PHA 5128 Dosing Optimization II

Spring 2013 · Case Study II

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1. Which combination of the following pharmacokinetic characteristics best describes the neonates compared to Adults?

1) Less total body water (% of body weight)

2) Decreased protein binding

3) Lower renal clearance

4) Longer gastric emptying time

A) 2&3&4

B) 2&4

C) 4 only

D) All of the statements are right

2. Calculate the creatinine clearance of following patients using Cockcroft-Gault equation.

(1) A female, 40 years old, 160 cm, 60 kg, has a concentration of serum creatinine of 1.2 mg/dL.

First to decide which body weight (IBW, TBW or ABW) would be used in the equation.

IBW=45+0.9(height in cm-150)=45+0.9(160-150)=45+9=54 kg

$$\frac{TBW}{IBW} = \frac{60}{54} \times 100\% = 111.1\% < 120\%$$

Since TBW is less than 120% of IBW, we should use TBW as dosing weight to calculate creatinine clearance

$$CL_{cr} = \frac{(140 - age) \times BW}{Cp_{cr} \times 85} = \frac{(140 - 40) \times 60}{1.2 \times 85} = 58.8\, ml/\min$$

(2) A male, 30 years old, 180 cm, 110 kg, has a concentration of serum creatinine of 2.5 mg/dL.

IBW=50+0.9(height in cm-150)=50+0.9(180-150)=77 kg

$$\frac{TBW}{IBW} = \frac{110}{77} \times 100\% = 142.9\% > 120\%$$

Since TBW is more than 120% of IBW, ABW is used

ABW=IBW+0.4(TBW-IBW)=77+0.4(110-77)=90.2 kg

$$CL_{cr} = \frac{(140 - age) \times BW}{Cp_{cr} \times 72} = \frac{(140 - 30) \times 90.2}{2.5 \times 72} = 55.1\, ml/\min$$

3. J. J. is a 55 years old male person with 75 kg weight and 176 cm height. He suffers from a severe urinary infection and the treatment suggested by the physician is 7 mg/kg gentamicin once daily IV infused over 30 minutes. Assuming his serum creatinine is 1.1 mg/dL and Vd=0.25L/kg, what is the measured peak gentamicin concentration 30 minutes after the infusion was ended and the measured trough gentamicin concentration 30 minutes before the new infusion at steady state?

IBW=50+0.9(height in cm-150)=50+0.9(176-150)=50+23.4=73.4 kg

$$\frac{TBW}{IBW}=\frac{75}{73.4}\times 100\%=102.2\%<120\%$$

So the TBW is used to calculate the creatinine clearance.

$$CL\approx CL_{cr}=\frac{(140-age)\times BW}{Cp_{cr}\times 72}=\frac{(140-55)\times 75}{1.1\times 72}=80.5\,ml/\min=4.8\,L/h$$

$$Vd=0.25\,L/kg\times 75kg=18.75L$$

$$k_e=\frac{CL}{Vd}=\frac{4.8}{18.75}=0.256h^{-1}$$

τ=24h and T=0.5h

$$C_{\max}=\frac{Dose}{Vd\times k_e\times T\times(\frac{1-e^{-k_e\tau}}{1-e^{-k_eT}})}=\frac{7\times 75}{18.75\times 0.256\times 0.5\times(\frac{1-e^{-0.256\times 24}}{1-e^{-0.256\times 0.5}})}=26.3\,mg/L$$

t_1=0.5h, t_2=24-0.5-0.5=23h

$$C^*_{\max}=C_{\max}\times e^{-k_et_1}=26.3\times e^{-0.256\times 0.5}=23.1\,mg/L$$

$$C^*_{\min}=C_{\max}\times e^{-k_et_2}=26.3\times e^{-0.256\times 23}=0.073\,mg/L$$

