PHA 5127 Dose Optimization I, Fall 2012, Case Study V Solution

If you have any questions regarding this case study, do not hesitate to contact Benjamin Weber (benjaminweber@ufl.edu). Please remember that attendance of the case study lecture is mandatory.

Problem 1

For the following situations, indicate whether the drug is: filtered, reabsorbed (if fully or if reabsorbed through transporters), or actively secrete. Assume that the GFR is 130mL/min and that the urine flow is 1.5mL/min.

1. Drug with f_u= 0.3 and a Cl_{ren}=39mL/min

   f_u*GFR=0.3*130mL/min=39mL/min

   Cl_{ren}= f_u*GFR → filtered

2. Drug with f_u=0.6 and a Cl_{ren}=30mL/min

   f_u*GFR=0.6*130mL/min=78mL/min

   Cl_{ren} < fu* GFR → reabsorbed

   f_u*urine flow=0.6*1.5mL/min=0.9mL/min

   (Cl_{ren}>f_u*urine flow) → not fully reabsorbed

3. Drug with f_u=0.05 and a Cl_{ren}=15mL/min

   f_u*GFR=0.05*130mL/min=6.5mL/min

   Cl_{ren}>fu* GFR → actively secreted

4. Drug with f_u=0.2 and a Cl_{ren}=0.3mL/min

   f_u*GFR=0.2*130mL/min=26mL/min

   Cl_{ren}<fu* GFR → reabsorbed

   f_u*urine flow=0.2*1.5mL/min=0.3mL/min

   Cl_{ren}=f_u*urine flow → fully reabsorbed

5. Drug with f_u=0.8 and a Cl_{ren}=0.3mL/min

   f_u*GFR=0.8*130mL/min=104mL/min

   Cl_{ren}<f_u* GFR → reabsorbed

   f_u*urine flow=0.8*1.5mL/min=1.2mL/min

   Cl_{ren}<f_u*urine flow → reabsorbed through transporters

Problem 2

T.T. (male, 6'3'' tall, 111 kg, 24 years old) shows a serum creatinine level of 1.3 mg/dL.

a) Use the Cockcroft-Gault-Equation to calculate his creatinine clearance and glomerular filtration rate (GFR). Comment on the renal function of T.T.?

$$\boldsymbol{IBW_{male} = 50kg + 2.3kg * 15 = 84.5kg}$$

$$\boldsymbol{TBW = 111kg} > IBW * 120\% = 84.5\boldsymbol{kg} * \boldsymbol{120\%} = \boldsymbol{101.4kg}$$

Thus, use ABW is Cockcroft-Gault-Equation.

$$\boldsymbol{ABW = IBW + 0.4 * (TBW - IBW) = 84.5kg + 0.4 * (111kg - 84.5kg) = 95.1kg}$$

$$\boldsymbol{CrCL_{male,obese} = \frac{(140 - age) * ABW}{72 * [Creatinine\ (Serum)]} =}$$

$$\boldsymbol{\frac{(140 - 24) * 95.1kg}{72 * \left[1.3\frac{mg}{dL}\right]} = 117.9\frac{mL}{min} = GFR}$$

The calculated (observed) GFR is close to the maximum GFR of 130 ml/min. Thus, the renal function of T.T. seems to be normal.

b) Why do we use the creatinine clearance to estimate the GFR?

- **Creatinine is mainly eliminated by renal processes**
- **Creatinine is cleared by glomerular filtration only**
  - **No active tubular secretion**
  - **No tubular reabsorption**
- **No plasma protein binding**

c) Drug A shows a plasma protein binding and tissue protein binding of 10% and 95%, respectively. Drug A is eliminated by hepatic (80%) and renal processes (20%). Calculate the total systemic clearance of drug A (in L/h) when administered to T.T.Assume that the drug is neither actively secreted nor reabsorbed.

$$\boldsymbol{CL_{ren} = f_u * GFR = 0.9 * 117.9\frac{mL}{min} = 106.1\frac{mL}{min} = 6.36\frac{L}{h}}$$

$$\boldsymbol{CL_{Total} = CL_{ren} + CL_{hep} = 6.36\frac{L}{h} + CL_{hep} = 6.36\frac{L}{h} + 0.8 * CL_{Total} =}$$

