Safety of moxifloxacin with special reference to the recent labelling change and benefit-risk ratio

Paul M. Tulkens, MD, PhD *
Professor of Pharmacology

Françoise Van Bambeke, PharmD, PhD
Professor of Pharmacology and Pharmacotherapy

Cellular and Molecular Pharmacology Unit
Université catholique de Louvain, Brussels, Belgium

http://www.facm.ucl.ac.be

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

Contents of the Presentation

- Is moxifloxacin safety an issue ?
  - overview
  - hepatic safety
  - cardiac safety (QTc)

- "Respiratory" Fluoroquinolones in todays' epidemiological situation and "what if" these would be no longer available (for appropriate use) ?

Safety profile of moxifloxacin vs. other antibiotics:

Methods

- Literature published in the English language and referenced in PubMed (US National Library of Medicine)

  keywords: name of the drug + "*safety*", "*side effect*", "*adverse effect*", or "*toxicity*", or the name of the specific side effect(s)

- US PI (labeling) and EU SPC (Summary of product characteristics)
- Sponsor's data (clinical studies and Periodic Safety Update Reports [PSUR])
- pharmacovigilance data (incl. "*case – non-case*" studies).

Keys

Bayer HealthCare
Bayer Schering Pharma

data compiled by and from Bayer's data

independent analysis by our research group

Safety data from published clinical trials *

- 6270 patients moxifloxacin
- 5961 patients comparator
  - **amoxicillin/clavulanic acid, cefuroxime, cefixime,**
  - **clarithromycin, azithromycin,**
  - **trovafloxacin, levofloxacin,**
  - **sulfamethoxazole**

Overal conclusion: no significant difference for

- Side effects
- Serious side effects

** Andriole et al. (2005) Drug Safety 28:443-53*

Side effects (non-serious) from clinical trials: moxi *vs.* comparators

event	Moxifloxacin: n (%)			comparators: n (%)		
	< 65 y (n=4939)	65-74 y (n=842)	> 74 y (n=489)	< 65 y (n=4732)	65-74 y (n=479)	> 74 y (n=435)
Tx effect	2161 (43.8)	382 (45.4)	221 (45.2)	2056 (43.4)	351 (44.2)	194 (44.6)
Drug effect	1344 (27.2)	183 (21.7)	111 (22.7)	1154 (24.4)	169 (21.3)	93 (21.4)
Nausea	381 (7.7)	40 (4.8)	19 (3.9)	260 (5.5)	35 (4.4)	11 (2.5)
Diarrhea	274 (5.5)	39 (4.6)	29 (5.5)	236 (5.0)	28 (3.5)	21 (4.8)
Vomiting	89 (1.8)	5 (0.6)	6 (1.2)	80 (1.7)	8 (1.0)	3 (0.7)
Dyspepsia	72 (1.5)	8 (1.0)	1 (0.2)	59 (1.2)	8 (1.0)	3 (0.7)
Liver test	58 (1.2)	11 (1.3)	3 (0.6)	55 (1.2)	6 (0.8)	9 (1.2)
Faltulence	37 (0.7)	2 (0.2)	1 (0.2)	25 (0.5)	4 (0.5)	6 (1.4)
GGTP ↑	8 (0.2)	0	0	11 (0.2)	1 (0.1)	5 (1.1)
Headache	91 (1.8)	12 (1.4)	4 (0.8)	101 (2.1)	12 (1.5)	4 (0.9)
Abdo. Pain	106 (2.1)	10 (1.2)	8 (1.6)	81 (1.7)	13 (1.6)	4 (0.9)
Asthenia	48 (1.0)	7 (0.8)	4 (0.8)	43 (0.9)	3 (0.4)	4 (0.9)
Dizziness	123 (2.5)	30 (3.6)	12 (2.5)	116 (2.5)	9 (1.1)	5 (1.1)
Insomnia	23 (0.5)	0	5 (1.0)	32 (0.7)	2 (0.3)	3 (0.7)
Rash	44 (0.9)	3 (0.4)	6 (1.2)	33 (0.7)	7 (0.9)	1 (0.2)
Taste perv.	45 (0.9)	7 (0.8)	5 (1.0)	67 (1.4)	18 (2.3)	9 (2.1)

Comparators: amoxi/clav, cefuroxime, cefexime, clarithro, azithro, trova, levo, sulfamethoxazole

Andriole et al. (2005) Drug Safety 28:443-53

Serious side effects from clinical trials: moxi *vs.* comparators

event	moxifloxacin: n (%)			comparators: n (%)		
	< 65 y (n=4939)	65-74 y (n=842)	> 74 y (n=489)	< 65 y (n=4732)	65-74 y (n=479)	> 74 y (n=435)
Any system	24 (0.5)	5 (0.6)	5 (1.0)	26 (0.5)	5 (0.6)	4 (0.9)
Body as a whole	11 (0.2)	1 (0.1)	0	9 (0.2)	1 (0.1)	0
CV	3 (< 0.1)	1 (0.1)	1 (0.2)	3 (< 0.1)	1 (0.1)	1 (0.2)
Dig.	4 (< 0.1)	0	1 (0.2)	5 (0.1)	2 (0.3)	1 (0.2)
Endo	1 (< 0.1)	0	0	0	0	0
Haemic	2 (< 0.1)	1 (0.1)	0	1 (< 0.1)	0	0
Metabolic	0	0	0	2 (< 0.1)	1 (0.1)	0
Nervous	1 (< 0.1)	0	0	2 (< 0.1)	0	1 (0.2)
Respir.	4 (< 0.1)	2 (0.2)	3 (0.6)	5 (< 0.1)	1 (0.1)	0
Skin	3 (< 0.1)	0	0	1 (< 0.1)	1 (0.1)	0
Senses	1 (< 0.1)	0	0	0	0	0
Urogenital	1 (< 0.1)	1 (0.1)	0	3 (< 0.1)	0	1 (0.2)

Comparators: amoxi/clav, cefuroxime, cefexime, clarithro, azithro, trova, levo, sulfamethoxazole

Andriole et al. (2005) Drug Safety 28:443-53

What created a (potential) alert ?

- Periodic Safety Update Reports
  - Part of the normal post-marketing activity of a drug manufacturer
  - Collation of all side effects brought to the knowledge of the sponsor and sent to the registration authorities

European Medicines Agency

June 1997
CPMP/ICH/288/95

Reevaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious. Therefore, Periodic Safety Update Reports (PSUR) present the worldwide safety experience of a medicinal product at defined times post-authorisation, in order to:

- report all the relevant new safety information from appropriate sources;
- relate these data to patient exposure;
- summarise the market authorisation status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety reevaluation;
- indicate whether changes should be made to product information in order to optimise the use of the product.

