Clinical pharmacokinetics of gentamicin

Situation 1A

A 30-year old, 70-kg, 172-cm woman with a serum creatinine of 0.9 mg/dL, has been admitted to hospital with a fever of unknown origin. The doctors would like to start her treatment with 250 mg of gentamicin over one-half hour infusion every 8 hours. Check if the above dosage regimen would be appropriate for the patient.

1. *Calculation of volume of distribution*

According to population data, the gentamycin volume of distribution is 0.25 L/kg and it should be adjusted for obesity > 20%

obesity = $\frac{(weight - IBW)}{IBW} \cdot 100\%$

IBW – ideal body weight

$\text{IBW}_{\text{women}} = 45.5 + 0.9 \times (\text{height in cm} - 152.4)$

$\text{IBW}_{\text{men}} = 50 + 0.9 \times (\text{height in cm} - 152.4)$

IBW = …….

obesity = ……

V_d = 0.25 [L/kg] × weight (or IBW in case of obesity)

V_d = ……[L]

2. *Calculation of gentamycin clearance*

The clearance of gentamycin is equal to the clearance of creatinine

$$Cl_{cr}^{male} = \frac{(140 - Age)(weight)}{72 \cdot (C_{cr}(mg/dL))}$$

$$Cl_{cr}^{female} = (0.85)\frac{(140 - age)(weight)}{72 \cdot (C_{cr}(mg/dL))}$$

Cl (mL/min) = …….

Cl (L/h) = ……

3. *Calculation of the gentamycin elimination rate constant K*

$$K = \frac{Cl}{V_d}$$

K = ……..[1/h]

4. *Calculation of C_{peak} and C_{trough}*

For calculation bolus model might be used. Take into consideration that the "peak concentration" is sampled 1 hour after the start of the infusion.

$$C_{trough} = \frac{D}{V} \cdot \frac{e^{-K \cdot \tau}}{1 - e^{-K \cdot \tau}} =$$

$$C_{peak+1h} = \frac{D}{V} \cdot \frac{e^{-K \cdot t_1}}{1 - e^{-K \cdot \tau}} =$$

Table 1. C_{trough} and C_{peak} monitoring targets during maintenance therapy with gentamicin

Therapeutic plasma concentration	(mg/L)
C_{peak}	5 - 8
C_{trough}	≤ 2

Conclusion:……
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5. *Design new dosing regimen allowing to obtain C_{trough} and C_{peak} values given in the table 1.*

$$D_{new} = \frac{C_{peak+1}^{\ desired}}{C_{peak+1}^{\ current}} \cdot D_{current}$$

New dose	τ	C_{peak+1}	C_{trough}

Situation 1 B

After administration of a designed new dose of gentamicin for the above-mentioned patient, drug concentrations were monitored. A peak plasma concentration obtained 1 hour after the start of an infusion was 10 mg/L and a trough concentration was 2.5 mg/L. Suggest a dosage regimen that will produce lower therapeutic gentamicin concentrations.

6. *Calculation of the patient elimination rate constant and clearance*

$$K = \frac{\ln\left(\frac{C_{peak+1h}}{C_{trough}}\right)}{\Delta t} =$$

$Cl = V_d \cdot K =$

7. *Calculation of D_{new}*

$$D_{new} = \frac{C_{peak+1h}^{desired} \cdot V \cdot \left(1 - e^{-K\tau}\right)}{e^{-Kt_1}} =$$

$$C_{trough} = \frac{D_{new}}{V} \cdot \frac{e^{-K \cdot \tau}}{1 - e^{-K \cdot \tau}} =$$

$$C_{peak+1h} = \frac{D_{new}}{V} \cdot \frac{e^{-K \cdot t_1}}{1 - e^{-K \cdot \tau}} =$$

1 C. Simulation of pharmacokinetic parameters

- Check if the designed regimen from Sec. 1B is appropriate using program for simulation of pharmacokinetic parameters.

Table 2. Values obtained using program for simulation of pharmacokinetic parameters

Dose (mg)	τ (h)	C_{peak} (mg/L)	$C_{peak+1h}$ (mg/L)	C_{trough} (mg/L)	C_{ave} (mg/L)

- Suggest an alternative dosing regimen allowing to obtain C_{peak} and C_{trough} monitoring targets.

