Fluoroquinolones: are they all the same (or not)?

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Université catholique de Louvain
Brussels, Belgium

Singapore

With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/7383/078554
Disclosures and slides availability

• Research grants
  – Theravance, Astellas, Cempra, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Debiopharm, Eumedica
  – Fund for Sientific Research (F.R.S.-FNRS), Federal Public Service "Public Health", Walloon and Brussels Regions, European Union (FP7 and JPIAMR)

• Speaker's honoraria
  – Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, Vifor
  – Flemish Education Program on Antibiotics (Opleidingsprogramma Antibioticabeleid Vlaanderen)

• Advisory Committees and Decision-making Bodies
  – US National Institutes of Health (*grant reviewing*)
  – General Assembly and former member of the Steering committee of EUCAST
  – External expert for the European Medicines Agency (EMA)
  – Former member Belgian Drug Reimbursement Committee (*CRM / CTG*)
  – Member of the Belgian Antibiotic Policy Coordination Committee (BAPCOC)
  – Governance of the EU program "DRIVE AB" (new economical framework for antibiotics)

Slides: http://www.facm.ucl.ac.be → Lectures
Belgium

10 millions inhabitants …

10 Nobel prizes (10/850)

• Peace
  - Institute of International Law, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)

• Literature
  - Maurice Maeterlinck, Ghent (1911)

• Medicine
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)

• Chemistry
  - Ilya Prigogyne, Brussels (1977)

• Physics
  - François Englert, Brussels (2013)
The Catholic University of Louvain in brief (1 of 4)

- originally founded in **1425** in the city of *Louvain* (in French and English; known as *Leuven* in Flemish)
The Catholic University of Louvain in brief (2 of 4)

• It was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's  Erasmus  Vesalius
The Catholic University of Louvain in brief (3 of 4)

- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…

Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("big bang")

(here in conversation with A. Einstein)

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…)

(here in front of a centrifuge)

- in 1968, the University was divided into
  - a French-speaking Université catholique de Louvain
  - a Flemish-speaking Katholieke Universiteit Leuven…
The Catholic University of Louvain in brief (4 of 4)

• The Flemish-speaking Katholieke Universiteit Leuven has remained in Louvain (Leuven) and is named in English "Catholic Universiteit Leuven".

• The French-speaking Université catholique de Louvain has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwé)

• Together, the two Universities have about 55,000 students
What do we do?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- one-line monitoring of $\beta$-lactams
- novel antibiotics (and last studied)
  - lipoglycopeptides (oritavancin…)
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacin…)
  - ketolides (solithromycin…)
  - oxazolidinones (tedizolid …)

www.facm.ucl.ac.be

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

www.isap.org

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young ...
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young …
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young …
What shall we discuss?

• The basics: how were quinolones invented? (are they different by design?)

• The real life in the lab: microbiological properties and risk of resistance… (or how to really differentiate them …)

• The real life in the doctor’s office: efficacy and tolerance… (is there a difference) ?

• Should we use the “best in class”? 

22/03/2016 Are all fluoroquinolones equal? -- Singapore
What shall we discuss?

• The basics: how were quinolones invented? (are they different by design?)

• The real life in the lab: microbiological properties and risk of resistance... (or how to really differentiate them ...)

• The real life in the doctor’s office: efficacy and tolerance... (is there a difference)?

• Should we use the “best in class”?
Mechanism of action of fluoroquinolones: the basics...
2 key enzymes in DNA replication:

DNA gyrase

Stabilize positive node → Break back segment → Reseal break on front side

Topoisomerase IV

bacterial DNA is supercoiled
A bit of history: from chloroquine to nalidixic acid...

1939
chloroquine

1958
7-chloroquinoline (synthesis intermediate found to display antibacterial activity)

1962
nalidixic acid
From nalidixic acid to the 1st fluoroquinolone

3 key modifications *...

1. broader Gram(-) activity
2. less protein binding (50%)
3. longer half-life (3-4h)

* 6-fluoro-7-pyrimidino-quinoleine

* Belgian patent 863,429, 1978 to Kyorin
From norfloxacin to ciprofloxacin and ofloxacin

* Ger. pat. 3,142,854 to Bayer AG, 1983
** Eur. pat. Appl. 47,005 to Daiichi, 1982
Levofloxacin is the active isomer of ofloxacin

Ofloxacin is a racemic mixture
50/50

Levofloxacin is the pure (-) S isomer of ofloxacin *

The active form of ofloxacin is the (-) S isomer
The (+) R isomer is inactive but toxic

* Eur. pat. 206,283 to Daiichi, 1987
The present "first generation" of fluoroquinolones ... 

- Nalidixic acid
- Oxolinic acid
- Flumequine
- Pipemidic acid

- Norfloxacin
- Ofloxacin
- Ciprofloxacin
- Levofloxacin

$t_{1/2}$

<table>
<thead>
<tr>
<th></th>
<th>activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 h</td>
<td>++</td>
</tr>
<tr>
<td>6 h</td>
<td>++</td>
</tr>
<tr>
<td>3-4 h</td>
<td>+++</td>
</tr>
<tr>
<td>6 h</td>
<td>++/++</td>
</tr>
</tbody>
</table>

Mainly anti Gram (-) activity

2 x more active than ofloxacin per g
How to improve the chemotherapeutic usefulness of the "first generation" fluoroquinolones

1. Maintain broad Gram(-) activity ?
2. Further Improve Gram(+) activity ?
3. Acquire activity against anaerobes ?
Activity against *S. pneumoniae*

- Ciprofloxacin: MIC = 0.5 - 2
- Moxifloxacin: MIC = 0.01 - 0.5
- Levofloxacin: MIC = 0.5 - 2

Hint: lower MICs = a more potent antibiotic!
Activity against *B. fragilis* (anaerobe)

- Ciprofloxacin: MIC = 2-128
- Moxifloxacin: MIC = 0.125-8
At this point …

Gram (-) 

ciprolfloxacin

Gram (+) 

anaerobes

moxifloxacin

levofloxacin

This is by design!
What shall we discuss?

• The basics: how were quinolones invented? (are they different by design?)

• The real life in the lab: microbiological properties and risk of resistance… (or how to really differentiate them …)

• The real life in the doctor’s office: efficacy and tolerance… (is there a difference) ?

