Moxifloxacin safety data review

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* also
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  Université de Mons/Hainaut, Mons, Belgium
- Former member of the EUCAST (European Committee for Antibiotic Susceptibility Testing) steering committee
- founding member and past-President of the International Society of Anti-infective Pharmacology

Fluoroquinolones and Respiratory Tract Infections, Beijing, China – 18 December 2016

With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/8979/086081

Apologies… 道歉

- I'm sorry that I cannot give this presentation in Chinese... 中文
- The Chinese language is very artistic and logical ...
  and I'd very much like to read famous Chinese authors in the text …
- But, in my country, I already use, daily, two languages, French and Dutch, with patients, family and friends …
- plus English in the laboratory ...
- So, I'll use English here, which I hope will be acceptable to you…

Location of the *Université catholique de Louvain* in Brussels

The buildings of the Faculties of Medicine and Pharmacy and the Hospital

The group of Pharmacology/Toxicology of antibiotics

Slides are available on http://www.facm.ucl.ac.be ➔ "Lectures"

Disclosures

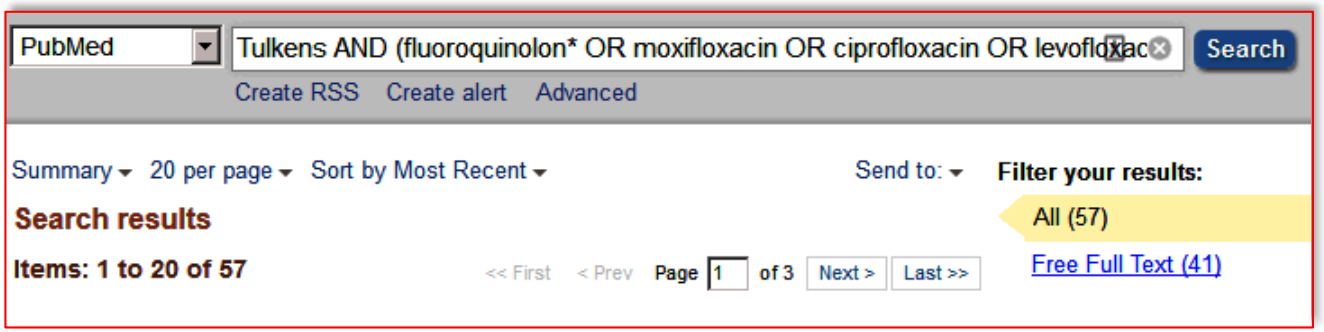
Financial support from

- the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
- *Université catholique de Louvain* for past personal support
- Commercial Relationships:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - European Medicines Agency (as expert for the agency and for Industry)

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

Why do I speak about fluoroquinolones ?

Because we published about fluoroquinolones



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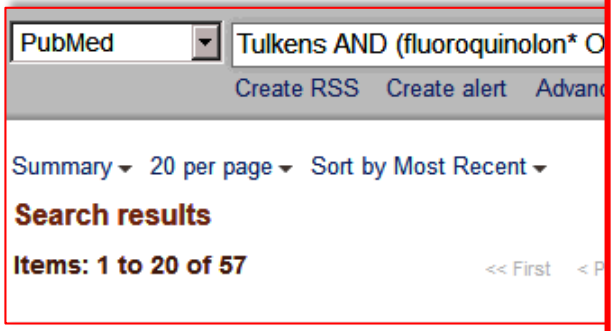


1990

Journal of Antimicrobial Chemotherapy (1990) **26,** *Suppl. B,* 27–39

Cellular uptake, localization and activity of fluoroquinolones in uninfected and infected macrophages

Marie-Béatrice Carlier[a], Bernard Scorneaux[a], Andrée Zenebergh[a,*], Jean-François Desnottes[b] and Paul M. Tulkens[a]

[a]Laboratoire de Chimie Physiologique, and International Institute of Cellular and Molecular Pathology, Université Catholique de Louvain, Avenue Hippocrate 75, Bte 75.49, B-1200 Bruxelles, Belgium; [b]Rhône-Poulenc Santé, Centre de Recherches de Vitry/Alfortville, 13, Quai Jules Guesde, B.P. 14, F–94403 Vitry s/Seine, France

2005

REVIEW ARTICLE

10.1111/j.1469-0691.2005.01131.x

Quinolones in 2005: an update

F. Van Bambeke[1], J.-M. Michot[1], J. Van Eldere[2] and P. M. Tulkens[1]

[1]Unit of Cellular and Molecular Pharmacology, Catholic University of Louvain, Brussels and [2]Department of Microbiology and Immunology, Rega Institute and Centre for Molecular Diagnostics, University Hospital, Catholic University of Leuven, Louvain, Belgium

Clin Microbiol Infect 2005; 11: 256–280

2012

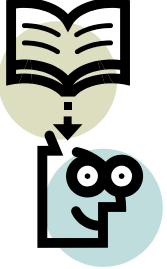
ORIGINAL RESEARCH ARTICLE

Drugs R D 2012; 12 (2): 71-100
1179-6901/12/0002-0071

Moxifloxacin Safety
An Analysis of 14 Years of Clinical Data

Paul M. Tulkens,[1] *Pierre Arvis*[2] and *Frank Kruesmann*[3]

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



Contents of the Presentation

- The warnings of the US Food & Drug Administration (FDA) and their context…
- 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).
- Adverse effects of moxifloxacin *vs* other agents
  - an overview of clinical trials
- The risk of bacterial failure
  - is moxifloxacin still active ?
- Conclusions

The warnings of the US food & Drug Administration

FDA News Release

FDA updates warnings for fluoroquinolone antibiotics

Limits use for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections

For Immediate Release

July 26, 2016

http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm513183.htm
Last visited: 3 Dec 2016

The warnings of the US food & Drug Administration

FDA News Release

FDA updates warnings for fluoroquinolone antibiotics

Limits use for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections

For Immediate Release

July 26, 2016

- *"Fluoroquinolones have **risks** and **benefits** that should be considered very carefully," said Edward Cox, M.D., director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research.*
- *"It's important that both health care providers and patients are aware of both the **risks** and **benefits** of fluoroquinolones and make an informed decision about their use."*

http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm513183.htm
Last visited: 3 Dec 2016

The warnings of the US food & Drug Administration

FDA News Release

FDA updates warnings for fluoroquinolone antibiotics

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For Immediate Release

July 26, 2016

- The labeling changes include an **updated Boxed Warning** and revisions to the **Warnings and Precautions section** of the label about the risk of disabling and potentially irreversible adverse reactions that can occur together. The label also contains new limitation-of-use statements to reserve fluoroquinolones for patients who do not have other available treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections.

http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm513183.htm
Last visited: 3 Dec 2016

The new US label of moxifloxacin

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRIAL NERVOUS SYSTEM EFFECTS and EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning

- **Fluoroquinolones, including AVELOX, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1) including:**
  - **Tendinitis and tendon rupture (5.2)**
  - **Peripheral Neuropathy (5.3)**
  - **Central nervous system effects (5.4)**

  Discontinue AVELOX immediately and avoid the use of fluoroquinolones, including AVELOX, in patients who experience any of these serious adverse reactions (5.1)
- **Fluoroquinolones, including AVELOX, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid AVELOX in patients with known history of myasthenia gravis (5.5).**
- **Because fluoroquinolones, including AVELOX, have been associated with serious adverse reactions (5.1–5.13), reserve AVELOX for use in patients who have no alternative treatment options for the following indications:**
  - **Acute bacterial sinusitis (1.6)**
  - **Acute bacterial exacerbation of chronic bronchitis (1.7)**

----------**RECENT MAJOR CHANGES**----------

Boxed Warning	7/2016
Indications and Usage (1.6, 1.7)	7/2016
Dosage and Administration (2.1)	7/2016
Warnings and Precautions (5.1)	7/2016

Tendinitis and tendon rupture

5.2 Tendinitis and Tendon Rupture

Fluoroquinolones, including AVELOX, have been associated with an increased risk of tendinitis and tendon rupture in all ages *[see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*. This adverse reaction most frequently involves the Achilles tendon, and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendons. Tendinitis or tendon rupture can occur within hours or days of starting moxifloxacin or as long as several months after completion of therapy. Tendinitis and tendon rupture can occur bilaterally.

- There were 2495 FDA's Adverse Event Reporting System (FAERs reports) of **tendon rupture** associated with currently approved FQs **since their respective introduction on the market and up to 2012** *(on a total of about 300 millions prescriptions).*
- Most FAERS reports were associated with **levofloxacin (n = 1555)** followed by **ciprofloxacin (n = 606)** and **moxifloxacin (n = 230)**
- Signal detection results for FQs using Empirical Bayes Geometric Mean (EBGM) were as follows:
  - **levofloxacin 55.2, 95% CI = 52.3 - 58.0**
  - **ciprofloxacin 20.0, 95% CI = 18.2 - 21.6**
  - **moxifloxacin 13.3, 95% CI = 11.7 - 15.1**
- **Most cases were in elderly in association with corticosteroids**

Arabyat *et al.* Expert Opin Drug Saf. 2015;14:1653-60 - PMID: 26393387

Peripheral neuropathy

5.3 Peripheral Neuropathy

Fluoroquinolones, including AVELOX, have been associated with an increased risk of peripheral neuropathy. Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones including AVELOX. Symptoms may occur soon after initiation of AVELOX and may be irreversible in some patients *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.2)]*.

A PubMed search yielded 2 references related to the use of moxifloxacin for treatment of tuberculosis

PubMed search made on 3 Dec 2016

Central nervous system toxicity

5.4 Central Nervous System Effects

Fluoroquinolones, including AVELOX, have been associated with an increased risk of central nervous system (CNS) reactions, including: convulsions and increased intracranial pressure (including pseudotumor cerebri) and toxic psychosis, Fluoroquinolones may also cause CNS reactions of nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression, and, suicidal thoughts or acts. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving AVELOX, discontinue AVELOX immediately and institute appropriate measures. As with all fluoroquinolones, use AVELOX when the benefits of treatment exceed the risks in patients with known or suspected CNS disorders (for example, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold *[see Drug Interactions (7.4)]*.

This was recognized and characterized by Bayer since the late 1990's

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1998, p. 1831–1836 Vol. 42, No. 7
0066-4804/98/$04.00+0

Determination of the Excitatory Potencies of Fluoroquinolones in the Central Nervous System by an In Vitro Model

GABRIELE SCHMUCK,* ANJA SCHÜRMANN, AND GERHARD SCHLÜTER
BAYER AG, Institute of Toxicology, 42096 Wuppertal, Germany

Received 29 December 1997/Returned for modification 25 February 1998/Accepted 6 May 1998

But the risk for moxifloxacin is low

5.4 Central Nervous System Effects

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1998, p. 1
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Determination of the Exci
in the Central Nervou

GABRIELE SCHMUCK,* ANJ
BAYER AG, Institute

Returne

Increase of the population spike amplitude of the pyramidal cells in the CA1 region of the hippocampus

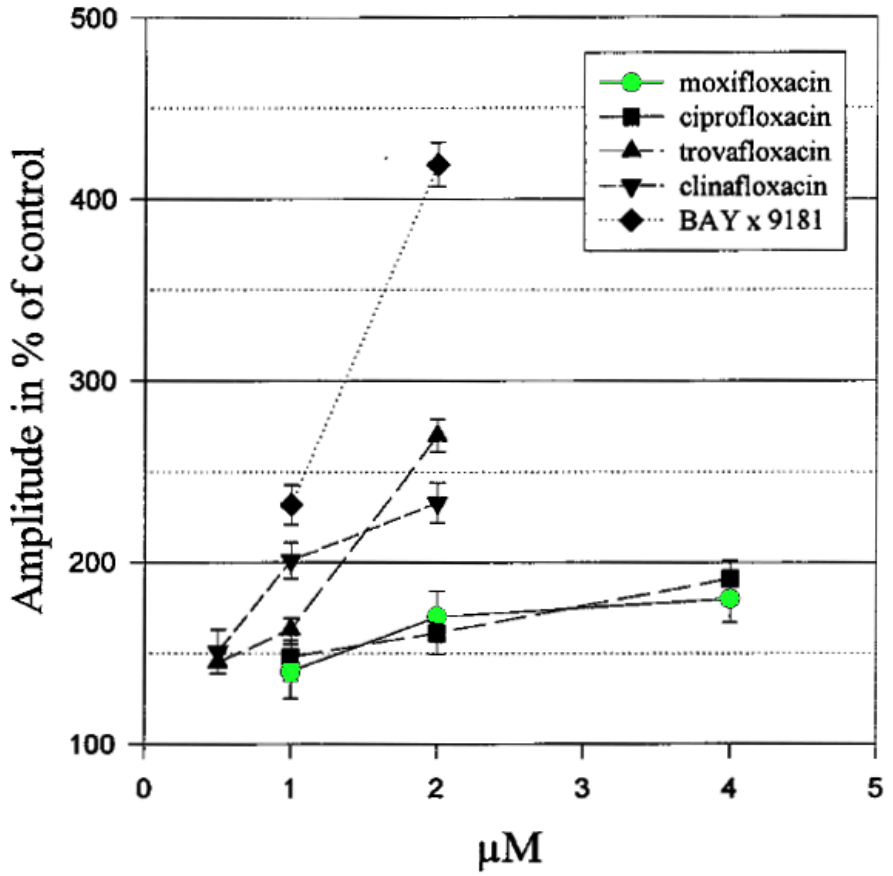


FIG. 1. Dose-response curves of selected fluoroquinolones. The concentration range tested was 0.5 to 4 µmol/liter. Each compound and concentration was tested with six individual brain slices from two animals. A statistically significant ($P < 0.01$) increase of the population spike amplitude (more than 125 to 130% in relation to the control level) could be shown in all experiments. Statistical analysis was done by one-way ANOVA followed by a *t* test.

