Revisiting the well-stirred model of hepatic clearance: $Q_H$, $CL_H$ and $F$ changing in the same direction

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This tutorial examines the relationship between CL, F, and hepatic blood flow ($Q_H$) quantitatively at oral and i.v. administration as an answer to the quiz set for KSCPT members. In case of oral dosing, when hepatic blood flow increases, the hepatic clearance (CL) and bioavailability (F) increases in high-extraction ratio drugs according to the well-stirred model equations for hepatic clearance:

$$CL_H = Q_H \times ER = Q_H \times f_u \times CL_{int}/(Q_H + f_u \times CL_{int})$$ and $$F = 1 - ER$$

Despite such a clear relationship, many students may feel it rather paradoxical that the increased CL (thus decreasing the AUC) causes increased F and thus the AUC (F∙Dose/CLH) remains unchanged. This tutorial clarifies that the degree to which CL increase fails to match that of the $Q_H$ increase, and thus the decreased ER (= CL/$Q_H$) that results in the increased F. Contemplating this simple, but seemingly paradoxical phenomenon may help students gain a deeper understanding of the first-pass effect.

Previous Quiz for Students: Paradox of hepatic clearance and bioavailability

The quiz below was announced to KSCPT members a couple of weeks ago. This tutorial was written to discuss the seemingly paradoxical phenomenon described in the quiz.

**Question:** Assume that we have a drug with a high hepatic extraction ratio (e.g., $f_u \times CL_{int} = 9 \times Q_H$). When hepatic blood flow increases by 1.5 times, the hepatic extraction ratio (ER) slightly decreases from 0.9 to 0.86 according to the well-known equation below. Thus, the $CL_H$ will increase by 1.4 times (from 0.9$Q_H$ to 0.86 x 1.5$Q_H$).

$$CL_H = Q_H \times ER = Q_H \times f_u \times CL_{int}/(Q_H + f_u \times CL_{int})$$

The bioavailability defined as $F = 1 - ER$ is then accordingly inflated (1.4 times increase; from 10% to 14%). Explain this simultaneous increase in bioavailability and $CL_H$. There is no problem in the equation. But why does F increase despite increased CL?

A simulated case based upon the equation ($Q_H$ at 1 L/min versus 1.5 L/min)

To address the question, we are to look into a simplified example as follows.

**<Case of Drug A>**

- Drug A is an extensively metabolized drug, which is eliminated only by hepatic metabolism, and its $f_u CL_{int}$ equals 9 x $Q_H$.
- Ignoring the hepatic arterial blood flow for simplicity, $Q_H$ the baseline portal blood flow of the subject was assumed to be 1 L/min.
- Drug A, given orally at 1500 mg, is completely absorbed by zero-order kinetics to arrive at the portal blood stream without any loss in the gut lumen or wall: instantaneous absorption to enterocytes subsequently followed by zero-order transfer to the portal venous blood at 100 mg/min.
- Let us see what happens to the CL$_H$ and F of drug A before and after the Q$_H$ is increased by 50% (1.5 L/min).

The example of calculating the CL$_H$ and F in relation with the Q$_H$ using the equation 1) in the quiz[1] is summarized in Table 1. According to the assumption, the hepatic arterial blood flow is ignored and the duration of zero-order absorption is 15 min at baseline and 10 min at 1.5 times-elevated Q$_H$ because of the portal venous transfer rate fixed to 100 mg/min. Thus, the drug...
Revisiting well-stirred model

Table 1. Changes in absorption-related parameters when \( Q_h \) increases in a high-extraction ratio drug A

