Case Study 6 2008

1. B.F. is 30 year old, 65 kg, 5'6" female patient to be started on gentamicin to treat a gram-negative infection. The target true maximum concentration is 8mg/L and the target true minimum concentration is 1mg/L. The clearance of the drug is equal to creatinine clearance and the Vd=0.25L/kg. This drug is typically given as a 30 minute IV infusion. Serum creatinine is 1.2mg/dL. This drug displays a two-compartment body model.

   A. Calculate the ke and half-life

   IBW=45.5+2.3*6=59.3kg
   TWB/IBW*100=65kg/59.3kg*100<120 this patient is not obese
   Clcr=(140-30)*65/(85*1.2)=70.10 mL/min=4.206L/hr
   Vd=0.25*65kg=16.25L
   Ke=4.206L/hr/16.25L=0.259hr^{-1}
   Half-life=0.693/ke=0.693/0.259hr^{-1}=2.68 hr

   B. Calculate the dosing interval. (Hint on your equation sheet tau (τ) is the dosing interval.)

   Tau=Ln(Cmax/Cmin)/ke+infusion time=Ln(8/1)/0.259+0.5hr=8.53~8hr. We can't use and 8.5 hr dosing interval because it's not practical. We round to 8 hours so it's given three times a day.

   C. Calculate the dose (mg).

$$D = C_{max(desired)} \cdot k_e \cdot V \cdot T \cdot \frac{\left(1 - e^{-k_e \cdot \tau}\right)}{\left(1 - e^{-k_e \cdot T}\right)}$$

   Dose=8mg/L*0.259 hr^{-1}*16.25L*0.5hr*(1-e^-0.259hr^{-1}*8hr)/(1-e^-0.259hr^{-1}*0.5hr) =121.145mg~120mg

   D. Once steady state was reached blood is drawn at 1 hr after the start of the infusion and 0.5 hr before the next infusion is started. The levels come back as 12mg/L and 4mg/L, respectively. Calculate the true Cmax and Cmin (these concentrations should be used to see if we are in the therapeutic window).

   Ke=ln(C2/C1)/(Δt)=Ln(12/4)/(6.5)=0.169hr^{-1}
   C=C0*e^(-ke*t)
   We are infusing the drug over 0.5 hr than the maximum concentration will be reached at the end of infusion.
   Cmax=C/e^(-ke*t)=12mg/L/e^(-0.169*0.5)=13.1mg/L
   Cmin=C0*e^(-ke*t)=4*e^(-0.169*0.5)=3.7mg/L

E. If trough concentration is not below at least 2mg/L there is a chance of toxicity. Please recommend a new dose using the information obtained and assuming that Vd is correct. (Meaning that the estimate of CL is incorrect).

Dose=8mg/L*0.169 hr^{-1}*16.25L*0.5hr*(1-e^-0.169hr^{-1}*8hr)/(1-e^-0.169hr^{-1}*0.5hr) =100.5~100mg

2. The next table shows the resulting pharmacokinetic parameters in this Patient 1. Let's assume a second patient will receive the same dose of this drug given orally as well. Both patients differ in the tissue and plasma protein binding to this drug. 100% of the drug in plasma and tissue is free for Patient 1. Contrary to this, in Patient 2, 50% of the drug present in tissue is free (fuT = 0.5) and 50% of the drug in plasma is free (fu=0.5). Ka is equal in both patients.

In the following table indicate whether the PK parameter will be higher, lower, or the same in patient 2 compared to patient 1.

PK parameter	Patient 1	Patient 2
Vd (L)	40	Same
CL (L/hr)	80	Same
Peak (mg/L)	5	Same
F	0.001	Increased

3. You wish to begin a patient on an oral formulation of Drug X and maintain an average plasma concentration of 15mg/L. You take the population average for Vd and Ke to be 10 L and 0.4hr^{-1}.

A. If the bioavailability is 70% and the normal dosing interval is 8 hours, what dose should we give?

CL=ke*Vd=0.4hr^{-1}*10L=4.0L/hr

Caverage=Dose*F/(CL*tau)
Dose=Caverage*CL*tau/F=15mg/L*4.0L/hr*8hr/(0.7)=685.71mg~700mg

B. After steady-state is reached the patient's blood is drawn and this patient has a supratherapeutic Cpaverage of 25mg/L. What is the patient's clearance?

Cl=Dose*F/(tau*Cpaverage)=700mg*0.7/(8hr*25mg/L)=2.45L/hr

C. At this concentration toxicity is a concern, calculate a new dose based on this clearance.

Dose=Caverage*CL*tau/F=15mg/L*2.45L/hr*8hr/(0.7)=420mg