Determination of pharmacokinetic/pharmacodynamic index for patients treated with high-dose vancomycin by continuous infusion

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Background

• a vancomycin $AUC_{24h}/MIC$ ratio $\geq 400$ (h$^{-1}$) is necessary for optimal therapy (Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42)

• we have to take into account *Staphylococci* with decreased susceptibility to vancomycin (Tenover FC et al. CID 2007; 44: 1208-1215)
  – associated with higher rates of clinical failure
  – not always detected by standard laboratory methods

• continuous infusion is easier for nursing and for therapeutic drug monitoring (TDM) than every 12h dosing (Wysocki et al AAC 2001; 45:2460-2467)
Aim of the study

Does high dose vancomycin, administered by continuous infusion, allow to attain an AUC$_{24h}$/MIC ratio $\geq$ 400 (h$^{-1}$) in patients with infections caused by organisms with increased MIC’s?
Which vancomycin serum concentration should we target?

**Efficacy**

- Geometric mean MIC = 1.75 mg/L
- VAN serum conc. (mg/L)
- 29.2
- 50

**Toxicity**

-Css vancomycin > 28 mg/L increased risk for nephrotoxicity [OR 21.236; P = 0.004]


Which vancomycin serum concentration should we target?

\[ C_{ss} = 25-30 \text{ mg/L} \]
Methods

• administration scheme
  – loading dose: 20 mg/kg
  – infusion rate: 2.5 g/day adapted to renal function and adjusted by a clinical pharmacist
Methods: (2)

- determination of total vancomycin serum levels:
  - CMIA: Architect®, Abbot Diagnostics, Solna, Sweden
- determination of MIC’s:
  - E-test: AB BIODISK, Solna, Sweden
Results

- patients: n=54 (40 documented infections)
- treatment duration:
  - 1 to 37 days
  - mean: 12 ± 10 days
- isolates
  - MRSA: 14
  - MSSA: 6
  - coagulase negative Staphylococci: 16
  - Other: 4
- MIC-range: 0.25 - 3 mg/L
Results (2)

vancomycin concentrations measured over time in patients treated by continuous infusion

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Target concentration range was reached and remained constant after 48h (infusion rate adjusted by a clinical pharmacist)

statue of Fred Bellefroid, Louvain
Results (3)

Important inter- and intra-individual variability in vancomycin serum concentrations measured despite dose adjustment by clinical pharmacist.
Results (4)

- \( \text{AUC}_{24h} / \text{MIC} \) ratio
  - mean: 525 +/- 83.4 h\(^{-1} \) [196 - 2684 h\(^{-1} \)]
  - \( \text{AUC}_{24h} / \text{MIC} \) of 400 h\(^{-1} \) was achieved in only 46% of cases
Results (5)

low target attainment in patients infected with organisms having MIC’s ≥ 1.5 mg/L
Conclusion

• high dose VAN by CI with dose adjustment by TDM did allow to maintain the mean VAN concentration within the target concentration range after the first 48h

• a high variability in VAN concentrations measured was observed despite dose adjustment by a clinical pharmacist

• due to this variability and the high prevalence of organisms with reduced susceptibility to VAN, an AUC$_{24h}$/MIC ratio $\geq 400$ (h$^{-1}$) was not reached in all patients

• patients infected with organisms having MIC’s $>1.5$ mg/L should be considered at risk for treatment failure

• the PK/PD data observed in this study further suggest that lowering the current susceptibility breakpoint of VAN is justified
  • EUCAST: susceptible if MIC $\leq 4$ mg/L
  • CLSI: susceptible if MIC $\leq 2$ mg/L
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