However, the German authorities asked for the sending of a "*Dear Dr Letter*" warning about severe hepatic toxicities…

- based on the identification of 48 cases of possibly moxifloxacin-related liver disorders with a fatal outcome…
- with 8 suspected cases of moxifloxacin-induced fatal hepatotoxicity
- with 3 for treatment of less severe indications (sinusitis, pharyngitis and acute bronchitis)

In our opinion, this "*Dear Dr Letter*" was largely ill-informative because

- all cases were only "possibly drug-related" or "suspected", with none certain…
- all patients had several other risk factors and co-morbidities …
- The letter failed to mention the denominator (i.e. that those 8 cases concerned a drug that had been given to more than 80 millions patients …

However, it was seen by many as a basis for a severe restriction of moxifloxacin …

So, we decided to look for additional comparative data about antibiotic-induced hepatotoxicity to assess the true significance of the warning…

Crude incidence rates of acute liver injury caused by non-fluoroquinolone antibiotics (observational studies)

(endpoint: international consensus *)

Antibiotic	population	Incidence rate / 100,000 users (CI 95 %)
cotrimoxazole	Saskatchewan Health Plan, Canada (1982-1986)	1.0 (0.2-5.7)
erythromycin	Saskatchewan Health Plan, Canada (1982-1986)	2.0 (0.7-5.9)
macrolides [a]	General practice research database, United Kingdom (1994-1999)	2.5 (0.9-5.4)
amoxicillin-clavulanic acid [b]	General practice research database, United Kingdom (1994-1999)	8.6 (2.4-14.6)

***** AAT/Alk. phos. ratio (hepatocellular: ≥ 5; cholestatic: ≤ 2 ; mixed: > 2 and < 5)

[a] clarithromycin similar to erythromycin; mostly short term and cholestatic; AOR = 6.1 [0.8-45.9]

[b] cholestatic or mixed, short and long-term (clavulanic acid main culprit); AOR = 94.8 [27.8-323]

De Valle et al (2006) Aliment. Pharmacol. Ther. 24:1187-95
Garcia Rodriguez (1996) 156:1327-32
Perez et al (1993) Epidemiology 4:496-501
de Abajo et al. (2004) Br. J. Clin. Pharmacol. 58:71-80

Relative risk of hepatic adverse event * of fluoroquinolones *vs.* macrolides and telithromycin in observational studies

(incidence calculated based on data from reporting systems)

Antibiotic class	Case patients	Non-case patients	Relative risk (CI 95 %)
fluoroquinolones	34 / 1069	865 / 22869	0.8 (0.6-1.2)
macrolides	46 / 1069	587 / 22869	1.7 (1.25 – 23)
telithromycin	20 / 2219	98 / 20667	1.82 (1.12 – 2.96)

* elevated liver function tests, jaundice, hepatocellular damage, liver failure

Motola et al (2007) Eur. J. Clin. Pharmacol. 63:73-9
Fluoroquinolones in Italy at the time of the survey and included in the analysis: levofloxacin, ciprofloxacin, moxifloxacin, lomefloxacin, norfloxacin, pefloxacin, rufloxacin, ofloxacin

Dore (2007) Drug Saf. 30:697-703

FDA reporting rate per 10,000,000 prescriptions (spontaneous reports)

Antibiotic class	Acute liver failure [a]
Levofloxacin	2.1 *
Moxifloxacin	6.6
Telithromycin	23
Trovafloxacin	58

[a] Empiric Bayes Geometric Mean (EBGM) study
www.fda.gov/ohrms/dockets/AC/06/slides/2006-4266s1-01-07-FDA-Brinker.ppt
presented December 2006 to FDA Advisory Committee

Liver failure was defined as "acute or severe liver injury with encephalopathy, liver transplant following acute illness, death in the setting of acute liver injury (hospital. with transam. elev., or hyperbilirubin., or clin jaund.)"

* The US labelling of levofloxacin includes warning against "potentially severe hepatotoxicity" (http://www.levaquin.com/levaquin/isi_index.html)

Hepatotoxicity: Conclusions

- There is no evidence from currently available data that reactions are more frequent than with comparators
  - Clinical and company-sponsored trials:
    - Apparent imbalance in drug-related “severe events” as per MSSO SMQ (see slides 7-9) is based on clinically non-severe, non-serious events; the number of serious, or clinically severe ADRs is too small for meaningful conclusions
  - Spontaneous reporting data:
    - No comparative statement possible from company data because of very low incidences
    - No signal in the Empiric Bayes Geometric Mean (EBGM) study conducted by FDA
    - In any case, amoxicillin-clavulanic acid and macrolides show a larger incidence of hepatic adverse reactions.

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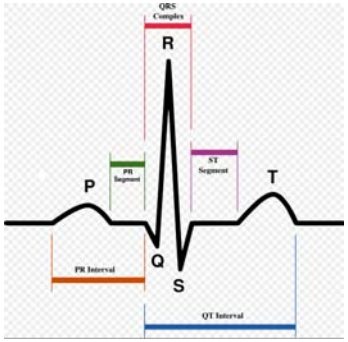
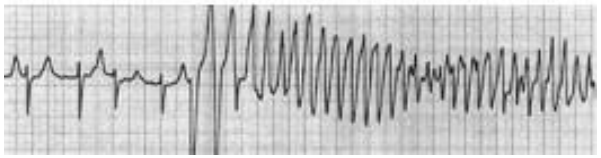
  - hepatic safety
  - cardiac safety (QTc)
- "Respiratory" Fluoroquinolones in todays' epidemiological situation
- How to see the recent labelling change ?

QTc interval: what is the problem ?

Moxifloxacin is known to cause modest QTc prolongation

➔ 6 – 7 msec in healthy volunteers, Phase II/III – po and Phase II/III – iv





European Medicines Agency

November 2005
CHMP/ICH/2/04

NOTE FOR GUIDANCE ON THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS
(CHMP/ICH/2/04)

… 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.*

* this includes erythromycin and clarithromycin (Balardinelli et al, TIPS (2003) 24:619-625)

Does moxifloxacin-induced QTc prolongation has clinical impact ?

