Respiratory Fluoroquinolones: Benefit-Risk profiles

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* also
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  Université de Mons, Mons, Belgium
• Former (2008-2010) member of the EUCAST (European Committee for Antibiotic Susceptibility Testing) steering committee
• Founding member and past-President (1998-2000) of the International Society of Anti-infective Pharmacology

Belgische Vereniging voor Pneumologie – Société belge de pneumologie -- 27-11-2010
Slides are available on http://www.facm.ucl.ac.be → "Lectures"
Starting points…

• What about guidelines …
  ▪ A quick overview of CAP guidelines

• What about Regulatory Authorities statements …
  ▪ EMEA 2007 referral procedure
Starting points…

• What about guidelines …
  ▪ A quick overview of CAP guidelines
    ➔ Fluoroquinolones are almost always proposed as second line antibiotics

• What about Regulatory Authorities statements …
  ▪ EMEA 2007 referral procedure
Starting points…

• What about guidelines …
  ▪ A quick overview of CAP guidelines

  ➔ Fluoroquinolones are almost always proposed as second line antibiotics

• What about Regulatory Authorities statements …
  ▪ EMEA 2007 referral procedure

  ➔ Use only if other antibiotics cannot be used
Contents of the Presentation

• All antimicrobials have associated toxicity risks …
  – Major non-serious and serious side-effects associated with the main antimicrobials used in the treatment of CAP ($\beta$-lactams, macrolides, tetracyclines, fluoroquinolones).

• Adverse effects of fluoroquinolones vs other agents
  – Overall … and specific aspects
  – Which risks for which patients ?

• And what about the efficacy ?

• Conclusions
All antimicrobials have associated risks *

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Frequent or serious side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>amoxicillin</td>
<td>• Anaphylactic reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clostridium difficile-associated colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestive tract: diarrhoea, nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CNS: agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness.</td>
</tr>
<tr>
<td></td>
<td>amoxicillin - clavulanic acid</td>
<td>• Anaphylactic reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clostridium difficile-associated colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatic toxicity, including hepatitis and cholestatic jaundice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestive tract: diarrhoea, nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CNS : agitation, anxiety, insomnia, confusion, convulsions, behavioural changes, and/or dizziness</td>
</tr>
<tr>
<td></td>
<td>cefuroxime</td>
<td>• Anaphylactic reactions and cutaneous eruptions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nephrotoxicity (aggrav. with loop diuretics)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatic toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clostridium difficile-associated colitis</td>
</tr>
<tr>
<td></td>
<td>ceftriaxone</td>
<td>• Anaphylactic reactions and cutaneous eruptions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestive tract:diarrhoea, nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clostridium difficile-associated colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hematologic disturbances (éosinophilia, leucopenia, granulopenia, thrombopenia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatic and biliary toxicities (precipitation of Ca++ salt)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CNS: cephalalgia, vertigo</td>
</tr>
</tbody>
</table>

* based on an analysis of the respective labelling (SmPC or equivalent)
All antimicrobials have associated risks *

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Frequent or serious side effects</th>
</tr>
</thead>
</table>
| Macrolides | clarithromycin | • Anaphylactic reactions  
• *Clostridium difficile*-associated colitis  
• Drug interactions (CYP450)  
• Hepatic toxicity, including hepatitis and cholestatic jaundice  
• Palpitations, arrhythmias including prolonged QTc  
• Digestive tract: diarrhoea, nausea, vomiting, abnormal taste  
• CNS: headache, confusion, … |
|          | azithromycin | • Anaphylactic reactions  
• *Clostridium difficile*-associated colitis  
• Drug interactions (CYP450), less frequent than with other macrolides  
• Hepatic toxicity, including hepatitis and cholestatic jaundice  
• Digestive tract: diarrhoea, nausea, abdominal pain  
• CNS: dizziness, fatigue, vertigo, …  
• Genitourinary: nephritis, vaginitis |
|          | telithromycin | • Anaphylactic reactions and allergic skin reactions  
• *Clostridium difficile*-associated colitis  
• Hepatotoxicity  
• Visual disturbance  
• Loss of consciousness  
• Respiratory failure in patients with myastenia gravis  
• QTc prolongation  
• Drug interactions (CYP450)  
• Digestive tract: diarrhoea, nausea, vomiting, dysguesia  
• CNS: headache, dizziness |

