ERRATUM

Due to a printing error, pages 1331 and 1334 in the article "Oral Bioavailability and First-Pass Effects" by K. C. Kwan (*Drug Metab. Dispos.* 25:1329–1336, 1997) were printed incorrectly. The corrected page 1331 is reprinted here. The first paragraph in column 2, page 1334 is reprinted on the next page.

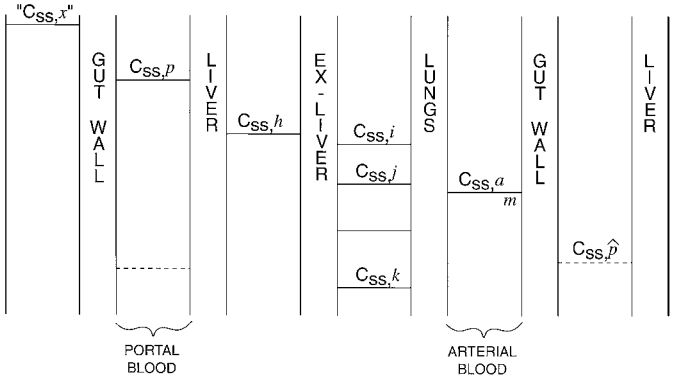

FIG. 2. *Schematic diagram of steady-state concentrations, C_{ss}, at sites of interest during a continuous perfusion of drug solution to the gastrointestinal tract at a constant rate.*

Lower case letter designation have the same meaning as in fig. 1. "$C_{ss,x}$" is the effective steady-state concentration at the absorption site *x*. See text for the definition of $C_{ss,\hat{p}}$.

that reaches the sampling site following $D^{iv,h}$. Hence,

$$F_S = \frac{CL'\ AUC_j^{D^{iv,h}}}{D^{iv,h}} = \frac{D^{ia,n}}{D^{iv,h}} \frac{AUC_j^{D^{iv,h}}}{AUC_j^{D^{ia,n}}} \tag{13}$$

Combining eqs. 11 and 13,

$$F_S \cong \frac{D^{ia,n}}{D^{iv,i}} \frac{AUC_j^{D^{iv,i}}}{AUC_j^{D^{ia,n}}} \tag{14}$$

Eq. 14 is experimentally preferable to eq. 13 in that a peripheral vein is more accessible than the hepatic vein. Moreover, the evaluation of F_S would entail only one additional treatment, $D^{ia,n}$, rather than two, $D^{ia,n}$ and $D^{iv,h}$.

Total body clearance, CL or CL′, may be calculated from serum, plasma, or blood concentration data as long as the same medium is used consistently in bioavailability assessment.

For clarity, ensuing discussions will dispense with F_S, the assessment of which can always be amended with an additional experiment. Furthermore, since all peripheral veins are interchangeable as sites of administration, the site qualifiers for D^{iv} are no longer necessary and will be dropped. The $D^{iv,p}$ designation is retained for drug administration to the hepatic portal vein, however. Whereas peripheral veins appear to be equivalent as sites of administration, they are not interchangeable as sampling sites. Conversely, peripheral sampling sites on the arterial side are equivalent, but administration to each artery engenders a unique first-pass effect. Therefore, data used to extract pharmacokinetic parameters should come from samples taken from a common venous sampling site. Data derived from samples taken from peripheral arteries are not similarly constrained. For this reason, subsequent developments will designate an artery *a* as the peripheral sampling site.

Measurements in the Portal and Peripheral Circulation. Concomitant measurements in the portal and peripheral blood provide a new dimension in experimental design. Suppose the gastrointestinal tract were subjected to a continuous perfusion at a constant rate of a drug solution of fixed composition. At steady state, blood concentrations C_{ss} at individual sampling sites become time invariant. Fig. 2 depicts steady-state concentrations at sampling sites of possible interest for a drug that is capable of being absorbed and the eliminating organs for which include the gut wall and the liver. The rate of drug delivery, R, from the gut lumen to the portal circulation can be estimated (23) by

$$R = Q_p(C_{ss,p} - C_{ss,\hat{p}}) \tag{15}$$

where Q_p is the blood flow rate in the hepatic portal vein, $C_{ss,p}$ is the observed concentration in portal blood at steady state, and $C_{ss,\hat{p}}$ is that part of $C_{ss,p}$ represented by drug returning from the general circulation. The difference between $C_{ss,p}$ and $C_{ss,\hat{p}}$, therefore, represents new contributions from the gut lumen. The relationship between $C_{ss,p}$ and $C_{ss,\hat{p}}$ can be visualized by rolling fig. 2 back on itself to form a cylinder wherein vertical bars representing "gut wall" and "liver" on the far right coincide with their counterparts on the left. In this alignment, $C_{ss,p}$ and $C_{ss,\hat{p}}$ appear in the same column representing the portal vein.

