Answers Case Study 2
PHA 5127
Fall 2005

Question 1:

An 50-year-old, male patient was admitted to hospital with gram-negative pneumonia infection, and was given an iv bolus of drug X. (200 mg). The drug concentrations at 2hr and 12hr after initial dose were reported as 7.1mg/L and 1.3mg/L. Assuming the drug follows one compartment body model with first-order elimination, please calculate the total Cl, AUC $_{0-\infty}$, Vd, $t_{1/2}$ for drug X.

Answer:

ke = ln (C_2/ C_1)/ ($t_1 - t_2$) = ln (1.3/7.1) / (2-12) = (-1.7) / (-10) = 0.17 /hr
$t_{1/2}$ = 0.693/0.17= 4.1hr
drug concentration at time zero: $C_0 = C_1 * \exp (ke * t) = 7.1 * \exp (0.17 * 2) = 10$mg/L
vd = Dose / C_0 = 200 / 10 = 20 L
Cl = ke * Vd = 0.17 * 20 = 3.4 L/hr
AUC $_{0-\infty}$ = Dose / Cl = 200/ 3.4 = 58.8 mg*hr/L

Question 2:

70-90% of quinidine is bound to plasma albumin and alpha-1-acid glycoprotein.
In patients with chronic liver disease plasma protein binding is decreased by 20%. How will the volume of distribution change? Use a plasma volume of 3 L and the fraction bound in plasma 80% (for normal patients), a tissue volume of 38 L and the fraction unbound in tissue 80% to calculate the volume of distribution in patients with liver disease.

Answer:

Vd = Vp + Vt * fu / fu_T
For patients with liver disease, only fu increase, all the other factors remain unchanged, as we can see from the equation, the Vd will increase.

0.8 * 0.8 = 0.64
fu = 1-0.64= 0.36 > normal patients' 20% free fraction
Vd = 3 + 38 * 0.36/0.8 =20.1 L

Question 3:

Researchers recently found out that grape fruit juice is CYP3A4 inhibitor. When taking together with grape fruit juice, the intrinsic hepatic clearance (CL int) of drug B is decreased by 20%. Main pharmacokinetic parameters of drug B were listed as following: Hepatic clearance (WITHOUT taking grape fruit juice), CL hep = 10 L / hr. Fraction unbound: fu = 0.4. Please calculate what is the new hepatic clearance, when drug B is taking together with grape fruit juice. Assume the hepatic blood flow is 90 L / hr.

Answer:

First, calculate the original CL int.

$CL = (Q_H * fu * CLint) / (Q_H + fu * CLint)$

$CL = (90 * 0.4 * CLint) / (90 + 0.4* CLint) = 10$

$CLint = 28.125 = 28.1$ L/ hr

Then, calculate the new CL hep.

$CL = (Q_H * fu * CLint) / (Q_H + fu * CLint) = 90 * 0.4 * 28.1 * 0.8 / (90 + 0.4 * 28.1 * 0.8) = 90 * 8.992 / (90 + 8.992) =$ 8.2 L/hr

Question 4:

Please answer the following questions with true or false:

a) for high extraction drugs:

1) In case of a increasing fraction unbound, the extraction ratio of the drug stays the same,

Answer:

TRUE, for high extraction drugs, $E \approx 1$, independent on fraction unbound

2) In case of increased hepatic blood flow, the clearance stays the same

Answer:

FALSE : for high extraction drugs , $CL_{hep} = E * Q \approx Q$, when Q increase, CL_{hep} increases

b) for low extraction drugs:

1) In case of increasing fraction unbound, the extraction ratio of the drug stays the same,

Answer:

FALSE: for low extraction drugs, $E \approx Cl_{int} * fu / Q$, when fu increase, E increases

2) In case increasing hepatic blood flow, the clearance of the drug stays the same.

Answer:

TRUE: for low extraction drugs, $Cl_{hep} \approx Cl_{int} * fu$, independent of liver blood flow

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