Moxifloxacin (possibly) – induced seizures are described

Iranian J Publ Health, Vol. 43, No.9, Sep 2014, pp.1291-1294

Case Report

Moxifloxacin Induced Seizures -A Case Report

*Jiana SHI [1, 2], *Huimin XU [1]*

1. *Dept. of Pharmacy, the Second Affiliated Hospital, School of Medicine, Zhejiang University, No. 88 Jiefang Road, Hangzhou 310009, China*
2. *Dept. of Pharmacy, Tongde Hospital of Zhejiang Province, Hangzhou 310012, China*

***Corresponding Author:** Email: xuhuiminze@126.com

(Received 23 May 2014; accepted 18 July 2014)

Abstract

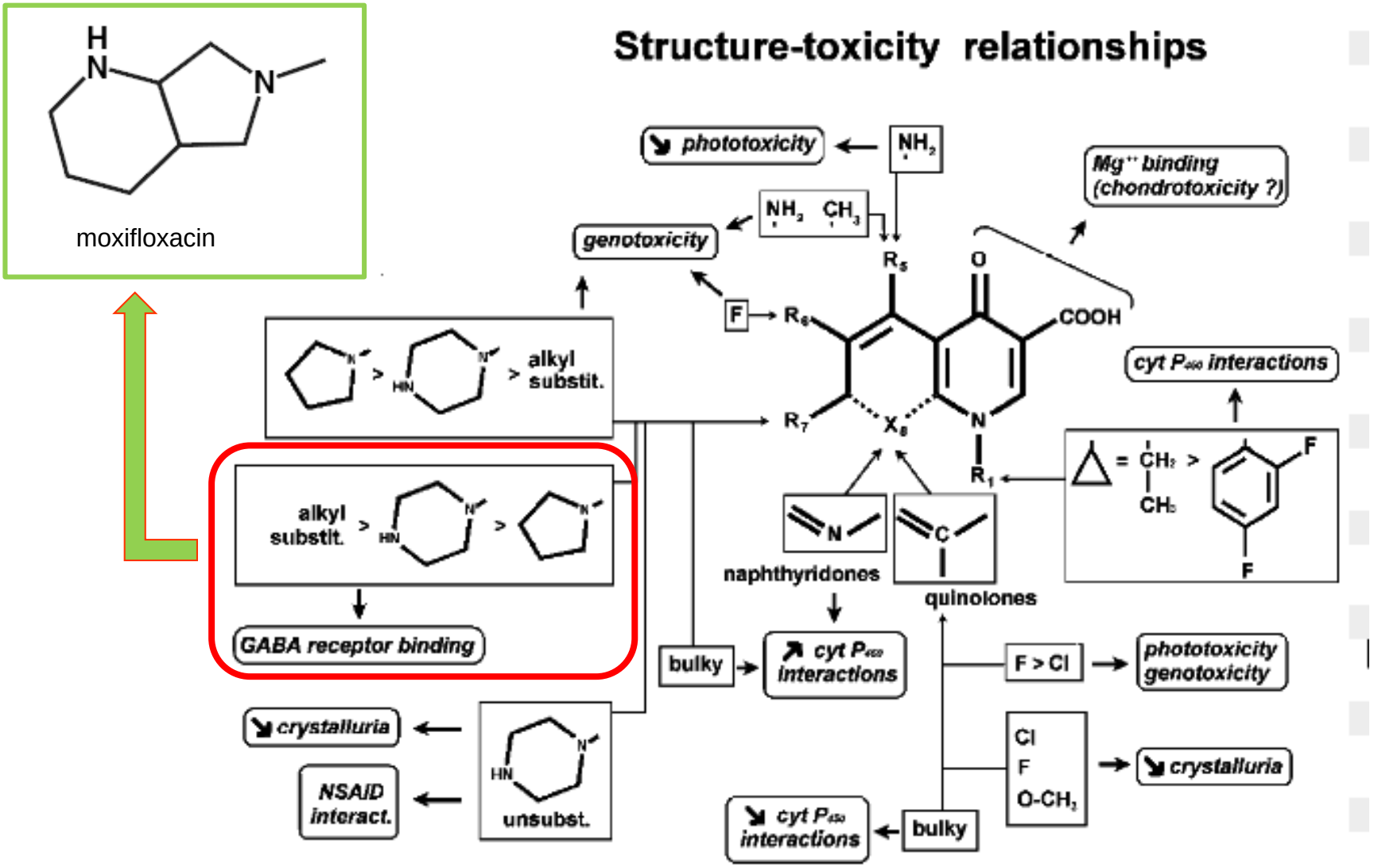
A 73-year-old female patient developed a generalized tonic-clonic seizure on the 6th day after treatment with moxifloxacin 400 mg daily intravenously for appendicitis. This patient had atrial fibrillation and history of a sur-gery for intracerebral hemorrhage, with impaired renal function and liver function, but without history of seizures. Moxifloxacin was discontinued and switched to cefuroxime. The patient remained seizure-free at discharge four days later. The naranjo adverse drug reaction probability scale score was 4, indicating a possible adverse reaction to moxi-floxacin. The potential risk factors related to moxifloxacin-induced seizures are discussed. It highlights that pre-existing central nervous system disease, elderly female with lower bodyweight and severe renal impairment may be the risk factors involved in moxifloxacin-induced seizures.

Keywords: Fluoroquinolones, Antibiotics, Moxifloxacin, Side effects, Seizures

Quoting:

"Moxifloxacin penetrates well through the blood-brain barrier, but lacks the specific structure toxicity relationships noted to induce seizures."

Fluoroquinolones structure-toxicity relationships and GABA receptor binding



Van Bambeke et al. Clin Microbiol Infect. 2005;11:256-280 - PMID: 15760423

Moxifloxacin drug interactions: the case of NSAIDs

7.4 Nonsteroidal Anti-Inflammatory Drugs

The concomitant administration of a nonsteroidal anti-inflammatory drug (NSAID) with a fluoroquinolone, including AVELOX, may increase the risks of CNS stimulation and convulsions *[see Warnings and Precautions (5.4)]*.

Drug Metab. Pharmacokinet. 24 (2): 167–174 (2009).

Regular Article

Quantitative Comparison of the Convulsive activity of Combinations of Twelve Fluoroquinolones with Five Nonsteroidal Antiinflammatory Agents

Jahye KIM[1], Hisakazu OHTANI[2], Masayuki TSUJIMOTO[1,†] and Yasufumi SAWADA[2,3,*]

[1]*Department of Medico-Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan*

[2]*Laboratory of Drug Informatics, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan*

[3]*Graduate School of Interdisciplinary Information Studies, The University of Tokyo, Tokyo, Japan*

Kim et al. Drug Metab Pharmacokinet. 2009;24:167-174 - PMID: 19430173

"Fluoroquinolone-induced CNS excitation is attributable to the inhibition of g-aminobutyricacid (GABA) binding to the GABAA receptor.

Some NSAIDs such as fenbufen, potentiate the blockade of the GABAA receptor by fluoroquinolones."

Moxifloxacin drug interactions: the case of NSAIDs

7.4 Nonsteroidal Anti-Inflammatory

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AVELOX, may increase the risks of CNS

Drug Metab. Pharmacokinet. 24 (2): 167–174 (2009).

Regular Article

**Quantitative Compari
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Five Nonsteroida**

Jahye KIM[1], Hisakazu OHTANI[2], M
[1]*Department of Medico-Pharmaceutica
Kyushu U
[2]Laboratory of Drug Informati
The Univer
[3]Graduate School of Interdisciplinary Inf

