Optimizing AMINOGLYCOSIDE dosage based on PK/PD

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With documents borrowed from Paul G. Ambrose, Institute for Clinical Pharmacodynamics, Ordway Research Institute, Albany, New York

With the support of Wallonie-Bruxelles-International
Pros and Cons of aminoglycosides

- High potency
- Concentration-dependent killing
- Synergy with β-lactams
- Cheap

- Perception of poor efficacy in some circumstances
- Nephrotoxicity
- Ototoxicity

Both efficacy and safety can be improved by appropriate dosing!
1. optimizing efficacy based on PK-PD
In vitro time-kill curves

Time and conc. – dependent killing

In vitro post-antibiotic effect

delay before regrowth

Animal PD model

Amikacin versus Gram-Negative Bacilli: efficacy

Neutropenic mice were inoculated with $10^6$ CFU/thigh of either *P. aeruginosa* (MIC = 4 mg/L) or *S. marcescens* (MIC = 8 mg/L) by Craig et al. IDSA, 2006.

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both AUC24h:MIC and Cmax:MIC dependent killing!
Animal PD model

Amikacin versus Gram-Negative Bacilli: PK-PD attainment rate

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Dosing Regimen</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>15 mg/kg/day</td>
<td>30 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>99.9</td>
<td>94.8</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>85.7</td>
<td>42.8</td>
<td>99.8</td>
</tr>
<tr>
<td>4</td>
<td>23.7</td>
<td>2.5</td>
<td>85.6</td>
</tr>
<tr>
<td>8</td>
<td>0.72</td>
<td>0</td>
<td>23.8</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PK-PD Target\(^1\)

- AUC\(_{\text{MIC}} = 59\)
- AUC\(_{\text{MIC}} = 96\)

Craig et al. IDSA, 2006.

stasis and a 1 log CFU reduction

stasis and a 1 log CFU reduction
Concentration is important in patients also …

Cmax/MIC > 8 !
in a TID treatment

Concentration is important in patients also …

Gentamicin and *Pseudomonas* bacteriemia

---

Zelenitsky et al. JAC 2003; 52:668-674
What have we learned from models?

- Aminoglycosides have a concentration-dependent pattern of bactericidal activity and prolonged persistent effects both *in vitro* and *in vivo*.

- **PK-PD Goal** of dosing: Maximize Concentrations!

  - Optimize peak (and AUC)
  - Once-a-day administration!
Meta-analysis:
Once-daily dosing has a lower risk of clinical failure

In favor to
Once-a-day

Estimate (95% confidence interval):

Klastersky et al 5
Hansen et al 14
Muijsken et al 15
Tulkens et al 16
Hollender et al 17
Mauracher et al 18
Sturm et al 19
De Vries et al 20
Nordstrom et al 7
Ter Braak et al 21
Giamarello et al 22
Marik et al 23
Van der Auwera et al 24
Vigano et al 25
Gonzalez et al 27
Maller et al 28
Prins et al 29
Rozdzinski et al 30
Vanhaeverbeek et al 31

0.76 (0.61 to 0.95)
0.83 (0.57 to 1.21)

0.70 (0.17 to 2.84)
1.30 (0.55 to 3.11)
0.09 (0.01 to 1.57)
0.50 (0.33 to 0.75)
0.20 (0.01 to 4.00)
2.84 (0.12 to 68.6)
0.67 (0.28 to 1.61)
1.25 (0.69 to 2.65)
0.46 (0.13 to 1.72)
1.01 (0.55 to 1.87)
1.05 (0.02 to 50.4)
0.20 (0.05 to 0.83)
1.46 (0.57 to 3.75)
1.00 (0.02 to 48.0)
0.32 (0.01 to 7.74)
0.08 (0.00 to 1.36)
0.20 (0.01 to 4.03)
1.90 (0.49 to 7.33)

