Therapeutic Drug Monitoring of Aminoglycosides

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Objectives

- Participants will be able to develop a therapeutic drug monitoring plan for aminoglycosides with or without serum concentration time data.
- Participants will be able to make appropriate decisions as to the need for therapeutic drug monitoring.
- Participants will be able to identify situations appropriate for series or peak/trough pharmacokinetic monitoring.
- Participants will be able to identify an appropriate schedule and time for aminoglycoside therapy.
- Participants will be able to identify appropriate peak and trough concentrations for conventional and single daily dosing strategies.
- Participants will be able to develop a plan to monitor the patient for successful resolution of infection or the development of adverse drug reactions to the aminoglycoside.

TDM

- Knowing what to do and getting it done in a hospital 24/7 are not one of the same
- Part of the art is knowing when to believe and when not to believe
- Need to be able to function without data, with data, or when data seems to be in question
- Always need a short term and long term plan
Aminoglycoside Patient Care Decisions

- Decide whether the following are appropriate:
  - Use alone or in combination with another antibiotic
  - Dose and Interval
  - Need for therapeutic serum concentration drug monitoring
    - Will aminoglycoside levels be needed?
    - What type of study if any is needed
    - How many and when should levels be obtained
  - How should patient be monitored
  - Duration of therapy

Initial Evaluation of Aminoglycoside Dose & Interval

- Aminoglycoside serum concentration time data (ASCTD) available
- No ASCT data available
  - Far more common situation
  - General rule for conventional aminoglycoside therapy (Assume adult with normal renal function)
    - Daily dose for gentamicin or tobramycin ~ 5 mg/kg/d
      - Amount per dose ~ 1.5 mg/kg or Single Dose Strategy
    - Daily dose for amikacin ~ 15 mg/kg/d
      - Amount per dose ~ 5 to 7.5 mg/kg

Evaluating Aminoglycoside Dose & Interval without ASCTD

- Parameters required for evaluation:
  - Age
  - Height in inches
  - Weight
  - Serum creatinine
Evaluating Aminoglycoside Dose & Interval without ASCTD

- 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)

Evaluating Aminoglycoside Dose & Interval without ASCTD

- Calculated Creatinine Clearance (Crcl) in ml/min
  - Method of Cockcroft and Gault
    - Male = ((140 – Age) * LBW) / (72 * 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

Critical Evaluation of Calculated Parameters

- LBW
  - Para or Quadraplegic patient or where LBW > ABW
- Creatinine Clearance (Crcl) this is an estimate
  - Elderly
  - Para or Quadraplegic patient
  - Nutrionally starved patients
  - Crcl not likely a linear function < 30 ml/min
- Caution
  - Dehydration or Overhydration
  - Bleeding
  - Going into or coming out of acute renal failure
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

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

Setting up Levels for TDM

- Pharmacokinetic Series Option
  - Patient does not have to be at steady state
  - Need to obtain trough level if not the first dose
  - Need a minimum of 2-3 levels post antibiotic infusion spaced over a period of ≥ 1.5 T1/2's
# Pharmacokinetic Studies

- Need to know the start and stop time of the aminoglycoside infusion
  - Drug must be administered at a constant rate
  - Infusion should include tubing flush
- Need to know the exact time when levels were drawn in relation to dose
- Should always critically evaluate the half-life and distribution volume generated from the pharmacokinetic study
  - Factor in likely renal function, obesity, etc vs result

# Dosage Recommendations

- Should always factor in the clinical condition of the patient
- The likely bacterial pathogen and level of sensitivity to chosen aminoglycoside
- The location of infection and how well the aminoglycoside is likely to concentrate at that site
- Anticipate future
  - Renal & fluid status
  - Likely duration of therapy

# Monitoring Plan

- Patient status, patient location, temperature and body weight
- Day to day clinical status
- Culture information
  - Both positive & negative results from all sites
  - WBC, BUN / Ser & other lab studies
  - X-rays or scans
- Fluid status, urine output, & ability to take orally food or medications
- Charting of doses and recording of levels
Critical Evaluation

- Interpret data in relation to patient
- Result real vs artifact (most often the problem)
  - Volume is a dose sensitive parameter
    - Preparation, administration or serum level handling error
    - Less drug than thought increases volume
    - More drug than thought reduces volume
    - Obese vs wasting, para/quadriplegic, 3rd spacing (pleural effusion, ascites etc) or overhydration (anasarca)
    - Stable fluid status vs massive IV fluids &/or blood products
    - May be a function of assay used
  - Half-life is a dose independent parameter
    - Method used trough/peak vs series pharmacokinetics
    - Young vs old, NRF vs ARF
    - Beta-lactam inactivation

- Double check entry of all data and calculations
- Evaluate final recommendation on basis of mg per Kg per dose and per day
- Before making recommendation to physician or in writing make sure patient data matches up with the chart
- Therapy should always be goal directed with monitoring plan for drug efficacy and toxicity
  - Plan for antibiotic alternatives

Example I

- 40 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 medical history of renal impairment or drug allergies.
- 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 level.
- 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?