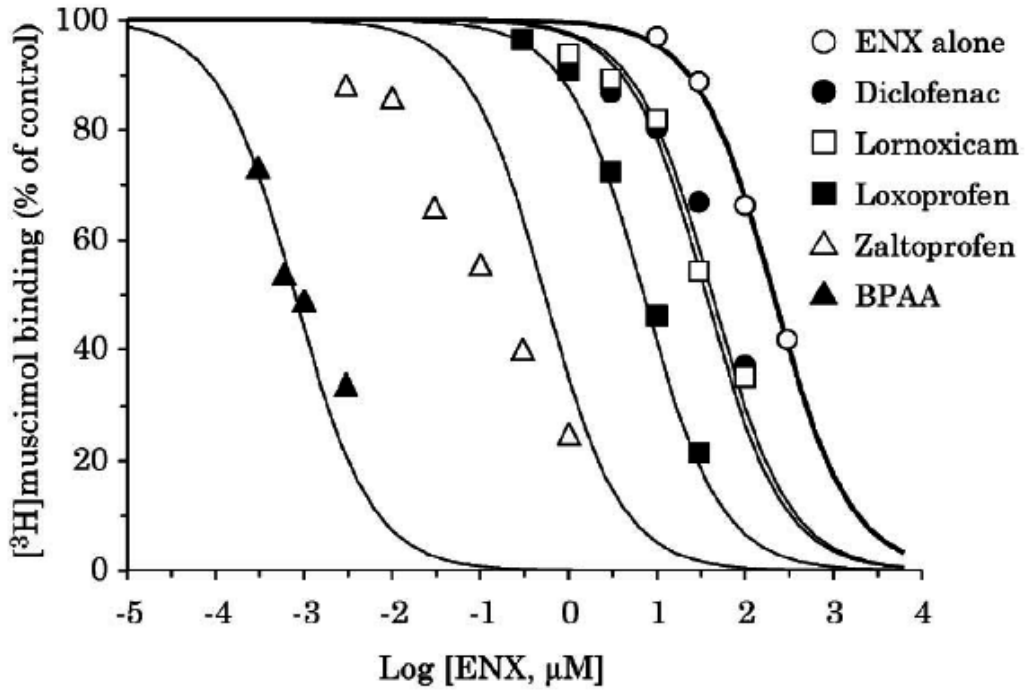


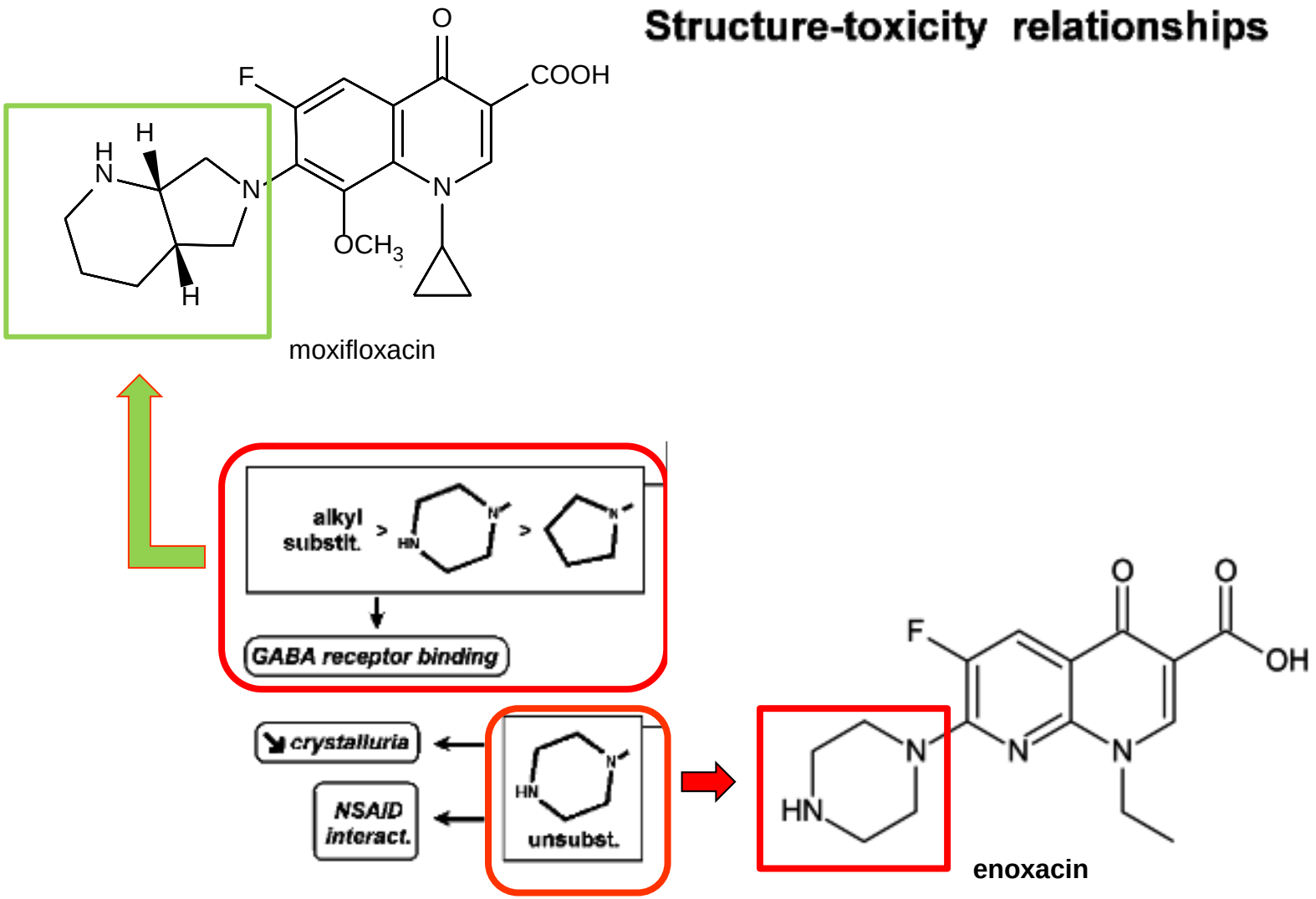
Fig. 2. Potentiation of the inhibitory effects of ENX on [^{3}H]muscimol binding by five NSAIDs
Various concentrations of unlabled ENX and [^{3}H]muscimol (10 nM) were incubated with synaptic plasma membrane for 30 min at 4°C, in the presence of 100 μM NSAID (n = 3). Error bars are omitted for clarity.

Kim et al. Drug Metab Pharmacokinet. 2009;24:167-174 - P

- ENX: enoxacin
- BPAA: 4-biphenylacetic acid (the active metabolite of fenbufen)

➢ ***The combination of 4-biphenylacetic acid with enoxacin was concluded to be one of the most hazardous***.

Fluoroquinolones structure-toxicity relationships and interactions with NSAIDs for GABA binding



Van Bambeke et al. Clin Microbiol Infect. 2005;11:256-280 - PMID: 15760423

An overall view of mechanistic effects

Current Medicinal Chemistry 2001, *8*, 371-384

Adverse Reactions to Fluoroquinolones. An Overview on Mechanistic Aspects

Angela De Sarro* and Giovambattista De Sarro

Istituto di Farmacologia, Facoltà di Medicina e Chirurgia, Università di Messina, Policlinico Universitario, Via Consolare Valeria, 98125 Messina, Italia

De Sarro & De Sarro. Curr Med Chem. 2001;8:371-384 - PMID: 11172695

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De Sarro & De Sarro. Curr Med Chem. 2001;8:371-384 - PMID: 11172695

Table 1. Severity of Adverse Effects Associated with Fluoroquinolones

Quinolones	Gastrointestinal reactions	CNS effects	Photo toxicity	Liver toxicity	Hypoglycaemia	Tendinitis	Cardio toxicity	Haemolitic syndrome
Ofloxacin	+	+						
Levofloxacin	++		+					
Norfloxacin	+	+						
Ciprofloxacin	+	++						
Moxifloxacin	+++	+	+					
Clinafloxacin		++++	++++		++			

The data from a meta-analysis of articles reported in the present manuscript are indicated.

The legend indicates the severity of adverse effects : + mild, ++ moderate, +++ severe, ++++ very severe.

Incidence of moxifloxacin adverse effects in the EU label

4.8 Undesirable effects

- Adverse reactions based on all clinical trials with moxifloxacin 400 mg (oral and sequential therapy) sorted by frequencies are listed below:
- Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.
- Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
- Frequencies are defined as:
  - common (≥ 1/100 to < 1/10)
  - uncommon (≥ 1/1,000 to < 1/100)
  - rare (≥ 1/10,000 to < 1/1,000)
  - very rare (< 1/10,000)

English text obtained from http://www.medicines.org.uk/emc/medicine/11841/SPC/Avelox+400+mg+film-coated+tablets
Cross-checked with the official Belgian SmpC (in French)

Incidence of moxifloxacin adverse effects in the EU label (1 of)

System Organ Class (MedDRA)	Common	Uncommon
Infections and infestations	Superinfections (resistant bacteria or fungi)	
Blood and lymphatic system disorders		Anaemia, Leucopenia(s) Neutropenia, thrombocytopenia Thrombocythemia Blood eosinophilia Prothrombin time prolonged/INR increased
Immune system disorders		Allergic reaction
Metabolism and nutrition disorders		Hyperlipidemia
Psychiatric disorders		Anxiety reactions Psychomotor hyperactivity/ agitation
Nervous system disorders	Headache Dizziness	Par- and Dysaesthesia Taste disorders Confusion and disorientation Sleep disorders (insomnia) Tremor Vertigo Somnolence

English text obtained from http://www.medicines.org.uk/emc/medicine/11841/SPC/Avelox+400+mg+film-coated+tablets
Cross-checked with the official Belgian SmpC (in French)

Incidence of moxifloxacin adverse effects in the EU label (2 of)

System Organ Class (MedDRA)	Common	Uncommon
Eye disorders		Visual disturbances incl. diplopia and blurred vision
Cardiac disorders	QT prolongation in patients with hypokalaemia	QT prolongation (see section 4.4) Palpitations Tachycardia Atrial fibrillation Angina pectoris
Vascular disorders		Vasodilatation
Respiratory, thoracic and mediastinal disorders		Dyspnea (including asthmatic conditions)
Gastrointestinal disorders	Nausea, Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation, Dyspepsia, Flatulence Gastritis Increased amylase
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (LDH increase) ↗ bilirubin, gamma-glutamyl-transferase, alkaline phosphatase

English text obtained from http://www.medicines.org.uk/emc/medicine/11841/SPC/Avelox+400+mg+film-coated+tablets
Cross-checked with the official Belgian SmpC (in French)

Incidence of moxifloxacin adverse effects in the EU label (2 of)

System Organ Class (MedDRA)	Common	Uncommon
Skin and subcutaneous tissue disorders		Pruritus, Rash, Urticaria, Dry skin
Musculoskeletal and connective tissue disorders		Arthralgia, Myalgia
Renal and urinary disorders		Dehydration
General disorders and administration site conditions		Feeling unwell (asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating

- Rare (≥ 1/10,000 to < 1/1,000) events include anaphylaxis and allergic oedema, depression and hallucination, seizures and peripheral neuropathies, tachyarythmia and syncope, cholestic hepatitis, tendonitis, and renal failure
- Very rare (< 1/10,000) events include psychotic reactions, torsade de pointe, hepatitis, bullous skin recations, tendon rupture

English text obtained from http://www.medicines.org.uk/emc/medicine/11841/SPC/Avelox+400+mg+film-coated+tablets
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Renal and urinary disorders		
General disorders and administration site conditions		

- **Most fluoroquinolone-associated seizures are linked to drug interactions, epilepsy, brain tumors, anoxia, and alcohol dependence…**
- **PubMed contains only case reports as clinical data for moxifloxacin**

- Rare (≥ 1/10,000 to < 1/1,000) events include anaphylaxis and allergic oedema, depression and hallucination, **seizures and peripheral neuropathies**, tachyarythmia and syncope, cholestic hepatitis, tendonitis, and renal failure
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FactMed Summary Statistics

- Reports of MOXIFLOXACIN causing NEUROPATHY: 6
- Reports of *any* side effect of MOXIFLOXACIN : 473
- Percentage of MOXIFLOXACIN patients where NEUROPATHY is a reported side effect: 1.2685%
- **No case of seizures was reported**

Source: http://factmed.com/report-MOXIFLOXACIN%20HYDROCHLORIDE-causing-NEUROPATHY.php

- Rare (≥ 1/10,000 to < 1/1,000) events include anaphylaxis and allergic oedema, depression and hallucination, **seizures and peripheral neuropathies**, tachyarythmia and syncope, cholestic hepatitis, tendonitis, and renal failure
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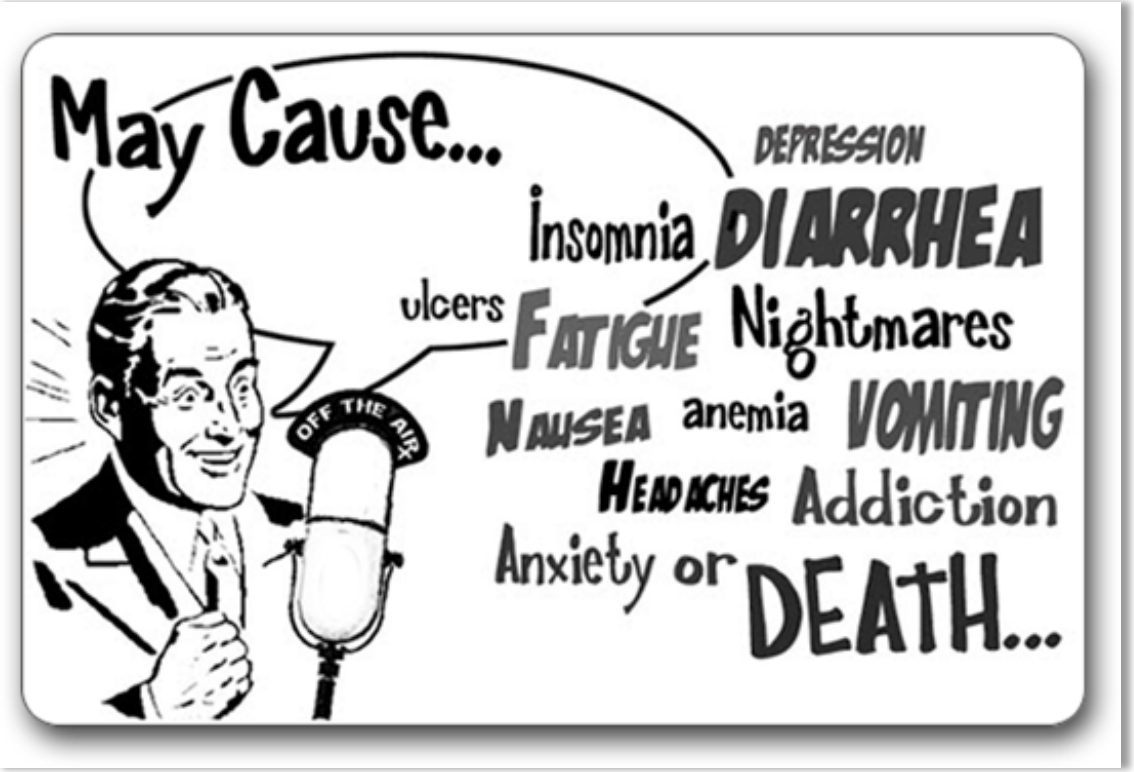
→ <u>Assuming causality</u>, it is mainly a problem of benefit / risk ratio

English text obtained from http://www.medicines.org.uk/emc/medicine/11841/SPC/Avelox+400+mg+film-coated+tablets
Cross-checked with the official Belgian SmpC (in French)

But fluoroquinolones are not alone for toxicities

Don't we hear this for many widely used drugs ?