Once-a-day Favors muliple dose

Favors once-a-day

Meta-analysis:
Once-daily dosing has a lower risk of clinical failure

Barza et al, BMJ 1996; 312:338-344
Dosing once-a-day in practice

Peak/MIC > 8

1. adequate mode of administration
   - i.v. administration

2. calculate the peak you need
   - minimal peak = MIC x 8

3. calculate the dose you need
   - peak = dose / Vd
   - dose = peak x Vd
Finding the appropriate dose ...

increase the unit dose to get the appropriate peak!

\[
\text{MIC} = 1 \text{ mg/L} \quad \text{C}_{\text{max}} = 8 \text{ mg/L} \quad 3 \text{ mg/kg}
\]

\[
\text{MIC} = 2 \text{ mg/L} \quad \text{C}_{\text{max}} = 16 \text{ mg/L} \quad 6 \text{ mg/kg}
\]

\[
\text{MIC} = 4 \text{ mg/L} \quad \text{C}_{\text{max}} = 32 \text{ mg/L} \quad 15 \text{ mg/kg}
\]

limit of \( G, T, N \) ??

limit of \( A, I \) ??

October 2011
PK-PD course - aminoglycosides

13
Setting up the limits of efficacy

Aminoglycosides 1st two rules of thumb...

- Anything with an MIC < 1 µg/ml will be treatable if in the indications...

- Efficacy may become a problem for MIC’s:
  - > 2 µg/ml for G, T, N (up to 6 mg/kg)
  - > 4 µg/ml for A, I (up to 15 mg/kg)

PK / PD “safe” breakpoints for AG:
- G, N, T : 2 µg / ml
- A / I : 4 µg / ml
### Setting up the limits of efficacy

**Aminoglycosides EUCAST breakpoints**

#### Enterobacteriaceae  
**EUCAST Clinical Breakpoint Table v. 1.3 2011-01-05**

<table>
<thead>
<tr>
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<th>Zone diameter breakpoint (mm)</th>
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<td>R &gt;</td>
<td>S ≥</td>
</tr>
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<td>Tobramycin</td>
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**Notes**
- Numbers for comments on MIC breakpoints
- Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents.
### Setting up the limits of efficacy

**Aminoglycosides EUCAST breakpoints**

**Enterobacteriaceae EUCAST Clinical Breakpoint Table v. 1.3 2011-01-05**

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**Notes**

Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of aminoglycosides. Aminoglycosides are given in combination with beta-lactam agents.

*amikacin may be given at very high doses reasonably safely*
Setting up the limits of efficacy

### Aminoglycosides EUCAST breakpoints

**Pseudomonas spp.**

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**Notes**

Numbers for comments on MIC breakpoints
Letters for comments on disk diffusion

1. Aminoglycoside breakpoints are based on once-daily administration of aminoglycosides are given in combination with beta-lactam agents.

This is to avoid splitting the wild type population in two.
EUCAST MIC distributions

Gentamicin / Pseudomonas aeruginosa
EUCAST MIC Distribution - Reference Database 2011-10-03

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC Epidemiological cut-off: WT ≤ 8 mg/L

Clinical breakpoints: ≤ 4 mg/L, > 4 mg/L

24384 observations (71 data sources)
2. Reducing toxicity based on PK-PD
The goal is to avoid toxicity while preserving efficacy!
Aminoglycosides nephrotoxicity incidence is highly variable among patient populations

Patients with nephrotoxic reaction after treatment with gentamicin

- young volunteers: Smith et al, 1982
- random hospital population: Smith et al., 1980
- critically-ill patients: Plaut et al., 1979
High doses in animals cause renal necrosis, tubular dysfunction, and renal failure associated with regeneration.

Fig. 1. Renal changes in Fischer 344 rats after gentamicin (40 mg/kg per day in two injections per day).
From Ref. 13.

Looking at the kidney with "plastic sections"
What does happen in the kidney proximal tubules?

