Role of Metabolites for Drugs That Undergo Nonlinear First-Pass Effect: Impact on Bioequivalency Assessment Using Single-Dose Simulations

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ABSTRACT: We investigated the effects of dose and intrasubject variability (ISV) on bioequivalence (BE) of a parent drug with a single metabolite formed by nonlinear first-pass. A BE simulation was done using a four-compartment model at doses of 17.5, 35.0, and 70.0 mg. ISV was set at either 10% or 20% for clearance and either 20% or 50% for the absorption rate constant, K_a. The ratio of $K_{a_{test}}/K_{a_{reference}}$ was fixed at 1.00 while fraction available ratios, $F_{test}/F_{reference}$, were varied from 1.00 to 1.25. Results showed the probability of passing the 90% confidence interval (CI) BE requirement for AUC_I, area-under-the-concentration curve to time infinity, and C_{max}, concentration maximum, were greater for the metabolite than the parent at all $F_{test}/F_{reference}$ ratios. For the parent, the probability of meeting BE criteria for AUC_I and C_{max} declined from 100% to 60% at the 70 mg dose as the ISV for K_a increased from 20% to 50% with an increased $F_{test}/F_{reference}$ ratio. For the metabolite, the probability of meeting BE criteria was above 80% for all doses and ISV values and $F_{test}/F_{reference}$ ratios less than 1.15. Results show that the parent, reflected absorption, is more informative for determining BE than the metabolite. Clinical data gave a similar result. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:515–523, 2010

Keywords: absorption; bioequivalence; first-pass metabolism; nonlinear pharmacokinetics; simulations

INTRODUCTION

The role of metabolites in bioequivalence (BE) determination has been extensively discussed[1,2] and continues to be a topic of interest despite the issuance of the FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations in March 2003.[3] The guidance proposed that metabolites should only be used to assess BE when the parent drug cannot be analyzed or if the metabolite is formed as a result of gut wall or presystemic metabolism and contributes meaningfully to safety and/or efficacy of the drug product. Overall, data for the metabolite are often considered to be supportive evidence of the therapeutic outcome when it is active. However, the metabolite will generally not be used to meet the BE criteria.

Although the Guidance for Industry referred only to the metabolite in general, the document

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makes no distinction between drugs that exhibit linear versus nonlinear first pass effects. Therefore, a question remains if the metabolite role in BE determination is indeed the same when the metabolite is formed by nonlinear first-pass pharmacokinetics (PK) as when formed by linear PK.[4–6] There have been few rigorous studies that have investigated the role of the parent drugs and the metabolite formed by a nonlinear first-pass effect in the determination of BE. Also, for linear drugs, it has been definitively shown *via* simulation and experimental data that single-dose (SD) studies are the most sensitive to changes in BE.[1,7] The objective of this article is to determine the effect of dose following SD on BE determination of the parent and its single metabolite formed by the liver nonlinear first-pass during absorption. In addition, the influence of intrasubject variability (ISV) in K_a on the P and M 90% CIs for a drug with a metabolite formed by a nonlinear first-pass effect was investigated. Based upon study results, it will be determined if the parent or the metabolite is the better indicator of BE following a SD.

MATERIALS AND METHODS

Monte Carlo Simulations

Model

A four-compartment nonlinear first-pass model (Fig. 1) was used to simulate parent drug and metabolite concentrations.

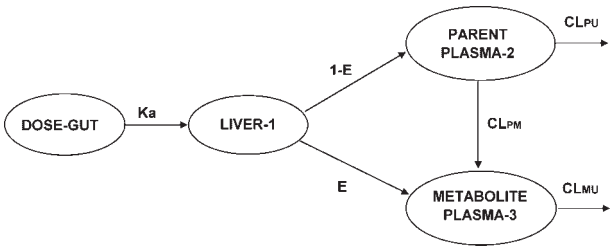

Figure 1. First-pass model used to simulate propranolol. The model is characterized by drug absorbed into the liver *via* K_a with E being extracted drug undergoing first-pass, with the $1-E$ fraction being available. The formed metabolite, F_m, and absorbed parent drug are further eliminated *via* renal clearance.

The model was described by the following differential equations:

$$\text{GUT} = A_1$$

$$\frac{\mathrm{d}\,\text{Dose}}{\mathrm{d}t} = -K_a A_1 \tag{1}$$

$$\frac{\mathrm{d}A_{\text{liver}}}{\mathrm{d}t} = K_a A_1 - ((E \times \text{CL}_{\text{int}}) + ((1-E) \times \text{CL}_{\text{int}})) \times C_{\text{liver}} \tag{2}$$

$$\frac{\mathrm{d}A_{\text{parent}}}{\mathrm{d}t} = ((1-E) \times \text{CL}_{\text{int}} \times C_{\text{liver}}) - \text{CL}_{\text{PU}} \times C_{\text{parent}} - \text{CL}_{\text{PM}} \times C_{\text{parent}} \tag{3}$$

$$\frac{\mathrm{d}A_{\text{metabolite}}}{\mathrm{d}t} = E \times \text{CL}_{\text{int}} \times C_{\text{liver}} + \text{CL}_{\text{PM}} \times C_{\text{parent}} - \text{CL}_{\text{MU}} \times C_{\text{metabolite}} \tag{4}$$

where A_1 is the amount remaining to be absorbed (dose at time zero), C_{liver} the concentration of parent drug in the liver, C_{parent} the concentration of parent drug in plasma, $C_{\text{metabolite}}$ the concentration of metabolite in plasma, A_{liver} the amount of drug in the liver, A_{parent} the amount of parent in plasma, $A_{\text{metabolite}}$ the amount of metabolite in plasma, $V_{\max}$ the maximum rate of elimination, K_m the concentration at one-half the maximum rate of elimination, CL_{int} the intrinsic clearance.

$$\text{CL}_{\text{int}} = \frac{V_{\max}}{K_m + C_{\text{liver}}}$$

$$1 - E = 1 - \frac{\text{CL}_{\text{int}}}{Q_H + \text{CL}_{\text{int}}}$$

$$E = \frac{\text{CL}_{\text{int}}}{Q_H + \text{CL}_{\text{int}}}$$

CL_{PU} is the renal clearance for parent, CL_{MU} the renal clearance for metabolite.

$$\text{CL}_{\text{PM}} = \frac{V_{\max}}{K_m + C_{\text{parent}}}$$

K_a is the absorption rate constant, Q_H the Hepatic blood flow-1500 mL/min.

Parameter values from a recent referenced study[8] were used for the simulations for propranolol and presented in Table 1.

K_a values were generated using a bivariate log normal distribution based upon the reference values in Table 1. The $K_{a_{\text{test}}}/K_{a_{\text{reference}}}$ ratio was