Alternative antibiotics associated risks *

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

* based on an analysis of the respective labelling (European SmPC or equivalent) for common and uncommon events

All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
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, dysgueusia • CNS: headache, dizziness

* based on an analysis of the respective labelling (European SmPC or equivalent) for common and uncommon events

Comparisons of hepatotoxicity risks of antibiotics

Antibiotic	population	Incidence rate (CI)		endpoint	reference
		per 100,000 users	per 100,000 prescriptions		
fluoroquinolones (w/o moxifloxacin)	Outpatient clinic, Sweden (1995-2005)	0.7 (0.5-1.1)		International consensus	[1]
moxifloxacin	Outpatient clinic, Sweden (1995-2005)	0.08 (0.0-0.5)		International consensus	[1]
cotrimoxazole	Saskatchewan Health Plan, Canada (1982-1986)	1.0 (0.2-5.7)	4.9 (0.9-27.6)	International consensus, hospitalisation	[2]
erythromycin	Saskatchewan Health Plan, Canada (1982-1986)	2.0 (0.7-5.9)	14.0 (4.8-41.2)	International consensus, hospitalisation	[2]
amoxicillin-clavulanic acid	General practice research database, United Kingdom (1991-1992)	22.5 (14.7-34.4)	17.4 (11.4-26.5)	International consensus	[3]

* see Van Bambeke & Tulkens Drug Saf. 2009;32:359-378 - PMID: 19419232 for full Table and details

1. De Valle et al. Aliment Pharmacol Ther 2006 Oct 15; 24(8): 1187-95
2. Perez et al. Epidemiology 1993 Nov; 4(6): 496-501
3. Garcia-Rodriguez et al. Arch Intern Med 1996 Jun 24; 156(12): 1327-32

An extensive review of hepatic toxicity of antibiotics

J Antimicrob Chemother 2011; **66**: 1431–1446
doi:10.1093/jac/dkr159 Advance Access publication 17 May 2011

Journal of Antimicrobial Chemotherapy

Hepatic safety of antibiotics used in primary care

Raúl J. Andrade[1,2] and Paul M. Tulkens[3,4]*

[1]Hepatology Unit, Gastroenterology Service, Virgen de la Victoria University Hospital Department of Medicine, University of Málaga, Spain; [2]Centro de Investigación Biomédica en Red de enfermedades hepáticas y digestivas (CIBERehd), Barcelona, Spain; [3]Cellular and Molecular Pharmacology & Centre for Clinical Pharmacy, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; [4]Human Biochemistry and Biochemical Pathology, Université de Mons, Belgium

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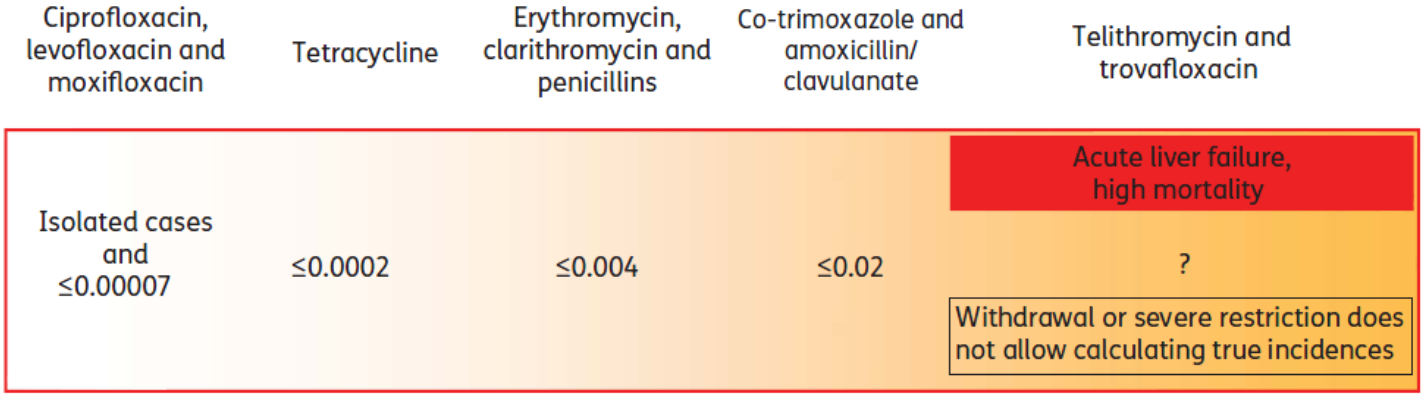
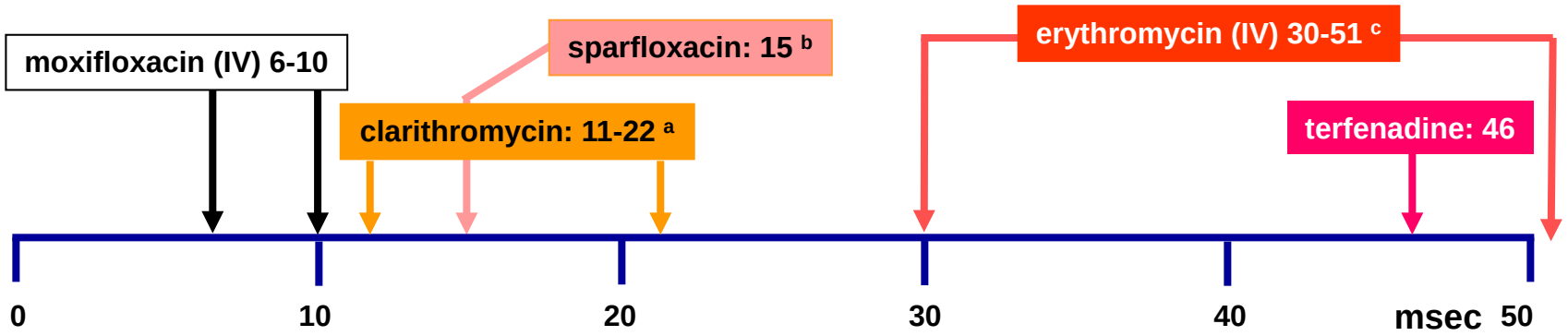


Figure 1. Hepatotoxicity risk of antibiotics (percentage of prescriptions for antibiotics with main indications for use in the community setting). Derived from references 32, 37, 40, 42, 44, 73, 89, 96 and 108. Excluding antibiotics used mainly for the treatment of tuberculosis.

Comparative cardiac safety of antibiotics

- Moxifloxacin IV produces a predictable increase in QT_C interval
- The frequency of cardiac adverse events and drug-related cardiac adverse events are similar for moxifloxacin- and comparator-treated patients
- **No increased risk** of cardiac morbidity or mortality was seen in hospitalised patients with CAP (including high risk ones) treated with IV moxifloxacin (**CAPRIE study**)

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



Ref.:[a] Carr et al. Antimicrob Agents Chemother. 1998; 42:1176-80; Germanakis et al. Acta Paediatr. 2006;95:1694-6.
[b] Jaillon et al. J Antimicrob Chemother. 1996; 37 Suppl A:161-7; Jaillon et al. Br J Clin Pharmacol. 1996; 41:499–503.c
[c] Tschida et al. Pharmacotherapy. 1996;16(4):663-74; Oberg et al. Pharmacotherapy. 1995;15:687-92

Risk factors for severe cardiac effects

Genetic risks
- LQTS 1-7
- Unidentified channelopathies

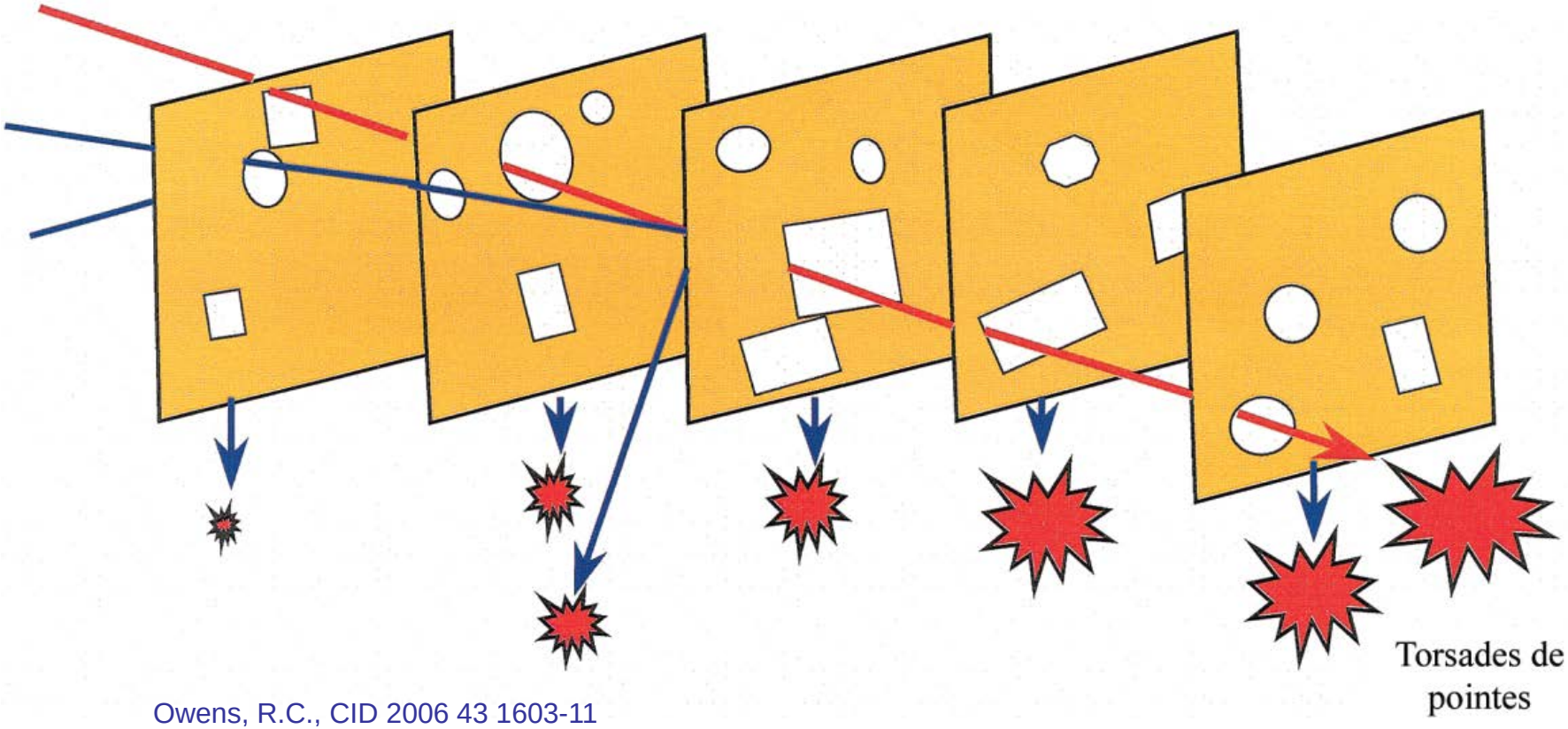
Underlying cardiac disease
- Bradycardia
- Congestive heart failure
- Myocardial ischemia
- Atrial fibrillation

Electrolyte derangements
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

Drug with QT liability given and failure to dose adjust in the presence of organ impairment
- Renal insufficiency
- Severe hepatic disease

Drug with QT liability and metabolic liability
- Genetic polymorphism
- Concurrent CYP inhibitor administered

Administration of multiple drugs with QT liability



Owens, R.C., CID 2006 43 1603-11

Risk of Torsade de pointes and inhibitors of CYP450 metabolism

Table 1

QT interval prolonging drugs metabolized by CYP 3A4, which may possibly interact both pharmacokinetically and phamacodinamically with macrolides and imidazole antifungals.