* based on an analysis of the respective labelling (SmPC or equivalent)

Carbonnelle et al., submitted
All antimicrobials have associated risks *

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Frequent or serious side effects</th>
</tr>
</thead>
</table>
| fluoroquinolones | levofloxacin | • Anaphylactic reactions and allergic skin reactions  
• *Clostridium difficile*-associated colitis  
• Hematologic toxicity  
• Hepatotoxicity  
• Central nervous system effects: headache, insomnia, dizziness, convulsions  
• **Musculoskeletal: tendinopathies**  
• Peripheral neuropathy  
• Prolongation of the QTc interval and isolated cases of torsade de pointes  
• **Digestive tract: nausea, diarrhoea** |
|                | moxifloxacin | • Anaphylactic reactions and allergic skin reactions  
• *Clostridium difficile*-associated colitis  
• **Musculoskeletal: Tendinopathies**  
• Peripheral neuropathy  
• Prolongation of the QT interval  
• Central nervous system effects: headache, insomnia, dizziness, convulsions  
• **Digestive tract: nausea, diarrhoea** |

* based on an analysis of the respective labelling (SmPC or equivalent)
All antimicrobials have associated risks *

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<th>Class</th>
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<th>Frequent or serious side effects</th>
</tr>
</thead>
</table>
| **tetracyclines** | doxycycline | • Anaphylactic reactions and allergic skin reactions  
• *Clostridium difficile*-associated colitis  
• Digestive tract: anorexia, glossitis, dysphagia, nausea, vomiting, diarrhoea  
• **esophagitis and esophageal ulcerations**  
• Blood cells: hemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia  
• Hepatotoxicity  
• **Photosensitivity** |

* based on an analysis of the respective labelling (SmPC or equivalent)

**Conclusions (# 1):**

- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the specific environment and for the specific patient
Contents of the Presentation

• All antimicrobials have associated toxicity risks …
  – Major non-serious and serious side-effects associated with the main antimicrobials used in the treatment of CAP (β-lactams, macrolides, tetracyclines, fluoroquinolones).
• Adverse effects of fluoroquinolones vs other agents
  – Overall … and specific aspects
  – Which risks for which patients
• And what about the efficacy ?
• Conclusions
Are fluoroquinolones more toxic in controlled clinical trials*?

<table>
<thead>
<tr>
<th></th>
<th>Moxifloxacin</th>
<th>Comparator</th>
<th>Moxifloxacin</th>
<th>Comparator</th>
<th>Moxifloxacin</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral, N (%)</td>
<td>Sequential, N (%)</td>
<td>Oral, N (%)</td>
<td>Sequential, N (%)</td>
<td>Oral, N (%)</td>
<td>Sequential, N (%)</td>
</tr>
<tr>
<td>Total</td>
<td>9394 (100)</td>
<td>9359 (100)</td>
<td>2934 (100)</td>
<td>2970 (100)</td>
<td>529 (100)</td>
<td>533 (100)</td>
</tr>
<tr>
<td>AE</td>
<td>4057 (43.2)</td>
<td>3950 (42.2)</td>
<td>1952 (66.5)</td>
<td>1927 (64.9)</td>
<td>149 (28.2)</td>
<td>133 (25.0)</td>
</tr>
<tr>
<td>ADR *</td>
<td>2257 (24.0)</td>
<td>2059 (22.0)</td>
<td>759 (25.9)</td>
<td>718 (24.2)</td>
<td>57 (10.8)</td>
<td>59 (11.1)</td>
</tr>
<tr>
<td>SAE</td>
<td>369 (3.9)</td>
<td>361 (3.9)</td>
<td>552 (18.8)</td>
<td>492 (16.6)</td>
<td>14 (2.6)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>SADR *</td>
<td>56 (0.6)</td>
<td>50 (0.5)</td>
<td>89 (3.0)</td>
<td>61 (2.1)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Fatal AE</td>
<td>33 (0.4)</td>
<td>44 (0.5)</td>
<td>121 (4.1)</td>
<td>119 (4.0)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Fatal ADR</td>
<td>3 (&lt;0.1)</td>
<td>4 (&lt;0.1)</td>
<td>4 (0.1)</td>
<td>5 (0.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

