Title

For hepatically cleared drugs, liver to blood KPUU at steady-state is always equal to FH , which exposes the deficiency of the present extended clearance concept equation

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FOR HEPATICALLY CLEARED DRUGS, LIVER TO BLOOD Kp_{uu} AT STEADY-STATE IS ALWAYS EQUAL TO F_H, WHICH EXPOSES THE DEFICIENCY OF THE PRESENT EXTENDED CLEARANCE CONCEPT EQUATION

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It has not been previously recognized that for an hepatically cleared drug at steady-state, Kp_{uu}, the ratio of the hepatic unbound concentration ($C_{u,Liver}$) to the systemic unbound concentration ($C_{u,Blood}$) is equal to F_H, the fraction of an oral dose that escapes first pass hepatic elimination. This is true since at steady- state the product of the systemic blood concentration (C_{Blood}) multiplied by the hepatic blood clearance ($CL_{H,Blood}$) is equal to $C_{u,Liver}$ multiplied by the intrinsic hepatic clearance of unbound drug, $CL_{int,Liver}$, i.e., $C_{H,Blood} \cdot CL_{H,Blood} = C_{u,Liver} \cdot CL_{\int ¿.¿}$This equality is valid independent of the mechanism of hepatic elimination. Substituting a clearance-intrinsic clearance equation into this equality allows $C_{u,Liver}/C_{u,Blood}$ to be determined. For example, when the equation previously believed to be the well-stirred model (WSM), $CL_{H,Blood,WSM} = Q_{Liver} \cdot f_{u,Blood} \frac{\cdot CL_{\int ¿}}{Q_{Liver} + f_{u,Blood} \cdot CL_{\int ¿}¿}$, where Q_{Liver} is hepatic blood flow and $f_{u,Blood}$ is fraction of drug unbound in the blood, is substituted into the equality, $Kp_{uu,WSM} = \frac{Q_{Liver}}{Q_{Liver} + f_{u,Blood} \cdot CL_{\int ¿}¿}$. There are a number of important aspects of this finding. First, Kp_{uu} for drugs where hepatic basolateral transporters are not clinically relevant is a function of hepatic blood flow except for very low CL_{int} compounds. Thus, for many drugs, an *in vitro* Kp_{uu} measurement may not be the correct value *in vivo*. Second, Kp_{uu} for such drugs is always less than or equal to 1.0. And third, since $F_H = 1 - \frac{CL_{H,Blood}}{Q_{Liver}}$, Kp_{uu} for such drugs is equal to F_H. Now consider the case where hepatic basolateral transporters are included in the hepatic clearance equation and hepatic clearance is described by the universally regarded Extended Clearance Concept (ECC) equation, when Q_{Liver} is much greater than CL_{int} and much greater than transporter influx (PS_{influx}) and efflux (PS_{efflux}) clearances. That is, $CL_{H,Blood,ECC} = f_{u,Blood} \cdot PS_{influx} \cdot \frac{CL_{\int ¿}}{CL_{\int ¿ + PS_{efflux}}¿}$; then, $Kp_{uu,ECC} = \frac{PS_{influx}}{CL_{\int ¿ + PS_{efflux}}¿}$. It can easily be shown for this ECC relationship that when Q_{Liver} is included in the clearance definition $F_H = Kp_{uu,ECC}$. As we have recently published, using Kirchhoff's Laws (KL) to derive the clearance equation when basolateral transporters are included in the hepatic clearance equation and Q_{Liver} is significantly greater than CL_{int} and greater than the basolateral transporter clearances, then $CL_{H,Blood,KL} = f_{u,Blood} \cdot (PS¿¿influx - PS_{efflux}) \cdot \frac{CL_{\int ¿}}{CL_{\int ¿ + (PS¿¿influx - PS_{efflux})¿}¿¿}$ and $Kp_{uu,KL} = \frac{(PS_{influx} - PS_{efflux})}{CL_{\int ¿ + (PS_{influx} - PS_{efflux})}¿}$. Once again it is easy to show when Q_{Liver} is included in the clearance definition that for this clearance equation $F_H = Kp_{uu,KL}$. Overall basolateral transporter clearances can quantitatively be either less or more than hepatic

elimination clearance. However, this cannot be true for the present ECC equation $Kp_{uu,ECC}$, when PS_{influx} is greater than ¿, which would result in predicted F_H>1. This supports the position that the ECC equation is not the proper approach when including hepatic basolateral transporters in hepatic clearance equations. There is even a greater benefit to the analysis presented here for the KL approach. If an accurate determination of Kp_{uu} can be made by experimental measurements, no easy task, then it would be possible, when transporters appear in the clearance equation, to predict hepatic blood clearance of a drug independent of requiring an intravenous dose clinical study.