Antiarrhythmics	Amiodarone (with roxithromycin [23]), quinidine (with erythromycin [116]), disopyramide (with clarithromycin [117, 118])
Antifungals	Fluconazole, ketoconazole, itraconazole, miconazole
Prokinetics	Cisapride (with clarithromycin, [119, 120], with erythromycin [121])
Antihistamines	Terfenadine (with erythromycin [122, 123], with troleandomycin [124]), astemizole (with erythromycin [125]), loratidine
Antipsychotics	Pimozide (with clarithromycin [126, 127]), chlorpromazine, haloperidol, ziprasidone, risperidone, clozapine, quetiapine
Immunsuppressive drugs	Tacrolimus
Opioid agonists	Methadone
Antimalarials	Quinine, chloroquine, halofantrine

Case reports on torsades de pointes or QT prolongation during coadministration of macrolide agents and other repolarization prolonging drugs are in brackets

Simkó et al., Infection 2008;36:194-206

The use of macrolides without paying attention to other drugs may put patients at risk …

All antimicrobials have associated risks …

Conclusions so far:

- 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**

Never say that …

but check for specific risks

And assess the benefit / risk ratio !

RTI: respiratory tract infection

Populations at risk *

Class	Drugs	Populations at higher risk of side effects
β-lactams	amoxicillin	• **Allergic patients**
	amoxicillin/ clavulanic acid	• **Allergic patients** • Erythematous skin rash: patients with mononucleosis • **Hepatic toxicity: patients with hepatic dysfunction** • Nephrotoxicity: elderly patients
macrolides	clarithromycin	• **Cardiac effects: patients taking other drugs with effects on QTc or class 1A or III antiarrythmics** • Pregnancy • Patients with severe renal impairment with or without coexisting hepatic impairment • **Patients taking drugs metabolized by CYP450**
	azithromycin	• **Hepatotoxicity: patients with liver failure**

* as defined by the corresponding labelling

The whole clinical trial moxifloxacin data base

ORIGINAL RESEARCH ARTICLE

Drugs R D 2012; 12 (2): 71-100
1179-6901/12/0002-0071

Moxifloxacin Safety

An Analysis of 14 Years of Clinical Data

Paul M. Tulkens,[1] *Pierre Arvis*[2] and *Frank Kruesmann*[3]

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

Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

Which patients and which comparators ?

Comparators	Patients (no.)					
	PO (N=21,298)		IV/PO (N=6846)		IV only (N=1860)	
	Moxifloxacin (N=10613)	Comparators (N=10685)	Moxifloxacin (N=3431)	Comparators (N=3415)	Moxifloxacin (N=937)	Comparators (N=923)
A. Double-blind studies						
β-lactams	2391	2104	1077	1034	408	390
β-lactams + macrolides	274	155	0	0	0	0
Fluoroquinolones	2246	2287[a]	444	457[b]	0	0
Macrolides	3659	2929	0	0	00	0
Other	1230	1168[c]	368	365[d]	180	181[e]
Total	**8822[h]**	**8643**	**1889**	**1856**	**588**	**571**
B. Open-label studies						
β-lactams	1318	1301	578	574	0	0
β-lactams + macrolides	186	190	0	0	0	0
β-lactams ± macrolides	0	0	532	549	0	0
Fluoroquinolones	263	270[f]	349	352[f]	349	352[f]
Macrolides	287	281	0	0	0	0
Other	0	0	456	463[g]	0	0
Total	**1791[h]**	**2042**	**1542**	**1559**	**349**	**352**

open-label and double-blind actively controlled clinical trials included in the clinical trial database of moxifloxacin 400 mg once-daily performed by the registration holder (currently Bayer HealthCare) as part of the phase II-IV programmes initiated, completed and with raw data reported to the sponsor between 1996 and 2010

Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

Global results

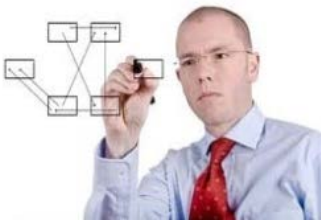
Double-blind studies

Event	Number (%) of patients with treatment					
	PO (N=17,465)		IV/PO (N=3745)		IV (N=1159)	
	MXF (N=8822)	Comp. (N=8643)	MXF (N=1889)	Comp. (N=1856)	MXF (N=588)	Comp. (N=571)
Adverse events (AE)	3782 (42.8)	3711 (42.9)	1202 (63.6)	1138 (61.3)	305 (51.8)	253 (44.3)
Adverse drug reactions (ADR)	2211 (25.0)	2026 (23.4)	455 (24.0)	439 (23.6)	85 (14.4)	83 (14.5)
Serious adverse events (SAE)	318 (3.6)	316 (3.6)	315 (16.6)	282 (15.1)	74 (12.5)	54 (9.4)
Serious adverse drug reaction (SADR)	47 (0.5)	48 (0.5)	53 (2.8)	46 (2.4)	9 (1.5)	7 (1.2)
Premature discontinuation due to AE	366 (4.1)	337 (3.8)	144 (7.6)	131 (7.0)	16 (2.7)	9 (1.5)
Premature discontinuation due to ADR	261 (2.9)	251 (2.9)	74 (3.9)	63 (3.3)	4 (0.6)	4 (0.7)
AE with fatal outcome	28 (0.3)	36 (0.4)	66 (3.4)	54 (2.9)	21 (3.5)	13 (2.2)
ADR with fatal outcome [a]	3 (<0.1)	4 (<0.1)	3 (0.1)	3 (0.1)	0 (0)	1 (0.1)

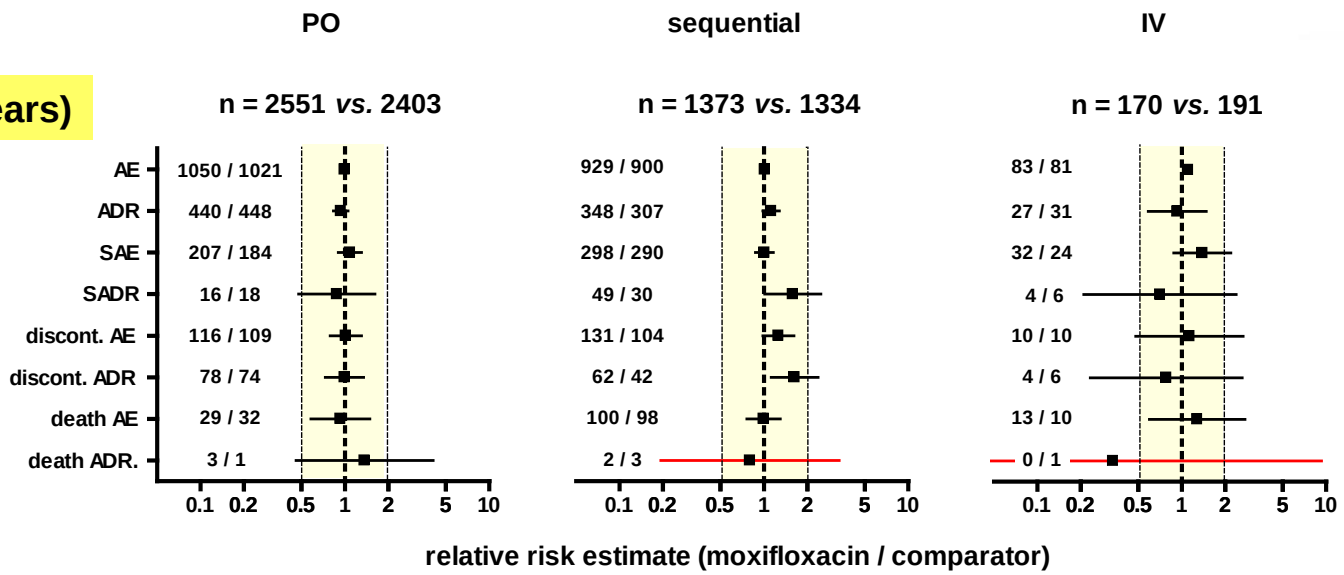
Simlar result for the open label studies

Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

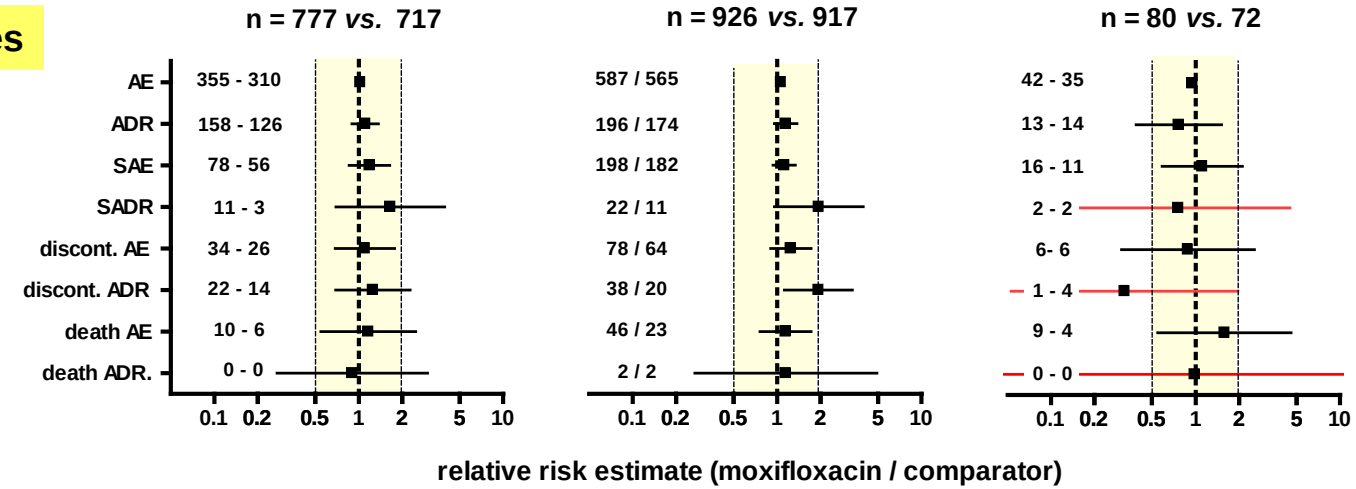
And for patients at risk ?



age (> 65 years)

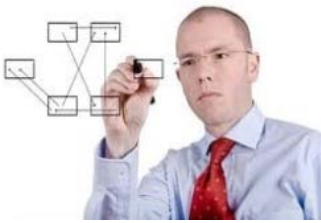


diabetes

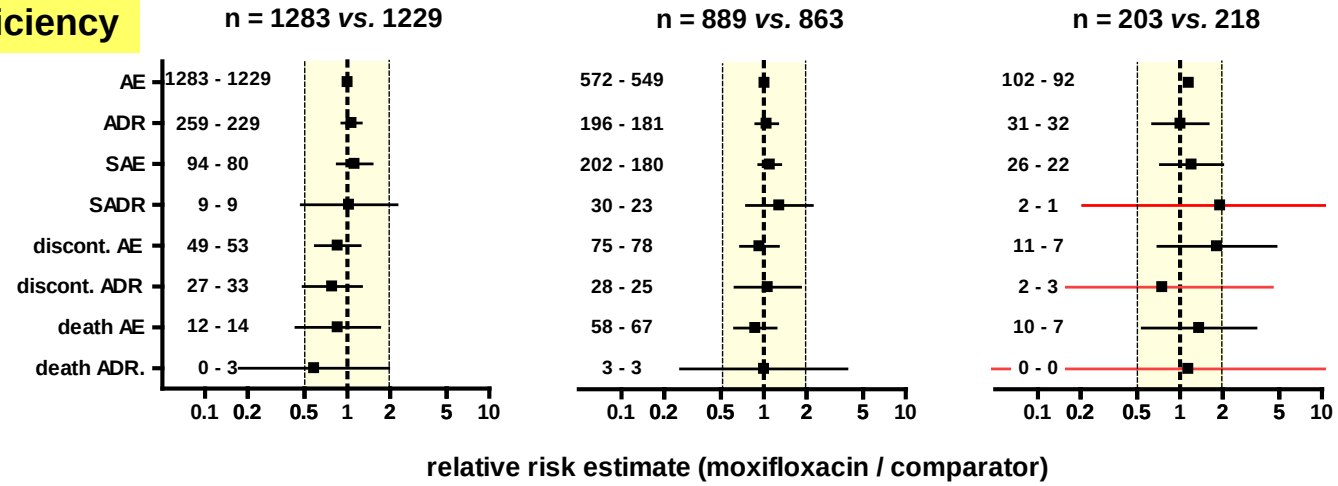


Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

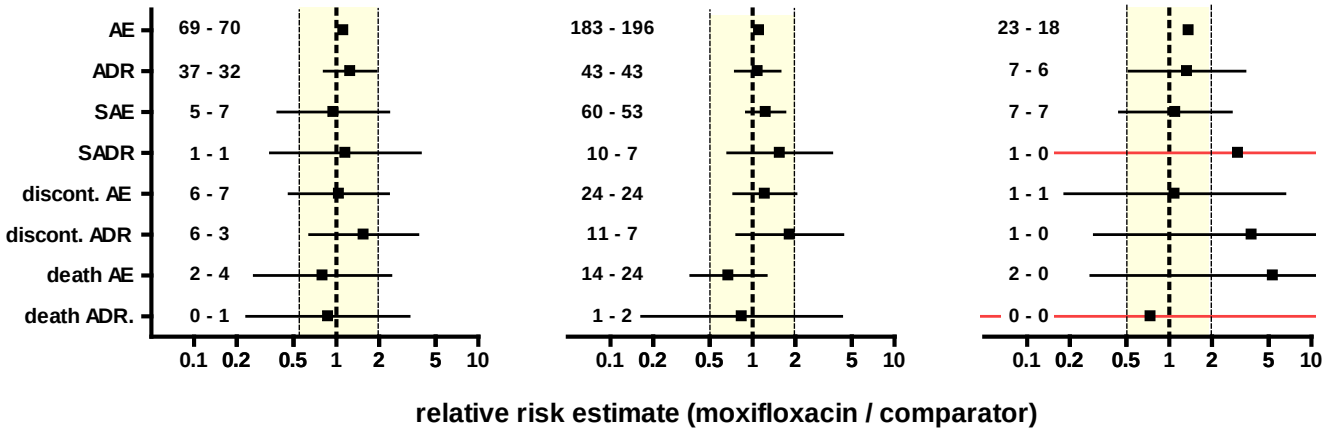
And for patients at risk ?