Agent	Serious cardiac events * (no. per 10 millions patients treated or as indicated)
Moxifloxacin	4 [a] (in 13 millions)
Ciprofloxacin	8
Ofloxacin	18
Levofloxacin	18
Gatifloxacin	27 (in 3 millions)
Sparfloxacin	> 100
Grepafloxacin	> 150

*** Torsades de Pointes, ventricular tachycardia, or bradycardia**

[a] current observed rate is 5.8 per 10 millions

Ianini (2004) Drug Benefit Trends (suppl) 34-41

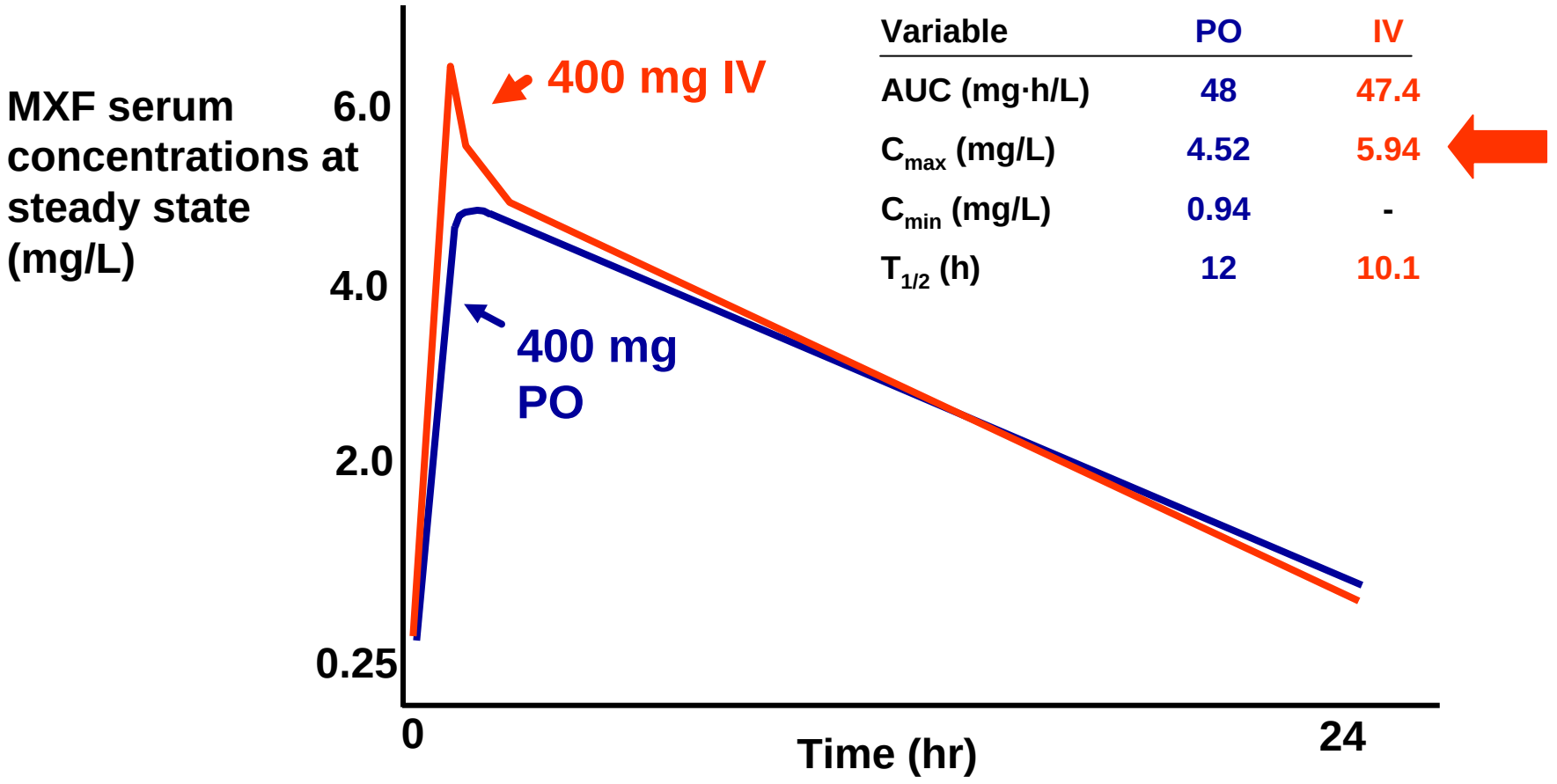
PSUR Bridging Report July 18, 2008

See also: Owens & Ambrose (2005) CID 41S2: S144-57

Falagas et al (2007) Int. J. Antimicrob. Ag. 29:374-9

Veyssier et al. (2006) Med. Mal. Infect. 36:505-12

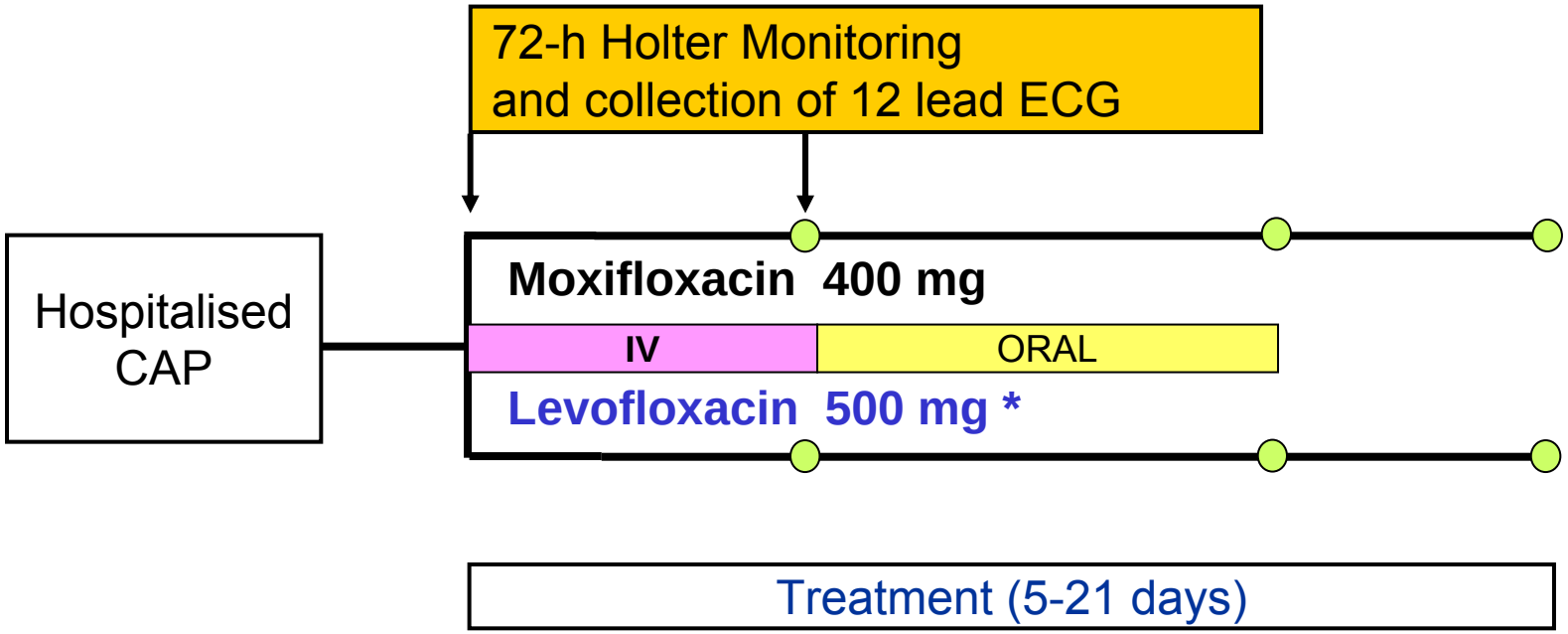
But is the risk not larger with the IV form ?



