AUC-Based Vancomycin Monitoring

A LEARNING CURVE

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Abstract #25
IRB Approved

Disclosures
• Danielle Trierweiler
• Potential conflicts of interest: none
• Sponsorship: none
• Proprietary Information or results of ongoing research may be subject to different interpretations
• This presentation is educational in nature and the speaker agrees to abide by the non-commercialism guidelines provided

Learning Objectives

At the end of this presentation participants should be able to...

1. Compare and contrast AUC-based therapeutic drug monitoring and traditional trough-only monitoring
2. Identify critical components of implementation of AUC-based monitoring of vancomycin

A Quick Review of the Literature

Murine Infection Models
Demonstrated AUC24:MIC is the optimal PK/PD parameter for vancomycin efficacy

2009 Vancomycin Guidelines
Established trough above 15 mcg/mL are associated with increased vancomycin-associated nephrotoxicity independent of other known risk factors

Bosso, et.al. 2011
Suggest troughs do not correlate well with AUC24:MIC and AUC24:MIC goal of ≥ 400 mcg*hr/mL can be achieved at lower troughs of 10-15 mcg/mL

Heil, et.al. 2018
Increasing data is being published to support AUC-based monitoring with an AUC24:MIC goal of 400-600 mcg*hr/mL

AUC-guided dosing and monitoring can be accomplished in one of two ways. One approach relies on the collection of two concentrations (one near steady-state, post-distributional Cmax at 1-2 hours post infusion and trough) during the same dosing interval and utilizing first-order PK equations to estimate the AUC. The preferred approach to monitor AUC involves the use of Bayesian software programs.

Therapeutic monitoring of vancomycin: A revised consensus guideline and review of the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society for Healthcare Epidemiology of America.

References

A Quick Review of the Literature

Table

<table>
<thead>
<tr>
<th>Year</th>
<th>Model</th>
<th>MIC Goal</th>
<th>Trough Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>-</td>
<td>15</td>
<td>10-15</td>
</tr>
<tr>
<td>2011</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2014</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>2018</td>
<td>-</td>
<td>-</td>
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Recommendation #1
Based on the current body of evidence of vancomycin PK/PD and clinical outcomes in patients with serious MRSA infections, a Bayesian-derived AUC:MIC ratio of 400 to 600 (assuming a vancomycin MIC of 1 mg/L) should be advocated as the target to achieve clinical efficacy while improving patient safety (I A+).

Recommendations #2 & 3
AUC-guided dosing and monitoring can be accomplished in one of two ways. One approach relies on the collection of two concentrations (one near steady-state, post-distributional Cmax at 1-2 hours post infusion and trough) during the same dosing interval and utilizing first-order PK equations to estimate the AUC. The preferred approach to monitor AUC involves the use of Bayesian software programs.
BREAKING NEWS

Recommendation #1
Based on the current body of evidence of vancomycin PK/PD and clinical outcomes in patients with serious MRSA infections, a Bayesian-derived AUC:MIC ratio of 400 to 600 (assuming a vancomycin MIC of 1 mg/L) should be advocated as the target to achieve clinical efficacy while improving patient safety (IA+).

Recommendations #2 & 3
AUC-guided dosing and monitoring can be accomplished in one of two ways. One approach relies on the collection of two concentrations (one near steady-state, post-distributional Cmax at 1-2 hours post infusion and trough) during the same dosing interval and utilizing first-order PK equations to estimate the AUC (trapezoidal rule). The preferred approach to monitor AUC involves the use of Bayesian software programs.

Our Study
IMPAKT OF A PHARMACIST-DRIVEN, AUC-BASED THERAPEUTIC DRUG MONITORING APPROACH ON OUTCOMES IN PATIENTS AT HIGH RISK FOR VANCOMYCIN-RELATED NEPHROTOXICITY.

Study Objectives
• Compare AUC-based therapeutic drug monitoring to traditional trough-targeted monitoring
• Validate an AUC-based dosing approach utilizing two-level kinetics and the trapezoidal rule, via a spreadsheet-based AUC calculator at Norman Regional Health System
• Determine whether there is an association between attaining a vancomycin trough level within a specified range and reaching a calculated AUC24/MIC of greater than 400 mcg*hr/mL

Methods
STUDY DESIGN AND PATIENT POPULATION

Norman Regional Health System
• Three campuses
  • Porter
  • Healthplex
  • Moore
• Acute care community hospital
  • ~ 400 beds
• Outpatient infusion center

Patient Population

Study Design
• Prospective pharmacokinetic study conducted at a 387 bed acute care community hospital
  
Inclusion
• 18 years of age
• Pharmacy dosing consult
• Reached steady state on a regimen

Exclusion
• Patients with renal impairment or instability defined as:
  • CrCl less than 30 mL/min using Cockcroft-Gault
  • Absolute increase of SCr of greater than 0.5 or a rise of greater than 50% in the first 48 hours
  • Pregnancy
Methods Continued

- Peak and trough vancomycin serum concentrations drawn at steady state
- AUC \(_{24}\) calculated using the trapezoidal rule via an Excel\textsuperscript{®}-based calculator
- AUC \(_{24}\) and trough values reviewed by a pharmacist
- Assess the need for intervention
- Patients also reviewed for vancomycin-related nephrotoxicity defined as:
  - Creatinine clearance less than 30 mL/min using Cockroft-Gault
  - Absolute increase in serum creatinine of greater than 0.5 mg/dL
  - A rise of greater than 50% following initiation of vancomycin therapy.

