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Symposium 5: TDM & Pharmacokinetics

Population pharmacokinetics modeling of vancomycin in non-critically ill pediatric patients

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Cuc Nguyen Thi
on behalf of research team
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Vancomycin – practical problems

**INTRODUCTION**

MIPD is a potential approach to address

- TDM: AUC-based estimated via Bayesian
- Recommendations related to using MIPD software

**ASHP REPORT**

Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring.

Evidence-based Guideline for Therapeutic Drug Monitoring of Vancomycin: 2020 Update by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society
Innovative approaches to optimizing in individual patients

Population pharmacokinetic model: important component part in MIPD software
- Developing model from the clinical data
- Selecting available model based on external validation & tweaking model (if possible)


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Clinical study design and data collection for popPK analysis of vancomycin

Sparse sampling strategy implemented in clinical practice setting:
- Serum concentrations of vancomycin obtained after the third dose.
- A set PK data including: 2 serum samples

<table>
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<th>Inclusion criteria</th>
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<tr>
<td>Subjects aged 1 month to 18 years (yr)</td>
</tr>
<tr>
<td>Receiving vancomycin for ≥ 48 hours (hr)</td>
</tr>
<tr>
<td>at least 1 serum vancomycin concentration</td>
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<table>
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<tr>
<th>Exclusion criteria</th>
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<tr>
<td>Subjects were on hemodialysis</td>
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<tr>
<td>Neonates, including prematures</td>
</tr>
<tr>
<td>Critically ill pediatric patient/in the intensive care unit (PICU)</td>
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Non-linear mixed-effects pharmacokinetic modeling & simulation: workflow

**METHODS**

**STEP 1: Optimizing structural model & statistical model**
- One-compartment *
- IIV: exponential
- RUV: additive/proportional/combined

Criteria: BICc index is smallest

**STEP 2: Covariate selection**
**SCM: stepwise approach**
- relationship: power
- Criteria:
  - forward inclusion: 
    \[ p < \sim 0.05; \Delta OFV > 3.84 \]
  - backward elimination: 
    \[ p < \sim 0.01; \Delta OFV > 6.64 \]

*: allometric weight model was applied for scaling PK parameter values

\[ P_i = P_{typ} \cdot \left( \frac{W_t}{W_{typ}} \right)^{PWR} \]

**STEP 3: Model diagnosis (internal validation)**
- GOF (goodness-of-fit)
- pcVPC (prediction-corrected Visual Predictive Check)
- PWRES/ NPDE vs. time, population predictions
- IWRES vs. individual predictions

Monolix software

\[ \text{Anderson et al 2006, Eur J Pediatr, 165(12):819–29} \]
Evaluate PTA in order to recommend dosage regimen:
• **Efficacy threshold:** $\text{AUC/MIC} \geq 400$, $\text{PTA} > 90\%$
• **Toxicity threshold:** $\text{AUC} > 600 \text{ mg.h/L}$, $\text{PTA} > 20\%$

**Methods**

**STEP 4: Simulation dosing regimens**

- **Model definition**
- **Treatments:**
  - 60 mg/kg/day
  - 75 mg/kg/day
  - 80 mg/kg/day
  - 90 mg/kg/day
  - 100 mg/kg/day
- **Covariates:** identified analysis process
- **Output:** probability of target attainment of dosing regimens
Exploratory data analysis: high variability VAN concentration

<table>
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<tr>
<th>Patient characteristics &amp; PK samples</th>
<th>Results (n = 27)</th>
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<tr>
<td>Age (years)</td>
<td>3.4 (2.1 – 7.8)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Baseline eGFR (mL/m/1.73m2)</td>
<td>206.2 ± 79.5</td>
</tr>
<tr>
<td>C1 (1-2 hrs after end of infusion)</td>
<td>18.7 (15.4 – 22.8)</td>
</tr>
<tr>
<td>C2 (30 ms prior to start of next dose)</td>
<td>7.0 (5.1 – 8.4)</td>
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Notes:
- Sampling strategy miss a lot of system distribution phase information
- Large interindividual variability was observed for both the observed C1 & C2 values
Formula:

\[
Cl(L/h) = Cl_{\text{pop}} \cdot (WT)^{\beta_1} \cdot \left(\frac{\text{Age}}{\text{Age}_{\text{med}}}\right)^{\beta_3} \cdot \left(\frac{\text{eGFR}}{\text{eGFR}_{\text{med}}}\right)^{\beta_4} \cdot e^{\eta_{Cl}}
\]

\[
V(L) = V_{\text{pop}} \cdot (WT)^{\beta_2} \cdot e^{\eta_{V1}}
\]

- WT: actual body weight
- Age\_med = 3.48 (median value of age)
- eGFR\_med = 194.5 (median value of eGFR)
Model diagnosis

GOF goodness-of-fit

\[ y = 1.008x + 0.1865 \]
\[ R^2 = 0.7057 \]

\[ y = 1.0949x - 0.9592 \]
\[ R^2 = 0.9035 \]

pcVPC

Internal validation: Model is useful

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Simulation dosing regimens

Probability of target attainment: AUC ≥ 400 (%)

Age and eGFR also contributed to variations in achieving the target AUC ≥ 400:
- PTA was dependent on the level of eGFR, or more precisely, decreasing with increasing eGFR.
- At the same eGFR level, PTA increasing with increasing age.

The empiric dosing of 45 mg/kg/day was inadequate to achieve the AUC/MIC target ≥ 400.
Doses ranging from **60 to 80 mg/kg/day** were necessary in children with normal renal function.
Simulation dosing regimens

Probability of target attainment: AUC < 600 mg.h/L (%)

With threshold related to safety, an inverse trend is observed...
Recommended dosing regimens

Selecting a weight-adjusted empiric vancomycin regimen should be based on: (1) age, (2) eGFR and (3) the local MIC distribution of MRSA to optimize treatment success while minimizing over-exposure and potentially adverse effects.
Conclusion:
▪ Population pharmacokinetic modeling: one-compartment, first-order elimination. Age, eGFR and weight were independent covariates on CL, and weight on Vd.
▪ Monte Carlo simulation: the initial dose of 60 mg/kg/day was adequate in most subjects with eGFR < 90 ml/min/1.73m². Higher dosing regimens 75-90 mg/kg/day were suggested for individuals with eGFR more than 90 ml/min/1.73m².

Perspectives:
▪ Advanced internal validation (bootstrap resampling techniques) and external validation popPK model
▪ Applying new recommended maintenance dose regimens and assess the probability of target attainment as well as the risk of nephrotoxicity. Integrating popPK model into the vancomycin precision dosing software based on AUC estimated Bayesian method
▪ Expand study pharmacokinetic to other special populations (critically ill patients, dialysis, neonates,...)

Lesson learned .......
“... In settings with limited resources, a sparse sampling strategy can be feasible as long as each step is carefully considered and executed.”
“....All models are wrong, but some are useful....”
Thank you for your attention!

Questions?
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