PHA5128 – Dose Optimization II
Case Study 2
Spring 2014

True or False

(1) For hydrophilic drugs, obesity would increase the volume of distribution in most cases. (F)

(2) Octanol/water lipid partition coefficient (LPC) is used to measure lipophilicity of a drug or compound. Drugs with higher LPC value tend to distribute in the adipose tissue, resulting in lower volume of distribution in obese patients. (F)

(3) An individual is considered obese when the body fat content is greater than 25% and 30% of total body weight (for men and women, respectively). (T)

(4) Body weight is a primary covariate of volume and clearance and is often referenced to a 70-kg person with allometry using a coefficient of 0.75 for clearance and 1 for volume of distribution. (T)

(5) Interspecies scaling principles, including physiologically based pharmacokinetic models and allometric scaled models, can be used for extrapolation of pediatric dosage regimens. (T)

(6) The modification of diet in renal disease (MDRD) method for estimating glomerular filtration rate (eGFR) is less accurate than the Cockcroft-Gault method in older and obese individuals. (F)

Compute the body surface area using the estimation based on body weight and the DuBois formula, as well as the creatinine clearance using the Cockcroft-Gault equation:

(1) Male, 45 years of age, 6'1" in height, 175 lbs in weight with a serum creatinine of 1.4 mg/dL

$$BSA = \left(\frac{TBW}{70}\right)^{0.7} \cdot 1.73 = \left(\frac{175 * 0.455}{70}\right)^{0.7} \cdot 1.73 = 1.89\, m^2$$

$$BSA = 0.007184 * TBW^{0.425} \cdot height^{0.725} = 0.007184 * \left(\frac{175}{2.2}\right)^{0.425} (73 * 2.54)^{0.725}$$
$$= 2.03\, m^2$$

$$IBW_{male} = 50 + 2.3(73 - 60) = 80\, kg$$

$$TBW = \frac{175}{2.2} = 79.5\, kg \sim IBW$$

$$CL_{cr} = \frac{(140 - age)BW}{72 \cdot SCr} = \frac{(140 - 45) \cdot 79.5}{72(1.4)} = 75\, mL/min$$

(2) Female, 64 years of age, 5'8" in height, 180 lbs in weight with a serum creatinine of 2.1 mg/dL

$$BSA = \left(\frac{TBW}{70}\right)^{0.7} \cdot 1.73 = \left(\frac{180 * 0.455}{70}\right)^{0.7} \cdot 1.73 = 1.93\, m^2$$

$$BSA = 0.007184 * TBW^{0.425} \cdot height^{0.725} = 0.007184 * \left(\frac{180}{2.2}\right)^{0.425} (68 * 2.54)^{0.725}$$
$$= 1.96\, m^2$$

$$IBW_{female} = 45 + 2.3(68 - 60) = 63.4\, kg$$

$$TBW = \frac{180}{2.2} = 82\, kg > 120\%\ of\ IBW$$

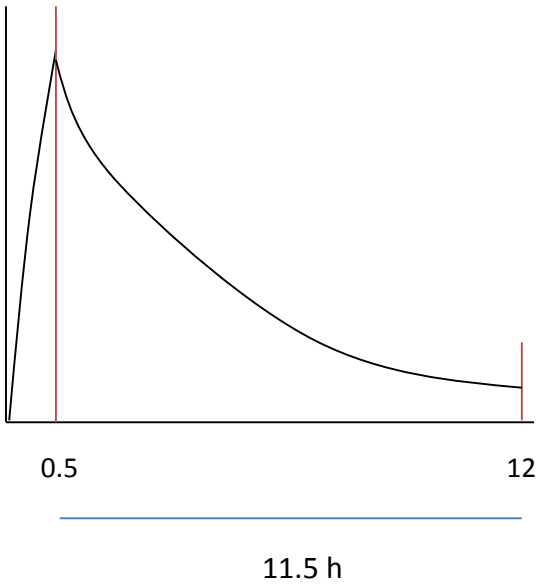
$$ABW = IBW + 0.4(TBW - IBW) = 63.4 + 0.4\left(\frac{180}{2.2} - 63.4\right) = 70.8\, kg$$

$$CL_{cr} = \frac{(140 - age)BW}{72 \cdot SCr} \cdot 0.85 = 0.85 \times \frac{(140 - 64) \cdot 70.8}{72(2.1)} = 39\, mL/min$$