• Should we use the “best in class” ?
A unbiased estimation of antibiotic activity (in the absence of resistance)

MIC distributions and epidemiological cut-off

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European and other countries, FESCI and ISC. The Steering Committee also consults on EUCAST proposals with experts within the fields of infectious diseases and microbiology, pharmaceutical companies and susceptibility testing device manufacturers.

EUCAST has a subcommittee on artificial susceptibility of...
MIC for Gram-negative bacteria: *E. coli* as an example

---

**Ciprofloxacin / Escherichia coli**

International MIC Distribution - Reference Database 2015-02-08

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

---

**Levofloxacin / Escherichia coli**

International MIC Distribution - Reference Database 2015-02-08

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

---

http://mic.eucast.org/Eucast2/regShow.jsp?id=1022

http://mic.eucast.org/Eucast2/regShow.jsp?id=1072

Last accessed: 8/2/2015
MIC for Gram-positive bacteria: *S. pneumoniae* as an example

**S. pneumoniae**

- **Moxifloxacin**
- **Levofloxacin**

### Moxifloxacin / Streptococcus pneumoniae
International MIC Distribution - Reference Database 2015-02-08

- MIC (mg/L) ranges from 0.002 to 64.
- Percent of isolates:
  - Moxifloxacin: 0.015625 to 64.
  - Levofloxacin: 0.015625 to 16.

### Levofloxacin / Streptococcus pneumoniae
International MIC Distribution - Reference Database 2015-02-08

- MIC (mg/L) ranges from 0.002 to 64.
- Percent of isolates:
  - Moxifloxacin: 0.015625 to 64.
  - Levofloxacin: 0.015625 to 16.

**http://mic.eucast.org/Eucast2/regShow.jsp?Id=1099**
**http://mic.eucast.org/Eucast2/regShow.jsp?Id=1310**

Last accessed: 8/2/2015
Anaerobes: *B. fragilis*

**MIC distributions for B. fragilis**

- **Moxifloxacin**
- **Levofloxacin**

**Percent of isolates**

- **Moxifloxacin**
- **Levofloxacin** (not recommended)

**MIC (mg/L)**

- 0.015625
- 0.03125
- 0.0625
- 0.125
- 0.25
- 0.5
- 1
- 2
- 4
- 8
- 16
- 32
- 64

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

**References:**


Last accessed: 8/2/2015
Killing abilities of fluoroquinolones: Are they all equal against susceptible strains?

*in vitro* kill curves: observations with *S. pneumoniae*

Fig. 1. Time kill curves of moxifloxacin versus levofloxacin against *S. pneumoniae* 7362 (average of 2 models).

Schafer et al. Diag Microb Infect Dis 2008; 60:155–161
Killing abilities of fluoroquinolones: Are they all equal against less susceptible strains?

Animal survival experiments (S. pneumoniae i.p. inoculations)

<table>
<thead>
<tr>
<th>strain</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR33118</td>
<td>0.12</td>
</tr>
<tr>
<td>FL2812</td>
<td>0.25</td>
</tr>
<tr>
<td>FL5629</td>
<td>4</td>
</tr>
</tbody>
</table>

**Hint:** lower dose (more to the left) → more potent antibiotic!

The risk for resistance to fluoroquinolones is to be “within the mutation selection window” …

$C_{\text{max}}$ and "Mutant Prevention Concentration" (MPC) …

$\text{MIC}_{99} = 0.8 \text{ mg/L}$ (in this example)

"Classic" bactericidal effect

Elimination of resistant organisms

$\text{MPC}_{10} = 9$

Dong et al: AAC 1999; 43:1756-1758
"Mutant Prevention Concentration …"

Surviving bacteria

MIC<sub>99</sub> = 0.8

Concentration that inhibits the majority of the organisms

MPC<sub>10</sub> = 9

A concentration of about 10 x the MIC is needed to prevent selecting resistant subpopulations!

Dong et al; AAC 43:1756-1758
MPC: moxifloxacin vs levofloxacin

~10 x the median MIC (0.125 mg/L)

~10 x the median MIC (1 mg/L)
Pharmacokinetics and “resistance” breakpoint vs. MIC

Levofloxacin 500 mg 1X / day
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
\[ \text{MIC}_{\text{max}} \sim 0.5 \]

Moxifloxacin 400 mg 1X / day
- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
\[ \text{MIC}_{\text{max}} \sim 0.5 \]

% of strains

Maximal MIC to avoid selection of resistance

resistance breakpoint
- AUC/MIC = 100
- peak/MIC = 10

MIC data: EUCAST MIC distributions (wild type)
PK data: US and EU labelling (typical values)
Hs resistance to moxifloxacin materialized: evidence for *S. pneumoniae* in Belgium from 1999 to 2014 *

*S. pneumoniae* susceptibility to moxifloxacin in Belgium

* Moxifloxacin was introduced in Belgium in 2001 and became the almost only fluoroquinolone used for RTI since 2004

From data of a national collection
- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S. pneumoniae* from clinically-confirmed CAP (n=132)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 312 in 2014)
- Data available yearly for 1999 through 2014 at [http://www.iph.fgov.be](http://www.iph.fgov.be)

Vanhoof et al. 19th ECCMID, Helsinki, 2009
Ceyssens et al. 35th RICA, Paris, 2015
Ceyssens et al. submitted
What shall we discuss?

- The basics: how were quinolones invented? (are they different by design?)
- The real life in the lab: microbiological properties and risk of resistance... (or how to really differentiate them ...)
- The real life in the doctor’s office: efficacy and tolerance... (is there a difference)?
- Should we use the “best in class”?
Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus that of Levofloxacin Therapy

Antonio Anzueto,1,2 Michael S. Niederman,3 James Pearle,4 Marcos I. Restrepo,1,2 Albrecht Heyder,5 and Shurjeel H. Choudhri,6 for the Community-Acquired Pneumonia Recovery in the Elderly Study Group*

1Department of Medicine, University of Texas Health Science Center, and 2Veterans Evidence Based Research Dissemination and Implementation Center, Department of Medicine, South Texas Veterans Healthcare System, San Antonio, Texas; 3Department of Medicine, Winthrop-University Hospital, Mineola, New York; 4California Research Medical Group, Fullerton, California; 5Carolina Research Specialists, Elizabeth City, North Carolina; and 6Bayer Pharmaceuticals, West Haven, Connecticut
Head to head comparison…

Clinical Infectious Diseases 2006;42:73-81.

Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus that of Levofloxacin Therapy.

Antonio Anzueto,1,2 Miroslav Vrabec,3,4 and Shurjeel H. Choudhry1

1Department of Medicine, University of Virginia Health System, Charlottesville, Virginia; 2Department of Radiology, University of Virginia Health System, Charlottesville, Virginia; 3Department of Medicine, University of Virginia Health System, Charlottesville, Virginia; 4Department of Medicine, University of Virginia Health System, Charlottesville, Virginia; and 5Bayer Pharmaceuticals, West Haven, Connecticut.

Hospitalised CAP

Visit 1
Day 1

Visit 2
(Day 3–5)

Test of cure + 5–21 days

Randomisation

12-lead ECG

Hospitalised CAP

72-h Holter monitor

12-lead ECG

Moxifloxacin 400mg q.d.

IV

PO

Levofloxacin 500mg q.d.

PO

IV
and results in a snapshot...

**Clinical outcomes**

<table>
<thead>
<tr>
<th>Clinical recovery rate</th>
<th>Clinical cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>97.9 (95% CI: 1.7, 14.1); P=0.01</td>
<td>92.9 (95% CI: -1.9, 11.9); P=0.2</td>
</tr>
</tbody>
</table>

**Clinical cure rate according to severity of CAP**

- **Mild/Moderate**
  - Moxifloxacin: 92.6, 113/122
  - Levofloxacin: 88.6, 101/114
- **Severe**
  - Moxifloxacin: 94.7, 18/19
  - Levofloxacin: 84.6, 22/26

Success rate (% of patients)
and results in a snapshot...

Clinical outcomes

Clinical recovery rate
(95% CI: 1.7, 14.1); P=0.01

Clinical cure rate
(95% CI: -1.9, 11.9); P=0.2

Success rate (% of patients)

Days 3-5

Test of cure

Moxifloxacin 400 mg daily was numerically superior to levofloxacin 500 mg daily

Clinical cure rate according to severity of CAP

Moxifloxacin 400 mg daily was numerically superior to levofloxacin 500 mg daily
Clinical Infectious Diseases 2008; 46:1499-509.

Moxifloxacin Monotherapy Is Effective in Hospitalized Patients with Community-Acquired Pneumonia: The MOTIV Study—A Randomized Clinical Trial

Antoni Torres, Javier Garau, Pierre Arvis, Jean Carlet, Shurjeel Choudhri, Amar Kureishi, Marie-Aude Le Berre, Hartmut Lode, John Winter, and Robert C. Read, for the MOTIV (MOxifloxacin Treatment IV) Study Group

1Servei de Pneumologia i Alergia Respiratoria, Institut Cliníc del Torax, Hospital Cliníc de Barcelona, IDIBAPS, Facultat de Medicina, Consorcio CIBER del área de Enfermedades Respiratorias (CIBERESP), and 2Hospital Mutua de Terrassa, University of Barcelona, Barcelona, Spain; 3Bayer Healthcare, Puteaux, and 4Intensive Care Unit and Infectious Diseases Department, Fondation Hôpital Saint-Joseph, Paris, France; 5Bayer Healthcare Pharmaceuticals, Toronto, Canada; 6Bayer Healthcare Company, Beijing, People’s Republic of China; 7Institute for Clinical Pharmacology, Charité-Universitätsmedizin, Berlin, Germany; and 8Department of Medicine, Ninewells Hospital and Medical School, Dundee, and 9Section of Infection, Immunity and Inflammation, Sheffield University Medical School, Sheffield, United Kingdom
Background to the study

- Designed to further demonstrate the **efficacy** and **safety** of moxifloxacin in CAP
- According to European (EMA; CPMP) guidelines
  - Potent comparator (ceftriaxone/levofloxacin b.i.d.)
  - Review of the data by **independent committees**
    (clinical response, chest X-ray, cardiac events)
  - Non-inferiority trial: can do as well as this combination?
What was done in MOTIV?

Patients with CAP & PSI score >II

Stratification

PSI III (<50%)

PSI IV & V (≥50%)

Clinical evaluation

Pre-therapy

Randomisation

C_{\text{max}} \text{ and ECG x3}
15 min post-dose, Day 1, Day 3

Moxifloxacin alone *

Levofloxacin/ceftriaxone **

Moxifloxacin alone *

Levofloxacin/ceftriaxone **

Days 3–5

Test of cure Days 4–14

Late FU Days 21–28

* moxifloxacin: 400 mg/day
** levofloxacin: 500 mg twice a day /ceftriaxone: 2g/day
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Moxifloxacin (N=291)</th>
<th>Ceftriaxone + levofloxacin (N=278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>66.0 ± 16.2</td>
<td>64.8 ± 16.7</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>191 (65.6)</td>
<td>164 (59.0)</td>
</tr>
<tr>
<td>Cardiac comorbidity, n (%)</td>
<td>89 (30.6)</td>
<td>90 (32.4)</td>
</tr>
<tr>
<td>Duration of CAP symptoms prior to enrolment, mean days ± SD</td>
<td>5.0 ± 3.5</td>
<td>4.6 ± 2.8</td>
</tr>
<tr>
<td>Failure on previous systemic antimicrobials, n (%)</td>
<td>39 (13.4)</td>
<td>40 (14.4)</td>
</tr>
<tr>
<td>Intensive care admission, n (%)</td>
<td>25 (8.6)</td>
<td>30 (10.8)</td>
</tr>
<tr>
<td>PSI distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III, n (%)</td>
<td>122 (41.9)</td>
<td>111 (39.9)</td>
</tr>
<tr>
<td>Class IV, n (%)</td>
<td>138 (47.4)</td>
<td>134 (48.2)</td>
</tr>
<tr>
<td>Class V, n (%)</td>
<td>31 (10.7)</td>
<td>33 (11.9)</td>
</tr>
</tbody>
</table>

All differences were non-significant
And what did you get?

