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Importance of metabolite data in bioequivalence studies – Sample size and power

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Purpose: to investigate whether the combined concentrations of the parent drug and its corresponding metabolite impacts the experimental design of bioequivalence studies.

Background: Bioequivalence studies have been used to establish equivalency of a generic drug product after modifying an existing formulation of an innovator product. Classically, bioequivalence assessment relies on the concept of average bioequivalence. In most cases, bioequivalence studies are carried out focusing on the measurement of the parent drug. The role of the emtabolite in bioequivalence remains a controversial issue. It has also been demonstrated that the application of the 0.80 – 1.25 bioequivalence limits to the sum of the parent compound and its active metabolite may have misleading results.

Methods: Data presented were obtained from several bioequivalence studies under fasting conditions for drugs that have active metabolites. The analytical method used was a validated LC-MS/MS method. Bioequivalence criteria of 80 – 125% were applied to the parent compound, the active metabolite, and the sum of the parent drug and the active metabolite. Pharmacokinetic data mainly AUC, T_{max}, C_{max}, and elimination half-life were reported.

Results: Similar results were obtained for the parent drug, metabolite, and the sum of the parent drug and metabolite for AUC. In the case of C_{max}, the intersubject variability for the metabolite and the sum of the parent and the metabolite was lower than that of the parent drug while the power of the bioequivalence decision was higher for the metabolite and the sum of the parent drug and the metabolite.

Conclusions: The power of estimating Cmax using the metabolite data was higher than for the drug alone so a more accurate decision can be made using the metabolite data. As a result of the higher power, the sample size can be lowered accordingly.

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