Therapeutic Drug Monitoring of Aminoglycosides

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Conventional vs Single Daily Dose for Aminoglycosides

- Gentamicin or Tobramycin
  - Conventional ~1.5 mg/Kg Q8H or ~5 mg/Kg/day
  - SDD ~7 mg/Kg as one dose every 24 Hrs
- Amikacin
  - Conventional ~5 mg/Kg Q8H or 7.5 mg/Kg Q12H
  - SDD 15 mg/Kg as one dose every 24 Hrs

Data Poor or Rich Environment

What to do when:

No data
Poor
Population data
Patient specific trough/peak data
Patient specific series PK data
Better

Evaluating Aminoglycoside Dose & Interval without ASCTD

- Parameters required for evaluation:
  - Age
  - Height in inches
  - Weight
  - Serum creatinine

Patient weight:
- Actual body weight (ABW)
- Lean body weight (LBW) in Kg
- Males = 50 + 2.3 (# inches over 5 feet)
- Female = 45 + 2.3 (# inches over 5 feet)
- Note if LBW > ABW use ABW
- Dosing body weight (DBW)
- For patients >30% over LBW
- DBW = LBW + 0.4 (ABW – LBW)

Calculated Creatinine Clearance(Crcl) in ml/min
- Method of Cockcroft and Gault
  - Male = ((140 – Age) x LBW) / (72 x Scr)
  - Female = 0.85 (Male)
- Transform Crcl into Kd using Detli method
  - Kd (Hr^{-1}) = 0.0024 (Crcl) + 0.01
- Transform Estimated Kd into T1/2
  - T1/2(Hrs) = 0.693 / Kd
Initial Evaluation for Conventional Aminoglycoside Therapy

- Peak concentrations should be ~ 10 x MIC of the likely bacterial pathogen
- Troughs should be as low as possible given the circumstances surrounding the patient
- Dose should be evaluated on a mg/kg/day basis and mg/kg per dose basis using the appropriate body weight parameter
- Dosing interval should be ~ 2 to 3 T1/2’s plus the hour for drug infusion
- Try to limit total course of therapy to < 5 days to reduce risk of nephrotoxicity or ototoxicity

The Sawchuk-Zaske Method

- One Compartment Modeling of Aminoglycoside Serum Concentration Time Data
- Method Originated at University of Minnesota, College of Pharmacy & Used Worldwide

Reference Parameters

- $t$ = Separation time between two points (Hours)
- $t'$ = Time of infusion (Hour)
- $K_o$ = Rate of infusion (mg/Hr)
- $T$ = Dosage interval (Hours)
- $V_d$ = Distribution Volume (L or L/Kg)
- $T_{1/2}$ = Half-life (Hrs)
- $K_d$ = Elimination rate constant (Hr$^{-1}$)
- $C_{p_{max}}$ = Peak concentration (mg/L or mcg/ml)
- $C_{p_{min}}$ = Trough concentration (mg/L or mcg/ml)
- $C_p$ = Reference concentration (mg/L or mcg/ml)
- $C_p(t)$ = Concentration of drug separated by $t$ from $C_p$

One Compartment Model

Aminoglycoside Added

$K_o$ (mg/Hr) Rate of Infusion (Dose/$t'$)

$K_d$ Aminoglycoside Lost

Assumption there are no other compartments & that all aminoglycoside distribution occurs during infusion

Elimination Constant ($K_d$) & Half Life ($T_{1/2}$)

$$K_d = \frac{(\ln X_1 - \ln X_2)}{(Time X_1 - Time X_2)}$$

$$T_{1/2} = \frac{\ln 2}{K_d}$$

For example:

- $K_d = \frac{(\ln 6 - \ln 3)}{(2 - 4)}$
- $T_{1/2} = \frac{\ln 2}{0.693/0.346}$

Resulting Serum Concentration Time Curve with One Compartment Modeling

$\ln C_p (mg/L)$

True Peak ($C_{p_{max}}$) = $C_p(0) * e^{-K_d t'}$

$C_p(t)$ = $C_p(0) * e^{-K_d t}$

Slope = $-K_d$

True Trough ($C_{p_{min}}$) = $C_p(0) * e^{-K_d 2}$
What Does $e^{-Kd*t}$ Do?

What then is $1 - e^{-Kd*t}$?