Compute the eGFR using the MDRD method. The patient characteristics are: Female, African American, 56 years of age, 90 lbs in weight, with serum creatinine of 1.1 mg/dL.

$$eGFR = 175 \cdot SCr^{-1.154} age^{-0.203} \cdot 0.742(if\ female) \cdot 1.212(if\ African\ American)$$
$$= 175 \cdot 1.1^{-1.154} 56^{-0.203} \cdot 0.742 \cdot 1.212 = 62 \frac{ml}{min}\ per\ 1.73\ m^2$$

A male patient is treated with 700 mg amikacin via IV infusion for 30 min twice-daily for several days. Assuming that steady-state is achieved, his plasma drug concentration was 20 mg/L at 1 hour after stopping infusion and 2 mg/L immediately prior to the next infusion. The patient has a body weight of 142 kg, and 195 cm in height, compute the clearance of amikacin in this patient.



$$k_e = -\frac{\ln(20) - \ln(2)}{1 - 11.5} = 0.22\ h^{-1}$$

$$Cp_{max} = \frac{20}{\exp(-0.22 * 1)} = 25\ mg/L$$

$$V_d = \frac{Dose}{k_e T} \cdot \frac{(1 - e^{-k_e T})}{Cp_{max} - (Cp_{min})e^{-k_e T}} = \frac{700}{0.22 * 0.5} \cdot \frac{1 - \exp(-0.22 * 0.5)}{25 - 2\exp(-0.22 * 0.5)} = 28.6\ L$$

Alternatively, the volume of distribution for amikacin

$$IBW_{male} = 50 + 0.9(195 - 150) = 90.5\ kg$$

$$TBW = 142\ kg$$

Volume of distribution of amikacin can be estimated from the body weight:

$$V_d = 0.26[IBW + 0.38(TBW - IBW)] = 0.26[90.5 + 0.38 * (142 - 90.5)] = 28.6\ L$$

To obtain the clearance,

$$CL = k_e \cdot V_d = 6.3\ L/h$$

Design a dosing regimen (dose and dosing interval) for gentamicin to achieve steady state peak and trough concentrations of 20 mg/L and 6 mg/L, respectively, assuming a short-term infusion of 30 min infusion duration. The approximate gentamicin volume of distribution is 0.3 L/kg. The patient characteristics are: female, 67 years of age, 5'8", 165 lbs, serum creatinine is 1.6 mg/dL. Use Cockcroft-Gault equation to estimate the clearance of gentamicin.

$$IBW_{female} = 45 + 2.3(68 - 60) = 63.4\ kg$$

$$TBW = \frac{165}{2.2} = 75\ kg < 120\%\ IBW$$

$$CL_{cr} = \frac{(140 - age)BW}{72 \cdot SCr} \cdot 0.85 = 0.85 \times \frac{(140 - 67) \cdot 75}{72(1.6)} = 40\ mL/min$$

$$CL_{gentamicin} = 40\frac{mL}{min} * \frac{60\ min/h}{1000\frac{mL}{L}} = 2.4\ L/h$$

$$V_d = 0.3\frac{L}{kg} * 75\ kg = 22.5\ L$$

$$k_e = \frac{CL}{V_d} = \frac{2.4}{22.5} = 0.107\ h^{-1}$$

$$\tau = \frac{\ln\left(\frac{C_{max}}{C_{min}}\right)}{k_e} + T = \frac{ln\left(\frac{20}{6}\right)}{0.107} + 0.5 \approx 12\ h$$

$$Dose = C_{\max(desired)} k_e V_d T \frac{1 - \exp(-k_e \tau)}{1 - \exp(-k_e T)}$$
$$= 20 \times 0.107 \times 22.5 \times 0.5 \times \frac{1 - \exp(-0.107 \times 12)}{1 - \exp(-0.107 \times 0.5)} = 334\ mg \sim 350\ mg$$

The dosing regimen is 350 mg q12h.