TDM OF AMINOGLYCOSIDES

LEC 9

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INTRODUCTION

- The aminoglycosides are bactericidal antibiotics used in the treatment of serious gram-negative infections.
- Because absorption from the gastrointestinal tract is poor, the aminoglycosides must be administered parenterally to achieve therapeutic concentrationsin the systemic circulation.

- In most instances, aminoglycosides are administered by intermittent intravenous (IV) infusions. The choice of an aminoglycoside dose is infuenced by the specific agent (e.g., gentamicin vs. amikacin), infection (e.g.,site andorganism), renal function, and weight or body composition of the patient.

PHARMACODYNAMICS OF AMINOGLYCOSIDES

- Aminoglycosides have been dosed multiple times a day.
- Bactericidal activity of the aminoglycosides has been demonstrated to be concentration dependent (i.e., plasma concentrations that exceed 10 times the minimum inhibitory concentration [MIC] or a given bacteria are more effective than concentrations just above the MIC).
- In addition to the concentration dependent killing, there is also a post-antibiotic effect that results in depressed bacterial growth after plasma concentrations have fallen below the MIC.

KEY PARAMETERS: Aminoglycoside Antibiotics

THERAPEUTIC SERUM CONCENTRATIONS		
Gentamicin, Tobramycin	Conventional dosing Peak 5–8 mg/L Trough < 2 mg/L	"Once-daily" dosing 20 mg/L Undetectable
Amikacin	Peak 20–30 mg/L Trough < 10 mg/L	60 mg/L Undetectable
V[a]		
Adults, Children > 12 yr Children 5–12 yr	0.25 L/kg 0.35 L/kg	
Cl		
Adults, Children > 12 yr Functionally anephric patients[c] Surgically anephric patients[c] Hemodialysis[c] Children ≤ 12 yr[b]	Equal to Cl_{Cr} 0.0043 L/kg/hr 0.0021 L/kg/hr 1.8 L/hr Equal to GFR	
AUC_{24}	70–100 mg · hr/L	Gentamicin and tobramycin (amikacin approximately threefold higher)
t½		
Normal renal function Functionally anephric patients	2–3 hr 30–60 hr	
fu (fraction unbound in plasma)	> 0.95	

S = 1

F=1

BIOAVAILABILITY (F)

The aminoglycoside antibiotics are highly water soluble and poorly lipid soluble compounds. As a result, they are poorly absorbed when administered orally and must be administered parenterally for the treatment of systemic infection

VOLUME OF DISTRIBUTION (V)

The volume of distribution of aminoglycosidesis ≈ 0.25 L/kg,

Because aminoglycosides distribute very poorly into adipose tissue, lean rather than total body weight (TBW) should result in a more accurate approximation of V in obese patients.

TIME TO SAMPLE

Correct timing of the sample collection is important because aminoglycoside antibiotics have a relatively short half-life and a small but significant distribution phase.

The most widely accepted guidelines recommend that samples for peak serum concentrations be obtained hour after the maintenance dose has been initiated.

EQUATION USED

$$Cl_{Cr} \text{ for Males (mL/min)} = \frac{(140 - \text{Age})(\text{Weight})}{(72)(SCr_{ss})} \quad \textbf{(Eq. 6.6)}$$

$$Cl_{Cr} \text{ for Females (mL/min)} = (0.85)\frac{(140 - \text{Age})(\text{Weight})}{(72)(SCr_{ss})} \quad \textbf{(Eq. 6.7)}$$

$$C = C_0\, e^{-Kt} \quad \textbf{(Eq. 6.10)}$$

where C_0 is the initial plasma concentration, C a concentration at some time t later, to

$$C_0 = \frac{C}{e^{-Kt}} \quad \textbf{(Eq. 6.11)}$$

In the above equation, t represents the time from the measured plasma concentration (C) to the earlier plasma concentration (C_0). T is equation is used to back-extrapolate a plasma concentration to the "clinical peak," which is 1 hour after the start of the infusion. T e "clinical peak" concentration has generally been used as a guide to aminoglycoside efficacy.

$$C_1 = \frac{(S)(F)(\text{Loading Dose})}{V}$$

$$C_1 = \frac{(S)(F)(\text{Loading Dose})}{V}(e^{Kt_1})$$

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

$$K = \frac{\ln \frac{C_1}{C_2}}{t}$$

$$Cl = (K)(V)$$

$$V = \frac{\frac{(S)(F)(\text{Dose})}{Css_1}}{(1 - e^{-K\tau})}(e^{-Kt_1})$$

, and serum creatinine.

$$Cl_{Cr} \text{ for Males (mL/min)} = \frac{(140 - \text{Age})(\text{Weight})}{(72)(SCr_{ss})}$$
$$= \frac{(140 - 50)(60\ \text{kg})}{(72)(1.5\ \text{mg/dL})}$$
$$= 50\ \text{mL/min}$$

$$Cl_{Cr}\text{(L/hr)} = (50\ \text{mL/min})\ \frac{60\ \text{min/hr}}{100\ \text{mL/L}}$$
$$= 3\ \text{L/hr}$$

QUESTION #1

R.W. is a 30-year-old, 70-kg, nonobese woman with a serum creatinine of 0.9 mg/dL. An initial gentamicin dose of 140 mg was in used IV over 30 minutes. Calculate the plasma concentration of gentamicin 1 hour after the infusion was started (i.e., 0.5 hour after the infusion was completed)

QUESTION #2

Outline the reasonable plans to determine the causes of toxicity by aminoglycosides, how to prevent it and what organ will be affected?

QUESTION #3

In what types of patients is it more appropriate to use the infusion equation for the prediction of aminoglycoside concentrations? When can the bolus dose model be used satisfactorily?

Q3/ ANSWERS

Because the difference between the results obtained from these two approaches is primarily related to the amount of drug cleared from the body during the infusion period,

- It is reasonable to assume that in patients with decreased renal function and longer aminoglycoside half -lives, the bolus dose model could be used satisfactorily.

- In patients with good renal function (e.g., young adults and children), use of the infusion model is more appropriate because these patients often have very short aminoglycoside half -lives

QUESTION #4

- C.I. is a 50-year-old, 60-kg man with a serum creatinine of 1.5 mg/dL, who is receiving 350 mg of amikacin IV over 0.5 hour every 8 hours at midnight, 8:00 a.m., and 4:00 p.m.
- He had a trough concentration of 6 mg/L obtained just before the 8:00 a.m. dose and a peak concentration of 15 mg/L obtained at 9:00 a.m. Assuming these peak and trough concentrations represent steady-state levels, calculate C.I.'s elimination rate constant, clearance, and volume of distribution.
- Evaluate whether these parameters seem reasonable and should be used to adjust C.I.'s amikacin maintenance dose

THANK YOU