Therapeutic Drug Monitoring of Aminoglycosides

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Objectives
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- 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 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?
    - Type of study if any is needed
    - How many and when levels to 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
    - 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)

- 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

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
    - Nutritionally 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

- 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 / Scr & 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

### Critical Evaluation

- 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/clavulanate 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?