Variable	PO	IV
AUC (mg·h/L)	48	47.4
C_{max} (mg/L)	4.52	5.94
C_{min} (mg/L)	0.94	-
$T_{1/2}$ (h)	12	10.1

Moxifloxacin package insert

CAPRIE Study (10872 - CAP study in elderly patients)
Design to test for cardiac safety



- very elderly (mean age >75 years)
- 60% patients with PSI Risk Class III or higher
- no difference in efficacy between groups

Anzueto A et al, Clin Infect Dis 2006.

* Low dose by EUCAST standards

CAPRIE Study (10872): Primary Composite Cardiac Safety End Point (Based only on Holter Monitor Findings [ECG])

Findings observed on Holter	Moxifloxacin N = 192 (%)	Levofloxacin N = 195 (%)
Nonsustained VT ≥10 sec, ≤30 sec	14 (7.3)	9 (4.6)
Sustained VT >30 sec	1 (0.5)	0 (0)
Torsade de pointes	0	1 (0.5)
Cardiac arrest	1 (0.5)[#]	0 (0)
Total patients with findings	**16** (8.3 [4.5 to 12.2])	**10** (5.1 [2.1 to 8.2])

VT: Ventricular tachycardia

[#] Respiratory failure following DNR orders

Relative risk = 1.262 (NS)
95% Confidence Interval: 0.9149 to 1.741

- no significant difference for primary composite safety variable between moxifloxacin and levofloxacin
- most Holter findings were asymptomatic (most often not reported as AEs by investigators)
- drug-related cardiac AEs reported in 2 (1%) of moxifloxacin- and 7 (3.5%) of levofloxacin-treated patients (P = NS)

Morganroth et al, Chest 2005; 128:3398

Data on secondary composite cardiac safety end points **Slide D**

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Independent assessment of CAPRIE study

- Analysis of the safety data of the CAPRIE study* failed to demonstrate significant occurrence of cardiac toxicity of moxifloxacin vs. the comparator in elderly patients

* Anzueto et al. Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus That of Levofloxacin Therapy Clin. Infect. Dis. 2006; 42:73–81

Table 3. Overview of adverse events for hospitalized elderly patients eligible who received moxifloxacin or levofloxacin for the treatment of community-acquired pneumonia.

Variable	No. (%) of patients: Moxifloxacin arm (n = 195)	Levofloxacin arm (n = 199)	P
Treatment-emergent adverse event	164 (84.1)	146 (73.4)	.01
Discontinued treatment due to adverse event	15 (7.7)	20 (10.1)	.5
Serious adverse event	46 (23.6)	45 (22.6)	.9
Death	15 (7.7)	11 (5.5)	.5
Any drug-related adverse event	51 (26.2)	45 (22.6)	.5
Drug-related adverse event reported by >1.5% of patients in either treatment group			
Diarrhea	11 (5.6)	10 (5.0)	1.0
Oral candidiasis	7 (3.6)	7 (3.5)	1.0
Nausea	3 (1.5)	4 (2.0)	1.0
Clostridium difficile infection/colitis	1 (0.5)	6 (3.0)	.1
Cardiac event	2 (1.0)	7 (3.5)	.2
Atrial fibrillation	0	3 (1.5)	
Ventricular tachycardia	1 (0.5)	1 (0.5)	
Acute myocardial infarction	0	1 (0.5)	
Atrial flutter	0	1 (0.5)	
Congestive heart failure	0	1 (0.5)	
Cardiorespiratory arrest	0	1 (0.5)	
Supraventricular tachycardia	1 (0.5)	0	
Torsade de pointes	0	1 (0.5)	
Chest pain	0	1 (0.5)	
Increased heart rate	0	1 (0.5)	

MOTIV Study : Incidence rates of adverse events considered to be possible surrogates for arrhythmia

Events	Moxifloxacin (N=368)		Comparator * (N=365)	
	n	(%)	n	(%)
Entire course of study therapy				
Any event – Any relationship	50	(13.6)	43	(11.8)
Any drug-related event	15	(4.1)	12	(3.3)
Day 1 (after 1st infusion)				
Any event – Any relationship	10	(2.7)	8	(2.2)
Any drug-related event	7	(1.9)	4	(1.1)

*** Ceftriaxone + Levofloxacin**

Bayer HealthCare
Bayer Schering Pharma

Why a 6-10 msec QTc prolongation without clinical signs ?

Literature search shows that the reason for discordance between QTc data and actual cardiac toxicity data may result from

- its relatively large IC_{20} towards the hERG* channel (31-35 µM; ~12.6 mg/L **free** drug [corresponding to a serum total concentration of ~ 25 mg/L]), with significant risk of TdP demonstrated in animals at 100 µM (40 mg/L free drug)
  (Chen et al., Br J Pharmacol. 2005;146:792-9.)**

  Quoting: "*the lack of TdP report by moxifloxacin in patients without other risk factors might be attributable to its well-behaved pharmacokinetic profile and other dose-limiting effects*."

  Infusion time (if > 30 min) is not of major concern.

- the fact that TdP is also related to at least one additional parameter (beat-to-beat alternations in monophasic action potential duration (MAPD) on which moxifloxacin has little effect
  (Wisialowski et al. J Pharmacol Exp Ther. 2006;318:352-9).

- absence of cytochrome P450 interactions (main cause for terfenadine or cisapride-induced TdP)
  (Roden DM. N Engl J Med 2004;350:1013-22.)

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* **h**uman **E**ther-a-go-go **R**elated **G**ene (KCNH2) encoding the Kv11.1 potassium ion channel responsible for the repolarising IKr current in the cardiac action potential.

** independently, Patmore et al. (Eur. J. Pharmacol. 2000; 406:449-452) showed rank order of potency sparfloxacin > grepafloxacin = moxifloxacin > ciprofloxacin.

