PHA 5128

Homework #2 (Answers)

1. The volume of distribution of diazepam in a group of normal subjects (59 kg, ideal body weight) was found to be 91 L. In another group of patients (104 kg), the volume of distribution was found to be 292 L. Derive an equation that allows estimation of the volume of distribution based on ideal and actual body weight. (2 POINTS)

   Normal: IBW (59kg) $\rightarrow$ 91L $\rightarrow$ 1.5 L/kg

   Excess: EBW(104-59 = 45kg) $\rightarrow$ 292-91 = 201 L $\rightarrow$ 4.5 L/kg (threefold of normal) (2 POINTS)

   $V_d = 1.5 \cdot (IBW + 3 \cdot EBW) = 1.5 \cdot IBW + 4.5 \cdot EBW$

2. Estimate the half-life of gentamicin in two male patients with normal renal function (CL=0.12 L/min) if their weight is 55 kg vs. 90 kg. Assume a height of 6'. (2 POINTS)

- Since clearance is given, only V_d remains to be found in order to calculate $t_{1/2}$ for the two patients. (remember $CL=ke*V_D$)
- Both patients are <120% IBW so use normal weight
  (To use these expressions, we must first calculate IBW for each patient:

$$\begin{aligned} IBW &= 50 + 2.3(\text{height in inches} > 60 \text{ in}) \text{ [kg]} \\ &= 50 + 2.3 \cdot (12) \\ &= 77.6 \text{ kg} \end{aligned}$$

  this is the IBW for both since both are 6'.)

- Volume of distribution for each patient is then:

$$V_d(55kg) = (0.25L/kg)(55kg) = 13.8L$$

$$V_d(90kg) = (0.25L/kg)(90kg) = 22.5L$$

- Half-lives may be calculated using the common expression relating Cl and V_d to k_e:

$$Cl = k_e \cdot V_d$$

$$\text{Or} \quad k_e = Cl/V_d$$

  And then applying $t_{1/2} = \dfrac{\ln 2}{k_e}$

  For the 55 kg patient,

$$k_e = \frac{Cl}{V_d} = \frac{0.12L/min}{13.8L} \cdot \frac{60min}{1hr} = 0.522hr^{-1}$$

$$t_{1/2} = \frac{\ln 2}{k_e} = \frac{0.693}{0.418hr^{-1}} = \underline{1.3hr}$$

  For the 90 kg patient,

$$k_e = \frac{0.12L/min}{22.5L} \cdot \frac{60min}{1hr} = 0.32hr^{-1}$$

$$t_{1/2} = \frac{0.693}{0.3478hr^{-1}} = \underline{2.2hr}$$

3. H.T. is a 69 year old male who is being treated for a post surgical wound infection (gram negative) with gentamicin for a 21 day course of antibiotics. He is currently day seven of gentamicin. He is 6 feet tall and weighs 172 lbs and has been experiencing a decline in his urine output for the last 24 hours. His SCr prior to antibiotic therapy was 0.9 mg/dl. But currently, his SCr increased to 1.3 mg/dL. You suspect that his renal function may be declining due to this aminoglycosides. It is known that gentamicin is eliminated almost entirely by the renal route, so creatinine clearance can be used as an estimate for gentamicin clearance. Calculate the new creatinine clearance. (2 POINTS)

$$\rightarrow 1.3 \text{ mg/dL} \rightarrow \quad CL_{cr} = \frac{(140-69)\cdot 77}{72\cdot 1.3} = 58 mL/\min$$

4. Drug A has the following average pharmacokinetic parameters: CL 0.24 ml/min/kg, Vd 0.16 l/kg, fb 93%, Fren 49%. For a 70 kg, 50 yo male patient with a serum creatinine of 0.8 mg/dl, calculate the necessary intravenous daily dose to produce an average unbound serum concentration of 15 mg/l. How would you have to modify the dose, if the patient develops renal problems and his serum creatinine rises to 2.4 mg/dl? (2 POINTS)

$CL = 0.24 \cdot 70 = 16.8$ mL/min = 1 L/h
$V_d = 0.16 \cdot 70 = 11.2$L
$CL_R = 0.49 \cdot 16.8 = 8.2$ mL/min = 0.49 L/h $\qquad$ $CL_{NR} = 0.51$ L/h

$$D = \frac{Cu \cdot CL \cdot \tau}{fu \cdot F} = \frac{15 \cdot 1 \cdot 24}{0.07 \cdot 1} = 5.1g$$

new $CL_R = 0.33 \cdot 0.49 = 0.16$ L/h
new CL = 0.51 + 0.16 = 0.67 L/h
new dose

$$D = \frac{15 \cdot 0.67 \cdot 24}{0.07 \cdot 1} = 3.4g$$

5. It is known from clinical experience that some patients do not show the expected analgesic effects after administration of codeine. Make a recommendation to screen for these patients to predict these treatment failures. (2 POINTS)

   Screen for CYP 2D6 deficiency

   → Genotyping or Phenotyping with debrisoquine