Original Research

Sex Effect on Average Bioequivalence

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ABSTRACT

Purpose: Generic formulations are by far the most prescribed drugs. This scenario is highly beneficial for society because medication expenses are significantly reduced after expiration of the exclusivity period conceded to the branded name drug. Correspondingly, these formulations must be adequately evaluated to avoid drug inefficacy and toxicity in the overall patient population. Bioequivalence studies are the only in vivo evaluation that a generic drug must overcome to reach the market. These clinical trials have not been exempt from underrepresentation of female subjects and a lack of sex-based analysis. Frequently, conclusions obtained in men are extrapolated to women. Furthermore, the obtained results are not analyzed to determine sex differences. The aim of this study was to discuss the effect that male and female differences in gastrointestinal physiology can have on bioequivalence conclusions and to show why a sex-based analysis must be conducted in these studies to improve the evaluation of generic drugs.

Methods: This discussion was based on observed sex differences in product bioavailability discrimination (sex-by-formulation interaction) and on residual variability through an analysis of average bioequivalence data previously reported by other researchers and data collected by our center. Bioequivalence studies of oral formulations, with a 2-period, 2-sequence, 2-treatment random crossover design performed in healthy subjects with at least 6 subjects of each sex, were included. In addition, the bioequivalence conclusion that would have been reached in each study if performed with only 1 sex was estimated.

Findings: The data reveal that differences in both product bioavailability discrimination and residual variability occur with a significant incidence in bioequivalence studies. In either C_{max} or AUC, a significant sex-by-formulation interaction was present in 1 of 3 reviewed studies, whereas differences in residual variability between sexes were significant for $>50\%$ of studies. Moreover, the performed estimations suggest that the reported bioequivalence conclusions were not verified in at least 1 sex for 1 of 3 studies and were not verified in men and in women for 1 of 6 studies.

Implications: This research shows that extrapolation of bioequivalence results from the male population to the female population is not always valid. Bioequivalence studies must therefore be performed with both male and female subjects in similar proportions. Sex-based analysis in bioequivalence can improve study design, enhance the representativeness of conclusions, and provide important information regarding formulation performance, thereby promoting the efficacy and safety of generic drugs. (*Clin Ther.* 2017;39:23–33)

Key words: sex-by-formulation interaction, bioequivalence, bioavailability, intrasubject variability, multisource drug products.

INTRODUCTION

Bioavailability can be addressed as the rate and extent at which a drug delivered via extravascular administration reaches the systemic circulation. It plays a major role in determining how exposed to a drug the body

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will be after a nominal dose is administered. Because pharmacologic effects are produced as a result of drug exposition, the therapeutic effectiveness of an extravascular drug will be conditioned by its bioavailability.

Multisource drugs that have the same strength of active ingredient under the same dosage form, administered by the same route of administration, can differ in drug bioavailability because of the influence of inactive ingredients and fabrication technology. Thus, in the process of introducing a generic product to the market, the manufacturer must show that the generic product provides bioavailability similar to that of the brand name drug. To achieve this goal, a bioequivalence (BE) study is performed; that is, a crossover clinical trial in which healthy subjects take both products, and the systemic drug exposure is compared. A test product is deemed bioequivalent when the mean pharmacokinetic parameters AUC and C_{max} are both within ±20% of the reference (brand name drug) mean value with a 90% confidence.[1]

At the moment of marketing authorization of a new drug, the innovator must provide preclinical and clinical evidence in support of the drug's safety and efficacy. Generic drugs are not required to replicate these extensive studies to enter the market. Instead, they follow an abbreviated application relying on the development and clinical experience accumulated through the use of the brand name drug. The only required in vivo assessment is the BE study. This approach enhances the relevance of BE, but it is highly beneficial for society because it considerably reduces medication expenses after expiration of the original drug's exclusivity period. In fact, generic drugs represented 88% of the total prescriptions dispensed in the United States in 2015 but only 28% of drug costs.[2]

Despite regulation agency guidelines regarding including similar proportions of male and female subjects when the drug is intended for use in both sexes,[3] the historical underrepresentation of female subjects in clinical evaluations and the lack of sex-based analysis persist, and BE studies are no exception.[4–9] Currently, the US Food and Drug Administration (FDA) guidelines for BE studies recommend that if the product is intended for use in both sexes, the sponsor should attempt to include similar proportions of male and female subjects in the study.[10] European Medicines Agency guidelines are laxer in this matter: "subjects could belong to either sex."[11] The World Health Organization guideline is in accordance with that of the FDA.[12]

Leaving aside the rationale of excluding women of childbearing age for safety concerns, reasons for this exclusion are as follows: (1) increased probability of adverse drug events in women[13] (eg, considering their lower mean weight, as every subject receives the same dose, women are likely to achieve higher drug exposure); (2) women take more medications[14] and could not satisfy inclusion/exclusion criteria; (3) women have been linked to a higher pharmacokinetic intraindividual variability secondary to the impact of sex hormones in drug disposition; and (4) conclusions reached in men can be extrapolated to women (as product comparisons are being made in the same subject, the study result should be independent of subject sex, even with sex-related pharmacokinetic differences). Enrollment of female subjects in these clinical trials could therefore be more difficult and increase the probability of subject dropout. In addition, under the rationale of the aforementioned points 3 and 4, a larger sample size will be required to make conclusions given the increased variability, and such additional effort would have no impact in BE conclusions.

The aim of the present commentary was to discuss why BE studies should be conducted with male and female subjects, why extrapolation of results from the male population to a female population is not always valid, the impact of excluding female subjects, and how to manage BE data taken from both sexes to increase the representativeness of conclusions and assess formulation interchangeability.

MATERIALS AND METHODS

This commentary is supported in the analysis of data previously reported by other researchers and data collected by our center. Data from the literature were taken from the Center for Drug Evaluation and Research of the FDA (Chen et al[6]). They reviewed 26 BE studies conducted with both sexes that reported the respective AUC and C_{max} test/reference (T/R) mean ratios and, with the exception of 1 study, the residual variability in the form of %CV. From those studies, 1 performed with a transdermal formulation is not discussed here. In addition, data from 8 studies performed in our research center and from 3 external BE studies (provided by study sponsors) are also presented. These 11 studies included at least 6 subjects of each sex and were performed under a typical average BE design: 2-period, 2-sequence, 2-treatment crossover with random assigned sequences, enrolling healthy subjects between 18 and 45 years of age