4. T.C. is a 64 kg, 169 cm, 35 years old female patient with a serum creatinine of 0.8 mg/dL. She is going to receive IV infusion of vancomycin over 1 hour for several days. After achieving steady state, the peak concentration obtained 30 minutes after the end of the infusion was 20 mg/L and a trough concentration obtained 30 minutes before the next dosing was 0.5 mg/L. What is the "true" peak and trough concentration at steady state? What dose and dosing interval would you recommend for her (Assume Vd=0.25 L/kg)?

$$C_{\max}^{*} = 20\,mg/L$$

$$C_{\min}^{*} = 0.5\,mg/L$$

So we need to obtain k_e value to calculate the C_{max} and $C_{min.}$ Before that, we firstly have to decide which dosing weight we have to use.

IBW=45+0.9(height in cm-150)=45+0.9(169-150)=62.1 kg

$\frac{TBW}{IBW} = \frac{64}{62.1} \times 100\% = 103.1\% < 120\%$ Thus, TBW is used to calculate the Vd

$$Vd = 0.25\,L/kg \times 64kg = 16L$$

$$CL \approx CL_{cr} = \frac{(140 - age) \times BW}{Cp_{cr} \times 85} = \frac{(140-35) \times 64}{0.8 \times 85} = 98.8\,ml/\min = 5.9\,L/h$$

$$k_e = \frac{CL}{Vd} = \frac{5.9}{16} = 0.369h^{-1}$$

t_1=0.5h, t_2=0.5h

$$C_{\max} = \frac{C_{\max}^{*}}{e^{-k_e t_1}} = \frac{20}{e^{-0.369 \times 0.5}} = 24.1\,mg/L$$

$$C_{\min} = C_{\min}^{*} \times e^{-k_e t_2} = 0.5 \times e^{-0.369 \times 0.5} = 0.4\,mg/L$$

$$\tau = \frac{\ln(\frac{C_{\max}}{C_{\min}})}{k_e} + T = \frac{\ln(\frac{24.1}{0.4})}{0.369} + 1 \approx 12h$$

$$Dose = C_{\max(desired)} \times k_e \times Vd \times T \times \frac{(1 - e^{-k_e \tau})}{(1 - e^{-k_e T})} = 24.1 \times 0.369 \times 16 \times 1 \times \frac{(1 - e^{-0.369 \times 12})}{(1 - e^{-0.369 \times 1})} = 455.6mg \approx 450mg$$

So the recommended dose is 450 mg and dosing interval is 12 hours.

5. A 3 months old infant is hospitalized with possible pneumonia. 3 mg Tobramycin was given every 8 hours with IV infusion over 30 min. The dosing time is 6 am, 2 pm and 10 pm. Several days later, the serum concentrations of tobramycin are tested using HPLC and listed as follows:

Time Point	Concentration
7 am	6.0 µg/ml
1 pm	2.0 µg/ml

Determine the half-life and volume distribution of tobramycin in this infant.

$$k_e = \frac{\ln \frac{C^*_{\max}}{C^*_{\min}}}{\Delta t} = \frac{\ln \frac{6.0}{2.0}}{6} = 0.183h^{-1}$$

$$t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.183} = 3.8h$$

t_1=0.5h, t_2=1h

$$C_{\max} = \frac{C^*_{\max}}{e^{-k_e t_1}} = \frac{6.0}{e^{-0.183\times 0.5}} = 6.6\,\mu g/ml$$

$$C_{\min} = C^*_{\min} \times e^{-k_e t_2} = 2.0 \times e^{-0.183\times 1} = 1.7\mu g/mL$$

$$Vd = \frac{Dose}{k_e \times T} \times \frac{(1-e^{-k_e T})}{(C_{\max} - C_{\min} \times e^{-k_e T})} = \frac{3}{0.183\times 0.5} \times \frac{(1-e^{-0.183\times 0.5})}{(6.6 - 1.7\times e^{-0.183\times 0.5})} = 0.57L$$