Therapeutic Drug Monitoring of Antibacterials

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No conflicts of interest to report.

Questions:

- What is the most important PK parameter for the first dose? Clearance (red) or Volume of distribution (green)?
- How long is the Post Antibiotic Effect or Post MIC Effect of an aminoglycoside? 2 hours (red) or 7 hours (green)?
- What is the most appropriate level for aminoglycoside clearance? 24-h level (red) or 12-h level (green)?

Outline presentation

- Case
- PK-PD principle
- Optimal sampling
- General approach for TDM

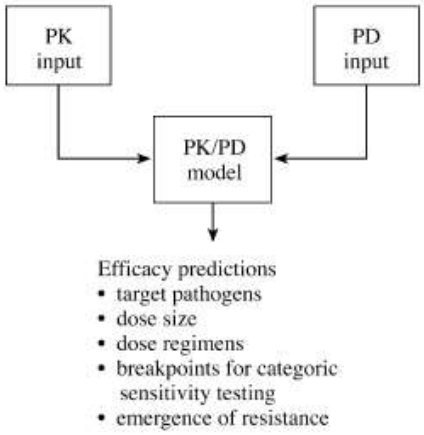
Case

- Patient (male, 64 years, 70 kg, serum creat 80 micromol/L) has an infection and must be treated with tobramycin
- Physician asks you:
  - Starting dose
  - Dosing interval
  - When to draw samples

You need

› Knowledge on PK/PD relationship for this antibiotic
› Knowledge of physiologic factors on PK for this antibiotic

For optimal dosing you need to integrate pharmacodynamics and pharmacokinetics



Back to the case

- General starting points:
  - MIC (tobramycin): 1,5 - 2 mg/L
  - For recovery from tobramycin induced renal toxicity C_{min} must be >5 hrs <0,5 mg/L
- What is the target for the peak concentration?
  - Calculate the dose.
- What is a safe dosing interval?

‘A priory’ dose regimen

- Standard first dose is calculated on the basis of
  - V which is calculated from Population PK valued for Vd and adapted to individual patient data (confounders: weight, height, age, sex)

- Dosing interval is calculated on the basis of
  - Individual estimation of clearance based on population value and confounders
  - Target value for trough level

Required data for the ‘a priory’ dose regimen:

- PK population parameters
  - Mean (Vd, CL, K12, K21)
  - standard deviation
- PK/PD determinants:
  - Peak/MIC (aminoglycosides)
  - AUC/MIC (vancomycin, fluorchinolones)
  - T above MIC (beta-lactam antibiotics)

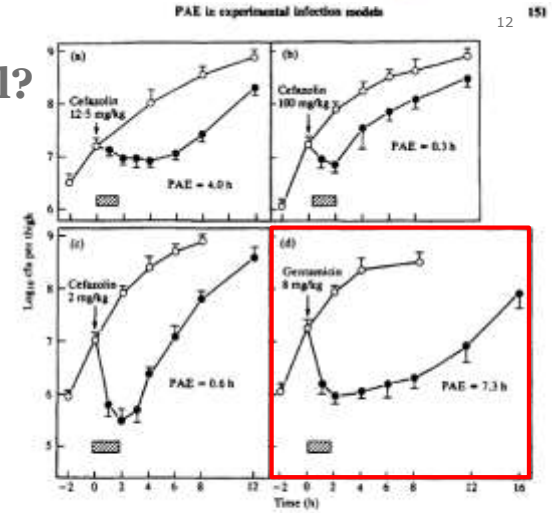
Dose:

- MIC: max 2 mg/L
  - Optimal C_{max} = 10 x MIC
  - Target C_{max} = 20 mg/L

- Volume of distribution: 0.25 – 0.4 L/kg
  - Dose: (0.25 to 0.4 L/kg) x 20 mg/L = 5 – 8 mg/kg (EUCAST advice 2016: 7 mg/kg)

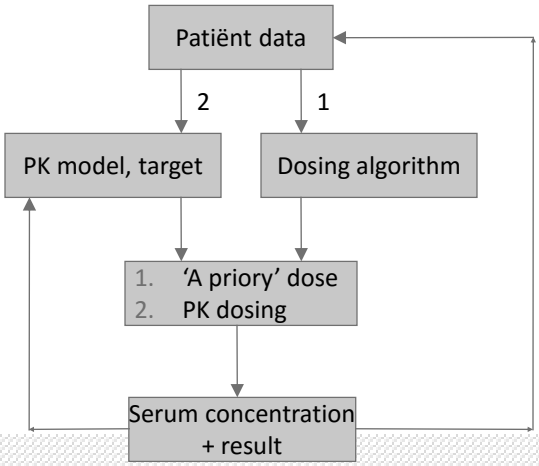
Dosing interval?

› Safe value for Cmin: 5-7 hrs <0,5 mg/L



Craig, JAC 1993

TDM schematic based on Bayes' principles:



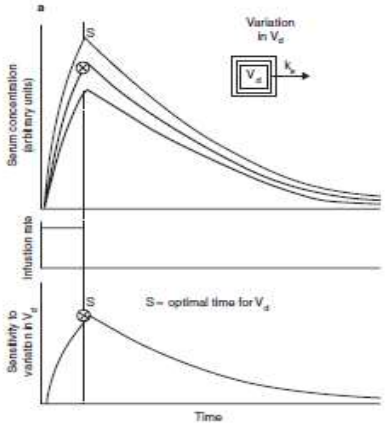
› Goal-oriented, model-based dosing:

- Patient characteristics
- Pharmacokinetic/ dynamic goals
- Pharmacokinetic model: covariates
- Reliability of the concentration data

When should you draw your samples?

Optimal sampling

- Why optimal sampling?
  - To reduce the number of blood samples
    - Reduce costs
    - Reduce burden and risk for the patient
- Which samples give the most information about the primary PK variables; Vd and clearance?

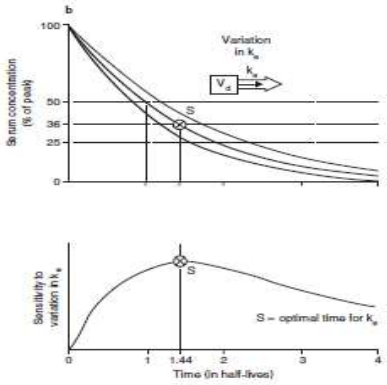


Volume of distribution:

› The result of the measurement of a blood sample immediately drawn after administration of an i.v. drug is the most sensitive to changes in the Vd

Clearance:

- The result of the measurement of a blood sample 1,44 x the half-life of a drug drawn after administration of an i.v. drug is the most sensitive to changes in the Cl



Practical protocol for tobramycin TDM

- Calculate ‘a priori’ dose based on BW
- Draw peak serum level 0.5 hrs after first dose
- Draw second level 1.44 x average $t_{1/2}$ after first dose
- Analyse the samples, calculate most probable individual PK parameters using Bayesian software
- Calculate next dose and dosing interval
- Repeat sampling

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Literature

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