Mechanism(s) of Torsade de Pointes (1)

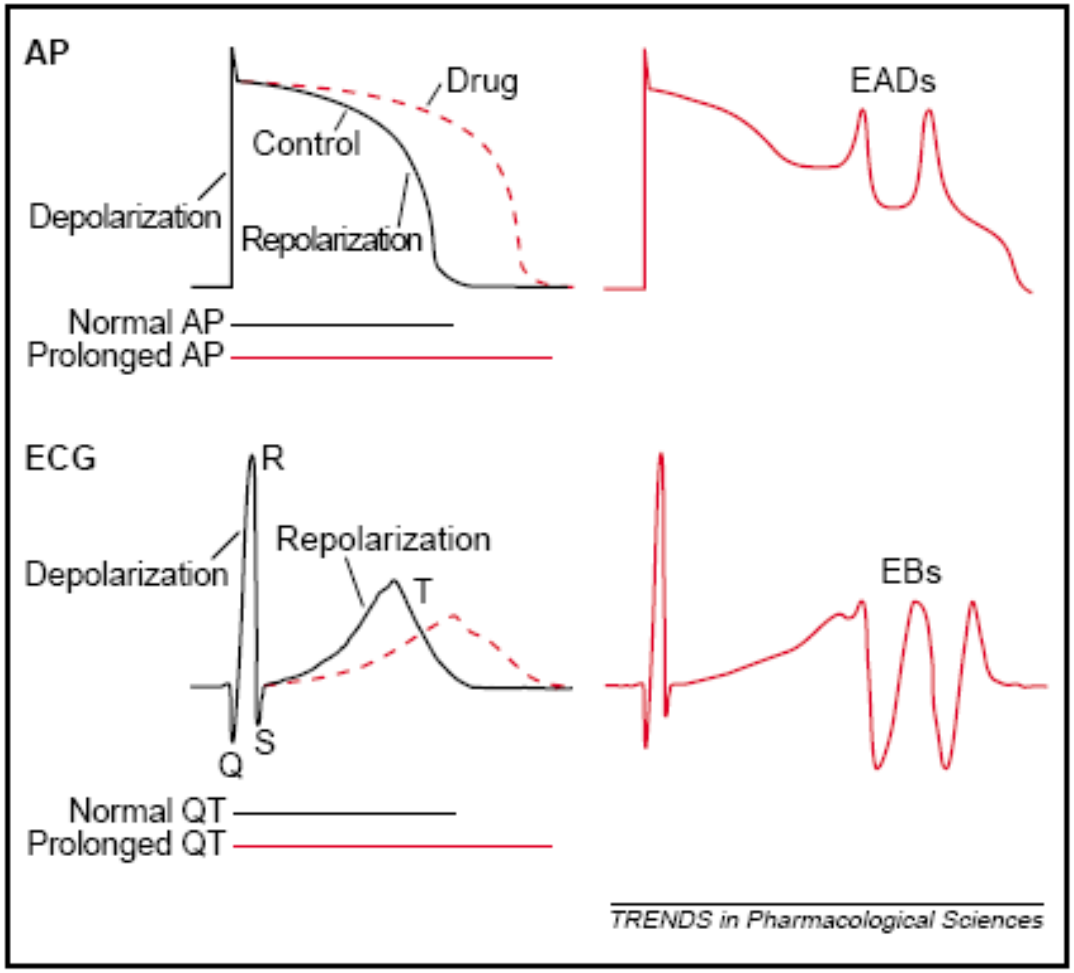


Figure 1. The relationship between ventricular transmembrane action potentials (APs) and the surface electrocardiogram (ECG). In the ECG traces the QRS and T waves denote the depolarization and repolarization, respectively, of the ventricles. The QT interval represents the time elapsed between the ventricular depolarization and repolarization. An increase in the duration of the AP (APD) is responsible for the prolongation of the QT interval. Shown on the left are the APs and ECG in the absence (control) and presence of a drug [e.g. a blocker of the rapid component of the delayed rectifier K^+ current (I_{Kr})] that prolongs the APD and consequently the QT interval. Shown on the right are two large early afterpolarizations (EADs) occurring during the repolarization phase of a prolonged AP, giving rise to two ectopic beats (EBs) in the ECG trace.

Balardinelli et al, TIPS (2003) 24:619-625

Mechanism(s) of Torsade de Pointes (2)