$Cp_t = Cp_0 * e^{-Kd*t}$

$\ln Cp (mg/L)$

$\ln Cp (mg/L)$

$4 mg/L$

$3 mg/L$

$4 mg/L$

$3 mg/L$

$Cp_t = Cp_0 * e^{-Kd*t}$

$\ln Cp (mg/L)$

$\ln Cp (mg/L)$

$4 mg/L$

$3 mg/L$

$4 mg/L$

$3 mg/L$

Using Monoexponential Equation to Solve For Dosing Interval (T)

$Cp_t = Cp_{max} * e^{-Kd*t}$

$Cp_{min} = Cp_{max} * e^{-Kd*(T-t')}$

Solve for $T = ?$

$\ln Cp (mg/L)$

$\ln Cp (mg/L)$

$4 mg/L$

$3 mg/L$

$4 mg/L$

$3 mg/L$

Why the Complicated Formula???

$Vd = \frac{Ko * (1 - e^{-Kd*t})}{Kd * (Cp_{max} - Cp_{min} * e^{-Kd*t})}$

$Vd = Dose / Cp$ or Change in Cp

In the Calculation of $V_d$ Note:

$K_d$ by nature has a negative value but in the term $e^{-Kd*t}$ you do not multiply $-K_d$ by a negative sign making the value positive

and

In the term $K_o/K_d$, $K_d$ here must be a positive value or you calculate a $-V_d$

Calculation of $V_d$

- Aminoglycoside does not enter the body as bolus but rather in a “zero order” process, an infusion rate (mg/Hr)
- Aminoglycoside is eliminated in a “first order” process, a constant percent per unit of time (50%/T1/2)
Aminoglycoside (AG) Pharmacokinetic Parameters

- $V_d$ is dose sensitive in that if the patient received less drug, $V_d$ will be overestimated & if patient receives more, $V_d$ will be smaller
- Value of $V_d$ may be result of blood loss, fluid or blood products being administered, 3rd spacing or drug inactivation
- Value of AG PK parameters may be a function of assay method used
- Half-life is dose independent if being evaluated ≥ 2 real post infusion values

Setting up Levels for TDM

- General requirements are that patient’s renal function and fluid status be stable
- Trough / Peak Option
  - Patient must be at steady state
    - Received drug for 3-5 T1/2’s
    - If T1/2 is short in relation to doing interval, the likelihood of having measurable trough is low
    - Nurse has administered drug on time and on schedule during the 3 to 5 T1/2 period
    - Note: If patient seriously ill with impaired renal function, clinician may not be able to wait for steady state

Need for Steady Conditions with Trough Peak Studies

- When flipping the pre-infusion concentration to use as 2nd post infusion point, must be the same distance from $C_{\text{max}}$
Example I

- 28 year old female, 6’ tall and weighs 75 Kg is admitted for treatment of pyelonephritis.
- Patient is started on gentamicin 400 mg QD and ampicillin 500 mg Q6H.
- Cultures of blood and urine are pending.
- Patient has no significant prior medical history
- She is not pregnant or breast feeding.
- Pharmacy receives a pharmacokinetic consult, what should be done for this patient?

Example II

- 50 year old male (6’ tall weight 85Kg) admitted for elective abdominal surgery eight days ago spikes temperature. Patient has no allergies and the serum creatinine has been 1.2 mg/dl.
- Patient is placed on ampicillin/sulbactam 3 Gm Q6H & gentamicin 140 mg Q8H.
- Prior to the 4th gentamicin dose, the night RPh orders a trough and peak gentamicin levels.
- Physician calls the DCP asking what should be done with the gentamicin dose.

Example III

- 24 year old male(5’10” tall & weighs 105Kg) involved in a MVA suffers multiple injuries.
- The patient is started on piperacillin/tazobactam 3.375 Gm Q6H & gentamicin 100 mg Q12H.
- Patient has positive blood & sputum cultures for *P. aeruginosa*.  Serum creatinine is 1 mg/dl.
- The physician contacts you wanting a pharmacokinetic study ASAP.  You find out the last dose was just given twenty minutes ago and proceed to obtain two post infusion levels, how should these data be evaluated?

Problem Set

Patient is a 40 year old female (5’10” tall, 69.5 Kg) who underwent intra-abdominal surgery for a ruptured appendix. She is placed on gentamicin 100 mg over an hour every eight hours and ampicillin/sulbactam 3 Gm every six hours. She has no allergies, not pregnant, or breast feeding. She has normal liver and renal function (serum creatinine 0.9 mg/dl).