Table 3. Alternative dosing regimen for gentamicin treatment

Dose (mg)	τ (h)	C_{peak} (mg/L)	$C_{peak+1h}$ (mg/L)	C_{trough} (mg/L)	C_{ave} (mg/L)

Which of the following parameters at most affect gentamicin steady state concentration: dose, time interval, creatinine clearance, volume of distribution, patient's weight, height, age?

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Situation 2.

A 40-year-old, 85-kg, 5 feet 5 inches -tall man was admitted to the hospital following an automobile accident. He was taken for abdominal surgery and postoperatively became hypotensive and required large volumes of fluid to maintain his blood pressure. Currently, he weighs 105 kg and has a serum creatinine of 2 mg/dL. Estimate dose to achieve peak gentamicin concentration ≥ 10 mg/L, if the drug would be given as intravenous infusion over 0.5 hour every 48 hours.

1. *Calculation of clearance*

Because the patient weighed 85 kg on admission we may suspect that he is obese

IBW_{male} = 50 kg + 2.3 kg × (height in inches > 5 feet)

IBW_{female} = 45 kg + 2.3 kg × (height in inches > 5 feet)

IBW = ……..

obesity = $\frac{(weight - IBW)}{IBW} \cdot 100\% =$

In obese patients clearance correlates better with IBW:

$$Cl(mL/\min) = \frac{(140 - age) \cdot IBW}{72 \cdot C_{cr}} =$$

Cl (L/h) =……

2. *Calculation of V_d*

V_d should be adjusted for obesity and/or alterations in extracellular fluid status.

A rapid increase in patient's weight is likely to be caused by fluid in the third space, which is common after operations.

V (L)= 0.25 (L/kg) × IBW + 0.1 × (Excess adipose weight) + (excess third space fluid weight)

excess adipose weight = initial body weight – IBW = ……

excess third space fluid weight = current weight - initial weight =……

V (L) = ……

3. Calculation of K

$K = \frac{Cl}{V_d}$ = ……

4. Calculation of the gentamicin dose

$$D_{new} = \frac{C_{peak+1h} \cdot V \cdot \left(1 - e^{-K\tau}\right)}{e^{-Kt_1}}$$

Conclusion:……
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Situation 3.

A 38-year-old, 70-kg man has been receiving IV gentamicin, 100 mg over one-half hour every 8 hours, for several days. A peak plasma concentration obtained 1 hour after the start of infusion was 8 mg/L, and a trough concentration obtained just before the initiation of a dose was 3 mg/L. The microbiology report revealed Pseudomonas aeruginosa with a minimum inhibitory concentration (MIC) of 1 μg/mL. Predict efficacy of the antibacterial therapy in the patient. Take into account that antibacterial effect of gentamicin is determined by PK/PD parameters: C_{peak}/MIC > 10 and AUC_{24}/MIC = 70 - 100.

$\frac{C_{peak}}{MIC} =$

1. *Calculation of K*

$$K = \frac{\ln\left(\frac{C_{peak+1h}}{C_{trough}}\right)}{\Delta t} =$$

2. *Calculation of Vd*

$$V_d = \frac{\frac{D}{C_{peak+1}}}{\left(1 - e^{-K \cdot \tau}\right)} \cdot e^{-K \cdot t_1} =$$

3. Calculation of clearance

$$Cl = V_d \cdot K$$

4. Calculation of AUC_{24}

$$AUC_{24} = \frac{D_{24h}}{Cl} =$$

$$\frac{AUC_{24h}}{MIC} =$$

Conclusion:……
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What dosage regimen would you recommend for the patient to ensure efficacy of the antibacterial therapy with gentamicin? Take into account that a dosing interval of approximately four to five half-lives maximizes the peak concentration and bactericidal activity while minimizing drug accumulation and toxicity.

5. *Calculation of $t_{0.5}$*

$$t_{0.5} = \frac{\ln 2}{K}$$

New dosing interval = …….

6. Calculation of D_{new}

$$D_{new} = \frac{C_{peak+1}^{desired} \cdot V_d \cdot \left(1 - e^{-K \cdot \tau}\right)}{e^{-K \cdot t_1}} =$$

7. Calculation of the PK/PD parameters

$$\frac{C_{peak}}{MIC} =$$

$$AUC_{24} = \frac{D_{24h}}{Cl} =$$

Conclusion:……
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