Update on PK/PD of antibiotics applied to critically ill patients: Focus on β-lactams and vancomycin

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The slides are available for download from http://www.facm.ucl.ac.be → Lectures
A quick reminder of drug pharmacodynamics...

- **\(E_{\text{max}}\)**: Maximal effect
- **\(E_{\text{50\%}}\)**: Intermediate effect
- **\(E_{\text{min}}\)**: Minimal effect

The graph shows the relationship between concentration and effect, with key points labeled for EC\(_{50}\) and the maximal effect. The equation for the intercept is given as \(\ln \text{EC}_{50} - 2\). The slope is \(\frac{E_{\text{max}}}{4}\).
In chemotherapy, aim for a maximal effect!

This is what you should aim for in chemotherapy.
Pharmacodynamics of antibiotics…

S. aureus

log extracellular concentration (X MIC)

Δ log CFU/mg prot. from time 0

oxacillin

gentamicin

$E_{\text{min}}$

$E_{\text{max}}$

It looks as if they are all concentration-dependent…

But here comes pharmacokinetics …

Weak concentration-dependence (max. effect over the $C_{\text{min}} - C_{\text{max}}$ range)

→ TIME will emerge as the main parameter in vivo

$C_{\text{min}} - C_{\text{max}}$

high concentration-dependence over the $C_{\text{min}} - C_{\text{max}}$ range

→ the time is less important than the actual concentration

• $C_{\text{min}} - C_{\text{max}}$: Principles and Practice of Infectious Diseases, 7th Ed. Mandell et al. eds., Elsevier
PK parameters governing the activity of antibiotics

- $C_{\text{max}} / \text{MIC}$
- $f_T > \text{MIC}$
- $\text{AUC}_{24h} / \text{MIC}$

Concentration vs. Time (h)

0 6 12 18 24
The three main groups of antibiotics

<table>
<thead>
<tr>
<th>Class</th>
<th>Driving PK/PD parameter</th>
<th>Symbol</th>
<th>What to do?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactams</strong></td>
<td>• time during which the free* concentration is &gt; MIC</td>
<td>$fT_{&gt;_{MIC}}$</td>
<td>• frequent administrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• extended/continuous infusion</td>
</tr>
<tr>
<td>aminoglycosides and fluoroquinolones</td>
<td>• free* concentration &gt; MIC → bactericidal rate</td>
<td>$fC_{max}/MIC$</td>
<td>• get a peak !</td>
</tr>
<tr>
<td></td>
<td>• free* AUC/MIC ratio → global effect</td>
<td>$fAUC_{24h}/MIC$</td>
<td>• total daily dose</td>
</tr>
<tr>
<td>most other antibiotics</td>
<td>• free* AUC/MIC</td>
<td>$fAUC_{24h}/MIC$</td>
<td>• total daily dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• schedule accord. to half-life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• continuous infusion</td>
</tr>
</tbody>
</table>

* For most antibiotics, only the free fraction is active
Fig. 2.6  Change in log\textsubscript{10} CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)
Beta-lactams …in a nutshell…

• Every antibiotic is concentration-dependent (simple pharmacological principle) …

• **BUT**, for β-lactams, activity if already optimal when the concentration exceeds the MIC by 3 to 4-fold, which is what easily happens with conventional administration… and bacteria with low MICs

• **AND**, having no post-antibiotic effect, β-lactams need to stay above the MIC (preferably 4-fold…) for the maximum time…

Medical controversies by H. Daumier (1808-1879)
PK/PD questions about β-lactams: PK/PD aspects

- How long above the MIC?
- How much above the MIC?
How long above the MIC for a typical β-lactam?

- **Mild and non-life-threatening infections**
  - 40%
  - cefotaxime
  - neutropenic mice
  - *K. pneumoniae*
  - lung infection

- **Serious, life-threatening infections**
  - 100%

Y-axis: Log$_{10}$ cfu per lung at 24 hours
X-axis: Time above MIC (%)
Typical pharmacokinetics of an IV β-lactam

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>serum concentration for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 g</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Single administration; half-life 2h ; \( V_d = 0.2 \text{ l/kg} \)
Simple optimisation of IV $\beta$-lactams for "difficult" organisms

- 2 g every 12 h
  - $T > MIC = 100\%$
  - if $MIC \leq 3\ mg/L$ !

