PHA 5127 Dose Optimization I

Case Study III

1. Drug A has an intrinsic clearance of 80,000 L/h and bioavailability of 1%. Drug B has 2% extraction ratio. If fraction of drug unbound in plasma reduces to half for both drugs, what change do you expect in the extraction ratio and oral bioavailability?

For Drug A, F=0.01, E=1-0.01=0.99, drug A is high extraction drug.

$F = \frac{Q_H}{Q_H + f_u * CL_{int}}$, for high extraction drug, $f_u * CL_{int} \gg Q_H$, $F = \frac{Q_H}{f_u * CL_{in}}$=0.01,

If fu'=fu*0.5, F'=0.02, E'=1-0.02=0.98

F: from 0.01 to 0.02; E: from 0.99 to 0.98

For high extraction drug, 50% decrease of fraction unbound in plasma will double the bioavailability but change of extraction ratio is little.

For Drug B, E=0.02, F=1-0.02=0.98, drug B is low extraction drug.

$E = \frac{f_u * CL_{int}}{Q_H + f_u * CL_{int}}$, for low extraction drug, $f_u * CL_{int} \ll Q_H, E = \frac{f_u * CL_{int}}{Q_H}$=0.02,

If fu'=fu*0.5, E'=0.01, F'=1-0.01=0.99

F: from 0.98 to 0.99; E: from 0.02 to 0.01

For low extraction drug, 50% decrease of fraction unbound in plasma will reduce extraction ratio by 50%, but change of bioavailability is little.

2. Patient 1 and 2 received a drug as an iv bolus injection at the same dose of 40mg. Pharmacokinetic and physiological parameters for two patients were calculated and shown in Table 1. (Assume liver blood flow is 80 L/h and drug is cleared only by hepatic metabolism.)

	Patient 1	Patient 2
C_0 (μg/ml)	0.5	0.5
fu	0.4	0.8
Vp (L)	3	3
VT(L)	38	38
AUC (μg/ml*h)	5	2.5
Ke (L/h)	0.1	0.2

The next table shows the parameters estimated from pharmacokinetc analysis.

Please circle the correct options in the column of patient 2 for each parameter whether the parameter CL, Vd, extraction ratio (E) and fraction of the drug unbound in tissue (fuT) will be larger (A), about the same (B), or will be smaller (C) than those estimates observed in Patient 1.

	Patient 1	Patient 2
Vd (L)	80	Larger (A), About the same (B), Smaller (C)
CL (L/h)	8	Larger (A), About the same (B), Smaller (C)
E	0.1	Larger (A), About the same (B), Smaller (C)
fuT	0.2	Larger (A), About the same (B), Smaller (C)

3. TRUE (T) or FALSE (F)

(1) If the volume of distribution increases, the clearance will always remain the same.

T F

(2) A drug with a large volume of distribution is likely to have a narrow therapeutic window.

T F

(3) A drug with a hepatic clearance of 0.15 L/min in healthy subjects with an average liver blood flow of 1.5 L/min. The expected hepatic clearance in a congestive heart failure patient with a liver blood flow of 1.1L/min but no change in other factors will be still close to 0.15 L/min.

T F