renal insufficiency

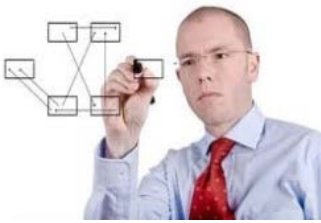


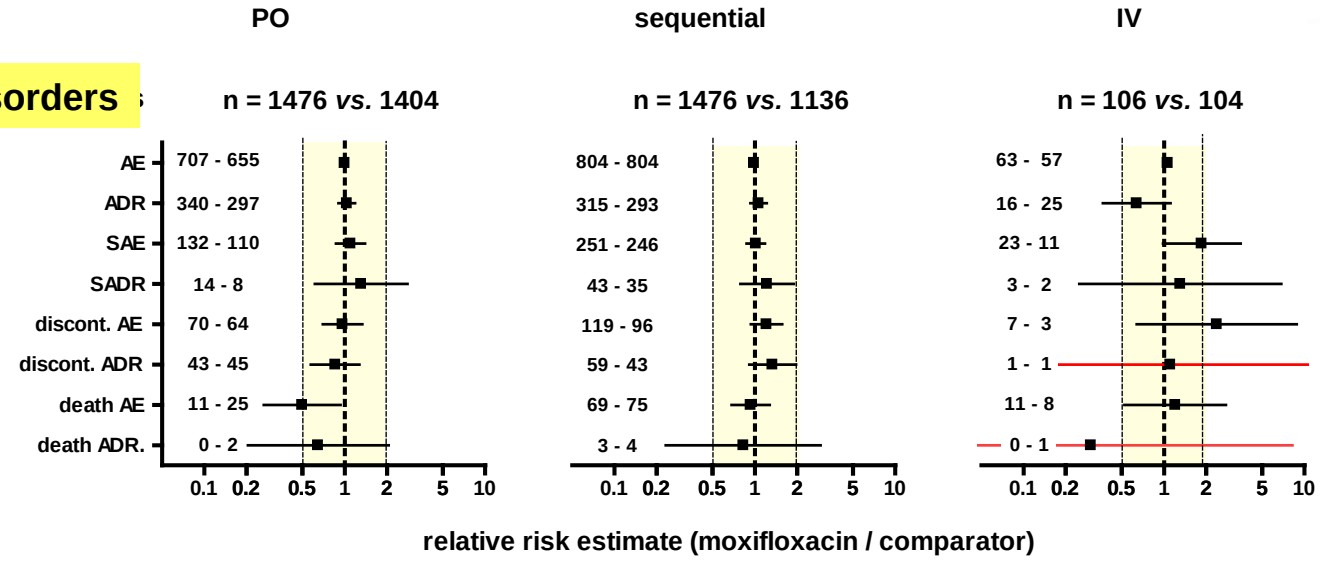
hepatic insufficiency

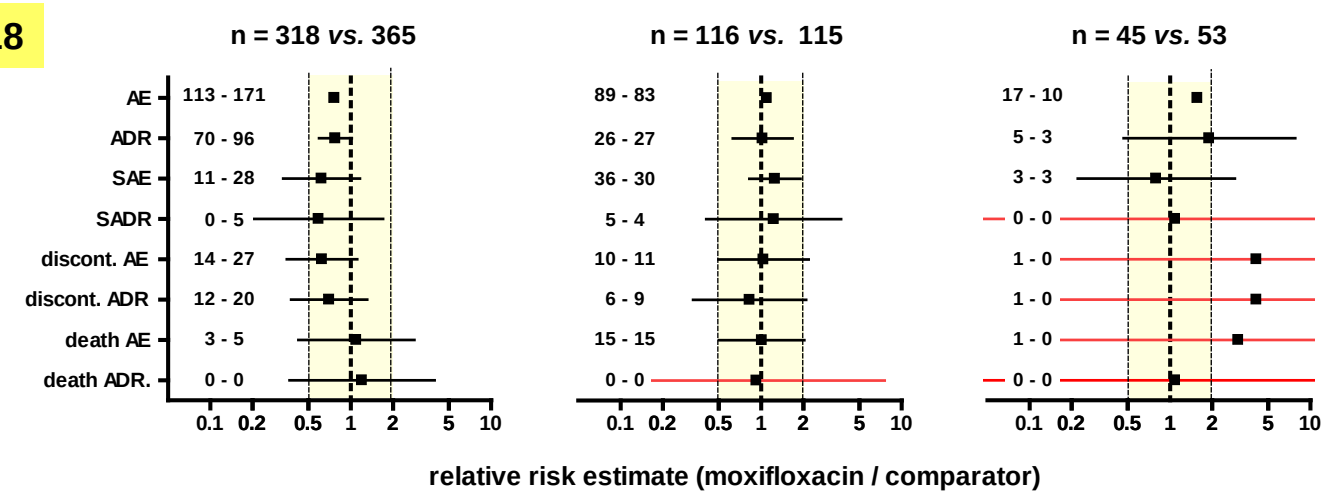


Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

And for patients at risk ?







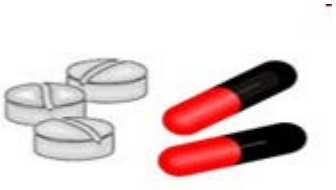
Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

Conclusions (at this point)

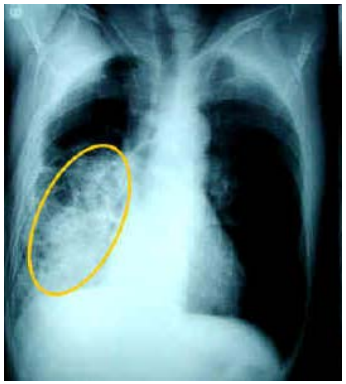
- The overall safety profile of moxifloxacin is similar to that of comparators in clinical trials
- More specifically, and with regard to recent questions:
  - Hepatic events reactions were very low and not superior in a statistically significant manner to comparators even if considering patients with hepatic disorders
  - While QTc prolongation were observed, no increase clinical adverse effects were seen even in patients with prexisting cardiac disorders vs. the comparator(s)
  - Specific toxicities (tendonitis, e.g.) remained exceedingly rare with no difference between moxifloxacin and the fluroquinolone comparator
  - Skin events were extremely rare and less frequent than with β-lactams

Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

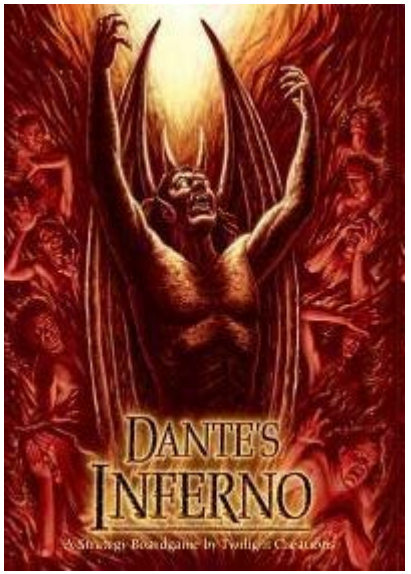
But what is "risk" ?



→ **side effects ?**



→ **therapeutic failure ?**

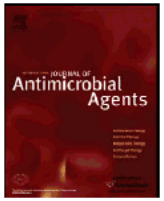


How does moxifloxacin compares with other antibiotics: the case of *S. pneumoniae*

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

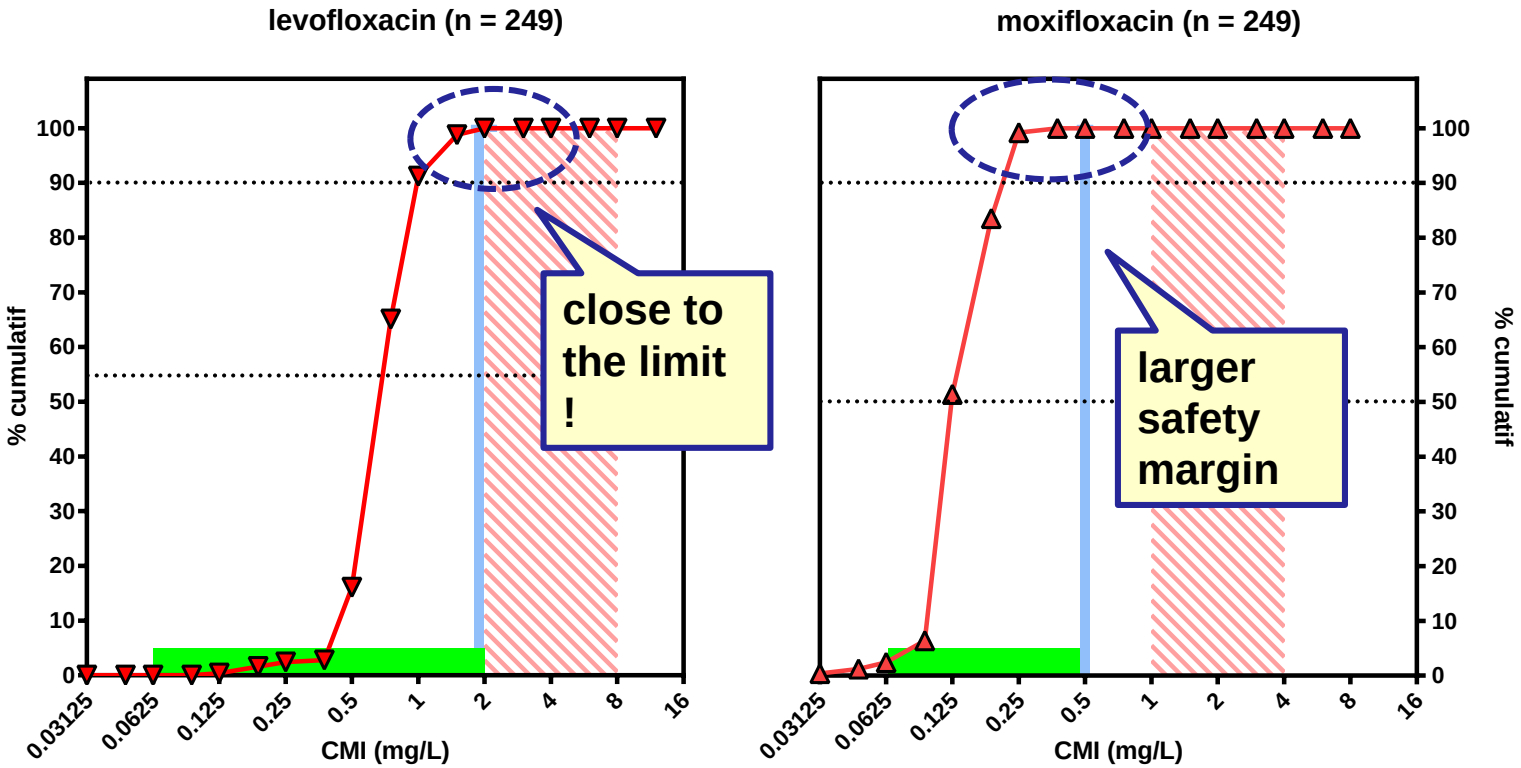


International Journal of Antimicrobial Agents 39 (2012) 208–216

Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium

Ann Lismond[a], Sylviane Carbonnelle[a,1], Jan Verhaegen[b], Patricia Schatt[c], Annelies De Bel[d], Paul Jordens[e], Frédérique Jacobs[f], Anne Dediste[g], Frank Verschuren[h], Te-Din Huang[i,2], Paul M. Tulkens[a,*], Youri Glupczynski[j], Françoise Van Bambeke[a]

How does moxifloxacin compares with levofloxacin for *S. pneumoniae* in CAP ?



