Interpretation of Area Under the Curve Measurements for Drugs Subject to Enterohepatic Cycling

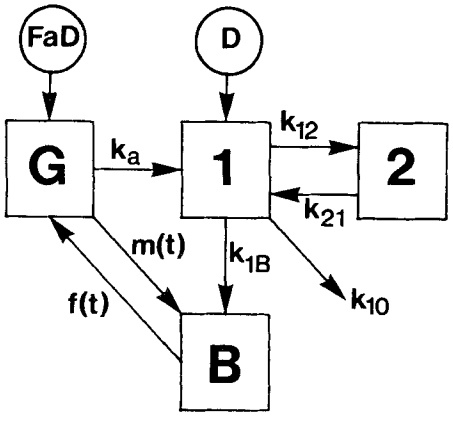
To the Editor:

It has been suggested in a recent publication that area under the plasma concentration–time curve (AUC) is dependent on the extent of enterohepatic cycling (EHC), that the ratio of AUC values for a drug that is cycled cannot be used as a relative measure of the extent of drug absorption, and that a model-independent approach cannot be used to calculate the fraction of the dose which reaches systemic circulation.[1] The authors come to these conclusions using a model of EHC which includes discontinuous transfer of drug from a storage compartment (i.e., the gallbladder) to the absorption compartment (i.e., the intestine). This model was fitted to concentration–time data after administration of cimetidine, and the effect of discontinuous gallbladder emptying on the area under the plasma concentration–time curve was investigated.

The purpose of this communication is to show that $AUC_{0-\infty}$ is independent of the time and time course of gallbladder emptying and that, contrary to the above conclusions, the ratio of AUC values can be used as a relative measure of the extent of drug absorption for such drugs. The model of EHC proposed by Veng-Pedersen and Miller[1] for cimetidine is used, but without the limitation of only one emptying of the gallbladder.

For this model, shown in Scheme I, compartment 1 represents the sampling compartment, 2 the peripheral compartment, G the compartment from which absorption takes place (the GI tract), and B the storage compartment (the gallbladder). Transfer of drug from the gut to the central compartment, from the central to the storage compartment, and between the central and peripheral compartments is assumed to be first order. No assumptions regarding the nature of the transfer of drug between compartments B and G are necessary to derive an expression for $AUC_{0-\infty}$. For this model there is no provision for a first-pass metabolism pathway that results in nonreversible formation of a metabolite.

The area under the curve for the amount of drug in compartment 1 over the time interval $t = 0$ to $t = \infty$, $AUAC_1$, is derived by integration of the differential equations for rate of change of the amount of drug in each compartment followed by solution of the resultant simultaneous equations for $AUAC_1$. If the rate of drug transfer from G to B is represented by an arbitrary function, $m(t)$, and that from B to G as $f(t)$, the following differential equations for the amount of drug in compartments 1, 2, B, and G can be written:



Scheme I

$$\frac{dA_1}{dt} = -(k_{10} + k_{12} + k_{1B})A_1 + k_A A_G + k_{21}A_2 \quad (1)$$

$$\frac{dA_2}{dt} = k_{12}A_1 - k_{21}A_2 \quad (2)$$

$$\frac{dA_B}{dt} = k_{1B}A_1 + m(t) - f(t) \quad (3)$$

$$\frac{dA_G}{dt} = -k_A A_G - m(t) + f(t) \quad (4)$$

To derive $AUAC_1$, both sides of eqs. 1–4 are multiplied by dt and integrated from time 0 to ∞. If we define

$$\int_0^\infty A_i\, dt = AUAC_i \quad (5)$$

and

$$\int_{iA_1^0}^{A^\infty} dA_i = A_i^\infty - A_i^0 \quad (6)$$

the resultant integrated equations are:

$$A_1^\infty - A_1^0 = -(k_{10} + k_{12} + k_{1B})AUAC_1 + k_A AUAC_G + k_{21}AUAC_2 \quad (7)$$

$$A_2^\infty - A_2^0 = k_{12}AUAC_1 - k_{21}AUAC_2 \quad (8)$$

$$A_B^\infty - A_B^0 = k_{1B}AUAC_1 + \int_0^\infty m(t)\, dt - \int_0^\infty f(t)\, dt \quad (9)$$

$$A_G^\infty - A_G^0 = -k_A AUAC_G - \int_0^\infty m(t)\, dt + \int_0^\infty f(t)\, dt \quad (10)$$

