

Title: Bioavailability of Drugs with Nonlinear Pharmacokinetics (PK) Can be Approximated by the Ratio of Doses that Provide Equal Areas under the Concentration-Time Curves (AUCs).

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Purpose: To propose an exact method and an approximation for model-independent calculation of bioavailability for drugs with nonlinear PK; to evaluate performance of the suggested approximation.

Methods: For drugs with linear PK, bioavailability of non-intravenous (IV) administration (e.g., subcutaneous (SC) bioavailability, F_{SC}) can be obtained as a ratio of dose-normalized AUCs following SC and IV doses. For drugs with nonlinear PK, direct application of this procedure may lead to significant under- or over-estimation of F_{SC} [1]. We observed that for any mammillary PK model true F_{SC} can be obtained as $F_{SC} = D_{IV}^T / D_{SC}$, where D_{IV}^T is the dose that needs to be administered via the variable-rate IV infusion to exactly mimic the concentration-time profile following SC dose D_{SC} . We then proposed the following approximation: $F_{SC} \approx D_{IV} / D_{SC}$, where D_{IV} is the IV dose that provides the same AUC as the SC dose D_{SC} . Simulations were conducted to evaluate applicability and bias of this approximation for drugs with the pharmacokinetics of typical monoclonal antibodies.

Results: The approximation under-estimated the true bioavailability by no more than 5-30% in the range of PK parameters typical for monoclonal antibodies, and it was always closer to the true value than F_{SC} computed as a ratio of AUCs at equal SC and IV doses. Dependence of bias on dose was U-shaped. Bias decreased with dose for $D_{SC} > 60$ mg. Bias was smaller for drugs with faster SC absorption and higher bioavailability. The approximation was more precise when steady-state doses that provide equal AUC values (AUC_{SS}) were used for calculation of F_{SC} .

Conclusions: Ratio of IV and SC doses that provide equal AUC or AUC_{SS} is a good approximation of the true bioavailability of monoclonal antibodies. This ratio underestimates the true bioavailability, with bias that decreases with increase of the absorption rate constant, true bioavailability, and SC dose.

References: [1] W Limothai, B Meibohm, Effect of Dose on the Apparent Bioavailability of Therapeutic Proteins that Undergo Target-Mediated Drug Disposition, AAPS 2011 Annual Meeting, Washington, DC