

PHA 5127 Dose Optimization I

Case Study III

1. A patient was given 200mg of a low extraction drug as an IV bolus injection and plasma concentration was monitored up to 72h. From concentration time profile, AUC_{∞} was estimated to be 18.18mg*h/L

(1) Estimate the renal clearance of this drug. (Assume there are only hepatic and renal clearance, and hepatic clearance of this patient is 10L/h)

$$CL = \frac{Dose}{AUC_{\infty}} = \frac{200}{18.18} \approx 11L/h$$
$$CL_{ren} = CL - CL_{hep} = 11 - 10 = 1 L/h$$

(2) If this drug is given to the other patient with liver function disease (half the normal function), please decide the given dose to this patient if we want to get same drug exposure (AUC_{∞}) as last patient. (Assume renal clearance of this patient is same as last patient)

$$CL_{hep} = f_u * CL_{int} = 10 L/h, \quad CL'_{int} = 0.5 * CL_{int}$$
$$CL'_{hep} = 0.5 * CL_{hep} = 5 L/h$$
$$CL' = CL'_{hep} + CL_{ren} = 5 + 1 = 6L/h$$
$$Dose' = CL' * AUC_{\infty} = 6 * 18.18 \approx 109 mg$$

So in order to reach same drug exposure, we need to give 109mg to this patient.

2. If the plasma protein binding increases by 50%, what changes (in percentage) you would expect in the extraction ratio and oral bioavailability of a) high extraction drug with 1% bioavailability and b) low extraction drug with 2% extraction ratio.

For high extraction drug, $F = \frac{Q_H}{f_u * CL_{int}} = 0.01$, $E_H = 1 - 0.01 = 0.99$

If $f_u' = 0.5f_u$, $F' = 0.02$, $E = 0.98$

So extraction ratio decreases only 1%, but bioavailability increases by 100%

For low extraction drug, $E_H = \frac{f_u * CL_{int}}{Q_H} = 0.02$, $F_H = 1 - 0.02 = 0.98$

If $f_u' = 0.5f_u$, $E'_H = 0.01$, $F' = 0.99$

So extraction ratio decreases 100%, but bioavailability increases by only 1%

3. Please categorize the following properties into A, B, C or D

A. High extraction drug; B. Low extraction drug; C. Both; D. Neither

Enzymes can metabolize both free drug and bound drug ___A___

Extraction ratio increases with reduced blood flow ___B___

Hepatic clearance will stay the same if the blood flow is reduced ___B___

Rate of extraction increases with increase in concentration of drug getting into liver ___C___

Hepatic clearance can be very close to liver blood flow ___A___

Diffusion of free drug into hepatocytes is important to hepatic clearance ___C___

4. TRUE (T) or FALSE (F)

1. Increase in liver blood flow can increase the clearance of low extraction drug based on equation $CL = Q * E$

T F

2. Liver enzyme inducers will increase oral bioavailability of a low extraction drug.

T F

3. For a drug with linear pharmacokinetics, clearance is proportional to the dose given

T F

4. For a high extraction drug that has predominant hepatic metabolism, the liver blood flow is a rate limiting step in its clearance.

T F