

Splanchnic Clearance and Its Relationship with Drug Elimination by the Liver and Gastrointestinal Tract

To the Editor:

Organ clearances are considered to be additive terms, yet this is not always the case. For example, splanchnic clearance is not simply the sum of hepatic and gastrointestinal clearances. Due to the anatomy and arrangement of blood flow within this region, splanchnic extraction and clearance are, instead, complex and hybrid terms. As such, a kinetic model was developed by Pang and Gillette¹ and subsequently reported by Lin et al.² describing the disposition of intravenously administered drugs that undergo both intestinal and hepatic metabolism. Thus, $CL_{spl} = CL_H + F_H CL_{GI}$, in which CL_{spl} is the splanchnic clearance, CL_H is the hepatic clearance, F_H is the fraction of drug escaping extraction on each pass through the liver, and CL_{GI} is the gastrointestinal clearance.

The splanchnic clearance equation is consistent with the contributions of hepatic and gastrointestinal elimination at their limits. As a result, if clearance by the gastrointestinal tract is absent (i.e., $CL_{GI} = 0$), then splanchnic clearance is simply equal to the hepatic clearance alone (i.e., $CL_{spl} = CL_H$). Further, if clearance by the liver is absent (i.e., $CL_H = 0$ and $F_H = 1$), then splanchnic clearance is simply equal to the gastrointestinal clearance alone (i.e., $CL_{spl} = CL_{GI}$). However, when hepatic and gastrointestinal elimination are both operative, it is very difficult to predict the overall effect on CL_{spl} because of the parallel as well as sequential perfusion of these two organs. This relationship is further complicated by concentration- or dose-dependent kinetics that may effect changes in clearance and/or extraction. To illustrate this point, we have examined this relationship in dogs using direct in vivo measurements of 5-fluorouracil (FUra) clearance by the liver, gastrointestinal tract, and splanchnic region. The surgical procedure, experimental methods, and results concerning the regional pharmacokinetics of FUra have been published elsewhere.³

Following intravenous infusions of FUra at five sequentially escalated dose rates (0.0625, 0.250, 0.750, 1.50 and 2.00 $\mu\text{mol}/\text{min}/\text{kg}$), values for CL_H (11.7, 11.8, 11.2, 11.0, and 9.88 $\text{mL}/\text{min}/\text{kg}$), F_H (0.225, 0.229, 0.298, 0.320, and 0.398), CL_{GI} (7.90, 7.26, 5.42, 4.98 and 3.42 $\text{mL}/\text{min}/\text{kg}$) and CL_{spl} (13.5, 13.5, 12.8, 12.6 and 11.2 $\text{mL}/\text{min}/\text{kg}$) were

reported, respectively. At the extremes of dose-rate (i.e., 0.0625 vs 2.00 $\mu\text{mol}/\text{min}/\text{kg}$), a substantial 57% reduction occurred in gastrointestinal clearance while a modest 16% reduction occurred in hepatic clearance. On the basis of these changes, one might be inclined to believe that splanchnic clearance would also decline to a large extent. However, the fraction escaping extraction by the liver was increased by a substantial 77%, thus attenuating the effect of a reduced gastrointestinal clearance. As a result, the overall splanchnic clearance of FUra was reduced by only 17% at the larger dose-rate. A final observation was that hepatic clearance assumed the major contribution to FUra's splanchnic clearance, regardless of dose-rate. Over the 32-fold range of dose-rates studied, clearance by the liver accounted for about 87% of drug elimination by the splanchnic region as a whole. Although this observation was specific for FUra, similar results would be predicted for other high hepatic extraction drugs because small values for hepatic availability ($F_H \leq 0.3$) would minimize the role of the gastrointestinal tract in systemic drug elimination.

References and Notes

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