<table>
<thead>
<tr>
<th>No.</th>
<th>Parameters</th>
<th>Unit</th>
<th>Baseline</th>
<th>( Q_h, \text{ 50%} \uparrow )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>( Q_h ) (Hepatic (portal) blood flow)</td>
<td>L/min</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>2)</td>
<td>( f_x \times CL_{int} )</td>
<td>L/min</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>3)</td>
<td>Dose</td>
<td>mg</td>
<td>1500</td>
<td>1500</td>
</tr>
<tr>
<td>4)</td>
<td>Absorption duration (0-order)</td>
<td>min</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>5)</td>
<td>Drug Concentration in portal blood</td>
<td>mg/L</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>6)</td>
<td>Rate of drug delivered to the liver (Rd)</td>
<td>mg/min</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>7)</td>
<td>( \text{ER} = \frac{f \times \text{CL}<em>{int} - \frac{f \times \text{CL}</em>{int}}{\text{Q}}}{\text{CL}_{int}} )</td>
<td></td>
<td>( 0.9 ) ((= \frac{0.1}{1+0.9}))</td>
<td>( 0.857 ) ((= \frac{0.1}{1+0.857}))</td>
</tr>
<tr>
<td>8)</td>
<td>( \text{CL} = \text{Q} \times \text{ER} )</td>
<td>L/min</td>
<td>0.9 (0.9 x 1)</td>
<td>1.29 (0.857 x 1.5)</td>
</tr>
<tr>
<td>9)</td>
<td>Hepatic elimination rate = Rd x ER (= CL x C)</td>
<td>mg/min</td>
<td>90 (100 x 0.9)</td>
<td>129 (150 x 0.857)</td>
</tr>
<tr>
<td>10)</td>
<td>Systemic absorption rate = Rd x (1-ER) = 6) – 9)</td>
<td>mg/min</td>
<td>10 (100 x 0.1)</td>
<td>21 (150 x 0.143)</td>
</tr>
<tr>
<td>11)</td>
<td>Absorbed amount = (10) x 4)</td>
<td>mg</td>
<td>150</td>
<td>214.5</td>
</tr>
<tr>
<td>12)</td>
<td>Bioavailability ( F = 11) \times 3) = 1 – ER</td>
<td>%</td>
<td>10</td>
<td>14.3 (43% ( \uparrow ))</td>
</tr>
<tr>
<td>13)</td>
<td>Clearance relative to blood flow ( (\text{CL}/Q_h) = \text{ER} )</td>
<td></td>
<td>0.9</td>
<td>0.857</td>
</tr>
</tbody>
</table>

Concentrations in the portal blood, while absorption was underway, were identical (100 mg/L) regardless of the \( Q_h \) change. Thus, the oral dose (1500 mg) is completely delivered to the liver in 15 or 10 min.

When you carefully read the equations in the Table 1 row by row, you may conclude that the increased \( F \) by the increased \( CL_{int} \) is a reasonable conclusion, not a paradox.

However, the question may remain – “What caused such a seemingly paradoxical phenomenon?” Although no mistake was found in the equations in Table 1, this simultaneous increase in \( F \) and \( CL_{int} \) is not easily acceptable using the common sense of pharmacokinetics.

A clue to resolve this confusion may be found in the extraction ratio \( \text{ER} = \text{CL}/Q_h \) in Table 1. The question “why does increased \( CL \) increase \( F \)” is better rewritten as “why does increased \( CL \) decrease \( \text{ER}? \)” to focus our topic: see how the \( \text{ER} \), or the ratio \( \text{CL}/Q_h \), differs by \( Q_h \) – the difference seems trivial (0.9 and 0.857). However, this clearly shows that the fraction of portal blood flow that escapes (by shunt or whatever mechanism) clearing by the liver enzymes increased by 43% (from 0.1 to 0.143). If the \( \text{CL}/Q_h \) were unity, 100% of the portal blood entering the liver would be cleared of the drug dissolved in it and the \( F \) would be 0, that makes the drug inappropriate for oral use. In real world settings, the \( \text{CL}/Q_h \) ratios for orally administered extensively metabolized drugs are near, but less than 1. The fraction of drug molecules escaping the first pass effect has always been > 0, albeit it may be rather small. When \( Q_h \) increases, the \( CL \) also increases, but at a slightly lower degree than the \( Q_h \) did and this ‘slight’ difference results in a ‘substantial’ increase in the \( F \). This relationship is more clearly demonstrated in Fig. 1. The relationship between \( CL \) and \( Q_h \) shown in Fig. 1 holds without regard to the absorption kinetics, i.e., first-order, zero-order, or otherwise.

