

SEX DEPENDENT PHARMACOKINETICS AND BIOEQUIVALENCE - TIME FOR CHANGE

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ABSTRACT

Bioequivalence studies have historically been performed largely in young males and then extrapolated to be applicable to both sexes at any age. This tendency continues today, yet a number of studies have shown that drug pharmacokinetics can be significantly different in women than in men, even as regards intra-patient variability. Some of our assumptions when treating women may not be accurate if we base our decisions on information obtained from studies conducted in men. Furthermore, women can have various physiological states that can affect drug disposition, and one of the most significant is pregnancy.

Key Words: *Pharmacokinetics, bioequivalence, absorption, intra-subject variability, adverse drug reactions, pregnancy*

Let's begin with a hypothetical scenario. A company would like to market a new generic equivalent of a product to treat biliary stasis during pregnancy. They need to perform bioequivalence studies against the originator drug. Bioequivalence is determined by measuring the systemic exposure to the test drug using the area under the concentration-time curve (AUC) and the maximum serum concentration achieved (C_{max}), comparing the findings to the reference or originator drug. The standard bioequivalence study design uses healthy adult subjects who are randomized to receive either the new drug or the reference product first and then crossed-over to receive the other drug, thus serving as their own controls. The AUC and C_{max} of the new generic drug must be within 80-120% of the reference product's parameters to be considered bioequivalent, i.e., within 20% above or below the reference standard. As is the current standard in the industry, the manufacturer conducts this bioequivalence (BE) study in 15 men, with an average age of 30, and determines that the new

drug is indeed bioequivalent to the originator product. As a regulator, would you approve this generic drug for treating biliary stasis during pregnancy? The current practice assumes that, because each subject serves as his own control for pharmacokinetics, the BE may not be affected. As will be argued below, this assumption is wrong.

Intra-subject Sex Variability

The United States Food and Drug Administration (US FDA) guidelines state: "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."¹ Unfortunately, typical BE studies are conducted almost exclusively in young, healthy adult male volunteers, even for drugs intended exclusively in women, and that this is the practice across the globe. The rationale is that each individual in the BE study acts as their own control, since they take both preparations and their results are compared.

Hence, being a man or a woman should not matter because the differences between the

two formulations, if they exist, will be apparent whether one studies either males or females.² This hypothetical principle is based on the assumption that intra-individual variability in BE—the difference in pharmacokinetics between the two drugs in the same individual and the variability in the results among the study subjects—is similar between men and women. But is it?

Chen and colleagues published a review in 2000, which reported on the analysis of 26 BE studies submitted to the US FDA’s Center for Drug Evaluation and Research.³ Each study must have involved at least 6 women and 6 men. From these studies 94 data sets were used: 47 for area under the concentration-time curve (AUC) and 47 for maximum serum concentration (C_{max}). Their analysis found statistically different results in intra-subject variability between the sexes in 6/47 drug data sets with respect to AUC and in 4/47 with respect to C_{max} .³ⁱ For example, for controlled-release alprazolam the coefficient of variation (CV) for intra-subject variability in AUC was about 5% in males and almost 30% in females: women had more variability than men. For cimetidine, it was about 16% in males and 10% in females: men had greater variability than women. Table 1 presents the range of ratios of test to reference geometric means for AUC and C_{max} for 3 drugs across the studies analyzed. With erythromycin, women had greater variability than men. With nitroglycerin there was a wide range across the sexes, and with NAPA men tended to have greater variability than women. It can be seen that intra-subject variability is not sex-dependent, however Chen’s data shows that females tend to have more variability.³

A larger CV and geometric mean differences indicate that larger numbers of study subjects are needed in order to confirm BE. Practically, this study indicates that sex differences may have major implications for the conduct and interpretation of BE studies for

certain drugs. For example, studies of alprazolam showed marginal intra-subject variability in males, therefore a small number of subjects would be needed to show bioequivalence in men. In contrast, among women, the variability jumps 6-fold, hence a much larger number of female subjects would be needed to show BE in women. However, we cannot predict the degree of variability between the sexes for drugs that were not tested, so the alprazolam example cannot be applied to erythromycin, for example. Among the studies analyzed in Chen’s paper, the C_{max} with erythromycin was 42% higher in men than in women.³ In this case, by testing men, a generic drug might be deemed bioequivalent, yet would achieve a 42% lower C_{max} than in women.

The implications are that one cannot draw general rules for sex differences in BE among drugs. Testing of drugs in non-representative populations of men and women may not appropriately indicate BE, because different drugs behave differently as regards sex-specific intra-individual differences.

TABLE 1
Test/reference geometric mean differences

Drug	Test/Reference Geometric Mean Differences (Male to Female)	
	AUC	C_{max}
Erythromycin	18%	42%
Nitroglycerin	-17 to 37%	-9 to 45%
N-acetylprocainamide (NAPA)	-13 to 4%	-17 to 0%

(From Chen ML, Lee SC, Ng MJ, Schuirmann DJ, Lesko LJ, Williams RL. Pharmacokinetic analysis of bioequivalence trials: implications for sex-related issues in clinical pharmacology and biopharmaceutics. Clin Pharmacol Ther. 2000;68(5):510-521.)