- 2 g every 8 h
  - $T > MIC = 100\%$
  - if $MIC \leq 12\ mg/L$

More frequent administrations is the best way to increase the activity of $\beta$-lactams in difficult-to-treat infections...

**PK / PD breakpoint for IV $\beta$-lactams**: $MIC \sim 8\ \mu g/ml$
**Where do you wish to be?**

<table>
<thead>
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<th>time (hours)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td><strong>6</strong></td>
<td><strong>6</strong></td>
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<tr>
<td>8</td>
<td>3</td>
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<tr>
<td>10</td>
<td>1.5</td>
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<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
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* Single administration; half-life 2h; $V_d = 0.2$ l/kg
But again, how much above MIC?

Figure 2 Relationship between concentration of ceftazidime and kill rate

The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

But do not forget about changes in MIC (low-level resistance) during treatment!

Change in MIC of antibiotics used in empiric antipseudomonal therapy (nosocomial pneumonia; intensive care units) towards the isolate identified before onset of therapy (D0) vs. the last isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using both raw and log₂ transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

More optimization to prevent emergence of resistance

Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam¹*, Kai-Tai Chang¹, Jian Zhou³, Kimberly R. Ledesma¹, Kady Phe¹, Song Gao³, Françoise Van Bambeke², Ana María Sánchez-Diaz³, Laura Zamorano⁴, Antonio Oliver⁴ and Rafael Cantón³

¹University of Houston, Houston, TX, USA; ²Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; ³Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCYIS), Madrid, Spain; ⁴University Hospital Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain


Simulation of serum concentration levels (hollow fivers model)
More optimization to prevent emergence of resistance

To prevent emergence of resistance, $C_{\text{min}}$ of $\beta$-lactams must stay $> 4 \times \text{MIC (mean)}$, which commands higher dosages...

**Figure 2.** Typical bacterial profiles for WT *P. aeruginosa*. Placebo control (a). Ceftazidime at 500 mg every 8 h ($C_{\text{min}}$/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h ($C_{\text{min}}$/MIC = 7.7) (c). Data are shown as mean ± SD.

**Figure 3.** Drug exposures ($C_{\text{min}}$/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold ($C_{\text{min}}$/MIC $\geq 3.8$) is depicted by the horizontal broken line.

Some discussion about $\beta$

- **$f_T > \text{MIC}$** is the driving parameter, but what is needed may vary between **40 to 100 %** depending upon the severity of the infection…

  ➔ providing a 100 % coverage may be particularly useful in severe infections (ICU, …) or $\beta$-lactams, activity if already optimal when the concentration exceeds the MIC by 3 to 4-fold, which is what easily happens with conventional administration… and bacteria with low MICs

- **4 x the MIC** provides optimal efficacy and prevention of resistance…

  ➔ This is what you may like to aim at in severe, difficult-to-treat infections, but lower values may be effective (not lower than 1 x the MIC, however…

OK!
There is growing evidence that standard antibiotic regimens may not provide adequate drug concentrations in ICU patients ...

Critically-ill patients

- Hyperdynamic states: Increased cardiac output, and clearance
  - Decreased plasma concentrations

- Altered fluid balance / Altered protein binding: Increased volume of distribution
  - Decreased plasma concentrations

- Renal and hepatic impairment: Decreased clearance
  - Increased plasma concentrations

- Organ support (RRT/ECMO): Increased volume of distribution / clearance
  - Increased/decreased plasma concentrations

**Pharmacokinetic alteration**

- Critically ill patients

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Hosthoff et al, Swiss Med Wkly. 2016;146:w14368
A. Abdulla et al: University Medical Center Rotterdam; eposter 069; ECCMID 2017

RRT: renal replacement therapy
ECMO: extra corporeal membrane oxygenation
Consequences of PK alteration

Critically ill patients

Pharmacokinetic alteration

Variability in antibiotic concentration

underdosing
Therapeutic failure/antibiotic resistance

Therapeutic antibiotic concentration
Therapeutic success

overdosing
Toxic effects

Hosthoff et al, Swiss Med Wkly. 2016;146:w14368
A. Abdulla et al: University Medical Center Rotterdam; eposter 069; ECCMID 2017
Continuous infusion ...

- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

What do we need to do in terms of PK/PD?
- What is the clinical evidence?
- What are the problems?
- How you do this in practice?
- Do you need to monitor blood levels?
Before we move further ..... 