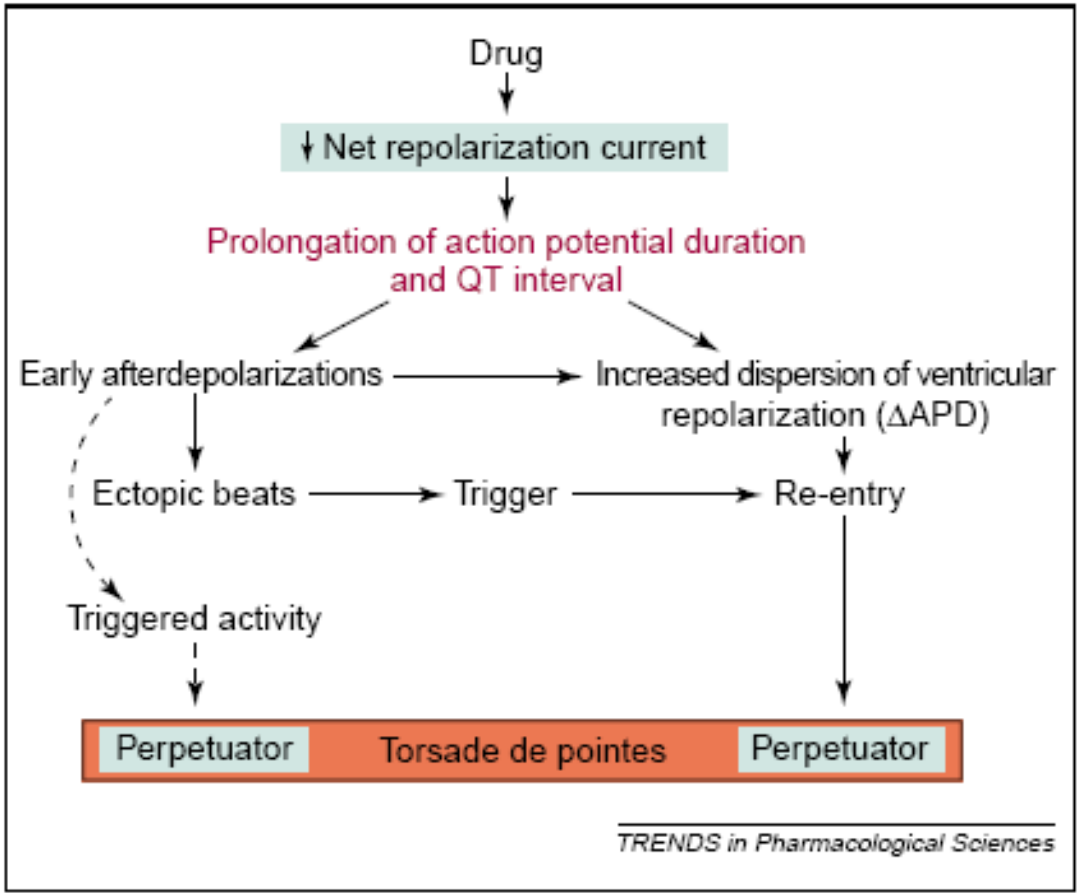


Figure 2. The major electrophysiological events known to play a role in the genesis of torsade de pointes (TdP). The drug causes a reduction in the net repolarizing current, which results in prolongation of the ventricular action potential duration (APD). Resulting early afterdepolarizations (EADs) generate ectopic beats that might serve as a trigger to initiate re-entry to perpetuate TdP. Alternatively, EADs might lead to triggered activity to perpetuate TdP (there is less consensus for this mechanism). Dispersion of ventricular repolarization refers to the differences in action potential duration (ΔAPD) across the left ventricular wall (transmural), between the left and right ventricles, or between the base and apex of the heart. The increase in spatial dispersion of ventricular repolarization leads to heterogeneity of refractoriness, which serves as a substrate for re-entry. Dashed arrows indicate pathways (mechanisms) with currently less supportive evidence than those indicated by solid arrows. See text for more details.

Balardinelli et al, TIPS (2003) 24:619-625

Mechanism(s) of Torsade de Pointes (3)

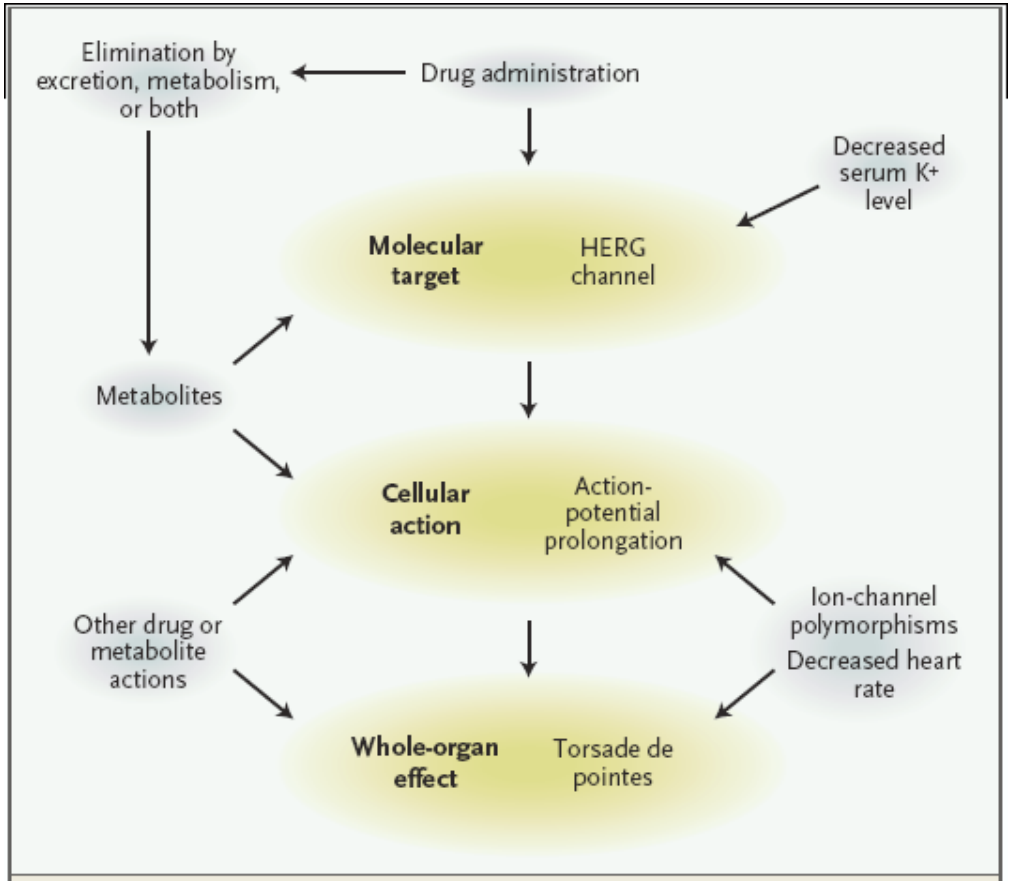


Figure 3. Effects of a Drug on Whole-Organ Function.

The effects of a drug on the function of an organ can be viewed as a cascade. The delivery of the drug to a molecular site of action is the first step. In each yellow area in the center of the figure, subsequent generic levels of action are shown on the left, with the specific example of drug-induced torsade de pointes on the right. Drug metabolites may also contribute to the clinical effects of the drug. At each level, physiological, genomic, or drug-specific or metabolite-specific properties may influence the drug effect that occurs; examples in the case of torsade de pointes associated with HERG blockade are shown on the right. A fundamental difficulty with toxic drug effects that occur at a low frequency is that an action at the level of a molecular target is an imperfect predictor of the effect on the whole organ.

Roden, NEJM 2004;350:1013-1022

Other antibiotics (with same indications) cause TdP

The macrolide antibiotics **erythromycin** and **clarithromycin** have been implicated in sudden death due to TdP. Proarrhythmia may be precipitated by Ikr blockade. In addition, these drugs are metabolized by and inhibit CYP3A4.53 They are especially dangerous for patients receiving another CYP3A4 inhibitor or a QT prolonging medication metabolized by CYP3A4…

(Gupta *et al.*, Am. Heart J. 2007;153:891-899: see also lee K.L. *et al.* Am. J. Med. 1998;104:395-96)
-- see also for **roxithromycin**: Promphan et a., PACE 2003; 26:1424–1426)

The multivariate adjusted rate of sudden death from cardiac causes among patients currently using **erythromycin** was twice as high (incidence-rate ratio, 2.01; 95 percent confidence interval, 1.08 to 3.75; P=0.03) as that among those who had not used any of the study antibiotic medications *[mainly amoxicillin]*.

(Way, R.A. et al., N Engl J Med 2004;351:1089-96)

QTc interval prolongation (605 ms) and torsades de pointes developed after the initiation of **levofloxacin**, 250 mg **intravenously** once daily. The patient was hypokalemic and mildly hypomagnesemic before the initiation of levofloxacin and at the time of occurrence of torsades de pointes.