Clinical cure at test of cure – overall

95% CI: -8.1, 2.2

Clinical cure at test of cure
PSI class IV–V

95% CI: -9, 5.8

253/291

250/278

Moxifloxacin
Ceftriaxone + levofloxacin

86.9
89.9

84.6
86.6

143/169
145/167

Moxifloxacin
Ceftriaxone + levofloxacin
And what did you get?

Clinical cure at test of cure – overall

moxifloxacin 400 mg daily was not inferior to a combination of levofloxacin 2 x 500 mg daily plus ceftriaxone 2 g daily
We all agree about efficacy, but what about side effects…

therapy ?

side effects ?
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>fluoroquinolones</td>
<td>levofloxacin</td>
<td>• Anaphylactic reactions and allergic skin reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <em>Clostridium difficile</em>-associated colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hematologic toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Hepatotoxicity (ALT-AST elevation [common])</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Central nervous system effects: headache, insomnia, dizziness, convulsions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Musculoskeletal: tendinopathies</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prolongation of the QTc interval (cardiac disorders [rare])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Hypoglycaemia (rare)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestive tract: nausea, diarrhoea</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td></td>
<td>• Anaphylactic reactions and allergic skin reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <em>Clostridium difficile</em>-associated colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Hepatotoxicity (ALT-AST elevation [common])</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Musculoskeletal: Tendinopathies</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prolongation of the QT interval (cardiac disorders [rare])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Central nervous system effects: headache, insomnia, dizziness, convulsions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestive tract: nausea, diarrhoea</td>
</tr>
</tbody>
</table>

* based on an analysis of the current respective labelling (European SmPC)
- common: 1/10 to 1/100
- rare: 1/1000-1/10000

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:
• For [community-acquired pneumonia], TAVANIC should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.
• Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.
A reasonable equilibrium for moxifloxacin?

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular
    (atypical pneumonia, tuberculosis)
- easy iv/po switch
- excellent oral bioavailability

- toxicity?
Moxifloxacin Safety
An Analysis of 14 Years of Clinical Data

Paul M. Tulkens, Pierre Arvis and Frank Kruesmann

1 Pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany

Based on the analysis of 14,681 patients treated with moxifloxacin vs. 15,023 patients treated with comparators
Side effects of moxifloxacin (clinical trials database)

Distribution of patients valid for the safety analysis, stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by comparator

<table>
<thead>
<tr>
<th>Study design and COMP</th>
<th>Treatment route [n]</th>
<th>IV/PO [n=6846]</th>
<th>IV only [n=1860]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO [n=21298]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MXF [n=10613]</td>
<td>COMP [n=10685]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactam</td>
<td>2391</td>
<td>2104</td>
<td>1077</td>
</tr>
<tr>
<td>β-lactam + macrolide</td>
<td>274</td>
<td>155</td>
<td>0</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>2246</td>
<td>2287\textsuperscript{a}</td>
<td>444</td>
</tr>
<tr>
<td>Macrolide</td>
<td>3659</td>
<td>2929</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1230</td>
<td>1168\textsuperscript{c}</td>
<td>368</td>
</tr>
<tr>
<td>Total</td>
<td>8822\textsuperscript{f}</td>
<td>8643</td>
<td>1889</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design and COMP</th>
<th>Treatment route [n]</th>
<th>IV/PO [n=6846]</th>
<th>IV only [n=1860]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO [n=21298]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MXF [n=10613]</td>
<td>COMP [n=10685]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactam</td>
<td>1318</td>
<td>1301</td>
<td>554</td>
</tr>
<tr>
<td>β-lactam + macrolide</td>
<td>186</td>
<td>190</td>
<td>0</td>
</tr>
<tr>
<td>β-lactam ± macrolide</td>
<td>0</td>
<td>0</td>
<td>532</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>263</td>
<td>270\textsuperscript{g}</td>
<td>0</td>
</tr>
<tr>
<td>Macrolide</td>
<td>287</td>
<td>281</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>456</td>
</tr>
<tr>
<td>Total</td>
<td>1791\textsuperscript{f}</td>
<td>2042</td>
<td>1542</td>
</tr>
</tbody>
</table>

PO= oral
IV = intravenous
MXF: moxifloxacin
COMP = comparator (see left column)

Tulkens et al., Drugs R D (2012) 12: 71-100
## Table III. Summary of safety data for patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by study design. An asterisk (*) indicates differences observed between treatment groups in disfavor of moxifloxacin that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups and for which the number of patients experiencing an event was ≥10 in either group.

<table>
<thead>
<tr>
<th>Study design and event</th>
<th>Treatment route [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Double-blind studies</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PO [n= 17465]</td>
</tr>
<tr>
<td>Any AE</td>
<td>3782 (42.9)</td>
</tr>
<tr>
<td>Any ADR</td>
<td>2211 (25.1)</td>
</tr>
<tr>
<td>SAE</td>
<td>318 (3.6)</td>
</tr>
<tr>
<td>SADR</td>
<td>47 (0.5)</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td>366 (4.1)</td>
</tr>
<tr>
<td>Premature discontinuation due to ADR</td>
<td>261 (3.0)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td>28 (0.3)</td>
</tr>
<tr>
<td>ADR with fatal outcome</td>
<td>3 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Open-label studies</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PO [n= 3833]</td>
</tr>
<tr>
<td>Any AE</td>
<td>764 (42.7)*</td>
</tr>
<tr>
<td>Any ADR</td>
<td>330 (18.4)*</td>
</tr>
<tr>
<td>SAE</td>
<td>104 (5.8)</td>
</tr>
<tr>
<td>SADR</td>
<td>12 (0.7)*</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td>70 (3.9)</td>
</tr>
<tr>
<td>Premature discontinuation due to ADR</td>
<td>51 (2.8)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>ADR with fatal outcome</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Side effects of moxifloxacin (clinical trials database)

- AE, ADR and SADR were mainly gastrointestinal disorders and "changes observed during investigations" such as asymptomatic QT prolongation.
- Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated diarrhoea were similar with moxifloxacin and comparators.