- gentamicin-treated: perfused kidney
- gentamicin-treated: unperfused kidney
Gentamicin accumulates in lysosomes of proximal tubular cells
Aminoglycoside entry in proximal tubular cells is via brush border binding...

binding to
• megalin  
  (Moeströp et al., 1995)
• acidic phospholipids  
  (Humes et al, 1983)

Silverblatt & Kuehen, Kidney Intern., 1979
Mice deficient in megalin do not accumulate gentamicin in kidney

Schmitz et al., J. Biol. Chem. 277:618-622, 2002
Mechanism of uptake

1. binding to brush border
2. accumulation in lysosomes
Intralysosomal gentamicin binds to phospholipids and causes phospholipidosis

Tulkens, Am. J. Med. 80:105-114, 1986
A first global hypothesis ?...
Gentamicin causes apoptosis at low, therapeutically-relevant dosages


Gentamicin-induced apoptosis can be reproduced with cultured kidney and non-kidney cells …

El Mouedden et al., Toxicol. Sci., 56:229-239, 2000
What is the mechanism of gentamicin–induced apoptosis and its relation to necrosis in kidney cortex?

FIG. 1. Ultrastructural alterations induced in proximal tubular cells during aminoglycoside treatment. (A) Control. Changes detected early on and at low doses (B) consist mainly of the enlargement of lysosomes, which most likely occurs by fusion of preexisting structures and which is caused by the progressive deposition of polar lipids which adopt a concentric lamellar disposition (myelin-like structures, most commonly referred to as myeloid bodies); the other subcellular structures are usually well preserved. Later changes or changes observed with high doses (C) include the apparent rupture of lysosomes (with the release of myeloid bodies in the cytosol), extensive mitochondrial swelling and damage, dilatation of the endoplasmic reticulum cisternae, shedding of the apical brush-border villi, pericellular membrane discontinuities, and the occurrence of apoptotic nuclei. These alterations do not necessarily coexist in all cells. The figure is adapted from reference 76 and is based on the typical descriptions given in references 38, 40, 71, 76, 77, 127, and 138.

Could lysosomal rupture cause apoptosis and necrosis?

Maldague et al., 1983

Servais et al., 2006
What Servais et al.'s experiment shows … (1 of 3)

AO diffuses and accumulates in lysosomes by proton trapping and becomes red because it is concentrated and at acid pH.
What Servais et al.'s experiment shows … (2 of 3)

GM also accumulates in lysosomes but by pinocytosis
What Servais et al.'s experiment shows … (3 of 3)

Gentamicin induces a liberation of AO which turns green upon dilution and at lower pH.

Is this membrane rupture or change of pH?
The recent demonstration of lysosomal rupture induced by gentamicin: use of Lucifer Yellow (1 of 5) *

LY accumulates in lysosomes by pinocytosis (non-diffusible) and is always green

The recent demonstration of lysosomal rupture induced by gentamicin: use of Lucifer Yellow (2 of 5)

GM also accumulates in lysosomes by pinocytosis as LY

The recent demonstration of lysosomal rupture induced by gentamicin: use of Lucifer Yellow (3 of 5)

gentamicin induces the liberation of LY which can only occur if membrane is damaged (non-diffusible; no effect of pH)

The recent demonstration of lysosomal rupture induced by gentamicin: use of Lucifer Yellow (4 of 5)

But LY is quickly effluxed through an export transporter, so that it never stays long in the cytosol ... and we did not see it ...

The recent demonstration of lysosomal rupture induced by gentamicin: use of Lucifer Yellow (5 of 5)

So, we added PB to block the efflux, and, then, we saw LY in the cytosol!

The recent demonstration of lysosomal rupture induced by gentamicin: results

The current hypothesis…

• gentamicin enters proximal tubular cells by megalin- and acid phospholipids mediated pinocytosis and ends up in lysosomes
• a minor part escapes lysosomes either by membrane destabilization (our hypothesis) or by retrograde transport (Molitoris' hypothesis) to reach the cytososol and the mitochondria … where it induces apoptosis and other toxic disturbances…

Reducing uptake by the kidney would result in reduced toxicity!

Once-a-day administration
Aminoglycoside toxicity is not linked to peak...
Aminoglycoside accumulation is kidney is saturable at clinically meaningful concentrations ...

