2} (h)</th>
<th>Nom.</th>
<th>Med. 90%</th>
<th>Pyr 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PYR proton</td>
<td>0.74-0.90</td>
<td>1.14</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>PYL</td>
<td>2.20-2.2</td>
<td>1.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLP</td>
<td>2.33-2.34</td>
<td>1.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PYM</td>
<td>5.31-5.07</td>
<td>3.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMP</td>
<td>4.33-4.37</td>
<td>3.67</td>
<td></td>
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</tr>
</tbody>
</table>

The new data demonstrate that doxylamine and Pyr metabolites show clear dose accumulation after a total dose of 40 mg/day. Some metabolites displayed 7-fold accumulation, along with increases elimination half-life. The complex metabolism of Pyr, including reversible metabolism presents difficulties in interpretation. However, the impact on safety of patients could be serious, considering that some off-label use of Diclectin up to 60 mg/day is reported.

**BE studies of Diclectin®: men vs women**

There is not time to show other recent studies and review of the doxylamine and pyridoxine bioequivalence information, but women tended to be more variable (intra-subject CV%) than men and there appeared to be a gender difference in the effect of food. However, there were insufficient data to indicate a formulation by gender interaction. Nonetheless, the accumulation information from the first multiple dose study of this drug in women suggests such information is of concern, especially if higher doses are being used off-label.
Conclusions

- Women are being included in PK studies for NDAs in accordance with ICH, FDA and HC guidances. Older drugs have been less studied. Few studies in pregnant women are available except for anti-virals and anti-malarials.
- Except for drugs used entirely in one gender, BE studies are supposed to include "representative numbers" of men and women. There is a problem with this in offshore CROs.
- A new look at BE studies to compare results in men & women would help determine if formulation by gender interactions are a problem. Body weight corrections do not remove all clearance differences.
- Questions remain about effects of pregnancy, menarche and menopause.
- There is less concern about BE than PK related to effect. (IMG)