<table>
<thead>
<tr>
<th>antibiotic</th>
<th>dose-response</th>
<th>influence of time</th>
<th>clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>weak</td>
<td>critical</td>
<td>• Exposure to the drug is the important factor</td>
</tr>
<tr>
<td>glycopeptides (*)</td>
<td></td>
<td></td>
<td>• Very high concentrations are unimportant</td>
</tr>
<tr>
<td>aminoglycosides</td>
<td></td>
<td>important</td>
<td>• Concentrations are important</td>
</tr>
<tr>
<td>fluoroquinolones (**)</td>
<td>limited</td>
<td></td>
<td>• The time of exposure is less important</td>
</tr>
</tbody>
</table>

* AUC_{24h}/MIC dependent but weak post-antibiotic effect

** C_{max} is also important to prevent emergence of resistance
Continuous infusion …

Infusion will push music to its limits

• Will push β-lactam efficacy to its maximum …
• by staying above the MIC indefinitely…

• What do we need to do in terms of PK/PD ?
• What is the clinical evidence ?
• What are the problems ?
• How you do this in practice ?
• Do you need to monitor blood levels ?
Continuous infusion of $\beta$-lactams in clinical practice

Pharmacokinetic and Pharmacodynamic Efficacies of Continuous versus Intermittent Administration of Meropenem in Patients with Severe Sepsis and Septic Shock: A Prospective Randomized Pilot Study.
PMID: 28485312 PubMed Article

Results by year

Search results
Items: 1 to 20 of 110

Format: Summary ▼ Sort by: Most Recent ▼ Per page: 20 ▼
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All (577)
Clinical Trial (110)
Free Full Text (145)
Continuous infusion of $\beta$-lactams: an overview...


Review

Continuous infusion of $\beta$-lactam antibiotics in severe infections: a review of its role

Jason A. Roberts$^{a,b}$, Jennifer Paratz$^{a,b}$, Elizabeth Paratz$^a$, Wolfgang A. Krueger$^c$, Jeffrey Lipman$^{a,b,*}$

$^a$ Burns Trauma and Critical Care Research Centre, University of Queensland, Brisbane, Australia
$^b$ Department of Intensive Care Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Australia
$^c$ Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, Tübingen, Germany

Received 16 January 2007; accepted 23 January 2007
Continuous infusion of β-lactams: an overview...

- The exact role of continuous infusion of β-lactam antibiotics in the treatment of severe infections remains unclear...
- However, increasing evidence is emerging that suggests potential benefits
  - better attainment of pharmacodynamic targets for these drugs
  - More reliable pharmacokinetic parameters in seriously ill patients
  - when the MIC of the pathogen is ≥4 mg/L (empirical therapy where the susceptibility of the pathogen is unknown)
- Clinical data supporting continuous administration are less convincing, but
  - Some studies have shown improved clinical outcomes from continuous infusion
  - none have shown adverse outcomes.
  - clinical and bacteriological advantage are visible in seriously ill patients requiring at least 4 days of antibiotic therapy.
- Seriously ill patients with severe infections requiring significant antibiotic courses (≥4 days) may be the subgroup that will achieve better outcomes with continuous infusion.

Continuous infusion …

- Will push β-lactam efficacy to its maximum …
- by staying above the MIC indefinitely…

But what do we need to do in terms of PK/PD?
- What is the clinical evidence?
- **What are the problems?**
- How you do this in practice?
- Do you need to monitor blood levels?
Problem no. 1: 
β-lactams are unstable molecules

chemical instability
Can instability be modulated?

- **yes** for penams and cephems, through
  - bulkiness and orientation of the C6/C7 substituent
    - in anchimeric assistance
  - presence of a C6 methoxy (temocillin)
    - in access of water
  - modulation of the C3 side-chain (cephems)
    - in electroattracting properties

- **difficult** for carbapenems (imipenem, meropenem...)
  - strong tension in the β-lactam ring induced by the fused 5-membered ring;
  - strong electroattracting properties of the C3 side chain
\[\text{**-lactam stability in a nutshell...} \]

- **Definition:** > 90% intact product (Pharmacopeia)
- **Conditions:** mimicking the total daily dose (commercial product) in 48 mL (motor operated syringe) water without pH adjustment and maintained at a fixed temperature (*)