By analogy to eq. 15, the total amount of drug that reaches the portal circulation from the gut following a single oral dose is

$$F_X\ F_G\ D^{po} = Q_p(AUC_p^{D^{po}} - AUC_{\hat{p}}^{D^{po}}) \tag{16}$$

$AUC_{\hat{p}}^{D^{po}}$ is not an experimentally observable entity, but its value can be deduced from the corresponding area measured in samples taken from a peripheral blood vessel, say, $AUC_{a,\hat{p}}^{D^{po}}$.

From an intravenous dose, one obtains $AUC_a^{D^{iv}}$ and $AUC_p^{D^{iv}}$. Since there is no lumenal source of drug after an intravenous dose,

$$AUC_{\hat{p}}^{D^{iv}} = AUC_p^{D^{iv}} \tag{17}$$

Furthermore, in a linear system with constant clearance between treatments, the ratio of $AUC_{\hat{p}}$ to AUC_a is invariant regardless of the route of administration and numerically equal to that following an iv dose; *i.e.*

$$\frac{AUC_{\hat{p}}^{D^{po}}}{AUC_a^{D^{po}}} = \frac{AUC_{\hat{p}}^{D^{ia,m}}}{AUC_a^{D^{ia,m}}} = \ldots = \frac{AUC_{\hat{p}}^{D^{iv}}}{AUC_a^{D^{iv}}} \tag{18}$$

Combining eqs. 16–18,

$$F_X\ F_G = \frac{Q_p}{D^{po}}\left[AUC_p^{D^{po}} - \frac{AUC_a^{D^{po}}}{AUC_a^{D^{iv}}}\ AUC_p^{D^{iv}}\right] \tag{19}$$

Given that

$$F_X\ F_G\ F_H = \frac{D^{iv}}{D^{po}}\ \frac{AUC_a^{D^{po}}}{AUC_a^{D^{iv}}} \tag{20}$$

dividing eq. 19 into eq. 20 yields

$$F_H = \frac{D^{iv}}{Q_p}\left\{\frac{AUC_a^{D^{po}}}{AUC_p^{D^{po}}\ AUC_a^{D^{iv}} - AUC_a^{D^{po}}\ AUC_p^{D^{iv}}}\right\} \tag{21}$$

Similarly, the amount of drug that reaches the portal circulation after a dose to the mesenteric artery is

$$F_G\ D^{ia,m} = Q_p(AUC_p^{D^{ia,m}} - AUC_{\hat{p}}^{D^{ia,m}}) \tag{22}$$

which, when combined with eqs. 17 and 18, yields

$$F_G = \frac{Q_p}{D^{ia,m}}\left(\frac{AUC_p^{D^{ia,m}}\ AUC_a^{D^{iv}} - AUC_a^{D^{ia,m}}\ AUC_p^{D^{iv}}}{AUC_a^{D^{iv}}}\right) \tag{23}$$

Finally, dividing eq. 23 into eq. 19, one obtains

$$F_X = \frac{D^{ia,m}}{D^{po}}\left\{\frac{AUC_p^{D^{po}}\ AUC_a^{D^{iv}} - AUC_a^{D^{po}}\ AUC_p^{D^{iv}}}{AUC_p^{D^{ia,m}}\ AUC_a^{D^{iv}} - AUC_a^{D^{ia,m}}\ AUC_p^{D^{iv}}}\right\} \tag{24}$$

Simultaneous measurement in the portal vein and a peripheral artery eliminates the need for an iv,p treatment. There are, however,

There is renewed interest in the use of the portal-to-peripheral concentration gradient as a measure of intestinal absorption (41–45). Notwithstanding the confounding effects of gut-wall metabolism, the validity of this approach depends on how closely the drug concentration profile measured in a peripheral blood vessel resembles that which is occurring at $\hat{p}$. Fig. 2 shows that steady-state concentrations at peripheral sampling sites *i*, *j*, *k*, and *a* may differ from each other and from the expected value at $\hat{p}$ for one drug at a fixed rate of input. The relative magnitudes at these same sites will differ from drug to drug since they depend on where drug elimination occurs and the relative contributions of each eliminating organ. After a single oral dose of drug, the difference in concentration between *p* and $\hat{p}$ varies with time and is proportional to the time course of change in drug input to the portal circulation; it starts at zero at time zero, goes through a series of finite values, and returns to zero eventually. Differences in concentration between *p* and peripheral sites *i*, *j*, *k*, or *a* must undergo similar changes with time but not coincidently with each other. Also unlike the differences between those at *p* and $\hat{p}$, they are not necessarily zero in the absence of input from the gut and, therefore, generally not proportional to the drug input profile. The remoteness with which concentrations at a peripheral site can emulate those at $\hat{p}$ suggests that the valid use of portal-to-peripheral concentration gradients *per se* would be limited. Empirically, applicability is limited to situations in which AUC's measured in the portal vein and the peripheral site after an iv dose are equal. In other words, differences in drug concentration between the portal and the peripheral blood are not indicative of ongoing absorption except in highly specialized situations, *e.g.* the drug is metabolically inert. They are especially inappropriate as indices of comparative absorption across compounds.