KEY
PHA 5128
First Exam
Spring 2010

1. Basic PK ____________
2. Basic PK ____________
3. Vancomycin _________
4. Basic PK ____________
5. Geriatrics ___________
6. Aminoglycosides __________
7. Gentamicin ___________
8. Amikacin ____________
9. Vancomycin ___________
10. Basic PK ____________
11. Basic PK ____________
12. Renal Disease _________
13. Gentamicin ___________
14. Geriatrics ________
1. Half life (t½) is a common parameter in PK study. A longer half-life of a drug will indicate:

A) a larger total body clearance.
B) more fluctuation can be expected at steady state.
C) a longer time to reach steady state
D) a shorter dosing interval to maintain a certain fluctuation.
E) a smaller volume of distribution

2. An investigational new drug is eliminated entirely by liver (hepatic) metabolism, with a clearance of 1.40 L/min in subjects with an average liver blood flow of 1.50 L/min. What would be its expected clearance in a congestive heart failure patient with a liver blood flow of 1.10 L/min but no change in hepatic extraction ratio?

A) 1.10 L/min
B) 1.50 L/min
C) 1.18 L/min
D) 1.03 L/min
E) Cannot be determined because the dose is not given.

Answer:
CLH = QH * E
E = CLH/QH = 1.4 L/min/1.5 L/min = 0.933
For CHF patient: QH = 1.1 L/min
CLH = QH *E = 1.10 L/min *0.933 = 1.03 L/min

3. What is the pharmacokinetic parameter that should be monitored for vancomycin therapy to achieve the desired efficacy?

A. Clearance
B. AUC
C. Peak concentration
D. Trough concentration
E. Vd
4. A 29-year-old male patient (75kg, 185cm) shows a creatinine clearance of 6 L/h. Calculate the serum creatinine concentration that has been measured to calculate his creatinine clearance of 6 L/h.

A. Not enough information provided to answer the question

B. 1.16 µg/dL

C. 19.27 mg/dL

D. 1.16 mg/dL

E. 19.27 µg/dL

\[ \text{IBW} = 50 + 0.9(185 - 150) = 81.5 \text{ kg} \]

TBW (75 kg) does not exceed 120% of IBW. Thus, TBW needs to be used in Cockcroft-Gault equation.

\[ \frac{6}{h} = 100 \text{ mL/min} \]

\[ 100 = \frac{(140 - 29) \times 75}{Cp_{Cr} \times 72} \]

\[ Cp_{Cr} = \frac{(140 - 29) \times 75}{100 \times 72} = 1.16 \text{ mg/dL} \]

5. Which of the following statements are TRUE?

1. The total body water (in % of body weight) in neonates is usually smaller than in adults

2. The glomerular filtration rate (GFR) in neonates is usually larger than in adults

3. The effect of body weight on volume of distribution does not depend on the lipophilicity of the drug

4. Aminoglycosides cannot pass membranes very well because of their low protein binding

A. 1

B. 2

C. 3

D. 4

E. None of the above
6. Which of the following statements about aminoglycosides are TRUE?

1. Therapeutic Drug Monitoring (TDM) is never recommended for aminoglycosides
2. Aminoglycosides are mostly cleared by the kidney
3. The creatinine clearance of a patient can be used to estimate his total systemic clearance
4. The volume of distribution of aminoglycosides is usually 0.25 L
5. Once-a-day dosing is never recommended for aminoglycosides

A  1, 5
B  2, 3
C  2, 3, 4
D  1, 2, 3, 4
E  2, 4
7. A 30-year-old, 75 kg, 180 cm, male patient with a serum creatinine level of 1.1 mg/dL received an initial gentamicin dose of 140 mg via IV infusion for 30 minutes. Calculate the plasma concentration of gentamicin 1 hour after the infusion was started.