**Key:**
- 37°C
- 25°C
- 4°C

<table>
<thead>
<tr>
<th>Molecule</th>
<th>≤ 6 h</th>
<th>12 h</th>
<th>24 h</th>
<th>&gt; 24 h</th>
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<tbody>
<tr>
<td>penicillin G</td>
<td>✔</td>
<td>🟢</td>
<td>🟡</td>
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</tr>
<tr>
<td>ampicillin</td>
<td>✔</td>
<td>🟢</td>
<td>🟡</td>
<td>🟢</td>
</tr>
<tr>
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<td>✔</td>
<td>🟢</td>
<td>🟢</td>
<td>🟡</td>
</tr>
<tr>
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<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
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<tr>
<td>cefepime</td>
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<tr>
<td>X imipenem</td>
<td>X</td>
<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
</tr>
<tr>
<td>X meropenem</td>
<td>X</td>
<td>🟢</td>
<td>🟢</td>
<td>🟢</td>
</tr>
</tbody>
</table>


Other references for indivual drugs in in Berthoin et al. (in preparation).
An example of how to cope with meropenem instability

Pharmacokinetic and Pharmacodynamic Efficacies of Continuous versus Intermittent Administration of Meropenem in Patients with Severe Sepsis and Septic Shock: A Prospective Randomized Pilot Study

Hui-Ying Zhao¹, Jian Gu², Jie Lyu¹, Dan Liu¹, Yi-Tong Wang³, Fang Liu¹, Feng-Xue Zhu¹, You-Zhong An⁴
¹Department of Critical Care Medicine, Peking University People’s Hospital, Beijing 100044, China
²Department of Pharmacy, Peking University People’s Hospital, Beijing 100044, China

Patients in the continuous group:
• 0.5 g loading dose
• 3 g of meropenem over 24 h

[To ensure] meropenem stability, 0.5 g was infused over 4 h … (thus 6 changes over 24h)
Problem no. 2:
\( \beta \)-lactams may be incompatible with other drugs if administered through the same line

\( \beta \)-lactam (typ. 8 g %)  
Drug X

1\(^{st}\) contact at high concentration (10 min)

2\(^{d}\) contact at 37°C at low concentration (1h)

direct examination (with viewer), HPLC, bioassay
Drug compatibility studies: example for ceftazidime

**Compatible:**

- **antiinfectives**
  - aminoglycosides, macrolides (diluted solutions), fluconazole
- **sedatives / anticonvulsivants**
  - ketamine, valproic acid, sufentanil, remifentanil, morphine
- **antihypertensives / diuretics**
  - urapidil, furosemide
- **varia**
  - aminoacid solutions (VAMIN)
  - insuline, methylprednisolone
  - isosorbide dinitrate
  - dopamine, adrenaline

Drug compatibility studies: example with ceftazidime

Non-compatible

- antibiotics
  - vancomycine (precipitation); macrolides (if concentrated)

- sedatives
  - propofol (trapping in emulsion); midazolam (precipitation)
  - piritramide (precipitation), phenytoïne (precipitation)

- antihypertensives
  - nicardipine (precipitation)

- varia
  - N-acetylcysteine (chemical inactivation)
  - dobutamine (if concentrated)
  - euphyllin (chemical inactivation)

Servais & Tulkens, AAC, 2001 Sep; 45(9):2643-7.
Baririan et al., JAC, 2003 Mar; 51:651-8.
Continuous infusion ...

- Will push β-lactam efficacy to its maximum ...
- by staying above the MIC indefinitely...

- What do we need to do in terms of PK/PD?
- What is the clinical evidence?
- What are the problems?
- **How you do this in practice?**
- Do you need to monitor blood levels?
Continuous infusion in practice
1. loading dose: the correct scheme *

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

Target serum concentration

loading dose

volume of distribution

\textbf{loading dose (in mg)} = C_t \text{ (mg/L)} \times Vd \text{ (L)}

The loading dose is only dependent upon the volume of distribution and is directly influenced by the weight of the patient and his/her medical situation.

Typical volumes of distribution of a $\beta$-lactam are between 0.2 L/kg (volunteers) and 0.4-0.5 L/kg (Intensive Care and burned patients).

