Letter to the Editor

In Vivo Assessment of Intestinal Drug Metabolism

Although the small intestine is regarded primarily as an absorptive organ in the uptake of orally administered drugs, it also has the ability to metabolize drugs by numerous pathways involving phase I and phase II reactions (1–3). Thus, the amount of an orally administered drug that reaches the systemic circulation can be reduced by both intestinal and hepatic metabolism. Drug metabolism before the drug entering the systemic circulation is referred to as presystemic or first-pass elimination. The pharmacokinetic consequences of first-pass elimination vary, depending on whether the drug is a high or low clearance compound, and on the relative contribution of intestinal and hepatic metabolism.

Several in vitro and in vivo methods have been established to determine the relative contribution of intestinal and hepatic metabolism to the overall first-pass elimination (4–6). The extent of intestinal and hepatic metabolism can be assessed by comparing the plasma AUC after portal vein infusion and oral administration. Evaluation of intestinal metabolism also is possible in patients with a portocaval anastomosis where portal blood bypasses the liver (7, 8) or in anhepatic patients during liver transplant surgery (9). However, these procedures are rarely used because of the ethical limitations and specialized surgical procedures that are involved.

In a recent paper entitled, “The Nifedipine-Rifampin Interaction: Evidence for Induction of Gut Wall Metabolism,” Holtbecker et al. (10) raised a number of interesting and important issues regarding intestinal metabolism. The authors attempted to estimate the intestinal and hepatic metabolism of nifedipine before and after rifampin induction in healthy volunteers. By comparing the plasma AUCs after intravenous and oral administration, the absolute bioavailability of nifedipine was found to decrease from 41.3% to 5.3% after 7 days of treatment with rifampin. Further kinetic analyses revealed that the intestinal ($E_i$) and hepatic ($E_h$) extraction ratios were increased from 0.218 and 0.474 to 0.758 and 0.674, respectively, as a consequence of rifampin induction. Thus, the authors concluded that the reduction of nifedipine bioavailability during enzyme induction is due mainly to rifampin-induced gut wall metabolism.

Unfortunately, the authors’ pharmacokinetic calculations are inappropriate and, therefore, their conclusion could be invalid! The authors erroneously assumed that intestinal metabolism does not contribute to the total clearance after intravenous administration. As a result, the hepatic extraction ratio ($E_h$) was calculated directly from the total clearance ($CL$) and hepatic blood flow ($Q_h$), according to the equation $E_h = CL/Q_h$ (10), without taking into account the intestinal metabolism. This leads to miscalculation of $E_h$ and, when used in the relationship $F_{bioavailability} = (1 - E_i)(1 - E_h)$, results in an inappropriate estimation of $E_h$.

A kinetic model describing the disposition of drugs that undergo both intestinal and hepatic metabolism has been developed by Gillette and Pang (11). The total body clearance ($CL_{total}$) and AUC after intravenous and oral dosing can be expressed as:

$$CL_{total} = CL_H + F_H \cdot CL_I$$

(1)

$$AUC_{i.v.} = \frac{Dose}{CL_H + F_H \cdot CL_I}$$

(2)

$$AUC_{p.o.} = \frac{f_{abs} \cdot F_H \cdot F_G \cdot Dose}{CL_H + F_H \cdot CL_I}$$

(3)

where $f_{abs}$ is the fraction of drug absorbed from the gastrointestinal lumen, and $CL_H$ and $CL_I$ are the organ clearances for the liver and intestine, respectively. $F_H$ and $F_G$ are the fractions of drug not metabolized by the liver and intestine, respectively. These terms can be expressed as:

$$CL_H = \frac{Q_h \cdot f_p \cdot CL_{int,h}}{Q_h + f_p \cdot CL_{int,h}}$$

(4)

$$CL_I = \frac{Q_i \cdot f_p \cdot CL_{int,i}}{Q_i + f_p \cdot CL_{int,i}}$$

(5)

and

$$F_H = \frac{Q_h}{Q_h + f_p \cdot CL_{int,h}}$$

(6)

$$F_G = \frac{Q_i}{Q_i + f_p \cdot CL_{int,i}}$$

(7)

where $Q_h$ and $Q_i$, respectively, are the blood flow to the liver and intestine; $f_p$ is the unbound fraction in plasma; and $CL_{int,h}$ and $CL_{int,i}$ are the intrinsic clearances of the liver and intestine, respectively. The $CL_{int}$ ($V_{max}/K_M$) is a measure of the degree to which the drug serves as a substrate for metabolic transformation.

By substitution of eqs. 4–7, eqs. 2 and 3 can be rewritten as:

$$AUC_{i.v.} = \frac{Dose}{f_p \cdot (F_H \cdot CL_{int,h} + F_H \cdot F_G \cdot CL_{int,g})}$$

(8)

$$AUC_{p.o.} = \frac{f_{abs} \cdot Dose}{f_p \cdot (CL_{int,h} / F_H + CL_{int,g})}$$

(9)

Both $CL_{int,h}$ and $CL_{int,g}$ can be increased by enzyme induction. However, upon close examination of eq. 8, increases in the $CL_{int,h}$ and $CL_{int,g}$ due to induction will be offset by the multipliers $F_H$ and $F_G$, which are <1 and will decrease due to induction. On the other hand, in eq. 9, the increase in the $CL_{int,h}$ upon induction will be amplified by dividing by $F_H$. It can be inferred that the increases in the $CL_{int,h}$ and $CL_{int,g}$ caused by enzyme induction will have minimal effect on the AUC of high clearance drugs after intravenous dosing. In contrast, the $AUC_{p.o.}$ is sensitive to changes in the $CL_{int,h}$ and $CL_{int,g}$, regardless of whether the drug is a high or low clearance compound.

Although the values of $Q_h$ and $Q_i$ can be obtained from the literature, and $f_p$ and $f_{abs}$ can be determined experimentally, exact solutions of $CL_{int,h}$ and $CL_{int,g}$ are not possible, based only on measurements of $AUC_{i.v.}$ and $AUC_{p.o.}$ However, a computer simulation of the effect of intestinal and hepatic enzyme induction on the disposition of drugs yields some useful information. Using eqs. 8 and 9,

Received January 31, 1997; accepted May 2, 1997.

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the effect of enzyme induction on the AUCs after intravenous and oral dosings were computed for high, intermediate, and low clearance drugs (figs. 1–3). The reported values of \( Q_h \) and \( Q_g \) are 1500 ml/min and 1200 ml/min, respectively. For the purpose of the simulation, the \( f_p \cdot CL_{int,h} \) is assumed to be 6000 ml/min for the high clearance drug, 2000 ml/min for the intermediate clearance drug, and 200 ml/min for the low clearance drug. The values of \( f_p \cdot CL_{int,g} \) are fixed at 50%, 10%, or 0% of \( f_p \cdot CL_{int,h} \) for all three classes of drugs. Furthermore, the degree of enzyme induction is assumed to be equal in the intestine and liver.

As shown in figs. 1–3, enzyme induction has a less profound effect on the AUC after intravenous dosing than that after oral administration, regardless of whether the compound is a high or low clearance drug.

**FIG. 1.** Simulated effect of enzyme induction on the AUC\(_{i.v.}\) (○) and AUC\(_{p.o.}\) (■) of a high clearance drug. The changes in the AUCs are expressed as percentage of the AUCs before induction. The value of \( f_p \cdot CL_{int,h} \) (6000 ml/min) is constant for (A)–(C), whereas the \( f_p \cdot CL_{int,g} \) is 3000 ml/min for (A), 600 ml/min for (B), and 0 ml/min for (C).

**FIG. 2.** Simulated effect of enzyme induction on the AUC\(_{i.v.}\) (○) and AUC\(_{p.o.}\) (■) of an intermediate clearance drug. The changes in the AUCs are expressed as percentage of the AUCs before induction. The value of \( f_p \cdot CL_{int,h} \) (2000 ml/min) is constant for (A)–(C), whereas the \( f_p \cdot CL_{int,g} \) is 1000 ml/min for (A), 200 ml/min for (B), and 0 ml/min for (C).

**FIG. 3.** Simulated effect of enzyme induction on the AUC\(_{i.v.}\) (○) and AUC\(_{p.o.}\) (■) of a low clearance drug. The changes in the AUCs are expressed as percentage of the AUCs before induction. The value of \( f_p \cdot CL_{int,h} \) (200 ml/min) is constant for (A)–(C), whereas the \( f_p \cdot CL_{int,g} \) is 100 ml/min for (A), 20 ml/min for (B), and 0 ml/min for (C).
drug. However, the differences between the changes (%) in the AUC \textsubscript{i,v} and AUC \textsubscript{p,o} are more dramatic for high clearance, compared with low clearance drugs (fig. 1 vs. fig. 3), even when intestinal metabolism is absent. Therefore, the mere observation of a greater change in the AUC \textsubscript{p,o} than the AUC \textsubscript{i,v} after enzyme induction does not necessarily reflect a greater degree of induction in the intestine. It should be noted that nifedipine is an intermediate clearance drug.

Because of backdiffusion of a drug from the intestinal circulation to the intestinal epithelial cells, the fraction of drug from the systemic circulation metabolized by the intestine may not be as great as that which occurs during absorption. Therefore, Minchin and Ilett (12) have suggested that an “effective intestinal blood flow” (\(\alpha \cdot Q_g\)), rather than the true intestinal blood flow (\(Q_g\)), should be used for the calculation of intestinal clearance, where the values of \(\alpha\) are dependent on the physicochemical properties of drugs. When an arbitrary effective intestinal blood flow (\(\alpha \cdot Q_g = 300\) ml/min) was used for the simulation, a similar pattern of changes in the AUC \textsubscript{i,v} and AUC \textsubscript{p,o} was observed, compared with those illustrated in figs. 1–3.

**Drug Metabolism I**

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**References**