<table>
<thead>
<tr>
<th>Study design and event</th>
<th>Treatment route [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Double-blind studies</strong></td>
<td><strong>PO [n= 17465]</strong></td>
</tr>
<tr>
<td>Any AE</td>
<td>3782 (42.9)</td>
</tr>
<tr>
<td>Any ADR</td>
<td>2211 (25.1)</td>
</tr>
<tr>
<td>SAE</td>
<td>318 (3.6)</td>
</tr>
<tr>
<td>SADR</td>
<td>47 (0.5)</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td>366 (4.1)</td>
</tr>
<tr>
<td>Premature discontinuation due to ADR</td>
<td>261 (3.0)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td>28 (0.3)</td>
</tr>
<tr>
<td>ADR with fatal outcome&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>3 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Open-label studies</strong></td>
<td><strong>PO [n= 3833]</strong></td>
</tr>
<tr>
<td>Any AE</td>
<td>764 (42.7)*</td>
</tr>
<tr>
<td>Any ADR</td>
<td>330 (18.4)*</td>
</tr>
<tr>
<td>SAE</td>
<td>104 (5.8)</td>
</tr>
<tr>
<td>SADR</td>
<td>12 (0.7)*</td>
</tr>
<tr>
<td>Premature discontinuation due to AE</td>
<td>70 (3.9)</td>
</tr>
<tr>
<td>Premature discontinuation due to ADR</td>
<td>51 (2.8)</td>
</tr>
<tr>
<td>AE with fatal outcome</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>ADR with fatal outcome&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

<table>
<thead>
<tr>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>age (&gt; 65 y)</strong></td>
<td>n = 2551 vs. 2403</td>
<td>n = 1373 vs. 1334</td>
</tr>
<tr>
<td>AE</td>
<td>1050 / 1021</td>
<td>929 / 900</td>
</tr>
<tr>
<td>ADR</td>
<td>440 / 448</td>
<td>348 / 307</td>
</tr>
<tr>
<td>SAE</td>
<td>207 / 184</td>
<td>298 / 290</td>
</tr>
<tr>
<td>SADR</td>
<td>16 / 18</td>
<td>49 / 30</td>
</tr>
<tr>
<td>discont. AE</td>
<td>116 / 109</td>
<td>131 / 104</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>78 / 74</td>
<td>62 / 42</td>
</tr>
<tr>
<td>death AE</td>
<td>29 / 32</td>
<td>100 / 98</td>
</tr>
<tr>
<td>death ADR.</td>
<td>3 / 1</td>
<td>2 / 3</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

<table>
<thead>
<tr>
<th>diabetes</th>
<th>n = 777 vs. 717</th>
<th>n = 926 vs. 917</th>
<th>n = 80 vs. 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>355 - 310</td>
<td>587 / 565</td>
<td>42 - 35</td>
</tr>
<tr>
<td>ADR</td>
<td>158 - 126</td>
<td>196 / 174</td>
<td>13 - 14</td>
</tr>
<tr>
<td>SAE</td>
<td>78 - 56</td>
<td>198 / 182</td>
<td>16 - 11</td>
</tr>
<tr>
<td>SADR</td>
<td>11 - 3</td>
<td>22 / 11</td>
<td>2 - 2</td>
</tr>
<tr>
<td>discont. AE</td>
<td>34 - 26</td>
<td>78 / 64</td>
<td>6 - 6</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>22 - 14</td>
<td>38 / 20</td>
<td>1 - 4</td>
</tr>
<tr>
<td>death AE</td>
<td>10 - 6</td>
<td>46 / 23</td>
<td>9 - 4</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 0</td>
<td>2 / 2</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

renal impairment

<table>
<thead>
<tr>
<th></th>
<th>PO n = 1283 vs. 1229</th>
<th>sequential n = 889 vs. 863</th>
<th>IV n = 203 vs. 218</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>1283 - 1229</td>
<td>572 - 549</td>
<td>102 - 92</td>
</tr>
<tr>
<td>ADR</td>
<td>259 - 229</td>
<td>196 - 181</td>
<td>31 - 32</td>
</tr>
<tr>
<td>SAE</td>
<td>94 - 80</td>
<td>202 - 180</td>
<td>26 - 22</td>
</tr>
<tr>
<td>SADR</td>
<td>9 - 9</td>
<td>30 - 23</td>
<td>2 - 1</td>
</tr>
<tr>
<td>discont. AE</td>
<td>49 - 53</td>
<td>75 - 78</td>
<td>11 - 7</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>27 - 33</td>
<td>28 - 25</td>
<td>2 - 3</td>
</tr>
<tr>
<td>death AE</td>
<td>12 - 14</td>
<td>58 - 67</td>
<td>10 - 7</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 3</td>
<td>3 - 3</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

Relative risk estimate (moxifloxacin / comparator)

hepatic impairment

<table>
<thead>
<tr>
<th></th>
<th>n = 146 vs. 163</th>
<th>n = 183 vs. 196</th>
<th>n = 46 vs. 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>69 - 70</td>
<td>183 - 196</td>
<td>23 - 18</td>
</tr>
<tr>
<td>ADR</td>
<td>37 - 32</td>
<td>43 - 43</td>
<td>7 - 6</td>
</tr>
<tr>
<td>SAE</td>
<td>5 - 7</td>
<td>60 - 53</td>
<td>7 - 7</td>
</tr>
<tr>
<td>SADR</td>
<td>1 - 1</td>
<td>10 - 7</td>
<td>1 - 0</td>
</tr>
<tr>
<td>discont. AE</td>
<td>6 - 7</td>
<td>24 - 24</td>
<td>1 - 1</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>6 - 3</td>
<td>11 - 7</td>
<td>1 - 0</td>
</tr>
<tr>
<td>death AE</td>
<td>2 - 4</td>
<td>14 - 24</td>
<td>2 - 0</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 1</td>
<td>1 - 2</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

Relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

<table>
<thead>
<tr>
<th>cardiac disorders</th>
<th>n = 1476 vs. 1404</th>
<th>n = 1476 vs. 1136</th>
<th>n = 106 vs. 104</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE</strong></td>
<td>707 - 655</td>
<td>804 - 804</td>
<td>63 - 57</td>
</tr>
<tr>
<td><strong>ADR</strong></td>
<td>340 - 297</td>
<td>315 - 293</td>
<td>16 - 25</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>132 - 110</td>
<td>251 - 246</td>
<td>23 - 11</td>
</tr>
<tr>
<td><strong>SADR</strong></td>
<td>14 - 8</td>
<td>43 - 35</td>
<td>3 - 2</td>
</tr>
<tr>
<td><strong>discont. AE</strong></td>
<td>70 - 64</td>
<td>119 - 96</td>
<td>7 - 3</td>
</tr>
<tr>
<td><strong>discont. ADR</strong></td>
<td>43 - 45</td>
<td>59 - 43</td>
<td>11 - 8</td>
</tr>
<tr>
<td><strong>death AE</strong></td>
<td>11 - 25</td>
<td>69 - 75</td>
<td>0 - 1</td>
</tr>
<tr>
<td><strong>death ADR.</strong></td>
<td>0 - 2</td>
<td>3 - 4</td>
<td>0 - 1</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

<table>
<thead>
<tr>
<th>BMI &lt; 18</th>
<th>n = 318 vs. 365</th>
<th>n = 116 vs. 115</th>
<th>n = 45 vs. 53</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE</strong></td>
<td>113 - 171</td>
<td>89 - 83</td>
<td>17 - 10</td>
</tr>
<tr>
<td><strong>ADR</strong></td>
<td>70 - 96</td>
<td>26 - 27</td>
<td>5 - 3</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>11 - 28</td>
<td>36 - 30</td>
<td>3 - 3</td>
</tr>
<tr>
<td><strong>SADR</strong></td>
<td>0 - 5</td>
<td>5 - 4</td>
<td>0 - 0</td>
</tr>
<tr>
<td><strong>discont. AE</strong></td>
<td>14 - 27</td>
<td>10 - 11</td>
<td>1 - 0</td>
</tr>
<tr>
<td><strong>discont. ADR</strong></td>
<td>12 - 20</td>
<td>6 - 9</td>
<td>1 - 0</td>
</tr>
<tr>
<td><strong>death AE</strong></td>
<td>3 - 5</td>
<td>15 - 15</td>
<td>1 - 0</td>
</tr>
<tr>
<td><strong>death ADR.</strong></td>
<td>0 - 0</td>
<td>0 - 0</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin (clinical trials database)

Comparison with other drugs?

A. oral therapy

1. moxifloxacin vs β-lactams

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk Estimate (Moxifloxacin / Comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 y</td>
<td>n = 909 vs 788</td>
</tr>
<tr>
<td>Diabetes</td>
<td>n = 282 vs 217</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>n = 347 vs 380</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>n = 47 vs 53</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>n = 526 vs 444</td>
</tr>
<tr>
<td>BMI &lt; 18</td>
<td>n = 70 vs 76</td>
</tr>
</tbody>
</table>

2. moxifloxacin vs macrolides

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk Estimate (Moxifloxacin / Comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 y</td>
<td>n = 1252 vs 942</td>
</tr>
<tr>
<td>Diabetes</td>
<td>n = 329 vs 255</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>n = 484 vs 427</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>n = 44 vs 64</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>n = 794 vs 623</td>
</tr>
<tr>
<td>BMI &lt; 18</td>
<td>n = 110 vs 114</td>
</tr>
</tbody>
</table>

Tulkens et al., Drugs R D (2012) 12: 71-100

(NO difference!)

22/03/2016 Are all fluoroquinolones equal? -- Singapore
Hepatotoxicity in large populations

Crude incidence rates of acute liver injury caused by antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>population</th>
<th>Incidence rate (CI)</th>
<th>endpoint</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoroquinolones</td>
<td>Outpatient clinic, Sweden (1995-2005)</td>
<td>0.7 (0.5-1.1)</td>
<td>International consensus</td>
<td>[1]</td>
</tr>
<tr>
<td>(w/o moxifloxacin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>Outpatient clinic, Sweden (1995-2005)</td>
<td>0.08 (0.0-0.5)</td>
<td>International consensus</td>
<td>[1]</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>Saskatchewan Health Plan, Canada (1982-1986)</td>
<td>1.0 (0.2-5.7)</td>
<td>International consensus, hospitalisation</td>
<td>[2]</td>
</tr>
<tr>
<td>erythromycin</td>
<td>Saskatchewan Health Plan, Canada (1982-1986)</td>
<td>2.0 (0.7-5.9)</td>
<td>International consensus, hospitalisation</td>
<td>[2]</td>
</tr>
<tr>
<td>amoxicillin-clavulanic acid</td>
<td>General practice research database,</td>
<td>22.5 (14.7-34.4)</td>
<td>International consensus</td>
<td>[3]</td>
</tr>
<tr>
<td></td>
<td>United Kingdom (1991-1992)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Hepatotoxicity from literature surveys

Hepatotoxicity risk of antibiotics
(percentage of prescriptions for antibiotics with main indications for use in the community setting)

Andrade & Tulkens, JAC (2011) 66: 1431–46
QTc prolongation

- Genetics
  - LQTS-1-LQTS-7
  - Unknown ion channel mutations

- Underlying cardiac disease
  - Ischemia
  - CHF
  - Bradycardia
  - Atrial fibrillation

- Electrolyte derangements
  - Hypokalemia
  - Hypomagnesemia
  - Hypocalcemia

- Organ impairment
  - Renal insufficiency
  - Severe hepatic disease

- $I_K$-blocking comedictions or CYP3A4 inhibitors
  - Macrolides/lincosamides
  - Quinolones
  - Azoles
  - Penicillins/tetracyclines
  - TMF-SMZ

Prescription of QT-prolonging drug (antimicrobials listed)

Owens & Ambrose CID (2005) 41:S144-157
EMA position

... the risk of arrhythmias appears to increase with the extent of QT/QTC prolongation.

- Drugs [with] QT/QTC interval by around 5 ms or less do not appear to cause TdP.
- ...data on drugs [with] QT/QTC interval by... 5 to < 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk.*

... decisions about [drug] development and approval will depend upon the morbidity and mortality associated with the untreated disease or disorder and the demonstrated clinical benefits of the drug, especially as they compare with available therapeutic modalities.