* assuming linear pharmacokinetics (almost always the case for $\beta$-lactams)
Continuous infusion in practice
1. loading dose: a simplified scheme

- Because β-lactams have a low intrinsic toxicity, transient overshooting may not be a major problem...
- Conventional treatments (discontinuous) is by means of bolus or short infusions...
- Why not giving the loading dose as a single bolus or short infusion of a classical dose (1-2 g)?
Continuous infusion in practice
2: infusion *

\[ C_{ss} = \frac{K_o}{Cl} \]

Target serum concentration

Clearance *

infusion rate

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

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance and not the weight of the patient

* assuming linear pharmacokinetics (almost always the case for β-lactams)
Continuous infusion in practice
2: infusion

During the infusion, the necessary dose (in 24h or per min) is only dependent upon the clearance and not the weight of the patient.
Continuous infusion …

- Will push β-lactam efficacy to its maximum …
  - by staying above the MIC indefinitely…

- What do we need to do in terms of PK/PD?
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- What are the problems?
- How you do this in practice?
- Do you need to monitor blood levels?

Infusion will push music to its limits
As a result, monitoring the serum levels of \(\beta\)-lactams has been proposed...
But available methods are slow and complex, and do not measure the free concentration...
Continuous Infusion of vancomycin?

PubMed search for "vancomycin AND continuous infusion".
How to optimize vancomycin treatment: the classical way

Basic pharmacodynamics of antibacterials with clinical applications to the use of $\beta$-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)
How to optimize vancomycin treatment: the classical way

\[ \text{AUC}_{24h} / \text{MIC} = 400 \]
Vancomycin TDM at CHU Mont-Godinne: how we did it...

- Allows good approximation of the $\text{AUC}_{24h}$.  
  - Peak level: 30-40 mg/L 2 h after the end of infusion.
  - Trough level: 5-10 mg/L just before the next dose.

Concentration (mg/L) at 3rd VAN dose (VAN BID 1g q12h) versus time (h):
But what about continuous infusion?

“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

AUC_{24h} /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?

**efficacy**

- **MIC = 1.5 mg/L**
- **25-30 mg/L**
- **28.0**
- **50**

Vancomycin CI: which serum concentration should we target?

**efficacy**

<table>
<thead>
<tr>
<th>VAN serum conc. (mg/L)</th>
<th>25-30 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC = 1.5 mg/L</td>
<td>28.0</td>
</tr>
<tr>
<td>400</td>
<td>24</td>
</tr>
</tbody>
</table>


**toxicity**

$C_{ss}$ vancomycin $> 28$ mg/L en increased nephrotoxicity risk

[OR 21.236; $P = 0.004$]

How to reach the serum target concentration target with CI?

1. loading dose: the correct scheme *

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

loading dose

**Target serum concentration**

**volume of distribution**

\[ \text{loading dose (in mg/kg)} = C_t \text{ (mg/L)} \times V_d \text{ (L/kg)} \]

\[ \text{loading dose (in mg/kg)} = 20 \text{ mg/kg} = 25 \text{ (mg/L)} \times 0.8 \text{ (L/kg)} \]

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

2: infusion *

\[ C_{ss} = \frac{K_o}{Cl} \]

**Target serum concentration**

**Clearance** *

**infusion rate**

**daily dose** (in mg) = 24 x clearance (L/h) x \( C_{ss} \)

**clearance of vancomycin** = 0.65 calculated creatinine clearance (Cockroft-Gault)

**daily dose** = 2754 mg = 24 x (0.65 x 6 L/h) x 27.5 mg/L

* assuming linear pharmacokinetics
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)
Total vancomycin serum concentrations

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

After increasing the rate of infusion (in 57% of patients) targeted value reached and maintained from 96h
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
Pros / Cons of continuous infusion
(beta-lactams / vancomycine)

- A more rational way of administering beta-lactams (and also applicable to other antibiotics for which the impact of concentration [once above x-fold the MIC] is low)
- Can be easier to use in hospital setting
- "Monitoring made easy" and more reliable *
- Can help containing costs *

* not addressed in this talk, but ask questions…
Pros / Cons of continuous infusion
(beta-lactams / vancomycin)

• The stability of each beta-lactam MUST be critically assessed under the conditions of practical use…

• Compatibility issues may make things quite complex unless a dedicated line is used

• use of motor-operated pumps (or pumps with similar reliability) is probably essential *

• High serum levels maintained for prolonged periods may be associated with toxicities (for vancomycin, levels > 28 mg/L have been associated with renal toxicity; for beta-lactams, levels > 80 mg/L have been associated with convulsions [cefepime]) *

* not addressed in this talk, but ask questions…
β- lactams and vancomycin continuous infusion

A brilliant idea....

But do not forget the problems...
Our experience with continuous infusion

- 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 β-lactams and 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 pharmacotheraphy?
  – 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., 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!!

The slides are available for download from http://www.facm.ucl.ac.be → Lectures