Continuous Infusion of Vancomycin in non-ICU Patients

Why, How and What's the Benefit?

These slides are from the public presentation of the Thesis of Els Ampe (Dr Pharm Sci.)
See the originals at
http://www.facm.ucl.ac.be/PhD_and_MSc_dissertations.htm#PhD_Theses
General introduction:

- glycopeptide AB isolated from a soil sample from Borneo containing *Amycolatopsis Orientalis* (1950’s)
- inhibits bacterial cell wall synthesis
- limitations
  - slow killing rate
  - limited tissue penetration
  - organisms with decreased susceptibility
  - higher doses lead to increased toxicity
- still 1st line treatment of most methicillin-resistant Gram-positive infections
General introduction
how to optimize vancomycin treatment

Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid. Craig W. et al., Infect Dis Clin N Am 17 (2003)

Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections
Moise-Broder P. et al., Clin Pharmacokinet 2004; 43 (13)
General introduction
how to optimize vancomycin treatment

AUC_{24h} / MIC = 400
General introduction
Vancomycin TDM at CHU Mont-Godinne at the start of the project

- **Concentration (mg/L) at 3rd VAN dose** (VAN BID 1g q12h)
  - **Peak level**: 30-40 mg/L 2 h after the end of infusion
  - **Trough level**: 5-10 mg/L just before the next dose

- **MIC**

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October 2017
vancomycin continuous infusion
Vancomycin administration and therapeutic drug monitoring (TDM) from a quality of care perspective
Vancomycin TDM at CHU Mont-Godinne at the start of the project

Time (h) | Peak level: 30-40 mg/L 2 h after the end of infusion
0 6 12

Conc. (mg/L) | Trough level: 5-10 mg/L just before the next dose
0 10 20 30 40

MIC

October 2017
vancomycin continuous infusion
Observational study – results

*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

40% incorrect sample timing
Observational study – results

Observed deviations (in min) from recommended sampling times at baseline.

vancomycin peak (n=49)

-150 to -90: 10%
-90 to -30: 10%
-30 to +30: 40%
+30 to +90: 20%
+90 to +150: 10%
> 150: 10%

vancomycin trough (n=83)

-60 to -30: 5%
-30 to +30: 60%
+30 to +60: 10%
+120 to +180: 20%
+60 to 120: 5%
> 180: 5%

*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose
### Observational study – results

**TDM process measures** for twice daily (BID; baseline) mode of administration of vancomycin

<table>
<thead>
<tr>
<th>Criterium</th>
<th>BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample timing within 30 min. from scheduled time</td>
<td>61.3% [81/132] (^a)</td>
</tr>
<tr>
<td>Implementation of TDM dose recommendations</td>
<td>32% [21/66]</td>
</tr>
<tr>
<td>Prescribed daily dose in accordance with hospital guidelines</td>
<td>17% [95/560]</td>
</tr>
<tr>
<td>% of serum levels in the recommended ranges</td>
<td>33.3% [37/112] (^b)</td>
</tr>
</tbody>
</table>

\(^a\) number of total observations (see Table 1 for the number of patients)

\(^b\) most deviations were towards lower than expected values (average: 20%)
Qualitative methods in healthcare

<table>
<thead>
<tr>
<th>Quantitative methods (clinical trials)</th>
<th>Qualitative methods (interviews, observations, notes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘how many’?</td>
<td>‘why?’ and ‘how?’ (hypothesis generating)</td>
</tr>
<tr>
<td><strong>what is the % of inappropriate TDM?</strong></td>
<td><strong>why/how does inappropriate TDM occur?</strong></td>
</tr>
<tr>
<td><strong>what is the impact of x on this %?</strong></td>
<td></td>
</tr>
<tr>
<td>large, random samples</td>
<td>small, purposive samples</td>
</tr>
</tbody>
</table>
Qualitative study – results

Emerging themes identified during the analysis of the transcripts of the focus groups and related to low TDM performance and deviations from local TDM guidelines during the baseline phase (BID).

