PHARMONITOR II

Optimisation of aminoglycosides dosage regimen with pharmacokinetics modeling

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NATIONAL SYMPOSIUM
20 years EEQ
Leuven, March 26th 2009
Why monitoring of aminoglycosides?

- Existence of a good PK/PD relationship both for activity and side-effects
- Need to optimize efficacy rapidly
- Pharmacoeconomic interest
Aminoglycosides
Pharmacodynamics

• Amikacin, gentamicin, tobramycin, netilmicin
• Bactericidal antibiotics against Gram negative (nosocomial infections, E. coli, pseudomonas aer., ...)
• Concentration-dependant activity, peak/CMI > 10
• Post-antibiotic effect (2-6h)
• Synergistic effect with ß-lactames
• Saturable cell penetration
Aminoglycosides
Administration mode

- Slow iv perfusion 0.5-1h
- Two dosage regimen with equivalent total daily dosage:
  - Conventional scheme twice daily (trend to disappear)
  - Once a day (to be recommended)
- Advantages of the «once a day»:
  - At least as efficient (PAE, conc dependant effect, synergy)
  - Theoretically reduced toxicity (saturation)
  - Nursing
  - Partial reduction of TDM
- Generally
  - The highest the peak ... the more efficient it is!
  - The lowest the trough... the safest it is!
Aminoglycosides
Side effects

• Multifactorial nephro- and ototoxicity
• toxicity depending on:
  – AUC
  – Trough concentrations ($C_0$, conc. before perf.) or progressive increase of the trough conc
  – Age
  – Total cumulated dosage and/or duration of treatment
  – Associated nephrotoxic drugs (e.g. calcineurin inhibitors...)
Aminoglycosides
Pharmacokinetics

- Oral bioavailability very poor (F <0.05)
- $t_{1/2\alpha}$: 12 min
- $t_{1/2\beta}$: 2-4 h
- $V_d$: 0.2-0.3 L/kg (adults), 0.4-0.8 L/kg (children)
- $Cl$: 100 mL/min or about 1.4 mL/min/kg (adults)
- Protein binding: <10%
- No metabolism
Proposed dosage regimen for amikacin in premature population

<table>
<thead>
<tr>
<th>Gestation age (week)</th>
<th>Vd (L/kg)</th>
<th>T1/2 (h)</th>
<th>Cl (mL/min/kg)</th>
<th>D (mg/kg)</th>
<th>Interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>0.7</td>
<td>12.2</td>
<td>0.73</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>28-31</td>
<td>0.66</td>
<td>8.4</td>
<td>0.87</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>31-34</td>
<td>0.61</td>
<td>7.7</td>
<td>0.98</td>
<td>18.5</td>
<td>30</td>
</tr>
<tr>
<td>34-37</td>
<td>0.57</td>
<td>6.7</td>
<td>1.09</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>37-41</td>
<td>0.52</td>
<td>5.5</td>
<td>1.15</td>
<td>15.5</td>
<td>24</td>
</tr>
</tbody>
</table>
## Aminoglycosides

### Advised serum concentrations at UCL-St Luc

<table>
<thead>
<tr>
<th>Conventional scheme BID</th>
<th>«Once a day» scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>• amikacin:</td>
<td>• amikacin:</td>
</tr>
<tr>
<td>- trough: &lt; 5 µg/mL</td>
<td>- trough: &lt; 2.5 µg/mL</td>
</tr>
<tr>
<td>- Calculated peak $T_0$: &gt;20-25 µg/mL</td>
<td>- Calculated peak $T_0$: &gt;45-50 µg/mL</td>
</tr>
<tr>
<td>• tobramycin:</td>
<td>• tobramycin:</td>
</tr>
<tr>
<td>- trough: &lt;1 µg/mL</td>
<td>- trough: &lt;0.5 µg/mL</td>
</tr>
<tr>
<td>- peak $T_0$: &gt;7-8 µg/mL</td>
<td>- peak $T_0$: &gt;15-20 µg/mL</td>
</tr>
<tr>
<td>• netilmicin:</td>
<td>• netilmicin:</td>
</tr>
<tr>
<td>- trough: &lt; 1 µg/mL</td>
<td>- trough: &lt; 0.5 µg/mL</td>
</tr>
<tr>
<td>- peak $T_0$: &gt;7-9 µg/mL</td>
<td>- peak $T_0$: &gt;15-20 µg/mL</td>
</tr>
<tr>
<td>• gentamicin:</td>
<td>• gentamicin:</td>
</tr>
<tr>
<td>- trough: &lt;1 µg/mL</td>
<td>- trough: &lt;0.5 µg/mL</td>
</tr>
<tr>
<td>- peak $T_0$: &gt;7-8 µg/mL</td>
<td>- peak $T_0$: &gt;15-20 µg/mL</td>
</tr>
</tbody>
</table>
Amikacin i.v. perfusion in a patient with normal kidney function
Aminoglycosides TDM