Patient Population

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Male Gender</th>
<th>Caucasian</th>
<th>Native American/Alaskan</th>
<th>Hispanic, African American</th>
<th>Average Age</th>
<th>Average Height</th>
<th>Average Weight</th>
<th>Average BMI</th>
<th>Absolute WBC</th>
<th>SCr</th>
<th>ID consult</th>
<th>Targeted Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>65/65 (58.5%)</td>
<td>58/65 (89.2%)</td>
<td>5/65 (7.69%)</td>
<td>1/65 (1.5%)</td>
<td>57</td>
<td>171.78 cm (67.6 inches)</td>
<td>92.02 kg (202.4 lbs)</td>
<td>35.97</td>
<td>14.02 *10(^9)/L</td>
<td>1.08 mg/dL</td>
<td>30/65 (46.1%)</td>
<td>16/65 (24.6%)</td>
</tr>
</tbody>
</table>

Risk Factors

- BMI > 30: 60/65 (30.7%)
- BMI > 40: 11/65 (16.9%)
- Concomitant piperacillin/tazobactam: 60/65 (90.0%)
- Diabetes: 26/65 (40.0%)

Definitions and Equations

- AUC \(_{24}\): Area under the curve over 24 hours
- MIC: Minimum inhibitory concentration
- Trapezoidal rule: Technique for approximating the area under a curve by calculating the area of individual trapezoids and then finding their sum
- Bayesian logic: using the knowledge of prior events to predict future events
- Bayesian software: software that uses population means to estimate AUC \(_{24}\) using a single level
- Cockroft-Gault equation: \[(140\text{-age})(\text{weight in kg})/(72\times\text{SCr})\] – multiply by 0.85 for females
- Matzke equation: \[K_{el} = 0.00083\times\text{CrCl} + 0.0044\]

Calculations

- Empiric Dosing Calculator
- Peak and trough levels drawn at steady state
- AUC \(_{24}\) calculated using trapezoidal equations via spreadsheet
- Three calculators
  - Same line
  - Around one dose
  - Dose between

Data Collection

- Impact of a Pharmacist
- Impact of AUC
- Impact of Vancomycin-related Nephrotoxicity

Danielle Trierweiler, Justin Booth, Norman Regional Health System, Norman, OK.
Baseline Data  
**Collected from October 1, 2018 – October 31, 2018**

<table>
<thead>
<tr>
<th>Trough (mg/mL)</th>
<th>Number of Patients</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>25</td>
<td>38.4%</td>
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<tr>
<td>10 – 15</td>
<td>36</td>
<td>54.6%</td>
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<tr>
<td>15 – 20</td>
<td>31</td>
<td>47.7%</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>10</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Average Trough: 11.7 mcg/mL

Data Collected

**Demographics and characteristics**
- Age, gender, race, height, weight, BMI, diagnosis of diabetes, indication, use of piperacillin/tazobactam

**Laboratory data**
- CBC, WBC, culture results (identification and susceptibility)

**Vancomycin administration**
- Doses, dosing intervals, times of administration, infusion times, and serum concentrations

**Measured outcomes**
- Calculated AUC, vancomycin-related adverse events

**Results**

**Results Continued**

**Results Continued**
Discussion

Impact of a Pharmacist-driven, AUC-driven monitoring approach on outcomes in patients at high risk for vancomycin-related nephrotoxicity. Danielle Trierweiler, Justin Booth, Norman Regional Health System, Norman, OK.

Implementation
- Getting Buy In
- Education
- Communication
- Inter-professional Collaboration
- Problem Solving
- Quality Assurance

Problem Solving
- Trough is less than 10 mcg/mL but AUC is high?
  - Consider smaller dose with increased frequency
- Who is at the highest risk for AKI?
  - Obesity
  - Diabetes
  - Concomitant use of piperacillin/tazobactam
- Trouble timing levels?
  - Alternative scheduling for levels

Limitations
- This study was not powered to evaluate patient-centered outcomes
- Use of Bayesian software programs is the recommended strategy for calculating AUC
- No control group comparisons
- No statistical evaluation

Future Directions
- Continue collection of AUC data and perform a retrospective cohort study to compare AUC-based monitoring to traditional trough only monitoring
- Compare spreadsheet based calculations to Bayesian software calculations of AUC
- Attempt to identify the patient population who would most benefit from AUC-based monitoring

Conclusions
- Use of AUC-based therapeutic drug monitoring provides pharmacists with additional information for clinical decision making when managing vancomycin
- This study shows that AUC-based monitoring using an Excel®-based calculator can be effectively implemented in a community health system
- Although further studies are needed to evaluate the impact of AUC-based monitoring on patient outcomes, the findings of this study suggest that trough levels exceeding 15 mcg/mL are not always necessary to achieve a goal AUC greater than 400 mcg/mL
Acknowledgements

• Justin Booth PharmD, BCPS, Research Preceptor
• Debbie Poland PharmD, BCPS, Residency Program Director
• Clinical Pharmacy Team at NRHS

Self Assessment

• The desired AUC24/MIC target for treatment of S. aureus is:
  • ≥ 600 mg·hr/L
  • ≤ 400 mg·hr/L
  • 400 – 600 mg·hr/L
  • 600 – 800 mg·hr/L

Self Assessment

• AUC-based vancomycin monitoring does not require a multidisciplinary approach.
  • True
  • False

Self Assessment

• AUC-based vancomycin monitoring does not require a multidisciplinary approach.
  • True
  • False

References