| Socio-cultural and structural elements | - inertia of practice  
|                                       | - lack of motivation and personal involvement  
|                                       | - insufficient interdisciplinary collaboration  
|                                       | - unclear definition of responsibilities  
|                                       | - ill-adapted techniques  
| Training and information              | - insufficient (post-) graduate education  
|                                       | - ‘teacher-centred’ learning approach  
|                                       | - incomplete and/or difficult to apply local guidelines  
|                                       | - conflict between local guidelines and external guidelines  
| harm-benefit ratio of TDM             | - patient too frail  
|                                       | - unnecessary samplings for the information gained |
Qualitative study – results

M2: “I'm convinced that there are pharmacokinetic calculations on which we will base [our next dosing] and which are erroneous because the sample drawing and the timing of the administration have not been made correctly, it is completely random, I mean…”

M1: “It is forbidden, on my ward, to follow the therapeutic recommendations of the laboratory, what the lab proposes.”

N2: “It represents a lot of additional samples for frail patients. Sometimes, I ask myself whether all these samples are necessary.”
Discussion

- combined observational and qualitative approach
  - identify factors related to poor performance.
- only “process measures”, no “outcome measures”
  - limited number of patients in the observational study (could not be extended for ethical reasons)
- studies performed in one single hospital prevents from generalization but the results can be decontextualized, this applies to:
  - similar baseline TDM scores have recently been observed in other European hospitals (Bailie GR *et al* Therapeutic Drug Monitoring 1988; vol: 10 p292-p295, Roustit M *et al* Scand J Infect Dis 2010; vol 42:177-184)
  - organisational and structural issues and aspects related to training including passive attitude towards learning have been identified elsewhere
- “Hawthorn effect”
how to optimize vancomycin treatment

“Continuous infusion is easier because it allows to control the duration of administration and samples can be taken at any time”
TDM of vancomycin by continuous infusion

AUC24h /MIC independent of the mode of administration

Concentration (mg/L)

Time (h)

continuous infusion

twice daily dosing
Vancomycin administration and therapeutic drug monitoring from a PK/PD perspective

Implementation of a Protocol for Administration of Vancomycin by Continuous Infusion: Pharmacokinetic, Pharmacodynamic and Toxicological aspects

E. Ampe, PharmD; B. Delaere, MD; J.D. Hecq, PharmD, PhD; P.M. Tulkens, MD, PhD; Y. Glupczynski, MD

vancomycin CI: which serum concentration should we target?

Data from a recent study point at a vancomycin $AUC_{24h}/MIC$ of at least 400 to obtain optimal clinical outcome in patients with $S. aureus$ lower respiratory tract infections (Moise-Broder et al., Clin Pharmacokinet. 2004;43(13):925-42)

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>minimal AUC (mg*L$^{-1}$*h)</th>
<th>target Css (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>16.6</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>33.3</td>
</tr>
<tr>
<td>4</td>
<td>1600</td>
<td>66.6</td>
</tr>
</tbody>
</table>
vancomycin CI: which serum concentration should we target?

![Diagram showing vancomycin serum concentrations](image)

- **MIC = 1.5 mg/L**
- **25-30 mg/L**

vancomycin CI: which serum concentration should we target?

**efficacy**

- VAN serum conc. (mg/L)
  - 50
  - 28.0
  - 25-30 mg/L
  - MIC = 1.5 mg/L

**toxicity**

- $C_{ss}$ vancomycin $> 28$ mg/L en increased nephrotoxicity risk
  - [OR 21.236; $P = 0.004$]

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How to reach the serum target concentration target with CI?
1. loading dose: the correct scheme *

\[ C_t = \frac{D_l}{V_d} \]

* assuming linear pharmacokinetics

**loading dose** (in mg/kg) = \( C_t \) (mg/L) x \( V_d \) (L/kg)

**loading dose** (in mg/kg) = 20 mg/kg = 25 (mg/L) x 0.8 (L/kg)
How to reach the serum target concentration target with CI?  
2: infusion *

$$\text{Target serum concentration}$$

$$C_{ss} = \frac{K_o}{Cl}$$

$$\text{Clearance} *$$

$$\text{infusion rate}$$

$$\text{daily dose} (\text{in mg}) = 24 \times \text{clearance} (\text{L/h}) \times C_{ss}$$

* assuming linear pharmacokinetics
How to reach the serum target concentration target with CI?