A  Not enough information is provided to answer the question

B  4.22 µg/mL

C  5.81 µg/mL

D  5.81 µg/L

E  4.22 µg/L

\[
C = \frac{Dose}{CL \times T} (1 - e^{-k \times T}) e^{-k \times t}
\]

\[
IBW = 50 + 0.9(180 - 150) = 77 \text{ kg}
\]

\[
TBW < 120\% \text{ of } IBW, \text{ thus use } TBW
\]

\[
CL = CL_{cr} = \frac{(140 - 30) \times 75}{1.1 \times 72} = 104.17 \text{ mL min}^{-1} = 6.25 \text{ L h}^{-1}
\]

\[
Vd = 0.25 \frac{L}{kg} = 18.75 \text{ L}
\]

\[
k = \frac{CL}{Vd} = \frac{6.25 \text{ L h}^{-1}}{18.75 \text{ L}} = 0.333 \frac{1}{h}
\]

\[
C = \frac{140 \text{ mg}}{6.25 \frac{L}{h} \times 0.5h} \left(1 - e^{-0.333 \frac{1}{h} \times 0.5h}\right) e^{-0.333 \frac{1}{h} \times 0.5h}
\]

\[
= 44.8 \frac{mg}{L} \times (0.153) \times 0.847 = 5.81 \frac{mg}{L} = 5.81 \frac{µg}{mL}
\]
8. Which dosing interval would you recommend for amikacin to treat a patient (CL=83.33 mL/min, 80 kg) that suffers from a pulmonary infection if the “true” peak and trough concentrations at steady state are supposed to be 30 mg/L and 5 mg/L, respectively? Assume a short-term infusion over 45 minutes

**A** 12 hours  
**B** 24 hours  
**C** 6 hours  
**D** 8 hours  
**E** Not enough information is provided to answer the question

\[
CL = 83.33 \frac{mL}{min} \approx 5 \frac{L}{h} \\
Vd = 0.25 \frac{L}{kg} \times 80 kg = 20 L \\
k = \frac{CL}{Vd} = \frac{5 \frac{L}{h}}{20 L} = 0.25 \frac{1}{h} \\
\tau = \frac{\ln \left( \frac{C_{\text{max}}}{C_{\text{min}}} \right)}{k} + T = \frac{\ln \left( \frac{30}{5} \right)}{0.25} + 0.75 = 7.91 h \approx 8 h
\]
9. P.J. (female, 52-year-old, 65 kg, 5’8” tall) has been admitted to Shands Hospital for treating a serious bacterial infection. Her serum creatinine is 2.4mg/dL. Please provide the physician the correct dosing regimen for vancomycin using the table provided.

a. 1000mg q 24 h
b. 1000mg q 12h
c. 1000mg q 8 h
d. 500 mg q 24 h
e. 500 mg q 12 h

IBW = 45.5 kg + 2.3 kgx8=63.9kg so use 65kg

\[
CL = \frac{140 - 52) \times 65 \text{kg}}{2.4 \times 72} = 33.1 \text{ mL/min}
\]

10. How will an increase in tissue binding affect the clearance (CL), bioavailability (F), AUC, and half-life (t1/2) of a low-extraction drug? (Please note that ⇔ means no change)

A: ↑ CL, ↓ F, AUC ↓, ↓ t1/2
B: ⇔ CL, ↑ F, AUC ↑, ⇔ t1/2
C: ⇔ CL, ⇔ F, AUC ⇔, ↑ t1/2
D: ↓ CL, ⇔ F, AUC ↑, ↑ t1/2
E: ↑ CL, ↑ F, AUC ↓, ↓ t t1/2
11. Chronic liver disease causes a 40% decrease in verapamil clearance. However, half-life of verapamil increases 4 fold in chronic liver disease. Clearly the volume of distribution has changed due to the chronic liver disease. What is the volume of distribution of verapamil in a patient with chronic liver disease? (Healthy population values: CL= 60L/h; VD= 300 L)

A. 200L
B. 480L
C. 720L
D. 480mL
E. 720mL

Healthy CL = ke · Vd
60 = ke · 300 L
ke = 0.2 L/h
t1/2 = 3.465 h
Hepatic CL 60% = 36 L/h
If t1/2 = 13.86
Vd= CL/ke = 30 /((0.693/13.86) = 720L
12. Drug A has the following average pharmacokinetic parameters: CL 0.24 ml/min/kg, Vd 0.16 l/kg, fb 93%, The renal clearance 49% of the total clearance. For a 70 kg, 50 year old 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 3 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?

Use 0.8 mg/dl for calculations.