AE: adverse event; ADR: adverse drug reaction; SAE: serious AE; SADR: serious ADR

* data for moxifoxacin (all clinical trials) (Tulkens et al., in preparation)
### Hepatic toxicity of antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Tetracycline</th>
<th>Erythromycin</th>
<th>Co-trimoxazole</th>
<th>Telithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Tetracycline</td>
<td>Erythromycin</td>
<td>Co-trimoxazole</td>
<td>Telithromycin</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Tetracycline</td>
<td>Erythromycin</td>
<td>Co-trimoxazole</td>
<td>Telithromycin</td>
</tr>
<tr>
<td>Amoxicillin/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clavulanate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Isolated cases and ≤ 0.00007

- ≤0.0002
- ≤0.004
- ≤0.02
- ≥0.02

#### Points of interest:

- **Simmons C.** Beware: antibiotic-induced hepatotoxicity is rare but deadly. Hosp Pharm 2002; 37:326-330
- **Health Canada.** Canadian Adverse Reaction Newsletter. 17, 1. 2007.
- **Carbon C.** Effets indésirables de la lévofloxacine: données des études cliniques et de la pharmacovigilance [In French (Levofloxacin adverse effects, data from clinical trials and pharmacovigilance); abstract in English]. Therapie 2001; 56(1):35-40.[PMID: PM:11322015]
Moxifloxacin QTc compared to other drugs

Moxifloxacin is used as a positive control for QT<sub>C</sub> effect(s) in Phase I studies because it offers a positive signal without risk of clinical adverse events to the volunteers.

And patients with pre-existing cardiac risk factors *?

oral treatment

vs β-lactams (n = 526 vs 444)

vs macrolides (n = 794 vs 623)

IV and sequential treatment

vs β-lactams (n = 438 vs 406)

vs macrolides (n = 175 vs 168)

- AE: adverse event;
- ADR: adverse drug related event;
- SAE: serious adverse event;
- SADR: serious adverse drug-related event;
- discont. AE: discontinuation of therapy due to an adverse event;
- death: death of the patient for any cause;
- death st. drug: death related to the study drug

* based on MedDRA 13.1 (potential cardiac disease [primary or secondary linkage]) excluding patients with congenital QT interval prolongation, uncorrected hypokaliemia, clinically significant bradycardia, left cardiac insufficiency or previous rhythm disturbances, and class Ia and III antiarrhythmics

Tulkens et al., in preparation
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# Populations at risk *

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Populations at higher risk of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>amoxicillin</td>
<td>• Allergic patients</td>
</tr>
<tr>
<td></td>
<td>amoxicillin/clavulanic acid</td>
<td>• Allergic patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Erythematous skin rash: patients with mononucleosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatic toxicity: patients with hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nephrotoxicity: elderly patients</td>
</tr>
<tr>
<td>macrolides</td>
<td>clarithromycin</td>
<td>• Cardiac effects: patients taking other drugs with effects on QTc or class 1A or III antiarrythmics</td>
</tr>
<tr>
<td></td>
<td>azithromycin</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients with severe renal impairment with or without coexisting hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients taking drugs metabolized by CYP450</td>
</tr>
<tr>
<td></td>
<td>telithromycin</td>
<td>• Hepatotoxicity: patients with liver failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Myopathies : co-administration of statins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients with severe renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Children (no studies so far)</td>
</tr>
</tbody>
</table>

