First-pass metabolism after oral drug administration does not only occur in liver, but also in epithelial cells of the gut wall mucosa [e.g. with the cytochrome P4503A4 (CYP3A4) substrates cyclosporin and midazolam]. For example, 43% of an intraduodenally administered dose of midazolam was extracted in intestinal mucosa in patients during the anhepatic phase of a liver transplantation, proving the importance of intestinal drug metabolism for low bioavailability of midazolam (1). Moreover, induction of intestinal metabolism of CYP3A4 substrates, such as cyclosporin and verapamil, was the major reason of reduced bioavailability of these drugs during coadministration of the enzyme-inducing agent rifampin (2, 3). These observations are in accordance with a marked increase in CYP3A content in intestinal epithelial cells during administration of rifampin to healthy volunteers (4).

Using a standard pharmacokinetic approach, which has been used for the estimation of intestinal and hepatic metabolism of cyclosporin, midazolam, and verapamil (2, 3, 5), we identified rifampin-induced prehepatic metabolism of the CYP3A4 substrate nifedipine as a major factor for reduced bioavailability during coadministration of rifampin to healthy volunteers (6).

These findings have been challenged by Lin et al. They present model simulations that confirm the well-known principle that enzyme induction in the liver and/or intestine has a greater effect on AUC after oral than intravenous administration, and this is more pronounced the higher the drug’s intrinsic clearance(s) (CLint). Thus, Lin et al. correctly point out that a larger change in AUCpo than AUCiv after enzyme induction does not necessarily indicate greater enzyme induction in the intestine than in the liver—a conclusion that we reached regarding the interaction between rifampin and nifedipine (6). In reaching this conclusion, we assumed that nifedipine’s systemic clearance after an intravenous dose only reflects hepatic elimination and that metabolism of systemically available drug by intestinal enzymes; in this case, CYP3A localized in the enterocyte is negligible. Lin et al. consider this not to be a valid assumption that leads to erroneous estimates of the extraction ratios of the intestine (Ei) and liver (Ep).

Modeling drug elimination by an organ such as the liver, where the vascular supply and metabolizing enzymes are intimately associated within the sinusoidal architecture, has been relatively successful (7). The well-stirred model applied by Lin et al. has, in fact, been widely used when considering organ elimination in the context of whole body pharmacokinetics. However, it is important to note that less success has been achieved as the level of functional reality has increased (i.e. the well-stirred model does not describe intraorgan characteristics and events very well). Given the different anatomy and vascularity of the intestine relative to the liver, application of the model to describe drug metabolism within this organ is not the trivial and simple extension provided by Lin et al. For example, after oral administration, absorbed drug undergoes vectorial transport in which it is first exposed to metabolizing enzymes such as CYP3A4 in the enterocytes of the microvilli before reaching the villous capillaries. On the other hand, for drug in the systemic circulation, the reverse pathway must be traversed. Unfortunately, the fraction of the mesenteric blood supply delivering drug to the enterocytes is not well-established, and it also varies, dependent on physiological factors (including digestion). Moreover, diffusion of drug from the villous capillaries to enzyme located at the apex of the enterocyte must occur. Thus, exposure of absorbed and systemic drug to the metabolizing enzyme may be considerably different. These and other considerations, contrary to the suggestion of Lin et al., have not yet allowed development of a substantiated and valid model to describe accurately drug elimination by the intestine after both oral and intravenous administration.

Several experimental findings, some of which we described (6), support our original assumptions and conclusions. For example, the hepatic clearance of midazolam—a drug that like nifedipine is completely metabolized mainly by CYP3A4 and also has an intermediate hepatic clearance—was estimated from in vitro measurement of its microsomal intrinsic clearance and appropriate scale-up to the whole organ (7). Comparison of this value with the drug’s estimated systemic clearance after intravenous administration showed excellent agreement, leading to the conclusion that the contribution of intestinal CYP3A4 to midazolam’s elimination from the systemic circulation was negligible (7). Subsequent studies performed during the anhepatic phase of liver transplantation confirmed this by finding that intestinal clearance of midazolam in the systemic circulation contributed on average <10% to the overall clearance of the drug (1). Moreover, pharmacokinetic analysis identical to that used by us to separate the relative contributions of intestinal and hepatic metabolism to nifedipine’s first-pass effect, also concluded that intestinal extraction is a major factor in midazolam’s bioavailability after oral administration, along with that by the liver (5). The same approach has also been applied to cyclosporin. Moreover, recently published data indicate that P-glycoprotein-mediated active secretion of drugs into the intestinal lumen might contribute to drug elimination in addition to intestinal CYP3A4 [for review, see Wacher et al. (8)]. Many substrates of CYP3A4 are also transported by P-glycoprotein, and both proteins are induced by rifampin (9). Assessment of intestinal drug metabolism derived from in vitro data as suggested by Lin et al. does not take this fact into account.

In summary, the model provided by Lin et al. is of theoretical interest. Considering that this model neglects the physiology of the gastrointestinal tract, it is not surprising that experimental and clinical data published do not support the approach by Lin et al.

References


