Early Bayesian Dose Adjustment of Vancomycin in Children: a Randomized Controlled Trial

R. Berthaud1,6, S. Benaboud1, M. Genuini2, S. Renolleau2, M. Oualha1,2, F. Lesage2, M. Castelle1, C. Briand2, S. Blanche1,3, S. Artru4, L. Norsa4, O. Boyer5, D. Hirt1, N. Bouazza1, JM. Treluyer1
1Paris Descartes University - Sorbonne Paris Cité University, Paris, France, EA 7323 - Pharmacology and Therapeutic Evaluation in pregnant women and children. 2Necker-Enfants Malades hospital - Assistance Publique-Hôpitaux de Paris, Paris, France, 2Pediatric Intensive Care Unit, 3Department of Pediatric Immun-hematology, 4Department of Pediatric Gastroenterology, 5Department of Pediatric Nephrology.

INTRODUCTION

- Methicillin-resistant staphylococcal infections are still a global burden.
- AUC/MIC is the PK parameter that best predicts vancomycin efficacy.
- Vancomycin pharmacological target is narrow and difficult to achieve because of a wide interindividual variability, especially in children.

Aim: to assess if an early Bayesian dose adjustment of vancomycin would increase the rate of target attainment, at the 24th hour of treatment.

METHODS

Study design
- Prospective randomized controlled trial with 2 parallel groups.
- Necker-Enfants Malades teaching hospital, from February 2016 to February 2017:
  - pediatric intensive care unit,
  - department of pediatric gastroenterology and hepatology,
  - department of pediatric immuno-hematology,
  - department of pediatric nephrology.

Inclusion criteria
- Age from 3 months to 17 years,
- Weight (Wt) > 4 kilograms,
- Serum creatinine (SCr) < 250 µmol/L,
- No renal replacement therapy at the time of inclusion.

Procedures
- Bayesian group
  - Randomization
  - 1st admin
  - Bayesian dose adjustment
  - TDM (Therapeutic Drug Monitoring)
  - H3
  - H6
  - H24
  - Follow-up
  - D7
- Control group

Figure 1 Procedures. TDM: Therapeutic Drug Monitoring.

Population based pharmacokinetic model

\[
CL = 0.248 * Wt^{0.75} * (0.48/SCr)^{3.61} * \ln\text{(Age)}/7.8^{0.995}
\]

\[
Vd = 0.636 * Wt
\]

CL: Vancomycin clearance (L/h); Vd: Volume of distribution (L);
SCr (mg/dL); Wt (kg); Age (d)

Primary Endpoint: Proportion of patients with \(400 \leq \text{AUC}_{0-24}/\text{MIC} \leq 800\) h.


RESULTS

Table 1 Patients baseline characteristics

<table>
<thead>
<tr>
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<th>Total n = 99</th>
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<tr>
<td>Median age, y (Min-Max)</td>
<td>4.5 (0.2-17.4)</td>
</tr>
<tr>
<td>Median weight, kg (Min-Max)</td>
<td>13.9 (4-85)</td>
</tr>
<tr>
<td>Median SCr, µmol/L (Min-Max)</td>
<td>26 (9-160)</td>
</tr>
</tbody>
</table>

Figure 3 Inclusions distribution: Per protocol population: Control: 42 patients / Bayesian: 40 patients.

Primary Endpoint

- 85% Patients in the target range at H24
- \(p = 0.007\)

Figure 4 Proportions of patients with a vancomycin exposure, for the first 24 hours of treatment, in the target range (n=82).

Target range: \(\text{AUC}_{0-24}/\text{MIC} \geq 400\) and \(\text{AUC}_{0-24}/\text{MIC} \leq 800\)

The most frequent reason of vancomycin initiation was the suspicion of central venous catheter-related bloodstream infection in 68% of patients.

Nephrotic drugs administered in association to vancomycin: only 19% of patients didn’t receive any other nephrotoxic drug, 56% of patients received \(\geq 2\) nephrotoxics.

Table 2 Iatrogenicity

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Bayesian</th>
<th>Total n=81</th>
</tr>
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<tbody>
<tr>
<td>Red man syndrome</td>
<td>2</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>SCr increase</td>
<td>6</td>
<td>4</td>
<td>12%</td>
</tr>
</tbody>
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No statistically significant difference.

CONCLUSION

- An early Bayesian dose adjustment of vancomycin significantly increase pharmacological target attainment in children at the 24th hour of treatment.
- Attaining quickly vancomycin target could improve the clinical outcome of methicillin-resistant staphylococcal infections.