* as defined by the corresponding labelling

Carbonnelle et al., submitted
<table>
<thead>
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<th>Class</th>
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<th>Populations at higher risk of side effects</th>
</tr>
</thead>
</table>
| fluoroquinolones  | levofloxacin | • **Tendon disorders**: elderly, patients taking corticoids, or with kidney, heart or lung transplants  
   |          | • Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia  
   |          | • CNS effects: patients at risk of epilepsy  
   |          | • Dysglycemia: diabetic patients  
   |          | • **Pregnancy, lactation, infants**          |
| moxifloxacin      |         | • **Tendon disorders**: elderly, patients taking corticoids, or with kidney, heart or lung transplants  
   |          | • Cardiac effects: elderly patients taking other drugs with effects on QTc or class 1A or III antiarrythmics, or with known QT prolongation or hypokaliemia  
   |          | • CNS effects: patients at risk of epilepsy  
   |          | • **Pregnancy, lactation, infants**          |
| tetracyclines     | doxycycline | • **Pregnancy, lactation, infants**          |

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Contents of the Presentation

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• Conclusions
Macrolides (alone) are no longer an option in Belgium …

S. pneumoniae prevalence (%) of macrolide-resistant and intermediate strains in 2008 in Belgium (CAP patients; n=249)

[Graph showing MIC (mg/L) vs. % isolates]

Lismond et al. ECCMID 2009 – poster 1099

http://www.eucast.org
β-lactams are reaching their limits in Belgium for CAP (which is the reason why physicians tend to use moxifloxacin more frequently)

About 15 % of isolates are "poorly susceptible" to amoxicillin and cefuroxime (requiring high dosages of these antibiotics) ...

99 % of isolates are below the breakpoint with the registered dosage of 400 mg 1 x day

Lismond et al., ECCMID 2008; Vanhoof et al, ECCMID 2009
Moxifloxacin MIC's against *S. pneumoniae* have not increased in Belgium from 1999 to 2008

*S. pneumoniae* susceptibility to moxifloxacin in Belgium

**Facts:**
- From data of a national collection * independent from our own collection (shown on the previous slide)
  - No change (and even improvement) in *S. pneumoniae* susceptibility to moxifloxacin from 1999 (pre-commercialization) to 2008 (7 years after launching **)
  - in 2008, 99.3 % isolates were still below the EUCAST breakpoint (0.5 mg/L) and at MIC values > 10-fold lower than the C$_{\text{max}}$.  

*Non invasive respiratory tract infections*  
**1st respiratory quinolone in BE**

Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 448 in 2008)  
http://www.iph.fgov.be  
Conclusions (1 of 2)

• The overall safety profile of fluoroquinolones (and moxifloxacin in particular) is similar or better than comparators
  – Hepatic events reactions are within range of other antibacterials, and lower than amoxicillin/clavulanic acid or macrolides
  – QTc prolongation is well characterized but cardiac events/TdP are not different from other fluoroquinolones and lower than those of macrolides
  – Class events (tendonitis, e.g.) are well known and can be taken care of
  – skin events are very rare and, in any case, much less frequent than with β-lactams
Conclusions (2 of 2)

• Fluoroquinolones are a useful alternatives when "1st line antibiotics" (for CAP or COPD) have problems;

• The safety profiles of higher doses of β-lactams or of levofloxacin is not well established

• Moxifloxacin is not causing excessive toxicity if prescribed for the correct indications and with due attention to the contraindications and warnings mentioned in the labeling

Disclosures

Financial support from
- the Belgian *Fonds de la Recherche Scientifique* (and other federal and regional funding agencies) for basic research on pharmacology and toxicology of antibiotics and related topics
- the Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice
- Pharmaceutical Industry for specific drug-related studies

Note:
- all work, irrespective the source of funding, is published in peer-reviewed journals and is available from our web site *
- P.M. Tulkens is member of the Committee organising public campaigns for appropriate use of antibiotics in Belgium since 2000 **

* [http://www.facm.ucl.ac.be/publicat_facm.htm](http://www.facm.ucl.ac.be/publicat_facm.htm)
** [http://www.antibiotiques.org/](http://www.antibiotiques.org/)

Selected publications in relation to this presentation: