

PHA 5127 Dose Optimization I

Homework III (10 points)

Due on Friday, 09/24/2010

1. A patient was given 800mg of a high extraction drug as an IV bolus injection and plasma concentration dropped from peak concentration of 2 mg/L with a rate constant of 0.2 h^{-1} . (4 point)

(1) Estimate the hepatic clearance and AUC_{∞} . (Assume there are only hepatic and renal clearance, and renal clearance of this patient is 8L/h)

$$V_d = \frac{Dose}{C_0} = \frac{800}{2} = 400L$$

$$CL = V_d * K_e = 400 * 0.2 = 80 \text{ L/h} \quad (0.5 \text{ point})$$

$$CL_{hep} = CL - CL_{ren} = 80 - 8 = 72 \text{ L/h} \quad (0.5 \text{ point})$$

$$AUC_{\infty} = \frac{Dose}{CL} = \frac{800}{80} = 10 \text{ mg} * \text{h/L} \quad (1 \text{ point})$$

(2) If the fraction unbound in plasma increases two fold, please determine the oral bioavailability of this drug. (Assume the liver blood flow of this patient is 80L/h and there is no other physiological change.)

$$CL_{hep} = Q_H * E, \quad E = \frac{CL_{hep}}{Q_H} = \frac{72}{80} = 0.9 \quad (0.5 \text{ point})$$

$$F = 1 - E = 0.1 \quad (0.5 \text{ point})$$

$$\text{For high extraction drug, } F \approx \frac{Q_H}{f_u * CL_{int}} \quad (0.5 \text{ point})$$

$$\text{If } f'_u = 2 * f_u, \quad F' = 0.5 * F = 0.05 \quad (0.5 \text{ point})$$

So the oral bioavailability of this drug is 5%.

2. Please predict changes on the pharmacokinetic parameters for a drug that is eliminated only through hepatic clearance after physiological changes happen (\uparrow , \downarrow , \leftrightarrow indicate increase, decrease and same): (0.25 point for each, 6 point)

Scenarios	High extraction drug			Low extraction drug		
	CL	F	$t_{1/2}$	CL	F	$t_{1/2}$
Increase in plasma protein binding	\leftrightarrow	\uparrow	\downarrow	\downarrow	\leftrightarrow	N/A
Increase in tissue binding	\leftrightarrow	\leftrightarrow	\uparrow	\leftrightarrow	\leftrightarrow	\uparrow
Increase in liver blood flow	\uparrow	\uparrow	\downarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow
Decrease in liver enzyme activity	\leftrightarrow	\uparrow	\leftrightarrow	\downarrow	\leftrightarrow	\downarrow