* this includes erythromycin and clarithromycin (Balardinelli et al, TIPS (2003) 24:619-625)
Torsade de pointe: comparison of risk

reporting rate of Torsades de pointe induced by antibiotics

<table>
<thead>
<tr>
<th>drug</th>
<th>No. of U.S. Cases Reported to the FDA</th>
<th>No. of Estimated Total U.S. Prescriptions (millions)</th>
<th>No. of Cases /10 Millions Prescriptions (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>moxifloxacin</td>
<td>0</td>
<td>1.4</td>
<td>0 (0-26)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>2</td>
<td>66</td>
<td>0.3 (0.0-1.1)</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>2</td>
<td>9.5</td>
<td>2.1 (0.3-7.6)</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>13</td>
<td>24</td>
<td>5.4 (2.9-9.3)</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>8</td>
<td>3</td>
<td>27 (12-53)</td>
</tr>
<tr>
<td>erythromycin</td>
<td>11 –17</td>
<td>151</td>
<td>0.7 -1.1</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>16 –31</td>
<td>90</td>
<td>1.8 -3.4</td>
</tr>
<tr>
<td>azithromycin</td>
<td>7 –10</td>
<td>124</td>
<td>0.6–1</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>1 -1</td>
<td>42</td>
<td>0.2 –1</td>
</tr>
</tbody>
</table>

*Van Bambeke & Tulkens, Drug Safety (2009) 32:359-78*

*used as negative control in RCT*

*FDA warning March 12, 2013*
# Tendinopathies: main features and incidence…

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>OBSERVATIONS/FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative quinolones reported</strong>&lt;sup&gt;6,9,13&lt;/sup&gt;</td>
<td>Ciprofloxacin (most commonly reported), norfloxacin, pefloxacin, ofloxacin, levofloxacin</td>
</tr>
<tr>
<td><strong>Associated risk factors</strong>&lt;sup&gt;11,31,32-37&lt;/sup&gt;</td>
<td>Age &gt;60 years, corticosteroid therapy, renal failure, diabetes mellitus, history of tendon rupture</td>
</tr>
<tr>
<td><strong>Relative risk of tendon disorders</strong>&lt;sup&gt;3,16,31&lt;/sup&gt;</td>
<td>1.7-fold increase for all tendinopathies 1.3-fold increase for tendon rupture 4.1-fold increase of Achilles tendon rupture 46-fold increase of tendon rupture with concurrent corticosteroid exposure 1.5-fold increase in tendon disorders if age &gt;60 years 2.7-fold increase in tendon rupture if age &gt;60 years</td>
</tr>
<tr>
<td><strong>Affected tendons</strong>&lt;sup&gt;11,33,14&lt;/sup&gt;</td>
<td>Achilles tendon most commonly affected (89.8% of cases) Multiple other tendons reported Up to 50% of cases with bilateral involvement Symptoms of tendinitis often precede tendon rupture by up to 2 weeks</td>
</tr>
<tr>
<td><strong>Latency period of tendinopathy</strong>&lt;sup&gt;3,4,5,15&lt;/sup&gt;</td>
<td>Median onset of 6 days (85% of cases within first month) Up to 50% of cases after fluoroquinolone discontinued</td>
</tr>
</tbody>
</table>

Tendinopathies…

- In 2005, all fluoroquinolones marketed in the US have received a black box label about tendinopathies.
**Tendinopathies…**

- But this is what we found for moxifloxacin in our survey of the whole clinical trial database

### Table VII. Incidence of selected treatment-emergent adverse events presented by Standard MedDRA Queries/ Bayer MedDRA Queries and preferred terms in patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only).

<table>
<thead>
<tr>
<th>SMQ/BMQ and preferred term</th>
<th>Treatment route [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO</td>
</tr>
<tr>
<td>Tendinopathies</td>
<td>11 (0.1)</td>
</tr>
</tbody>
</table>

PO= oral  
IV = intravenous  
MXF: moxifloxacin  
COMP = comparator

*very rare and no difference*  
*no case*

*Tulkens et al., Drugs R D (2012) 12: 71-100*
Levofloxacin (LEVAQUIN) Cases Lead Antibiotics

While antibiotics rank among the safest drugs we monitor, levofloxacin (LEVAQUIN) was suspect in more reports of serious injury than any other antibiotic. Most cases involved tendon rupture and other muscle, tendon and ligament injuries. Case reports of this problem substantially outnumbered those for two chemically similar drugs—ciprofloxacin (CIPRO), with greater volume of prescriptions, and moxifloxacin (AVELOX), with somewhat less frequent medical use.
Tendinopathies: incidences (revisited)...

Table 2. Tendon disorders for fluoroquinolone antibiotics 2010q2.

<table>
<thead>
<tr>
<th></th>
<th>Levofloxacin</th>
<th>Ciprofloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Rx (millions)*</td>
<td>2.1</td>
<td>5.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Case Reports</td>
<td>246</td>
<td>105</td>
<td>93</td>
</tr>
<tr>
<td>% Direct to FDA</td>
<td>52%</td>
<td>71%</td>
<td>42%</td>
</tr>
<tr>
<td>% Health Professionals</td>
<td>53%</td>
<td>59%</td>
<td>76%</td>
</tr>
<tr>
<td>Tendon Disorders (HLT)</td>
<td>93</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>All Musculoskeletal</td>
<td>156</td>
<td>62</td>
<td>20</td>
</tr>
</tbody>
</table>

*IMS Health National Prescription Audit ™ 2010

(AVELOX), with somewhat less frequent medical use.

Last accessed: 20/02/2015
Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin
Comparison with Other Fluoroquinolones and Other Antibacterial Classes

Françoise Van Bambeke and Paul M. Tulkens
Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

The data show that using moxifloxacin, in its accepted indications and following the corresponding guidelines, should not be associated with an excessive incidence of drug-related adverse reactions, provided the clinician takes care in identifying patients with known risk factors and pays due attention to the contraindications and warnings mentioned in the labelling.
What shall we discuss?

- The basics: how were quinolones invented? (are they different by design?)

- The real life in the lab: microbiological properties and risk of resistance… (or how to really differentiate them …)

- The real life in the doctor’s office: efficacy and tolerance… (is there a difference) ?

- Should we use the “best in class”? 

What shall we discuss?

- The basics: how were quinolones invented? (are they different by design?)
- The real life in the lab: microbiological properties and risk of resistance… (or how to really differentiate…)
- The real life in the doctor’s office: efficacy and tolerance… (is there a difference?)
- Should we use the “best in class”? 