• Blood drawing without anticoagulant
  – Before perfusion (trough)
  – 1h after end of perfusion (observed peak)
    In each case, the timing doesn’t matter much (flexibility for nursing), but the final timing should be accurately reported
• Avoid iv contaminations
• Mention accurate times of blood drawing, of initiation of perfusion and approximation of end of perfusion
• Mention accurately dose and interval (and of previous dose)
• Provide minimal clinical or biometric data: age, size, weight, creatinine, pathology such as
  – Transplantation, dialysis, chemotherapy, burned, cystic fibrosis, neutropenic, etc…
meccin preseptére:
Dr. M. DE MEYER
NEPOLOGUE U22
Service de Transplantation Sédale
1 2613 71 580

CLINIQUE universitaires saint-luc
MONITOrI:n therapeutiQuE DE MEDICAMENTS ()
Tél.: 02.764.67.00 - 02.764.68.30
837 M LD 68105 P.W.


PATIENT

Poids (kg): 68 kg
Taille (cm):

☐ Postopératoire
☐ Grippé renal
☐ Greffe hépat.
☐ Greffe card.
☐ Greffe moelle os.
☐ Insuff. rénale
☐ Insuff. hépat.
☐ Insuff. card.
☐ Dialyse
☐ Fumer
☐ Alcoolisme
☐ Enceinte
☐ Odorante, Ascite
☐ Mucoviscidose
☐ Prématuré
☐ Brûlé
☐ Septicémie

Résultats biologiques

Plasma:
Urée (mg/dl):
Creat (mg/dl):
Protéines (g/dl):
Bilir. dir. (mg/dl):
Bil. tot. (mg/dl):
K (mEq/L):

Sang:
G.B. (mm3):
Hb (g/dl):

Microbiologie:
Flore:

MEDICAMENTS

CARDIOTONIQUES
DIGO
DIGO

ANTHYMUSIQUES
AMIO
AMIO

ANALECTIQUES RESPIRATOIRES
THEO
THEO

IMMUNOSUPPRESSEURS
CIST
CIST

CYTOSTATIQUES
METO
METO

ANTIBIOTIQUES
AMIKâ
AMIK

UTILISATION EN SOINS INTENSIFS
DIAZ
DIAZ

VIGNETTE

URGENCE

DATE: 22/05/07
HORAIRE:
Prél. 0 à 8 h 20 min
Prél. 1 à 10 h 05 min
Prél. 2 à h min
Prél. 3 à h min

Remarques:
 Tube enveloppé d’une feuille d’aluminium.
 Voir verso.

U22
22/05/07
601127
L25780R

UNITE DE SOINS / N° LIT:
Date, heure du prélèvement:

☐ P +
☐ Extra Muros

CLINIQUEs universitaires saint-luc

VOIE D’ADMINISTRATION

Heure :
☐ per os.:
☐ I.v.:
☐ I.m.:
☐

parution temps:
début:
fin:

DIVERS **

SLI

PRELEVEMENT(S) **

3 juin
8 h 35 min
3 juin
9 h 15 min

VIGNETTE

DANGER

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Pharmacoeconomic perspective based on individualized therapies

• St Luc costs: > 400,000€/yr (amikacin and vancomycine)
• In case of efficient TDM (times, dosage, PK,..): reduction of
  – Hospitalisation and treatment duration
  – Total cumulated antibiotic dose
  – Side effects
• Cost saving estimated > US$ 725.00 per patient
  – Double blind studies Crist et al. Therap Drug Monit, 9,306-10, 1987
Pharmacoeconomic perspective based on individualized therapies