Cycle-Dependent Changes in Bioequivalence

Another important difference between men and women, as related to BE, is the fluctuating hormonal status of women along the menstrual cycle, which may affect the absorption, distribution, metabolism, and secretion of different drugs. For example, Flores Pérez and colleagues found that several pharmacokinetic parameters for

ⁱ Table III from Chen et al. is missing data lines for Procainamide SR and its metabolite, NAPA.³ The text refers to 6 statistically significant results for AUC, where Procainamide SR and its metabolite, NAPA, would be added to the 5 already marked in the table. One of these excluded data sets showed a statistically different result between men and women, as noted in the article. (Confirmed in communication with ML Chen, June 14, 2013.)

ranitidine were changed depending upon the phase of women's menstrual cycles.⁴ That is, not only did bioavailability of ranitidine differ between

Sex Differences in the Effect of Non-medicinal Ingredients

Often, a generic drug may differ from the reference formulation with respect to the presence and levels of inactive ingredients. For example, Ashiru and colleagues showed that polyethylene glycol enhanced the bioavailability in men of ranitidine in a liquid formulation.⁵ Various concentrations of polyethylene glycol increased bioavailability of ranitidine in men from 6% to 63% above control. In contrast, among women, these same concentrations decreased bioavailability by 8% to 24% below control.

The Clinical Impact of Sex differences in BE

Considering the Flores Pérez and Ashiru studies,^{4,5} if a ranitidine BE study were performed only in men, the dose of the generic product compounded with polyethylene glycol would have to be up to 60% lower as compared to the reference drug. If this ranitidine product were then applied to use in women (as is done for almost 100% of studies today), the reduced dose of the generic product, and its up to 24% decrease in bioavailability in women, would render the dose grossly subtherapeutic and possibly ineffective.

Adverse Drug Reactions

As noted by Don Mattison in his presentation, women appear to experience more drug-related adverse events than men.⁶⁻⁹ Some reasons for this have already been discussed, such as women taking more drugs than men, reporting more adverse events, and having differences in physiology. There can also be differences in absorption of a drug that are related to its formulation and excipients, such as in the ranitidine example above.⁵ Given these and other factors, bioequivalence studies that do not have sufficient power and adequate numbers of female subjects, may not adequately reflect or represent the disposition of drugs in women. The consequences of this shortcoming in most BE studies may result in inconsistencies in drug effectiveness and an increased risk of adverse drug

men and women, but it also differed in the same group of women at different phases in their cycle.

reactions. A 2001 US government report noted that 8 of 10 drugs withdrawn from the market between 1997 and 2000 "posed greater health risks for women than for men".¹⁰

Why Are Female Subjects Orphaned from Bioequivalence Studies?

Perhaps our cultural history can shed some light on why very few women have been included in BE studies. Before the 20th century, men performed women's roles in the theatre as a reflection of sexual puritanism. Until the mid-20th century women were not allowed to vote in some countries (and they still cannot do so in some parts of the world). There was the belief that men "knew" what was "good for women".

From the perspective of drug manufacturers, including women in studies might be perceived as presenting a problem in that they could become pregnant. Yet BE studies are short, so this should not be an issue. The current regulatory reality is not resolving the issue of women's underrepresentation in BE studies. In fact, the U.S. FDA's recommendation to include both male and female study subjects may even aggravate the situation. Combining the sexes would probably mean small numbers of each, resulting in insufficient power for either and not providing representative results. And studying a drug intended for women in a mixed population is not better. There are numerous relevant factors causing sex differences in drug disposition.¹¹

During pregnancy both volume of distribution (Vd) and renal clearance are increased. These two parameters tend to reduce plasma concentrations of drugs. For drugs with a low therapeutic index (ratio of therapeutic dose to toxic dose) these changes may be important. Furthermore, a woman's physiology will change over the course of pregnancy, so, for example, a woman in her 1st trimester is different in her 3rd, with much faster renal clearance as well as greater metabolic action of different cytochrome enzymes.

Gastric emptying and small intestine motility are reduced in pregnancy due to elevation of progesterone levels. The result may be an

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increase in the time needed to reach a drug's maximum serum concentration (T_{max}) and may reduce C_{max} . In many cases the effects on total bioavailability can be relatively minor and will be less important with repeated dosing. However, treatments relying on single doses may be less effective, such as with analgesics and anti-emetics, where T_{max} and C_{max} are relevant to therapeutic effect. These changes are important for clinicians to keep in mind.

Due to a reduction in hydrogen ion secretion and an increase in mucus production, there is an increase in gastric pH during pregnancy. This may increase the ionization of weak acids, tending to reduce their absorption more than that of weak bases. Drugs administered by inhalation may have enhanced absorption due to increased cardiac output and tidal volume increasing alveolar uptake. For example, as a result, dose requirements for volatile anesthetic agents, such as halothane, are reduced in pregnancy. Drug absorption from intramuscular delivery is usually enhanced by increased tissue perfusion secondary to vasodilation. And a practical problem for drug absorption is the nausea and vomiting associated with up to 80% of pregnancies.

In summary, some of our assumptions when treating women may not be accurate if we base our decisions on information obtained from studies conducted in men. Furthermore, women can have various physiological states that can affect drug disposition, and one of the most significant is pregnancy.

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