Azalides revisited: Why the single dose?
The pharmacologist's answer …

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  Catholic University of Louvain, Brussels, Belgium
- International Society of Antiinfective Pharmacology (ISAP)
The patient's views …

• Once daily makes it easier for me, Doc…
  – Enoxaparin … (Thromb Res. 2004;114(3):149-53)
  – …
They can't be all wrong...
The patient's views …

• A short treatment of my infections is what I want …if it works …

  – 3 days is (clinically) similar to 5-10 days for UTI
    (Cochrane Database Syst Rev. 2005 Apr 18;(2):CD004682.)

  – Ultrashort (4 days) eradication of H. pylori

  – 5 days for acute sinusitis …
    (Treat Respir Med. 2004;3(5):269-77.)

  – Less than 7 days for community-acquired pneumonia.
    (Clin Infect Dis. 2004 Sep 1;39 Suppl 3:S159-64).
They can't be all wrong either…

You are better soon..

Yes, 3 days are enough…
The doctor's view …

• Compliance is inversely proportional to the number of takes (and drugs) per day …

  – Type-2 diabetes mellitus
    (Clin Ther. 2004 Dec;26(12):2066-75)

  – Once-daily didanosine
    (Antivir Ther. 2004 Jun;9(3):335-42)

  – Valproate and control of epilepsy …
    (Epilepsy Behav. 2003 Dec;4(6):710-6)

  – $\beta$-blocker and chronic glaucoma
    (J Fr Ophtalmol. 2003 Sep;26(7):668-74).
The pharmacologist's key question …

- What do you need for "once-daily"?
  - long serum half-life?
  - high, sustained tissue levels?
  - Some sort of pharmacodynamic parameter???

Hint: do aminoglycosides have the two first properties?

Second hint: what if you have all three properties?
Pharmacodynamic properties of antibiotics

Available antibiotic can be divided in 3 groups

- time - dependent (T > MIC)
- AUC / MIC - dependent
- both AUC / MIC AND peak / MIC -dependent
Azithromycin has an long serum half-life …

Table 3. Main Pharmacokinetic Properties of Macrolide Antibiotics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max &lt;/sub&gt; (mg/l)</td>
<td>3</td>
<td>6.8</td>
<td>6.8</td>
<td>0.2-0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>T&lt;sub&gt;max &lt;/sub&gt; (h)</td>
<td>1.9-4.4</td>
<td>2</td>
<td>2.7</td>
<td>3-5</td>
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<tr>
<td>T&lt;sub&gt;1/2 &lt;/sub&gt; (h)</td>
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<td>8-13</td>
<td>4.4</td>
<td>42</td>
<td>35-40</td>
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Mulazimoglu, Tulkens, and Van Bambeke: Macrolides.
In: Antimicrobial Therapy and Vaccines (Volume II) Editors: Victor L. Yu, Rainer Weber & Didier Raoult
http://www.antimicrobe.org
Pharmacokinetic parameters

- Peak / MIC
- AUC / MIC
- Time > MIC

Pic

Vallée
Antibiotics Group # 2
(after W.A. Craig, 2000; revised 2003)

Antibiotics with time-dependent effects, with little or no influence of the concentration BUT with persistent effects

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycopeptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>azalides</td>
<td>24h AUC / MIC ratio</td>
<td>Optimize the quantity of AB administered</td>
</tr>
<tr>
<td>fluconazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PK/PD vs. efficacy

Table 4. Pharmacodynamics of azithromycin versus macrolide-susceptible and -resistant *S. pneumoniae* (AUC$_{0-24}$/MIC)

<table>
<thead>
<tr>
<th>Isolate/MIC</th>
<th>Serum (free drug)</th>
<th>ELF (free drug)</th>
<th>MEF (free drug)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>AUC$_{0-24}$/MIC</td>
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<tr>
<td>11771/0.06</td>
<td>36.7</td>
<td>153</td>
<td>153</td>
</tr>
<tr>
<td>11888/0.06</td>
<td>36.7</td>
<td>153</td>
<td>153</td>
</tr>
<tr>
<td>12808/2.0</td>
<td>1.1</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>3860/4.0</td>
<td>0.6</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>12629/8.0</td>
<td>0.3</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>3910/16.0</td>
<td>0.14</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>1217/32.0</td>
<td>0.07</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>2670/256</td>
<td>0.002</td>
<td>0.07</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Assumption made that protein binding in ELF and MEF was the same as serum (fraction unbound 0.5). E, eradicated; R, regrowth; ↓0.2, 0.2 log$_{10}$ cfu/mL decrease; ↓0.5, 0.5 log$_{10}$ cfu/mL decrease.