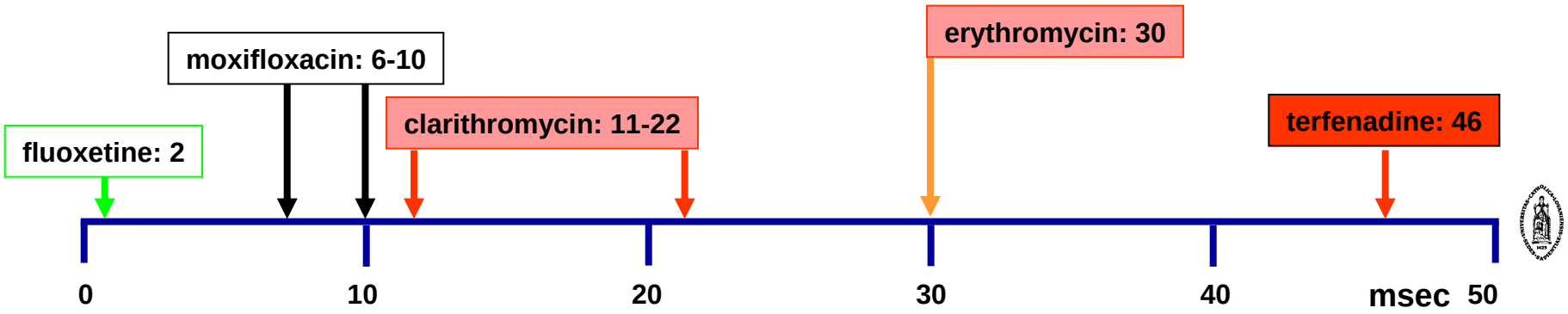
(Amankwa K et al. Clin Pharmacol Ther. 2004 Mar;75(3):242-7)

Moxifloxacin IV Cardiac Safety

- IV moxifloxacin produces a predictable increase in QTc interval. The mean increase is similar and largely overlaps that of PO moxifloxacin
- No clinical study has demonstrated an increased risk of serious cardiac events after moxifloxacin (400 mg – PO or IV)
- the QTc prolongation induced by moxifloxacin is actually too small and this parameter is not the only one to consider to assess the risk of TdP or other major cardiac toxicity.

Moxifloxacin is used as a positive control for QTc effect(s) in Phase I studies because it offers a positive signal without risk of clinically meaningful adverse effect !

- other well known drugs cause even more prolonged QTc interval (and reported TdP) !



Respiratory fluroquinolones in

todays' epidemiological situation:

What if ?

What if fluoroquinolones are made "impossible to prescribe" ?

➔ **significant problems in several EU countries because of resistance to other, often recommended antibiotics**

	Resistance of *S. pneumoniae* (%) in 2005 *			
Country	**Penicillins [1]**	**Macrolides [2]**	**Tetracyclines [2]**	**MDR [3]**
France	49.2	50.1	41.1	40.8
Spain	40.1	30.1	27.6	26.7
Italy	24.5	48.1	37.5	18.8
Mean EU	24.0	24.6	19.8	15.8

* Pneumococcal isolates (n = 1974) recovered from patients with community-acquired respiratory tract infections in 15 European countries (Eur J. Clin. Microbiol. Infect. Dis., 2007;26:485-490)

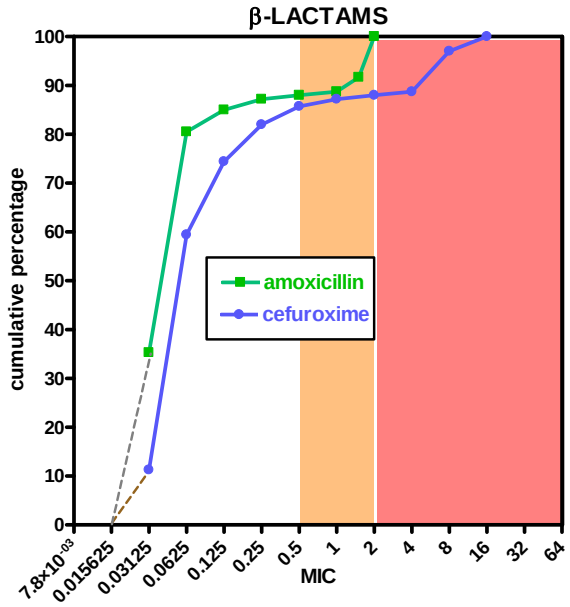
[1] intermediates and full-resistant (intermediates require high doses)

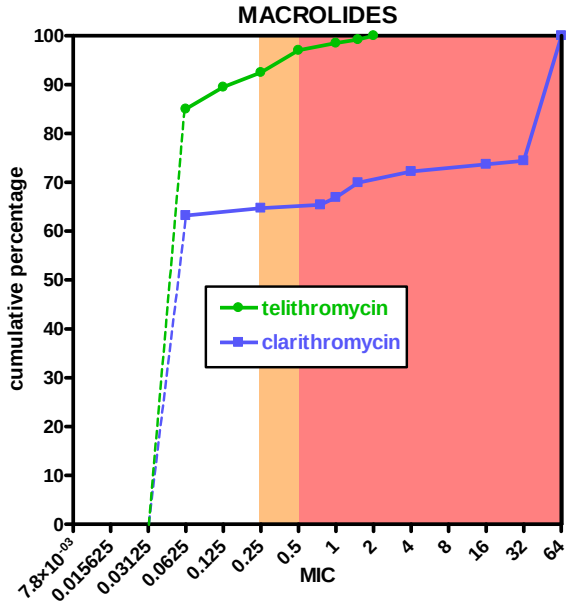
[2] full and crossed resistance to all macrolides except telithromycin

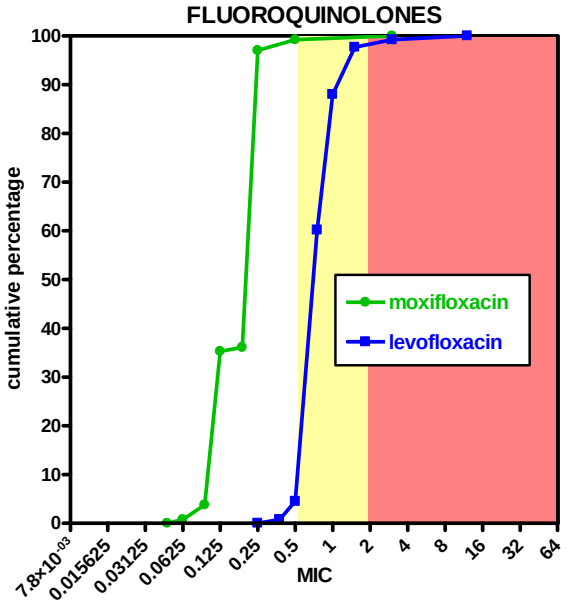
[3] penicillin (I or R) plus resistance to 2 or more other classes of antibiotics