Destache et al. Ther Drug Monit 12, 419-26, 1990

- Prospective randomized study
- 75 adult patients under aminoglycosides with TDM/PK
- 70 adult patients under aminoglycosides as control group
- 2 homogenous groups in age, sex, size and Appache score

<table>
<thead>
<tr>
<th></th>
<th>Hospitalisation duration (h)</th>
<th>Febrile episodes duration (h)</th>
<th>Direct cost/patient (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group TDM/PK</td>
<td>322</td>
<td>50</td>
<td>7102</td>
</tr>
<tr>
<td>Control Group</td>
<td>442</td>
<td>92</td>
<td>13758</td>
</tr>
<tr>
<td>p</td>
<td>0.08</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>


Aminoglycosides TDM

- Immunoassays
- TAT: ±15 min
- PK calculation: ±10 min/patient
- Social security coverage: B350 (isolated assay without calculation) or B1000 (minimal 2 assays, which should allow pharmacokinetics evaluation and dosage regimen advice)
One compartment PK open-model

\[ t^{½β} = 0.693/k_e \]

\[ V_d = \frac{K \cdot (1 - e^{-(ke \cdot T)})}{k_e \cdot (C_{max} - C_{min} \cdot e^{-(ke \cdot T)})} \]

\[ t = -\frac{1 \cdot \ln(C_{ss, min\ cible}) + T}{k_e \cdot C_{ss, max\ cible}} \]

\[ K = \frac{C_{ss, max\ cible} \cdot V_d \cdot k_e \cdot 1 - e^{-(ke \cdot t)}}{1 - e^{-(ke \cdot T)}} \]

- \( t^{½β} \): elimination half-life
- \( V_d \): volume of distribution
- \( t \): dosage interval
- \( K \): dose/hour

Variation in \( t^{½β}, V_d, t \) and \( K \) according to:
- age (ex. premature, elderly...)
- pathology (ex. Renal insufficiency, cystic fibrosis, burned...)
Pharmonitor II
Major advantages of the upgrade version

- New version distributed freely to all belgian clinical lab interested, by the ISP-WIV, together with basic training
- Possibility to online connection with most LIS
- More customized version
  - Choice of the analytical units
  - Available in 3 languages (dutch, french and english)
  - Choice of GFR calculation (MDRD, Cockcroft Gault, Schwartz)…
- Provides a better traceability (users login, supervisors login, keeping track of all steps, …)
- Final report could be printed or sent as pdf
- Will be a first platform for further developments (other drugs, multicompartment modelling, PopPK,…)
Example of interest: last proficiency testing for amikacin

- R/7534: Amikacine: A 51 yrs old man (70 kg - normal kidney function) is under 1000 mg amikacin/day 'once a day', since Dec 10 2008. A new 30 min perfusion is initiated on Dec 12 at 8h30. Two blood drawings are performed. Both are after the perfusion. The first is at 10h55 and corresponds to the QC sample. The second is drawn at 15h displayed a concentration of 10.1 µg/mL (17.2 µmol/L).

- Questions:
  - What is the amikacin concentration in the sample R/7534?
  - Select a protocol?
    - Inadequate or non-interpretable sampling
    - Adequate treatment
    - Toxic treatment
    - Infra-therapeutic or non-efficient treatment
# Results from 105 centres

## AMIKACIN - d (%) : 20.0

Conversion factor : \( \mu \text{mol/L} / 1.71 = \mu \text{g/mL} \)

<table>
<thead>
<tr>
<th>METHOD</th>
<th>Median ( \mu \text{mol/L} )</th>
<th>SD ( \mu \text{mol/L} )</th>
<th>CV %</th>
<th>Median ( \mu \text{g/mL} )</th>
<th>N labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>001 Non-Isotopic Abbott TDx</td>
<td>49.42</td>
<td>2.54</td>
<td>5.1</td>
<td>28.90</td>
<td>26</td>
</tr>
<tr>
<td>003 Non-Isotopic Roche Integra</td>
<td>47.97</td>
<td>2.74</td>
<td>5.7</td>
<td>28.05</td>
<td>32</td>
</tr>
<tr>
<td>005 Non-Is. - Roche Hit / Mod / cobas c</td>
<td>50.36</td>
<td>1.98</td>
<td>3.9</td>
<td>29.45</td>
<td>32</td>
</tr>
<tr>
<td>006 Non-Isotopic Syva Emit</td>
<td>44.76</td>
<td>3.45</td>
<td>7.7</td>
<td>26.17</td>
<td>12</td>
</tr>
<tr>
<td>011 Non-Isotopic Abbott - Architect/Aeroset</td>
<td>54.21</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>050 Home made</td>
<td>50.45</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Global results (all methods and all measuring systems)</strong></td>
<td>49.76</td>
<td>3.17</td>
<td>6.4</td>
<td>29.10</td>
<td>105</td>
</tr>
</tbody>
</table>