2: infusion *

\[ \text{In} = \text{infusion} \]

\[ \text{Out} = \text{clearance} \]

once a bath is at the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which must be equal: in = out...)

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance.
2. Clinical evaluation: study outline

- eligible patients (n=130)
  - discontinuous infusion (n=18)
  - CrCl <30 mL/min (n=13)
  - moribund patients (n=5)

- enrolled patients (n=94)

- clinical evaluation

- toxicity (n=94)
  - neutropenic fever [n=12]
  - concomitant infection at another site [n=10]
  - unconfirmed diagnosis [n=12]

- efficacy (n=59)
  - neutropenic fever [n=12]
  - concomitant infection at another site [n=10]
  - unconfirmed diagnosis [n=12]
2. Pharmacokinetic evaluation: study outline

- MIC determination (n=52) → enrolled patients (n=94)
- enrolled for PK analysis (n=56) → insufficient PK data (n=11)
- PK evaluable patients (n=48) → detailed PK analysis
- PK/PD evaluable patients (n=32)

*a signed informed consent for additional blood sampling
*b standard of care only
2. Relationship between $\text{AUC}_{24h}/\text{MIC}$ and clinical efficacy: outline

enrolled for PK analysis (n=56)\(^a\)

PK evaluable patients (n=48)

no MIC available

PK/PD evaluable patients (n=32)

multiple bacteria or multiple antibiotics (n=12)

correlation
PK/PD – clinical outcome of vancomycin (n=20)

\(^a\) signed informed consent for additional blood sampling

\(^b\) standard of care only
4. Efficacy in clinically evaluable patients (n=59)

- clinical cure:
  (i) disappearance of all major signs of infection;
  (ii) normalization of body temperature;
  (iii) marked decrease of CRP.
- at EOT and at 6 months
- assessment retrospectively validated by 2 ID physicians

Diagram:
- Cure (74.6%)
- Failure (15.3%)
- Improvement (10.2%)
3. Toxicity

Adverse events observed in all enrolled patients (n = 94).

- at least 1 adverse event: 13.8%
- nephrotoxicity ‘possible’ ADE multiple RF
- treatment discontinuation in only 2 cases

2 or 3 documented increases in serum creatinine level; increase of 0.5 mg/dL OR ≥ 50% increase from baseline after several days of vancomycin therapy.
7. Total vancomycin serum concentrations

target concentration reached at time 0 h

total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)
7. Total vancomycin serum concentrations

A total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)

- decline to 20 mg/L within 6h (initial infusion rate to low)
7. Total vancomycin serum concentrations

A total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)

After increasing the rate of infusion (in 57% of patients), targeted value reached and maintained from 96h
7. Total vancomycin serum concentrations

- deviations of >10 mg/L according to the recommended range
  - ➔ if increased CCrCl (threshold at >104 mL/min)
  - ➔ if concomitant use of diuretics

B
successive vancomycin serum levels values in individual patients with > 3 determinations after the first 96h of treatment (n = 52)
8. Free (unbound) vancomycin serum concentrations (n=30)

large variation in the free/total concentration ratio among individual samples
8. Free (unbound) vancomycin serum concentrations (n=30)

The correlation between free and total concentrations was satisfactory at the population level ($r^2=0.77$).
9. AUC\textsubscript{24h}/MIC predictive of clinical success/failure (n=20)

- Recursive partitioning analysis
- best AUC/MIC split value separating failure from success:
  - 667 (total serum concentration)
  - 452 (free serum concentration)
Discussion