A. The old dose is 500mg, the new dose is 300mg

B. The old dose is 1000mg, the new dose is 700mg

C. The old dose is 2000mg, the new dose is 700mg

D. The old dose is 1000mg, the new dose is 300mg

E. The old dose is 500mg, the new dose is 700mg

\[ CL = 0.24 \times 70 = 16.8 \text{ mL/min} = 1 \text{ L/h} \]
\[ V_d = 0.16 \times 70 = 11.2 \text{ L} \]
\[ CL_R = 0.49 \times 16.8 = 8.2 \text{ mL/min} = 0.49 \text{ L/h} \]
\[ CL_{NR} = 0.51 \text{ L/h} \]
\[ \text{new } CL_R = 0.33 \times 0.49 = 0.16 \text{ L/h} \]
\[ \text{new } CL = 0.51 + 0.16 = 0.67 \text{ L/h} \]

\[ D = \frac{Cu \cdot CL \cdot \tau}{f_u \cdot F} = \frac{3 \times 1 \times 24}{0.07 \times 1} = 1028 \text{ mg} \]

New dose \[ D = \frac{Cu \cdot CL \cdot \tau}{f_u \cdot F} = \frac{3 \times 0.67 \times 24}{0.07 \times 1} = 689.14 \text{ mg} \]
13. A patient was given 80 mg gentamicin over 30 minutes (i.v.) from 8:00 to 8:30 am. The following two serum levels were measured: 7.5 μg/ml at 9:00 am and 0.9 μg/ml at 3:30 pm. Calculate the peak concentration at 8:30 AM and the trough concentration at 4 PM.

A. \( C_{\text{max}} = 8.85 \mu g/mL; C_{\text{min}} = 1.06 \mu g/mL \)
B. \( C_{\text{max}} = 8.62 \text{mg/L}; C_{\text{min}} = 1.06 \text{mg/L} \)
C. \( C_{\text{max}} = 8.85 \mu g/mL; C_{\text{min}} = 0.76 \mu g/mL \)
D. \( C_{\text{max}} = 6.55 \mu g/mL; C_{\text{min}} = 0.76 \mu g/mL \)
E. \( C_{\text{max}} = 8.85 \text{mg/mL}; C_{\text{min}} = 1.06 \text{mg/mL} \)

\[
k_e = \frac{\ln \left( \frac{7.5}{0.9} \right)}{6.5} = 0.33 h^{-1}
\]

the peak concentration at 8:30 AM:
\[
C_{\text{max}} = \frac{7.5}{e^{-0.33 \cdot 0.5}} = 8.85 \mu g/mL
\]

the trough concentration at 4 PM:
\[
C_{\text{min}} = 0.9 \cdot e^{-0.33 \cdot 0.5} = 0.76 \mu g/mL
\]

14. Which combination of the following pharmacokinetic changes best describes the elderly and neonates? (These groups share similar PK characteristics.)

1. Low renal clearance
2. Longer half-lives
3. Low metabolic clearance
4. Decreased protein binding
5. Relatively less body water

A. 1 & 4
B. 1, 2, 3 & 4
C. 1, 3, 4 & 5
D. 1, 4, & 5
E. all of the above
Once-a-day Aminoglycosides

Aminoglycosides

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<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
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<tr>
<td>$V_d$ [L/kg]</td>
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<tr>
<td>$CL$ [L/h/kg]</td>
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<td>$S$</td>
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<td>$C_{max}$ [mg/L]</td>
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<td>$C_{min}$ [mg/L]</td>
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<tr>
<td></td>
<td>&lt;10 (A)</td>
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</table>

Dosing Weight
- IF $TBW>1.2 \times BW$: $BW + 0.4 \times (TBW - BW)$
- Third Space Fluids: Add to $V_d$ (IL/kg)

Detti Equation:
- $k = 0.00293 \times CL_{cr} \times [mL/min] - 0.014$ [h⁻¹]
Vancomycin Pharmacokinetics

Poor absorption from GI tract (oral only used for *C. difficile* colitis)

\[ Vd = 0.17 \cdot \text{age} + 0.22 \cdot \text{TBW} + 15 \text{ [L]} \]  
(or 0.7 L/kg)

Good tissue penetration  
(except bile, eye, noninflamed meninges)

80-90% eliminated by kidneys

\[ t_{1/2} \]

Adults: 6-7 hours  
Infants/Children: 2-4 hours  
Newborn: 6-10 hours

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Figure 1. Detroit Receiving Hospital and University Health Center vancomycin dosing nomogram. (Revised 5/99)