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<td>8-13</td>
<td>4.4</td>
<td>42</td>
<td>35-40</td>
</tr>
<tr>
<td>$V_d$ (l/kg)</td>
<td>0.64</td>
<td>3-4</td>
<td>11</td>
<td>23-31</td>
<td></td>
</tr>
<tr>
<td>Bioavailability</td>
<td>25-60 %</td>
<td>72-85 %</td>
<td>55 %</td>
<td>6-14%</td>
<td>37%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>65-90</td>
<td>73-96</td>
<td>40-70</td>
<td>15-30</td>
<td>12-40</td>
</tr>
<tr>
<td>Tissue/serum concentration</td>
<td>0.5</td>
<td>1-2</td>
<td>3-8</td>
<td>20-30</td>
<td>50-1150</td>
</tr>
<tr>
<td>$AUC$ (mg.h/l)</td>
<td>4.4-14</td>
<td>70</td>
<td>4.1</td>
<td>3.8</td>
<td>2-3.4</td>
</tr>
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Mulazimoglu, Tulkens, and Van Bambeke: **Macrolides.**

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Accumulation of azithromycin in cells

TABLE 1. Uptake of azithromycin and erythromycin by various phagocytic cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Antibiotic</th>
<th>Differential&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Antibiotic uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I/E</td>
<td>µg/10&lt;sup&gt;7&lt;/sup&gt; cells</td>
</tr>
<tr>
<td>Human PMNs</td>
<td>Azithromycin</td>
<td>4.9</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Murine PMNs</td>
<td>Azithromycin</td>
<td>3.9</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Murine alveolar macrophages</td>
<td>Azithromycin</td>
<td>5.9</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Rat alveolar macrophages</td>
<td>Azithromycin</td>
<td>5.5</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Murine resident peritoneal macrophages</td>
<td>Azithromycin</td>
<td>15.5</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cells were incubated for 2 h with 10 µg of the antibiotic per ml.

<sup>b</sup> Ratio of azithromycin uptake to erythromycin uptake. All values are statistically significant.

Gladue et al., AAC 33:277-82, 1989
Azithromycin is subject to P-gp-mediated efflux from macrophages…

Kinetics of uptake (A) and release (B) of azithromycin in J774 murine macrophages with (open squares) or without (closed squares) 20 µM verapamil.
Intracellular localization of azithromycin
Mechanism of accumulation...

pH 7.4
AZH₂⁺⁺ ➔ AZH₂⁺⁺
AZ ➔ AZ

pH 7.0
AZ ➔ AZ
AZH⁺ ➔ AZH⁺

pH 5.4
AZ ➔ AZ
AZH⁺ ➔ AZH⁺
AZH₂⁺⁺ ➔ AZH₂⁺⁺
3-days exposure of cells to azithromycin is associated with slower release...

![Graph showing cellular azithromycin levels over time with comparison between + and - azithromycin treatments.](image)

$t_{1/2} \approx 24h$

Azithromycin binds to (and is released from) phospholipids …

Azithromycin interaction with phospholipids is visible

Atomic force microscopy allows to probe the surface of bilayers

Azithromycin interaction with phospholipids is visible

**AFM on DOPC:DPPC 1:1 bilayers:**

- DPPC gel domains (white) in DOPC fluid matrix (dark);
- eight difference: $1.10 \pm 0.05$ nm

- Addition of azithromycin + 60 mn: only one uniform fluid phase visible

**Actions of the azithromycin on bilayers:**
- interaction of azithromycin with polar head groups
- fluidification of DPPC at the DOPC-DPPC interface
- decrease of the enthalpy associated to the gel-fluid phase transition
- enhancement of the fluctuations of the bilayers by mecanical effect of the insertion of azithromycin molecules between the polar head of DOPC molecules,

Intracellular infection …

*C. trachomatis*:
- urethritis, cervicitis
- trachoma

*C. pneumoniae*
- pneumonia
Intracellular infection ...
Azithromycin has pharmacological potentials ... and success in short treatments

Once-daily azithromycin for 3 days compared with clarithromycin for 10 days for acute exacerbation of chronic bronchitis: a multicenter, double-blind, randomized study.

Swanson RN, Lainez-Ventosilla A, De Salvo MC, Dunne MW, Amsden GW.

Defining the optimum treatment regimen for azithromycin in acute tonsillopharyngitis.

Cohen R.

Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis.

Henry DC, Riffert E, Sokol WN, Chaudry NI, Swanson RN.
Azithromycin in single dose…

A randomized, multicenter, double blind, double dummy trial of single dose azithromycin versus high dose amoxicillin for treatment of uncomplicated acute otitis media.

Azithromycin in single dose...

The demographic and behavioural profile of women with cervicitis infected with Chlamydia trachomatis, Mycoplasma hominis and Ureaplasma urealyticum and the comparison of two medical regimens.

Guven MA, Gunyeli I, Dogan M, Ciragil P, Bakaris S, Gul M.

Mass treatment with single-dose azithromycin for trachoma.

Conclusions …

• Azithromycin has the pharmacological potential of being a once-daily / single dose drug …
• Clinical trials are encouraging …
• This may be beneficial to
  – patients
  – public health
  – public economies …
What next …

I simply threwed ideas …

Maybe, like those ones…