- Steady state target concentration reached and maintained
- Efficacy comparable to other studies
- Acceptable safety profile despite higher target range (25-30 mg/L)
- High inter- and intra-patient variability => need for TDM
- Limited number of patients, heterogeneous patient population, no prospective control group
- Re-evaluation of initial infusion rate
- Higher AUC\textsubscript{24h}/MIC-ratio of 667 necessary for optimal efficacy in our context … MIC of 1 mg/L is probably the limit for vancomycin…
Observational study – results after implementation of CI

TDM process measures for twice daily (BID; baseline) mode of administration of vancomycin

<table>
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<tr>
<th>Criterium</th>
<th>BID</th>
<th>continuous infusion</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Sample timing within 30 min. from scheduled time</td>
<td>61.3% [81/132]</td>
<td>97.0% [217/224]</td>
<td>p&lt;0.0001*</td>
</tr>
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<td>Implementation of TDM dose recommendations</td>
<td>32 % [21/66]</td>
<td>94.4% [205/218]</td>
<td>p&lt;0.0001*</td>
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<td>Prescribed daily dose in accordance with hospital guidelines</td>
<td>17% [95/560]</td>
<td>86% [1395/1622]</td>
<td>p&lt;0.0001 **</td>
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<td>% of serum levels in the recommended ranges</td>
<td>33.3% [37/112]</td>
<td>66.8% [159/238]</td>
<td>p&lt;0.0001*</td>
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* Fisher exact test two sided
** Chi-square two sided (because of the large number of observations)

*a* number of total observations (see Table 1 for the number of patients)

*b* most deviations were towards lower than expected values (average: 20 %)
qualitative study – results one year after the end of the study

Implementation of CI by physicians

<table>
<thead>
<tr>
<th></th>
<th>mean (%)</th>
<th>min-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of CI</td>
<td>99</td>
<td>95-100</td>
</tr>
<tr>
<td>Follow-up TDM</td>
<td>96</td>
<td>95-100</td>
</tr>
<tr>
<td>recommendations</td>
<td></td>
<td></td>
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qualitative study – results one year after the end of the study

### Global satisfaction of HCP with CI

<table>
<thead>
<tr>
<th></th>
<th>Global satisfaction score* ( /5)</th>
<th>min-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians** (n=7)</td>
<td>4.5</td>
<td>4-5</td>
</tr>
<tr>
<td>nurses (n=10)</td>
<td>4.3</td>
<td>3.5-5</td>
</tr>
<tr>
<td>laboratory personnel (n=8)</td>
<td>4.4</td>
<td>4-5</td>
</tr>
</tbody>
</table>
Qualitative study – results after implementation of CI

M7: “Before even trough samples were obtained incorrectly. They were often just performed together with the other blood sampling without taking care of correct sample timing. Now with CI, samples are always performed correctly.”

M7: “We follow dose recommendations. In my opinion treatment follow up is better now and I feel patients are treated correctly.”

N1: “We perform just one sampling in the morning for all the scheduled blood analysis. We hardly ever perform additional samples for TDM only anymore.”
Final conclusions

- Hospital-wide implementation of CI is feasible and well accepted by health care professionals.
- Centralized preparation facilitated nursing and was perceived as contributing to the quality of care.
- Clinical Pharmacists can play an important role in the development and implementation of transversal quality improvement strategies.
- CI may help optimizing vancomycin usage in the absence of pharmacokinetic services and may improve the quality of these services if available.
Perspectives

• application to other area’s of pharmacotherapy?
  – from a ‘quality of care’ perspective:
    • factors underlying inappropriateness identified in other area’s of drug therapy
    • intervention proved positive impact on quality of administration and TDM
  – from a PK/PD perspective:
    • special patient populations (hyperclearance, morbidly obese patients, patients infected with a certain type of organism…)
    • Other AUC or time-dependent drugs (e.g. β-lactams, antifungals…)
    • ‘On line’ monitoring
  – from a clinical/hospital pharmacist perspective:
    • standardization of drug preparation/administration
    • opportunities for clinical pharmacy services (TDM recommendations, drug incompatibilities…)
  – from a hospital administrator perspective
    • cost-effective?
Thank you for your attention!!