Mean value: 29.09 µg/mL
At time 1.91 h after perfusion

There was 10.1 µg/mL
At time 6 h after perfusion

## Interpretation for AMIKACIN

<table>
<thead>
<tr>
<th>Interprétation - Interpretatie</th>
<th>N</th>
<th>Median ( \mu \text{g/mL} )</th>
<th>pct/all</th>
<th>pct/diag</th>
<th>consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prélèvement inadéquat/résultat non interprétable</td>
<td>71</td>
<td>49.59</td>
<td>67.6%</td>
<td>69.6%</td>
<td>X</td>
</tr>
<tr>
<td>Traitement adéquat</td>
<td>17</td>
<td>49.76</td>
<td>16.2%</td>
<td>16.7%</td>
<td></td>
</tr>
<tr>
<td>Infra-thérapeutique</td>
<td>11</td>
<td>49.76</td>
<td>10.5%</td>
<td>10.8%</td>
<td></td>
</tr>
<tr>
<td>aucune</td>
<td>3</td>
<td>45.83</td>
<td>2.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>toxique</td>
<td>3</td>
<td>51.47</td>
<td>2.9%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>105</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results from 105 centres

- Most centres considered the case as non-interpretable (because unusual sampling times), and would recommend new sampling and new analyses...
- In fact, as far as accurate sampling times and dosage information are provided, the case can be evaluated.
- According to the Pharmonitor II calculations, extrapolated peak and trough concentrations would be 47.7 and 0.15 µg/mL, respectively, corresponding to a possibly acceptable scheme (depending on target values in application in the centre).
Dear Colleagues,

Please find below the results of the tests required for your patient OKUZA Philippe born on 10/02/1968.

**Current treatment**
- Antibiotic administered: AMIKACIN 400
- Regimen (dose/interval) administered: 1000 mg / 24 h

<table>
<thead>
<tr>
<th>Measured conc. (quantified)</th>
<th>Desired conc. (target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 h after adm. 28000 µg/mL</td>
<td>Cmin: 2.000 µg/mL</td>
</tr>
<tr>
<td>60 h after adm. 10100 µg/mL</td>
<td>Cmax: 50.000 µg/mL</td>
</tr>
</tbody>
</table>

**Results of the therapeutic**

<table>
<thead>
<tr>
<th>Measured conc. (quantified)</th>
<th>Calculated conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmin: 0.108 µg/mL</td>
</tr>
<tr>
<td></td>
<td>Cmax: 47.796 µg/mL</td>
</tr>
</tbody>
</table>

**Calculated PK parameters**
- $V_e$: 0.20 (L/kg)
- $CL$: 1.21 (ml/min/kg)
- $T_{1/2}$: 2.57 h
- AUC: 196.25 (mg/mL)

**Protocol and proposed treatment**

- Regimen (dose/interval) administered: 1000 mg / 24 h

*Proposée de maintenir le même schéma posologique*
Conclusions

- Aminoglycosides are critical dose drugs
- Isolated serum concentrations appear poorly contributive both to treatment efficacy - and to global economy
- PK-TDM (min 2 blood specimen) is recommended but need proper nursing and clinical lab training
- Pharmonitor II appears a useful tool to clinical labs, and meets the growing interests to improve the “value added” of laboratory results
  - Knowledge service
  - Interpretation of results
  - Cost efficiency,…
<table>
<thead>
<tr>
<th>Groupe</th>
<th>Durée moy (j)</th>
<th>Dose totale (mg)</th>
<th>Coût / patient ($US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDM</td>
<td>5.9</td>
<td>1258</td>
<td>1812</td>
</tr>
<tr>
<td>Contrôle</td>
<td>10.3</td>
<td>1981</td>
<td>2537</td>
</tr>
</tbody>
</table>

\( p < 0.001 < 0.001 < 0.05 \)

Thanks for your attention