$$\boldsymbol{CL_{Total}(1 - 0.8) = 6.36\frac{L}{h}}$$

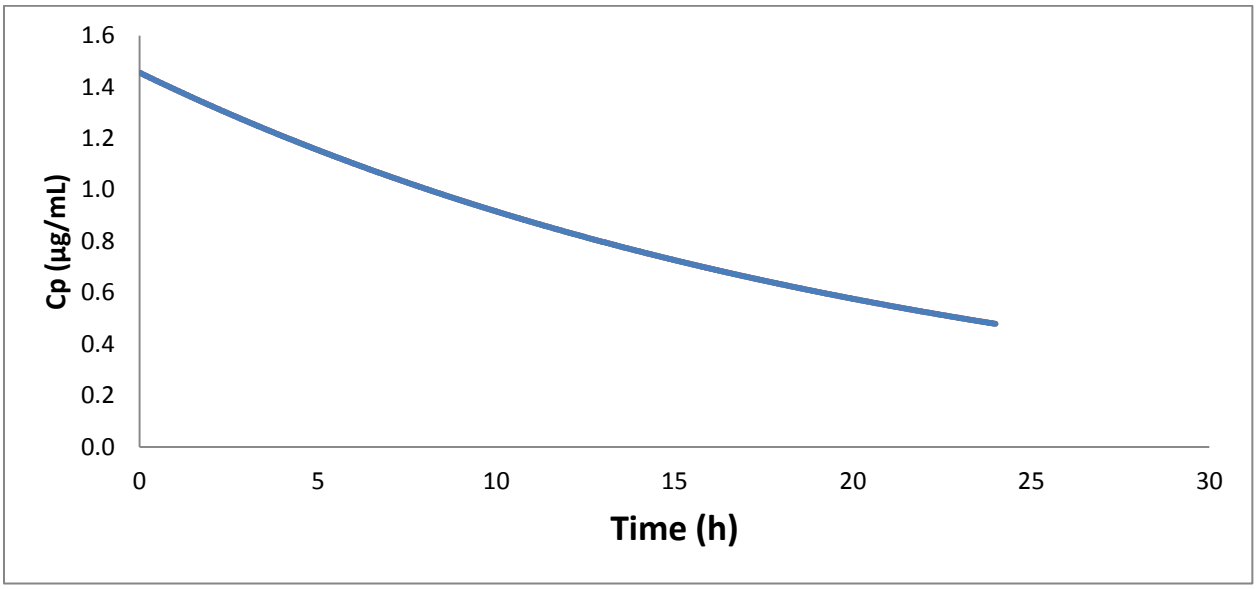
$$\boldsymbol{CL_{Total} = \frac{6.36\frac{L}{h}}{0.2} = 31.8\frac{L}{h}}$$

d) Graph the plasma-concentration time profile for the first 24 hours when 1000mg of drug A are administered to T.T. via an IV bolus injection. Assume that the drug is immediately distributed throughout the body, crosses membranes easily, and that all elimination processes are first-order processes.

$$\boldsymbol{Vd = 3L + 38L * \frac{f_u}{f_{u,T}} = 3L + 38L * \frac{0.9}{0.05} = 687L}$$

$$\boldsymbol{k_e = \frac{31.8 \frac{L}{h}}{687L} = 0.0463 \frac{1}{h}}$$

$$\boldsymbol{C(t) = \frac{Dose}{VD} * e^{-k_e * t} = \frac{1000mg}{687L} * e^{-0.0463 * t}}$$



Problem 3

Which properties does a drug need to have in order to demonstrate the following? Explain briefly.

a) Active tubular secretion
b) Glomerula secretion
c) Passive tubular reabsorption

Active tubular secretion: As active transporters are mainly anionic or cationic transporters, drugs which are actively secreted must be bases or acids.

Glomerula filtration: Drugs which are filtrated must fall below a certain molecular weight size. I.e. proteins are not filtrated in the glomerulus because of their large molecular weight.

Passive tubular reabsorption: Neutral lipophilic drugs are reabsorbed easily. Passive tubular reabsorption of bases or acids depends on the pH of the urine. Hydrophilic drugs tend not be reabsorbed extensively.

Problem 4

TRUE (T) or FALSE (F)

For a high extraction drug, liver blood flow is important to both hepatic clearance and oral bioavailability.

T F

For low extraction drug, f_u (fraction of unbound drug in plasma) is important to both hepatic clearance and oral bioavailability.

T **F**

Basic drugs that are polar in their unionized form, the extent of re-absorption depends on the degree of its ionization.

T **F**

Secretion is indicated when renal clearance is larger than GFR*f_u.

T F

It is possible for renal clearance to be close to the kidney blood flow.

T F

Assuming no plasma protein binding, the renal clearance equals the urine flow when full reabsorption occurs.

T F