In any case, we find that the increase in \( CL \) increased the amount of drug eliminated per unit time (row 9 in Table 1), but it was not sufficient to completely counterbalance the accelerated entry of drug to the liver and keep the \( \text{ER} \) as it was (0.9). In other words, accelerated absorption (\( Q_h \uparrow \)) caused accelerated elimination (\( CL \uparrow \)), but the degree of \( CL \uparrow \) was not exactly equal to that of \( Q_h \uparrow \).

An analogy of brown bears hunting salmon may help students who are not completely satisfied with the explanation above (let us put aside the fact that the salmon swim against the flow, unlike drug molecules). That is, say 1500 salmon (instead of 1500 mg of drug A) are swimming upward to their spawning ground (Fig. 1). At a waterfall along their way, they jump up at a rate of 100 salmon per minute. Bears waiting at the waterfall catch 90 of them every minute and only 10 salmon (10%) make it to their destination. Ultimately, 150 out of 1500 salmon will survive. In the case where the salmon accelerate their jumping rate to 150 salmon/min as if employing the ‘salmon-wave attack’, the bears will be able to catch more salmon (129 salmon) every minute by the equation 1, but more (21 salmon, 14.3% of 150) will escape thanks to the ‘salmon-wave’ tactics – more salmon are caught by bears per minute, but more escape! Ultimately, 210 of the 1500 salmon survived by the time all of the 1500 salmon finished jumping up the waterfall of the ‘liver’. That is how the increased \( CL \) (90 to 121 salmon/min) caused increased \( F \) This is also mentioned in the textbook as the decrease in the time drug spends in the liver.[2]

What happens to the AUCs in the scenario?

If the increased \( Q_h \) remains as is (1.5 L/min) until the absorbed drug A is almost completely eliminated, the AUC will
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be calculated as: $AUC_{QH} = dose \times F/CL = 1500 \times 0.143/1.286 = 1166 \text{ mg/L min}$, identical to the $AUC_{\text{baseline}} = dose/CL = 1500 \times 0.1/0.9 = 167 \text{ mg/L min}$. However, it is not common for the $Q_H$ to remain increased, rather, it generally returns to its baseline at some time after the meal when the $Q_H$ is increased by the effect of the meal. In that case, because the CL also returns to the baseline, the effect of increased $F$ may result in increased $AUC$ (Fig. 2). This is clearly demonstrated in a previous PK report of oral and i.v. propranolol (a high extraction ratio drug) given under fasted and fed conditions.[3]

What happens to the AUCs when the scenario uses an i.v. route instead of oral?

The answer is simple: $AUC_{\text{i.v.QH}} = dose/CL = 1500/1.286 = 1166 \text{ mg/L min}$, compared with the $AUC_{\text{i.v.baseline}} = dose/CL = 1500/1.286 = 1166 \text{ mg/L min}$.

Figure 1. Analogy of salmon hunting.
The high-extraction ratio drug A in our scenario was illustrated as salmon and hepatic enzymes eliminating the drug as brown bears catching the salmon. A fish symbol in the figure roughly represents 10 salmon (= 10 mg of drug A). A) number of survivors: 150 (10 escaped salmon/min x 15 min jumping), B) number of survivors: 210 (21 escaped salmon/min x 10 min jumping).

Figure 2. PK profile changes by hepatic blood flow changes in a drug with high-extraction ratio (Drug A in our scenario).
1500/0.9 = 1667 mg/L·min. The difference in AUCs is obvious in the case of i.v. dosing because the seemingly paradoxical increase in F is not involved (Fig. 2).

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Conflict of interest
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References