Giuliano et al., J. Pharm. Exp. Ther., 1986
Nephrotoxicity and schedule of administration …
the first large scale clinical trial

- 141 predominantly elderly patients with severe bacterial infections.
- All patients received once-daily doses of 2 g ceftriaxone, in addition to netilmicin.

"Netilmicin-induced toxicity may be reduced by using once-daily dosing regimens and limiting the duration of treatment."

And auditory alterations …

no. of patients [over 20 in each group] with lesions* and total no. of frequencies affected

<table>
<thead>
<tr>
<th></th>
<th>low tone (0.25-8 kHz)</th>
<th>high tone (10-18 kHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>amikacin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q24h</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>q12h</td>
<td>0</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

**netilmicin**

<table>
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<th>low tone (0.25-8 kHz)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>q24h</td>
<td>0</td>
<td>3 (7)</td>
</tr>
<tr>
<td>q8h</td>
<td>2 (3)</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

* loss of 15dB or more over baseline (max. loss recorded: 30 dB)

Tulkens *et al.*, 1989
Avoiding (or reducing) the toxicity

**Aminoglycosides 3d rule of tumb...**

give them once-a-day to reduce toxicity
- 1h peaks of 12-18 µg/ml for G, T, N
- 1h peaks of 20-30 µg/ml for A, I

**Increase interval (⇒ 36h, ⇒ 48h) in case of renal failure before reducing the unit dose...**

**Once-daily dosing of aminoglycoside antibiotics**

Fisman, DN; Beth Israel Deaconess Med Ctr; Div Infect Dis; Harvard Univ, Sch Publ Hlth, INFECTIOUS-DISEASE-CLINICS-OF-NORTH-AMERICA. JUN 2000
3. Monitoring
Monitoring recommendations for the once-a-day…: peak and trough values...

- **peak** (1h post infusion)
  - G, T, N : 18 - 24 mg/l
  - A, I : 25 - 50 mg/L

- **trough** (before next dose)
  - G, T, N : < 1 mg/ L
  - A, I : < 2 mg/L

Monitoring is probably unnecessary for short duration therapies… except for efficacy…

the difficulty, however, is to have good peaks
Do not minimize the difficulties of a "good peak"

A "Clinical Pharmacy" study about the peak and through levels of amikacin in a Belgian University Hospital

eligible patients: 102

inclusion: 94 patients

111 treatments

vancomycin: 46

peak: 44

amikacin: 65

trough: 62

exclusions:
• 2 for inability to perform observation
• 6 for limited life expectancy

Ampe et al., in preparation
Do not minimize the difficulties of a "good peak"

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exclusions:
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Ampe et al., in preparation
Points to consider for a "good peak"

1. the "time" of the real peak is highly dependent of your rate of infusion

Data for amikacin:
- \( D = 15 \text{ mg/kg} \)
- \( V_d = 0.25 \text{ L/kg} \)
- \( ka = \text{variable} \)
- \( ke = 0.346 \text{ h}^{-1} (t_{1/2} = 2h) \)

\[ C = \frac{D}{V_d} \times \frac{ka}{(ka-ke)} \times \left[ e^{-ke \times t} - e^{-ka \times t} \right] \]
Points to consider for a "good peak"

2. and the timing of the sample is even more critical

Data for amikacin:

- D = 15 mg/kg
- \( V_d = 0.25 \text{ L/kg} \)
- \( ka = \text{variable} \)
- \( ke = 0.346 \text{ h}^{-1} (t_{1/2} = 2\text{h}) \)

\[
C = \frac{D}{V_d} \times \frac{ka}{(ka-ke)} \times [e^{-ke \times t} - e^{-ka \times t}]
\]
The American Approach: Look for 8 h …

All that is less variable at 8 h!

