Evaluation of a rate-adjusted area under the curve method to reduce the impact of variability in bioequivalence testing

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Abstract

Aim: To quantify the utility of the rate-adjusted area under the concentration curve method in increasing the probability of a correct and conclusive outcome of a bioequivalence (BE) trial for highly variable drugs when clearance (CL) varies more than volume of distribution (V). Methods. Data from a large population of subjects were generated with variability in CL and V parameters and used to simulate a two-period, crossover BE trial. The 90% confidence interval for formulation comparison was determined following BE assessment using the area under the concentration curve (AUC) ratio test, and the proposed rate-adjusted AUC ratio method. An outcome of bioequivalent, non-bioequivalent or inconclusive was then assigned in relation to predefined BE limits. Results: We illustrate the utility of the rate-adjusted AUC method for BE testing when CL varies more than V. The approach is expected to enhance the probability of correctly assigning BE or non-BE and to increase study power to further reduce the risk of an inconclusive trial. Conclusions: The rate-adjusted AUC method represents a simple and readily applicable approach to enhance the BE assessment of drug products when CL varies more than V.

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