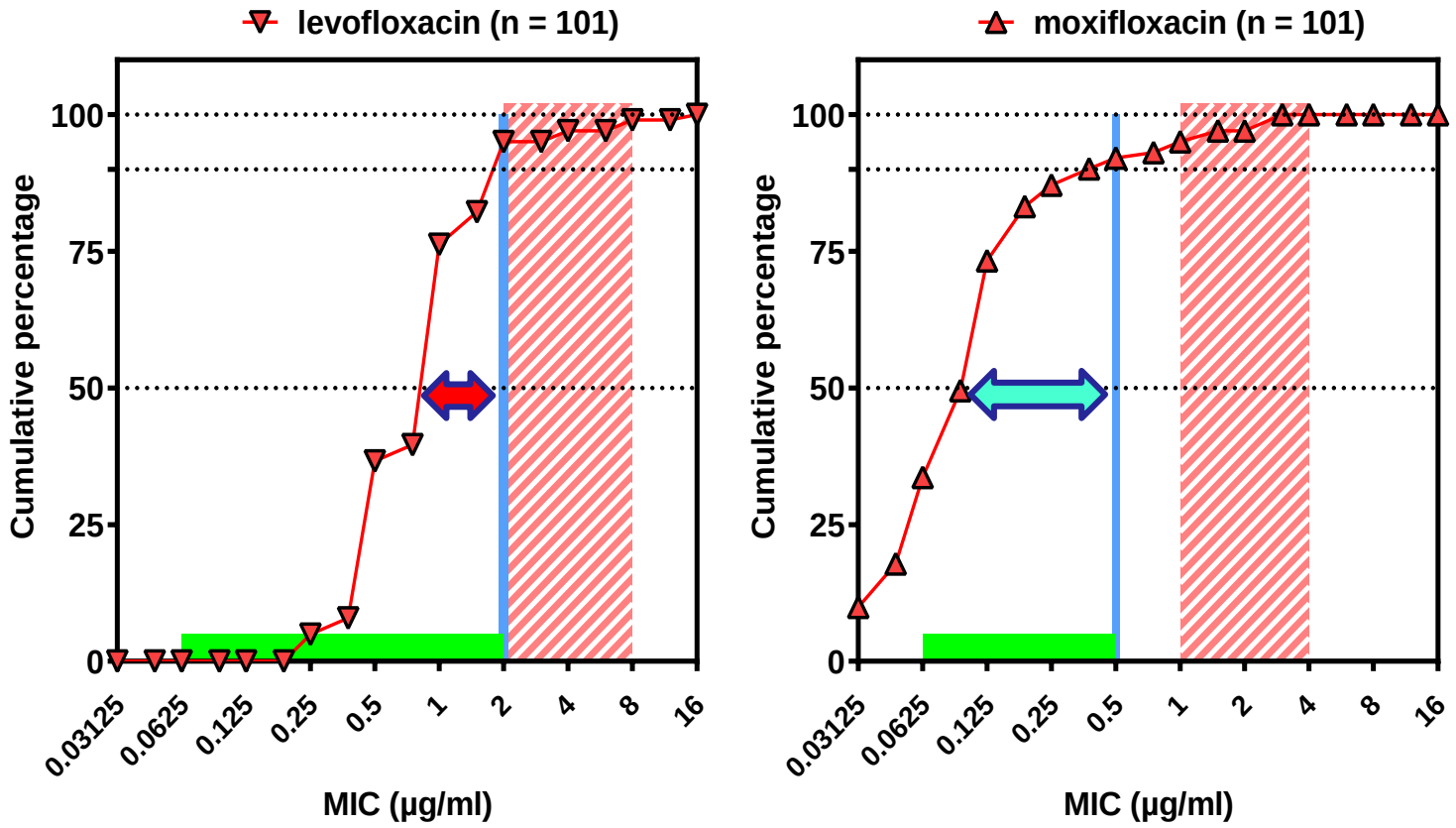
Consequences:

1. levofloxacin is "at the limit" (and should better be used at 750 mg QD or 500 mg BID)

2. moxifloxacin provides a better safety and minimizes the risk of emergence of resistance

Lismond *et al*. Int J Antimicrob Agents. 2012;39:208-16 - PMID: 22245497

And what about COPD (2006-2013) ?



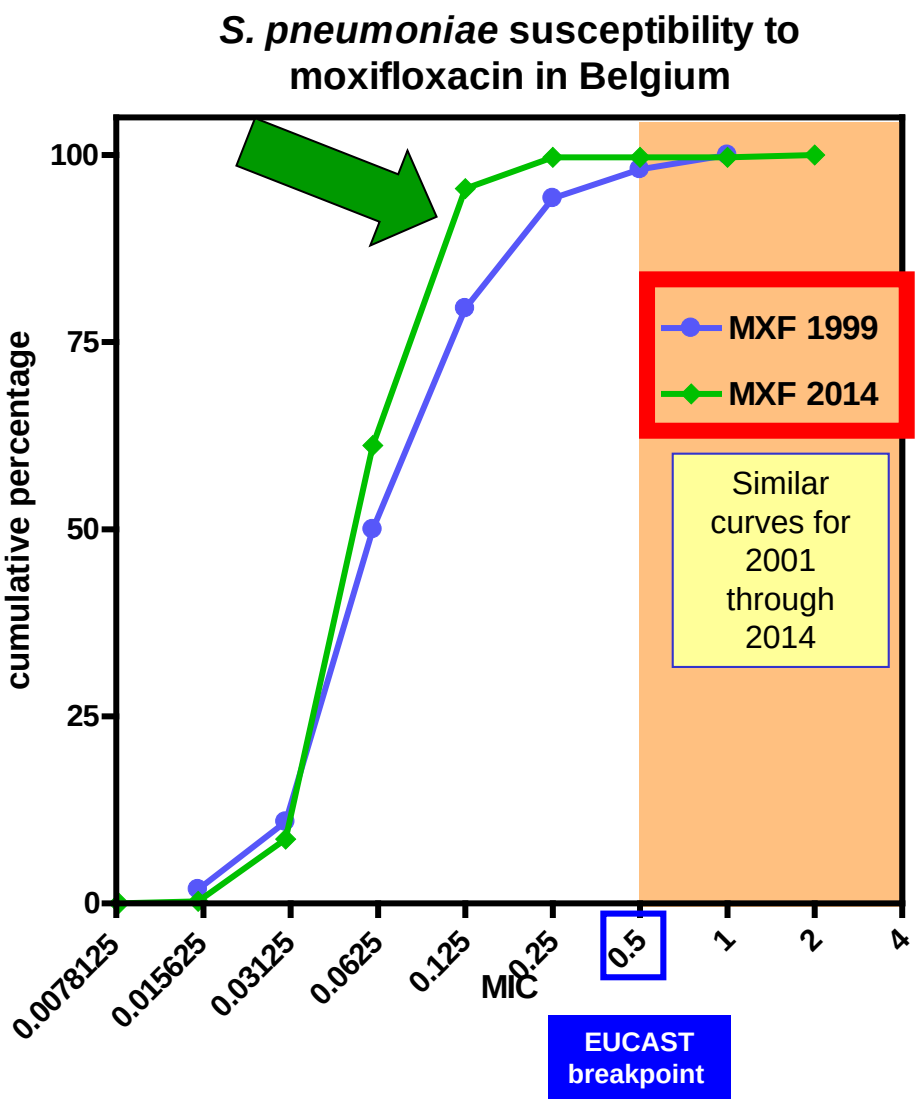
Consequences:

1. levofloxacin starts lagging beyind and gets very close even to CLSI breakpoint

2. moxifloxacin is not immune but still shows a much wider safety margin

Vandevelde *et al.* Int J Antimicrob Agents 2014;44:209-17 - PMID: 25123808.

Hs resistance to moxifloxacin materialized: evidence for *S. pneumoniae* in Belgium from 1999 to 2014 *



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

From data of a <u>national</u> 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

Vanhoof *et al*. 19th ECCMID, Helsinki, 2009
Ceyssens *et al*. 35th RICAI, Paris, 2015
Ceyssens et al. PLoS One. 2016;11:e0154816 - PMID: 27227336

Conclusions (Altogether)

- Moxifloxacin has kept over years an excellent activity against *S. pneumoniae* (and wil be effective against *S. aureus* up to an MIC of 0.125-1 mg/L) and should, therefore stand a as a useful alternative when so-called "*1st line antibiotics*" (for CAP, COPD or skin infections) have "stopped to work"

- The safety profile of moxifloxacin at 400 mg/day remains excellent with no statistically or medically significant difference with comparators (used often at a lower dose than recommended today)

- Thus, and based on all available evidence, the use of moxifloxacin should not be vitiated by excessive toxicity **if it is prescribed for the correct indications and with due attention to the contraindications and warnings mentioned in the labeling**

Van Bambeke & Tulkens Drug Saf. 2009;32:359-378 - PMID: 19419232
Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

The Flemish Painter Hieronymus Bosch (c1450-1516) presented his fantasies in the tryptic "The Last Judgment" (c1510-15, Akademie, Vienna)

Thus, in a nutshell …

LEADING ARTICLE

Drug Safety 2009; 32 (5): 359-378
0114-5916/09/0005-0359/$49.95/0

Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin

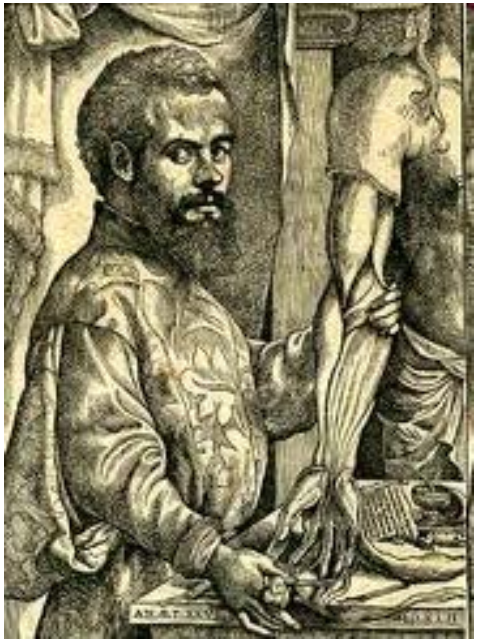
Comparison with Other Fluoroquinolones and Other Antibacterial Classes

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.

Please, ask questions …



be critical,
ask for facts !