Data for amikacin:

- $D = 15 \text{ mg/kg}$
- $V_d = 0.25 \text{ L/kg}$
- $ka = \text{variable}$
- $ke = 0.346 \text{ h}^{-1} \ (t_{1/2} = 2h)$

$C = \frac{D}{V_d} \times ka \times \frac{ka}{ke} \times [e^{-ke \times t} - e^{-ka \times t}]$
The American Approach: Look for 8 h

Still some variation but will less influence the calculation….

Data for amikacin:
D = 15 mg/kg
V_d = 0.25 L/kg
ka = variable
ke = 0.346 h^{-1} (t_{1/2} = 2h)

\[ C = \left( \frac{D}{V_d} \right) \times \frac{ka}{(ka-ke)} \times \left[ e^{-ke \times t} - e^{-ka \times t} \right] \]
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination).

Let us first see Vd

Data for amikacin:
D = 15 mg/kg
Vd = variable
ka = 2.772 h⁻¹ (t₁/₂ = 15 min)
ke = 0.346 h⁻¹ (t₁/₂ = 2h)
Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let us first see V_d and zoom at 8h …

you will detect easily an abnormal V_d
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination).

Let now see the elimination (K_e)

Data for amikacin:
D = 15 mg/kg
V_d = 0.25 L/kg
ka = 2.772 h^{-1} (t_{1/2} = 15 min
ke = variable
The American Approach: Look for 8 h

Now, the important point is to detect patients with highly abnormal Vd and/or highly abnormal Ke (elimination)

Let now see the elimination ($K_e$)

You do not even need to zoom!
The Hartford study (gentamicin)


Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients

DAVID P. NICOLAU,1,2,3,* COLLIN D. FREEMAN,1,3† PAUL P. BELLIVEAU,1,3‡ CHARLES H. NIGHTINGALE,3,4 JACK W. ROSS,2 AND RICHARD QUINTILIANI2,5

Department of Pharmacy,1 Office for Research4 and Department of Medicine,2 Division of Infectious Diseases, Hartford Hospital, Hartford, Connecticut 06102; School of Pharmacy, University of Connecticut, Storrs, Connecticut 062683; and School of Medicine, University of Connecticut, Farmington, Connecticut 060325

Received 11 April 1994/Returned for modification 2 October 1994/Accepted 8 January 1994
The Hartford study (gentamicin)

FIG. 2. Simulated concentration-versus-time profile of once-daily (7 mg/kg q24h) and conventional (1.5 mg/kg q8h) regimens for patients with normal renal function.

The Hartford study (gentamicin): recalculated for you …

**gentamicin**

*model of Nicolau et al. (1995)*

\[ C = \left( \frac{D}{V_d} \right) \times \frac{ka}{(ka - ke)} \times \left[ e^{-ke \times t} - e^{-ka \times t} \right] \]

- **D** = 7 mg/kg
- **V_d** = 0.25 L/kg \([CI_{95}=0.22-0.29]\)
- **ka** = 2.72
- **ke** = 0.18 \((t_{1/2} = 3.85 \text{ h})\)
The Hartford study (gentamicin)

FIG. 3. Simulated concentration-versus-time profile of once-daily 7- and 5-mg/kg regimens for patients with various Clcrs.

Take it easy : Hartford method
(Nicolau’s nomogram for gentamicin)

Take it easy: Hartford method (Nicolau’s nomogram for gentamicin)

1. obtain a single random blood sample between 6 and 14 h after the start of the infusion
Take it easy: Hartford method
(Nicolau’s nomogram for gentamicin)

1. Obtain a single random blood sample between 6 and 14 h after the start of the infusion

2. Place value in nomogram
Take it easy: Hartford method
(Nicolau’s nomogram for gentamicin)

1. obtain a single random blood sample between 6 and 14 h after the start of the infusion

2. Place value in nomogram

3. read interval corresponding to the zone of the nomogram
Take home message

• Maximize peak to increase efficacy and reduce toxicity
• Administer once-a-day
• Measure MIC and calculate the dose that is needed
• Reduce treatment duration as much as possible
• Do monitoring if
  - treatment > 5 days
  - special populations
  - risk factors
  - co-administration of other nephrotoxic drugs