Why not leaving this to the discussion?
but remembering:
- 400 mg once daily
or
- 2 x 500 mg daily
or … (have your pick!)

22/03/2016
Thank you for your attention!

And ask questions
Ternary complex
DNA - enzyme - fluoroquinolone

"GyraseCiproTop" by Fdardel - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:GyraseCiproTop.png#mediaviewer/File:GyraseCiproTop.png
Last accessed: 8/2/2015
Resistance to fluoroquinolones: the basics

decreased permeability

efflux pump

DNA gyrase

Topoisomerase

mutation of the enzymes and/or DNA protection
Chemistry and Activity

This is where it all began..
From norfloxacin to ciprofloxacin and ofloxacin

* Eur. pat. Appl. 47,005 to Daiichi, 1982
From norfloxacin to ciprofloxacin

norfloxacin

cyclopropyl to increase potency

ciprofloxacin *

* Ger. pat. 3,142,854 to Bayer AG, 1983
The "first generation" of fluoroquinolones

1960
- Nalidixic acid
- Oxolinic acid
- Cinoxacin
- Pipemidic acid

1970
- Norfloxacin
- Pefloxacin
- Ofloxacin
- Ciprofloxacin
- Fleroxacin
- Rufloxacin

1980
- improved anti Gram (-) activity
- t_{1/2} activity
  - 3-4 h ++
  - 11 h +
  - 6 h ++
  - 3-4 h +++

22/03/2016
Ternary complex
DNA - enzyme - fluoroquinolone

COVALENTLY CLOSED CIRCULAR DNA

DNA GYRASE catalytic subunits

DNA GYRASE ATP binding subunits

FLUOROQUINOLONES:
4 stacked molecules

(Shen, in Quinolone Antimicrobial Agents, 1993)
Fluoroquinolones are the first entirely man-made antibiotics: do we understand our molecule?

Don’t panic, we will travel together....
The pharmacophore common to all fluoroquinolones
Nalidixic acid *

- typical chemical features of fluoroquinolones (a, b, c)
  - BUT a naphthyridone (N at position 8:)
- limited usefulness as drug
  - narrow antibacterial spectrum (Enterobacteriaceae only)
  - short half-life (1.5h)
  - high protein binding (90%)

* Belg. pat. 612,258 to Sterling Drugs, 1962
The “second generation” fluoroquinolones

- Temafloxacin $^a$
- Sparfloxacin $^b$
- Grepafloxacin $^c$
- Gatifloxacin $^d$

- Gram (-);
- improved Gram (+)

anti-anaerobe

---

The “third / fourth generation” fluoroquinolones

- Clinafloxacin \(^a\)
- Trovafloxacin \(^b\)
- Moxifloxacin \(^c\)
- Gemifloxacin \(^d\)

Resistance must first be assessed by MIC distributions

- Resistance of Gram-negative (ciprofloxacin/levofloxacin) is widespread and must be assessed locally (often ward by ward)

MIC distributions of fluoroquinolones against P. aeruginosa in the Academic Hospital of the University of Leuven, Belgium

- Oflox, Levo, Cipro
Resistance must first be assessed by MIC distributions

• Conversely, resistance of Gram-positive is variable
  – High for MRSA (co-resistance frequent)
  – Low for *S. pneumonia* (especially for moxifloxacin; close to breakpoint for levofloxacin)

MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)

Resistance must first be assessed by MIC distributions

- Conversely, resistance of Gram-positive is variable
  - High for MRSA (co-resistance frequent)
  - Low for *S. pneumonia* (especially for moxifloxacin; close to breakpoint for levofloxacin)

MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)

Short Communication

Impact of poor compliance with levofloxacin and moxifloxacin on respiratory tract infection antimicrobial efficacy: A pharmacokinetic/pharmacodynamic simulation study

N. Carral\textsuperscript{a}, J.C. Lukas\textsuperscript{a,b}, I. Oteo\textsuperscript{a}, E. Suarez\textsuperscript{a,*}
A very recent paper...

Impact of poor compliance of respiratory tract infections: A pharmacokinetic/pharmacodynamic analysis

N. Carral a, J.C. Lukas a, b, I. Otterbein c, a

Table 1
Interindividual variability of $fAUC_{0-24h}$ for levofloxacin (LFX) and moxifloxacin (MOX), estimated for various drug dosing regimens in simulated patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (S.D.)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24h}$ (mg h/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFX 500 mg q24 h</td>
<td>45.78 (3.72)</td>
<td>37.21–57.13</td>
</tr>
<tr>
<td>LFX 750 mg q24 h</td>
<td>68.68 (5.58)</td>
<td>55.82–85.69</td>
</tr>
<tr>
<td>LFX 500 mg q12 h</td>
<td>91.57 (7.34)</td>
<td>77.66–115.48</td>
</tr>
<tr>
<td>MOX 400 mg q24 h</td>
<td>43.63 (8.60)</td>
<td>26.43–72.20</td>
</tr>
</tbody>
</table>
A very recent paper...

Impact of poor community-acquired respiratory tract infection on antimicrobial use: A pharmacokinetic-pharmacodynamic approach

N. Carral, J.C. Lukas

Short Communication

Contents lists available at ScienceDirect

Target attainment rate for S. pneumoniae

- **LVX 500 mg q12h**
  - (MIC = 1 mg/L)

- **MXF 400 mg q24h**
  - (MIC = 0.25 mg/L)

90%
A very recent paper...

Impact of poor community-acquired respiratory tract infection with Streptococcus pneumoniae: A pharmacokinetic-pharmacodynamic evaluation

N. Carral, J.C. Lukas

To be as protective, you need a twice daily dosing with levofloxacin.
What differentiates fluoroquinolones?

Results with *S. pneumoniae*

Fluoroquinolone AUC/MIC ratios for *S. Pneumoniae*
Is there a molecular basis for a lesser emergence of resistance with moxifloxacin?

A C8-methoxy group lowers the MPC for an N-1-cyclopropyl-fluoroquinolone.

FULL PRESCRIBING INFORMATION

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the NorA or pmrA genes seen in certain Gram-positive bacteria.

Last accessed: 8/2/2015