Vesalius – Anatomy *

All slide are available on http://www.facm.ucl.ac.be → Lectures

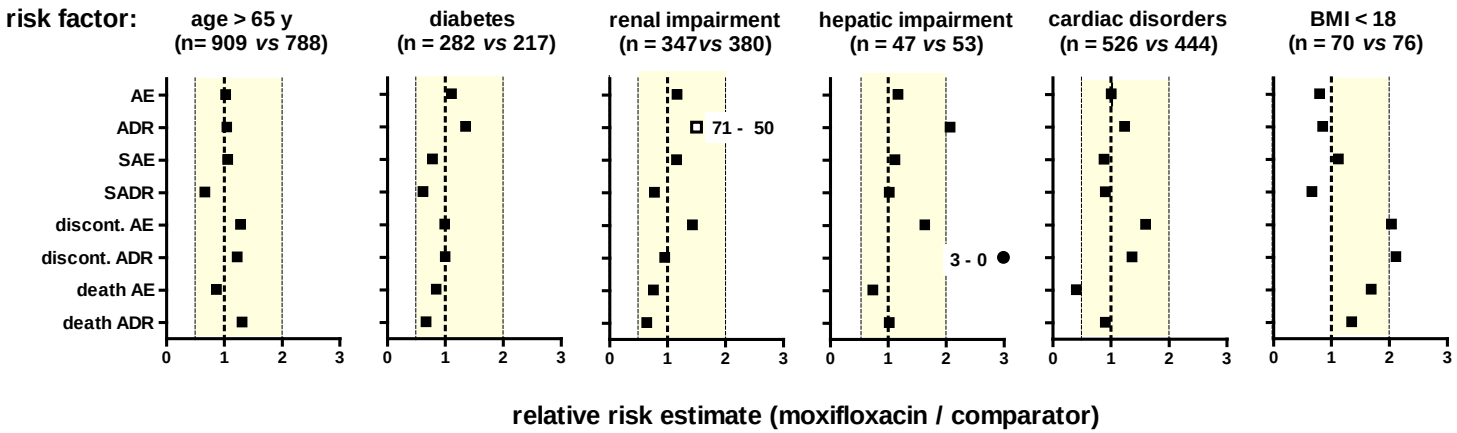
* *ANDREAE VESALII Bruxellensis Scholae "De humani corporis fabrica libri septem"* is a set of books on human anatomy written by Andreas Vesalius and published in 1543. It represented a major advance in the history of anatomy by moving from reiteration of past statements to actual observations

Backup

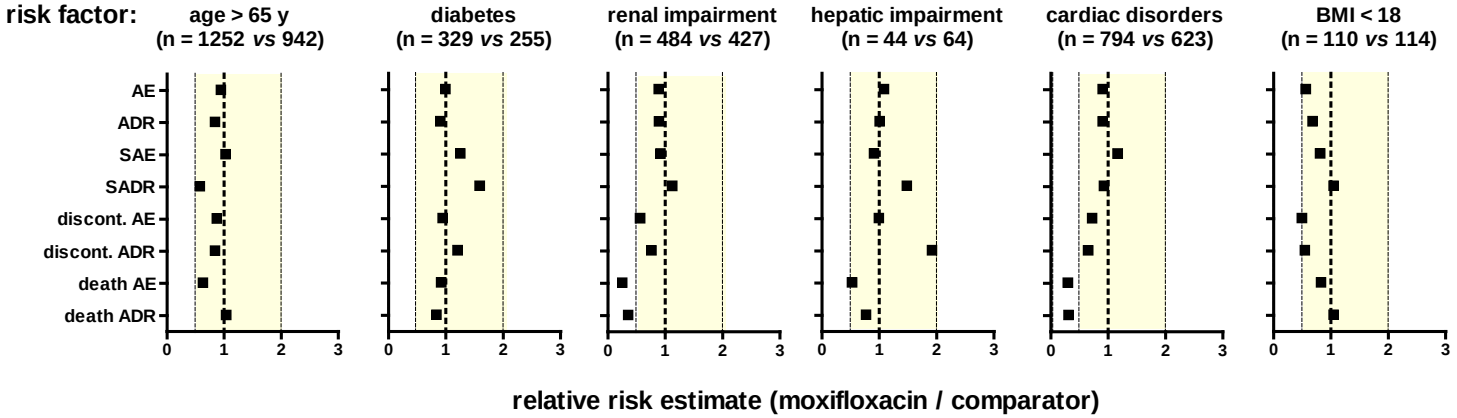
And what if we compare drugs ?

A. oral therapy

1. moxifloxacin *vs* β-lactams



2. moxifloxacin *vs* macrolides

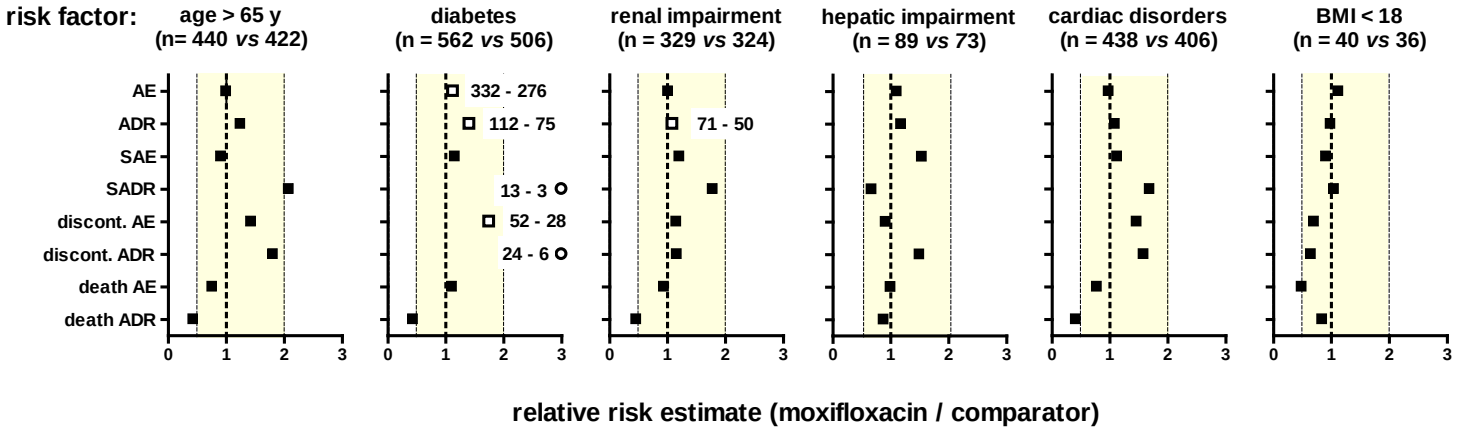


Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

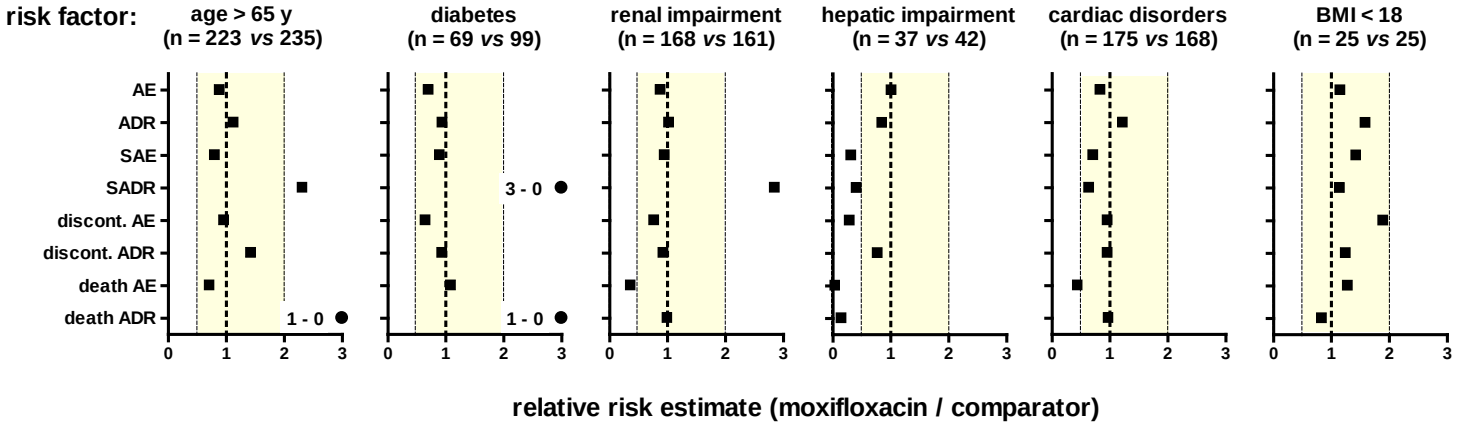
And what if we compare drugs ?

B. sequential therapy

1. moxifloxacin *vs* β-lactam alone



2. moxifloxacin *vs* β-lactam alone or combined with a macrolide

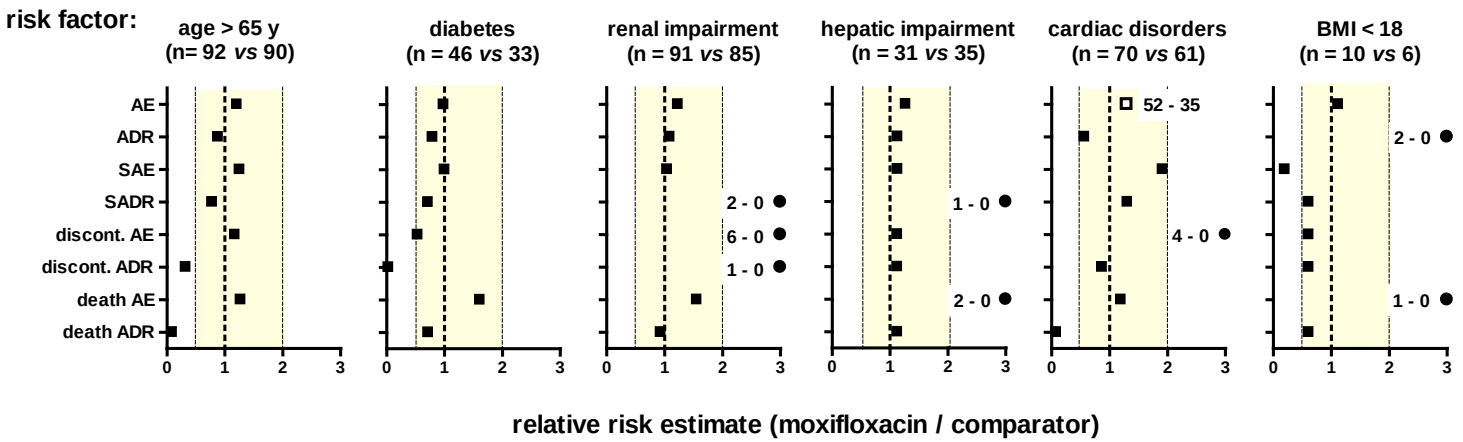


Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866

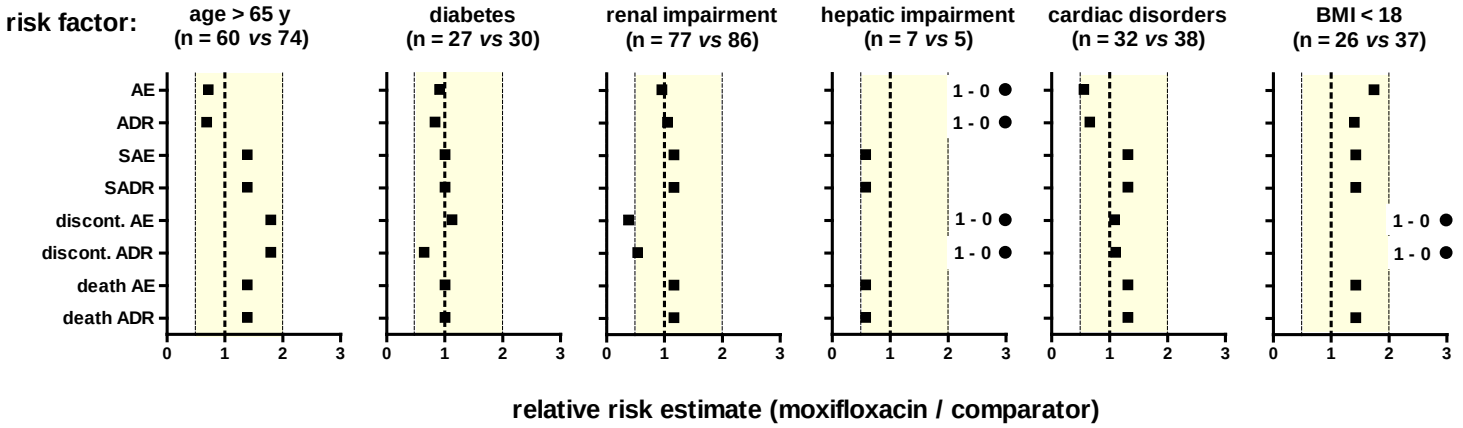
And what if we compare drugs ?

C. intravenous therapy

1. moxifloxacin *vs* β-lactam



2. moxifloxacin *vs* another fluroquinolone



Tulkens et al. Drugs R D. 2012;12:71-100 - PMID: 22715866