After bolus intravenous administration of drug (dose = D), $A_1^0 = D$ and all other initial and final conditions are 0. After oral administration of drug (dose = F_aD; F_a = fraction of the dose available for absorption from compartment G to either 1 or B), $A_G^0 = F_aD$ and all other initial and final conditions are 0. If the appropriate initial and final conditions are substituted, eqs. 7–10 can be rewritten and the resultant series of equations solved for $AUAC_1^{iv}$ and $AUAC_1^{po}$. Area under the plasma concentration–time curve, $AUC_{0-\infty}$, is simply the quotient of the respective $AUAC_1$ and the apparent volume of the central compartment, V_1:

$$AUC_{0-\infty} = \frac{AUAC_1}{V_1} \quad (11)$$

The resultant expressions for AUC_1^{iv} and AUC_1^{po} are:

$$AUC_1^{iv} = \frac{D}{k_{10}V_1} \quad (12)$$

and

$$AUC_1^{po} = \frac{F_aD}{k_{10}V_1} \quad (13)$$

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The ratio of areas after oral and intravenous bolus administration of drug is:

$$\frac{AUC_1^{po}}{AUC_1^{iv}} = F_a \quad (14)$$

Equations 12–14 demonstrate two important aspects of bioavailability that pertain to this model in which all of the drug (and drug conjugates) reaching the gallbladder is recycled (or hydrolyzed and recycled). First, $AUC_{0-\infty}$ is independent of the cycling process. An explanation for the discrepancy between the results shown above and those of Veng-Pedersen and Miller lies in the different assumptions used to derive AUC. These authors derived an equation for the time course of drug concentration in the central compartment. In order to do this, an assumption regarding the time course and frequency of drug transfer from the storage compartment (B) to the intestine (compartment G) must be made. Veng-Pedersen and Miller chose to allow one instantaneous transfer. $AUC_{0-\infty}$ was then derived through integration of the equation for the time course of drug concentration in the sampling compartment. Conceptually, after one gallbladder emptying, drug will continue to accumulate in this storage compartment. If the gallbladder is not "allowed" to empty again, only a fraction of the dose leaves the body, since drug remains in the gallbladder. The fraction of the dose which accumulates in the gallbladder after this single emptying will depend on the extent of recycling. Therefore, an expression for $AUC_{0-\infty}$ derived with these restrictions will also depend on the extent of recycling. However, contrary to these conclusions, it has been demonstrated that when elimination of the entire dose from the body is followed, $AUC_{0-\infty}$ is independent of the cycling process. This has also been shown for other, more complex models of EHC.[2] Therefore, as long as methods are developed to assess accurately $AUC_{0-\infty}$, these measurements can be used to calculate clearance, bioavailability, and/or bioequivalence without correction for cycling.

Second, it is peculiar to the case of enterohepatic cycling that when the drug extracted by the liver is cycled and not metabolized to a noncycling moiety, this extraction does not decrease systemic availability. Classically, we think of systemic availability as the product of the fraction of an oral dose available for absorption and that fraction which bypasses extraction in its first pass through the liver, $1 - E$. However, when there is cycling, drug which is extracted by the liver is transported to bile (or conjugated and transported into bile) and stored until the gallbladder contracts to release drug (or conjugate) into the intestine where it is again available (or hydrolyzed and available) for absorption. On the first pass through the liver $F_a(1 - E)D$ reaches the systemic circulation and F_aED is cycled through the hepatobiliary system and subsequently reabsorbed quantitatively into the portal circulation. On the second, third, and nth passes through the liver $F_a(1 - E)ED$, $F_a(1 - E)E^2D$, and $F_a(1 - E)E^{n-1}D$ are the respective amounts which reach the systemic circulation. The systemic availability, F, therefore, is the sum of the dose fractions which reach the systemic circulation with each cycle:

$$F = F_a(1 - E)(1 + E + E^2 + E^3 + \ldots) \quad (15)$$

However, when $x < 1$:

$$1 + x + x^2 + x^3 + \ldots = (1 - x)^{-1}$$

And, since $0 < E < 1$, eq. 15 can be rewritten:

$$F = \frac{F_a(1 - E)}{(1 - E)} = F_a \quad (16)$$

It is evident from the above analysis that events which lead to EHC of drug do not reduce systemic availability, provided that reabsorption of cycling drug is complete.

Thus, it has been demonstrated that model-independent methods can be used to calculate the fraction of the dose which reaches the systemic circulation, F. The model-dependent method proposed by Veng-Pedersen and Miller may lead to inaccurate estimates of F. When applied to the analysis of cimetidine data,[1] a mean value of 0.64 was calculated for F which agrees well with the values of 0.62 and 0.59[3] obtained with the ratio of areas calculated using the trapezoidal rule. However, when applied to the analysis of ranitidine data,[4] a mean value of 0.70 was obtained for F in comparison to a value of 0.58 obtained using the ratio of areas. Hence, for ranitidine, the model-dependent method gives a falsely high estimate of F.

In summary, contrary to statements previously appearing in the literature, model-independent methods can be used to calculate F for drugs subject to EHC as long as $AUC_{0-\infty}$ is accurately measured.

References and Notes

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