PHA 5127 Dose Optimization I
Case Study IV Solution

Problem 1

A female patient (6'0'' tall, 65.5 kg, 35 years old) shows a serum creatinine level of 1.1 mg/dL.

a) Use the Cockcroft-Gault-Equation to calculate her creatinine clearance and glomerular filtration rate (GFR).

$$\boldsymbol{IBW_{female} = 45.5kg + 2.3 * 12 = 73.1kg}$$

$$\boldsymbol{TBW = 65.5kg} < IBW = 73.1\boldsymbol{kg}$$

Thus, use TBW is Cockcroft-Gault-Equation.

$$\boldsymbol{CrCL_{female} = 0.85\frac{(140 - 35) * 65.5}{72 * 1.1} = 73.8\frac{mL}{min} = GFR}$$

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

- **Mainly eliminated by renal processes**
- **Only glomerular filtration**
  - **No active tubular secretion**
  - **No tubular reabsorption**
- **No plasma protein binding**

c) Drug A shows a plasma protein binding and tissue protein binding of 20% and 30%, respectively. Drug A is eliminated by hepatic (20%) and renal processes (80%). Calculate the total systemic clearance of drug A (in L/h) when administered to the patient. Assume that the drug is neither actively secreted nor reabsorbed.

$$\boldsymbol{CL_{ren} = 0.8 * 73.8\frac{mL}{min} = 59\frac{mL}{min} = 3.54\frac{L}{h}}$$

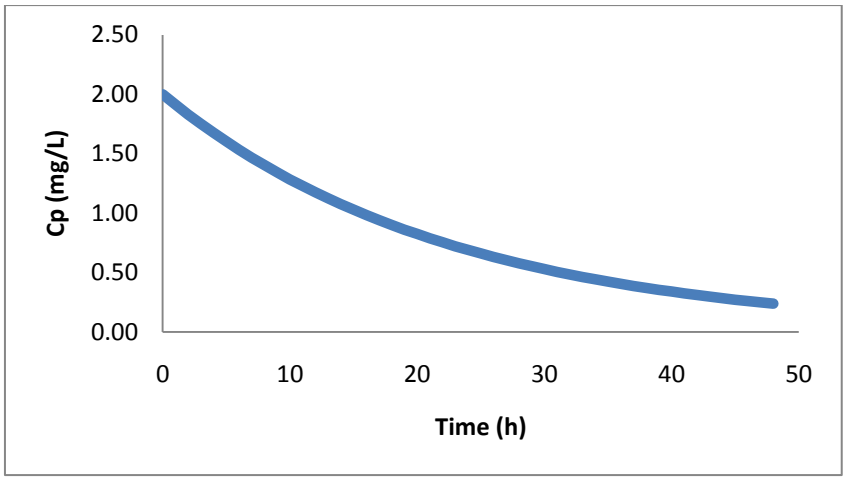
$$\boldsymbol{CL_{Total} = \frac{3.54\frac{L}{h}}{0.8} = 4.43\frac{L}{h}}$$

d) Graph the plasma-concentration time profile for the first 48 hours when 200mg of drug A are administered to the patient via IV bolus injection. A blood sample taken at the time of injection showed a plasma concentration of 2mg/L. Assume that the drug is immediately distributed throughout the body and that all elimination processes are first-order processes.

$$\boldsymbol{Vd = \frac{Dose}{C_0} = \frac{200mg}{2\frac{mg}{L}} = 100L}$$

$$k_e = \frac{4.43\frac{L}{h}}{100L} = 0.0443\frac{1}{h}$$

$$C(t) = 2\frac{mg}{L}e^{-0.043\frac{1}{h}*t}$$



Problem 2

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 3

Sketch the relationship between the following PK metrics and Dose for linear and non-linear pharmacokinetics.

a) CL vs. Dose
b) Vd vs. Dose
c) AUC vs. Dose
d) K_e vs. Dose