Suppose you are given three options to optimize gentamicin dose:
1) Use demographic and laboratory information above to estimate Kd, T1/2, Dose, and Interval.
2) Trough and peak study off 2nd dose
3) Trough and peak study 2nd day

Aminoglycoside Parameter Estimates

\[
LBW = 45 + 2.3 \times 10 = 68 \text{ Kg} \\
LBW \sim ABW \\
CrCl = 0.85 \frac{[(140-40) \times 68]/(72 \times 0.9])}{92.2 \text{ ml/min}} \\
Kd = (0.0024 \times 89.2) + 0.01 = 0.224 /\text{Hr} \\
T1/2 = 0.693/0.224 = 3.09 \text{ Hrs} \\
\text{Dosing Interval} = 2-3 \text{ T1/2’s } + t’ \\
\text{Gentamicin dose} \sim 1.5 \text{ mg/Kg or } \sim 4.5 \text{ mg/Kg/Day}
\]
Serum Sampling Options

- 2nd Dose
  - 100mg infused 0800-0900
  - Pre level 0745
  - Post level 0915

versus

- 2nd Day
  - 100mg infused 0800-0900
  - Pre level 0745
  - Post level 0915

- What can be done with these data?

Need for Steady Conditions with Trough Peak Studies

2nd Day Study

Time 0745 Level = 0.9 mg/L
Time 0915 Level = 6.2 mg/L

$K_d = (\ln X_1 - \ln X_2) / (\text{Time } X_1 - \text{Time } X_2)$

$6.2 \text{ mg/L} \quad K_d = (\ln 6.2 - \ln 0.9) / (0.25 - ???) = -0.2969$

$T_{1/2} = \ln 2 / K_d$

$T_{1/2} = 0.693/0.2969 = 2.334 \text{ Hrs}$

How Could the 2nd Dose Study be Fixed?

Volume of Distribution

- Correct pre level for start of infusion
  $C_{p_{\text{min}}} = 0.6 \; e^{-0.3322*0.25} = 0.5521 \text{ mg/L}$
- Trough in non-steady state conditions is used only in calculation of Vd.
- Trough in non-steady state conditions cannot be used as a post infusion point

- Correct 1st post level for true peak
  $C_{p_{15\text{ min post}}} = C_{p_{\text{max}}} \; e^{-0.3322*0.25}$

$5.3/ e^{-0.3322*0.25} = C_{p_{\text{max}}} = 5.76 \text{ mg/L}$

- Could make corrections for peak and trough using graph
\[ V_d = \frac{K_o}{K_d} \left( 1 - e^{(-K_d*t')} \right) \]
\[ V_d = \frac{100 \text{ mg}}{0.3322 \text{ Hrs}} \left( 1 - e^{(-0.3322*1.0)} \right) \]
\[ V_d = 15.87 \text{ L} \]

Note: \( K_d \) by nature has a negative value but in the term \( e^{(-K_d*t')} \)
You do not multiply \(-K_d\) by a negative sign making the value
positive also in the term \( K_o/K_d \). \( K_d \) here must be a positive value
or you calculate a - \( V_d \).

**Adjustment of \( C_{p_{\text{max}}} \) & \( C_{p_{\text{min}}} \) at Steady State**

- Your patient is a 54 yr old (5 foot 2 inch) female (58 Kg)
  who is being treated for pyelonephritis. Serum creatinine 1.1 mg/dl.
- You have just completed a pre/post study at steady state. Gentamicin 80 mg is infused over an hour every eight
  hours. The extrapolated peak and trough are 6.2 mg/L and 0.8 mg/L, respectively. If the dose were increased to
  120 mg Q8H, What are the new trough and peak concentrations?

**Desired \( C_{p_{\text{max}}} \) & \( C_{p_{\text{min}}} \): Resultant Dose & Dosing Interval**

\[ T = -\frac{L}{K_d} \ln C_{p_{\text{min}}} + t' \]
\[ \ln C_{p_{\text{max}}} \]

\[ \frac{C_{p_{\text{max}}} = \frac{K_o}{K_d} \left( 1 - e^{(-K_d*t')} \right)}{V_d \left( 1 - e^{(-K_d*T)} \right)} \]

\[ C_{p_{\text{min}}} = C_{p_{\text{max}}} \cdot e^{(-K_d(T - t'))} \]