PHA 5127 Dose Optimization I

Case Study II

1. Patient 1 and 2 received a drug as an iv bolus injection. Pharmacokinetic and physiological characteristics, such as dose, fraction of the drug unbound in plasma and tissue, and volume of plasma and volume of the tissue water in these patients are shown below. **(Assuming other condistions are same between these two patients)**

Table1: Input parameters

	Patient 1	Patient 2
Dose (mg)	40	40
fu	0.9	0.2
fuT	0.3	0.5
Vp (L)	3	3
VT(L)	38	38

The next table shows the resulting pharmacokinetic parameters in Patient 1.

Please circle the correct options in the column of patient 2 for each parameter whether the parameter Vd, Peak concentration of free drug, CL, Ke, $t_{1/2}$, AUC will be larger (A), about the same (B), or will be smaller (C) than those estimates observed in Patient 1.

Table2: Output parameters

	Patient 1	Patient 2
Vd (L)	117	Larger (A), About the same (B), Smaller (C)
Free Peak (μg/ml)	0.3	Larger (A), About the same (B), Smaller (C)
CL (L/h)	89	Larger (A), About the same (B), Smaller (C)
Ke (1/h)	0.76	Larger (A), About the same (B), Smaller (C)
$t_{1/2}$ (h)	1	Larger (A), About the same (B), Smaller (C)
AUC (μg/ml*h)	0.449	Larger (A), About the same (B), Smaller (C)

2. Please caculate how many $t_{1/2}$ does it take to get rid of more than 95% of drug out of body?

Solution A:

$X = X_0 * e^{-k*t}, \quad X \leq 0.05X_0$

$e^{-k*t} \leq 0.05, \quad -k*t \leq ln0.05 = -2.996, \quad k*t \geq 2.996$

$k = \frac{0.693}{t_{1/2}}, \quad t = n * t_{1/2}$

$\frac{0.693}{t_{1/2}} * n * t_{\frac{1}{2}} = 0.693 * n \geq 2.996, \quad n \geq 4.323$

Solution B:

100%→50%→25%→12.5%→6.25%→3.125%

So it takes 5 half life to get rid of more than 95% of drug out of body.

3. TRUE (T) or FALSE (F)

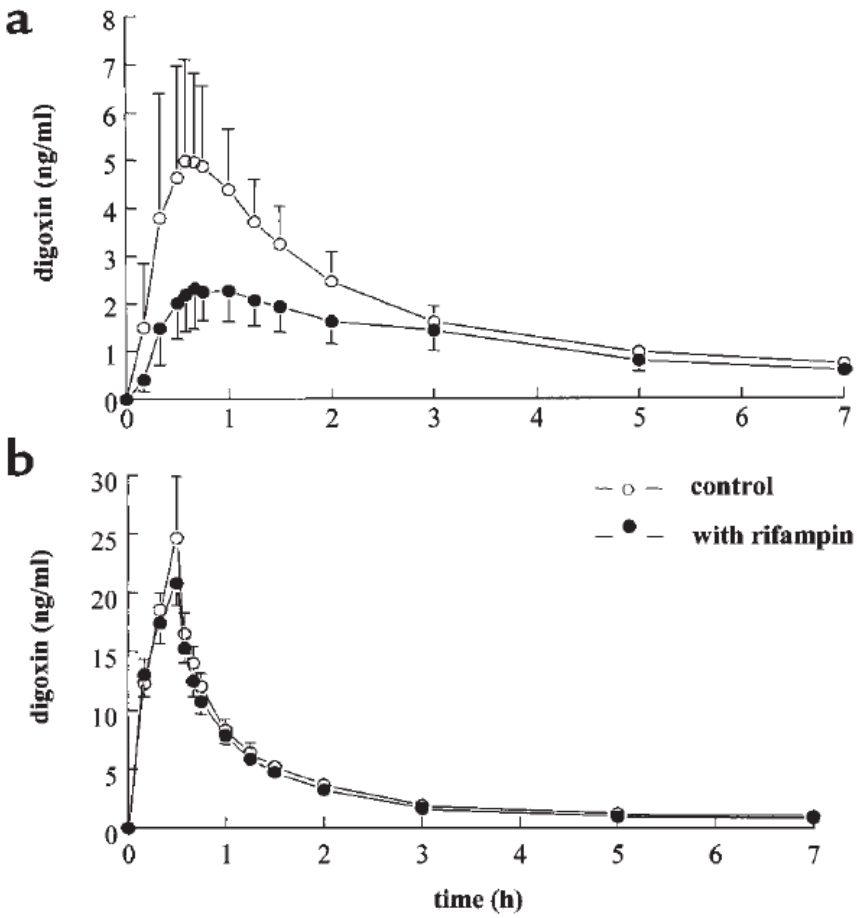
(1) The same drug was given to two patients and their elimination half life is 6h and 9h. The dose should be increased in the patient with half life of 9h.

T F

(2) It is impossible for drug to cross the membrane against concentration ingredient.

T F

4. A clinical study was conducted to investigate interaction between digoxin and rifampin. Researchers compared single-dose (1mg oral and 1mg intraveous) pharmacokinetics of digoxin before and after coadministration of rifampin in volunteers. The AUC of oral digoxin (shown in figure a) was significantly lower during rifampin treatment; the effect was less pronounced after intravenous administration of digoxin (shown in firgure b). Clearance and half life of digoxin were not altered by rifampin. Digoxin has been identified as a substrate of intestinal P-glycoprotein (P-gp) and rifampin can induce the intestinal P-pg expression. Please explain the observation.



The pharmacokinetic consequences of this interaction are explained by a transporter-based mechanism. After absorption into the enterocyte, digoxin was pumped back into the lumen via P-gp, so digoxin AUC after oral administration was reduced greatly, especially during the first 3 hours. As more and more drug was absorbed, concentrations after 3h between intravenous and oral administraton were very close. Digoxin plasma concentration after intraveous administration was less affected by rifampin, as only a minor fraction of the dose will reach the enterocytes.