An example for community *S. pneumoniae* in Belgium

Cumulative MIC distribution in 133 cases of confirmed infection against EUCAST breakpoints (http://www.eucast.org)







- amoxicillin: 0 % > R
  but at high dose
- cefuroxime: 13 % > R

- telithromycin: 8 % >R
- clarithromycin: 35 > R

- levofloxacin: 1 % > R
  bur at high dose
- moxifloxacin: 0 % R

Lismond et al (2008) ECCMID P1747
(Similar observations in two other Belgian independent centres [Louvain - Pasteur Institute])

Conclusions

- The safety profile of "respiratory" fluoroquinolones remains largely acceptable and not worse than that of several other comparators if SmPC (labelling) warnings are taken in due consideration
  - Hepatic events, bullous skin, and clinical cardiac events are not different from comparators (incl. levofloxacin)
  - ➔ Consistent with peer-reviewed published literature
- Restricting moxifloxacin specifically is, in my view, counter-productive and against Public Health interest because it will drive use of the remaining antibacterials with their own risks
  - ➔ safety profiles of high doses of beta-lactams and levofloxacin are potentially worse than that of moxifloxacin;
  - ➔ macrolides or tetracyclines are no longer an option in many EU countries and are not free from toxicities.

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

Note:

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

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* Bauraind et al. JAMA. 2004 Nov 24;292(20):2468-70.

Backup slides

Stevens Johnson syndrome and toxic epidermal necrolysis caused by antibiotics

Rare effect (based on labelling or SPC)
Results of a PubMed search for case report (July 2008) yields

1 for moxifloxacin [a] ; ~ 25 for other fluoroquinolones; ~ 40 for β-lactams;
~ 6 for macrolides; ~ 15 for cotrimoxazole; ~ 13 for vancomycin

[a] Nori *et al*., Arch Dermatol. 2004;140:1537-8

Relative risk for Stevens Johnson syndrome and toxic epidermal necrolysis (incidence calculated based on data from reporting systems)

Antibiotic class	Case patients	Non-case patients	Relative risk (CI 95 %)
macrolides	6 / 245	5 / 1147	1.6 (0.2-13)
aminopenicillins	15 / 245	12 / 1147	6.7 (2.5-18)
fluoroquinolones *	11/ 245	5 / 1147	10 (2.6-38)
cephalosporins	14 / 245	3 / 1147	14 (3.2-59)
sulfonamides	32 / 245	1 / 1147	172 (75-396)

* not including moxifloxacin (not yet commercialized)

Roujeau et al (1995) NEJM 333:1600-7

Resistance of *S. pneumoniae* in Europe

Table 1 Antimicrobial resistance rates in *Streptococcus pneumoniae* in 15 European countries during 2004–2005

Country	No. of isolates	Percent resistant (I+R)[a]					
		Penicillin	Erythromycin	Tetracycline	TMP-SMX	Ciprofloxacin	MDR[b]
France	309	49.2	50.1	41.1	35	0.7	40.8
Greece	7	57.1	57.1	28.6	42.9	0	42.9
Italy	208	24.5	48.1	37.5	42.3	7.2	18.8
Slovak Republic	44	52.3	36.4	31.8	45.5	2.3	34.1
Croatia	68	30.9	19.1	20.6	41.2	0	14.7
Spain	232	40.1	30.2	27.6	35.8	1.7	26.7
Poland	137	23.4	20.4	28.5	48.2	4.4	13.9
Slovenia	103	25.2	11.7	14.6	29.1	1	8.7
Finland	91	25.3	27.5	16.5	22	6.6	14.3
UK	135	8.2	16.3	6.7	9.6	0.7	4.4
Germany	185	5.4	16.8	11.9	13	0	3.8
Sweden	170	9.4	8.8	10	10.6	2.4	6.5
Norway	72	5.6	6.9	9.7	8.3	1.4	4.2
Denmark	89	0	8.9	1.1	6.7	1.1	0
Netherlands	124	4	11.3	10.5	10.5	0.8	3.2
Total	1974	24.0	24.6	19.8	26.7	2.0	15.8

[a] Resistance based on MIC interpretive criteria of CLSI [11]

[b] Penicillin resistance (I+R) plus resistance (I+R) to at least two other classes of antimicrobial agents

I Intermediate, *R* resistant, *TMP-SMX* trimethoprim-sulfamethoxazole, *MDR* multidrug resistant

Eucast MIC breakpoints (mg/L) http://www.eucast.org

- **Definitions**:
  - **Clinically Susceptible (S)**
    a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic succes
  - **Clinically Intermediate (I)**
    a micro-organism is defined as intermediate by a level of antimicrobial agent activity associated with uncertain therapeutic effect. It implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physically concentrated or when a high dosage of drug can be used; it also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.
  - **Clinically Resistant (R)**
    a micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure**.**

Drug	S (susceptible)	R (resistant)
amoxicillin	0.5	2 [1]
cefuroxime	0.5	1 [2]
telithromycin	0.25	0.5
clarithromycin	0.25	0.5
levofloxacin	2 [3]	2 [3]
moxifloxacin	0.5	0.5

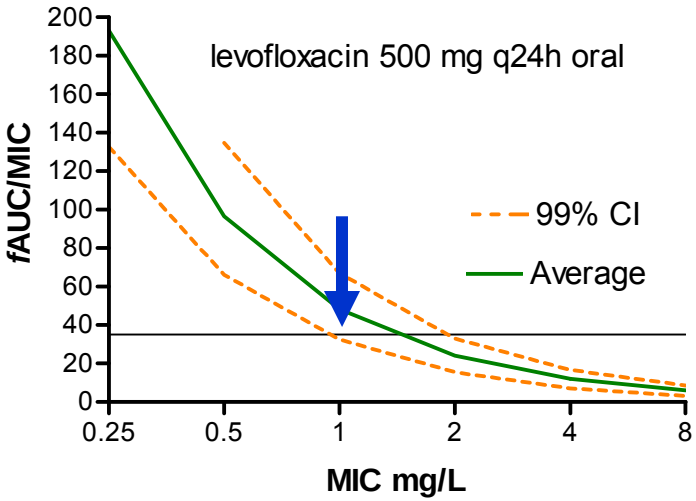
[1] from 0.5 to 2 if dose is increased to 3 g/day

[2] lower proposed value (0.25 mg/L; still unofficial) for cefuroxime axetil (oral form) on account of its bioavailability

[3] values for levofloxacin relate to high dose therapy (0.750 to 1 g/day).

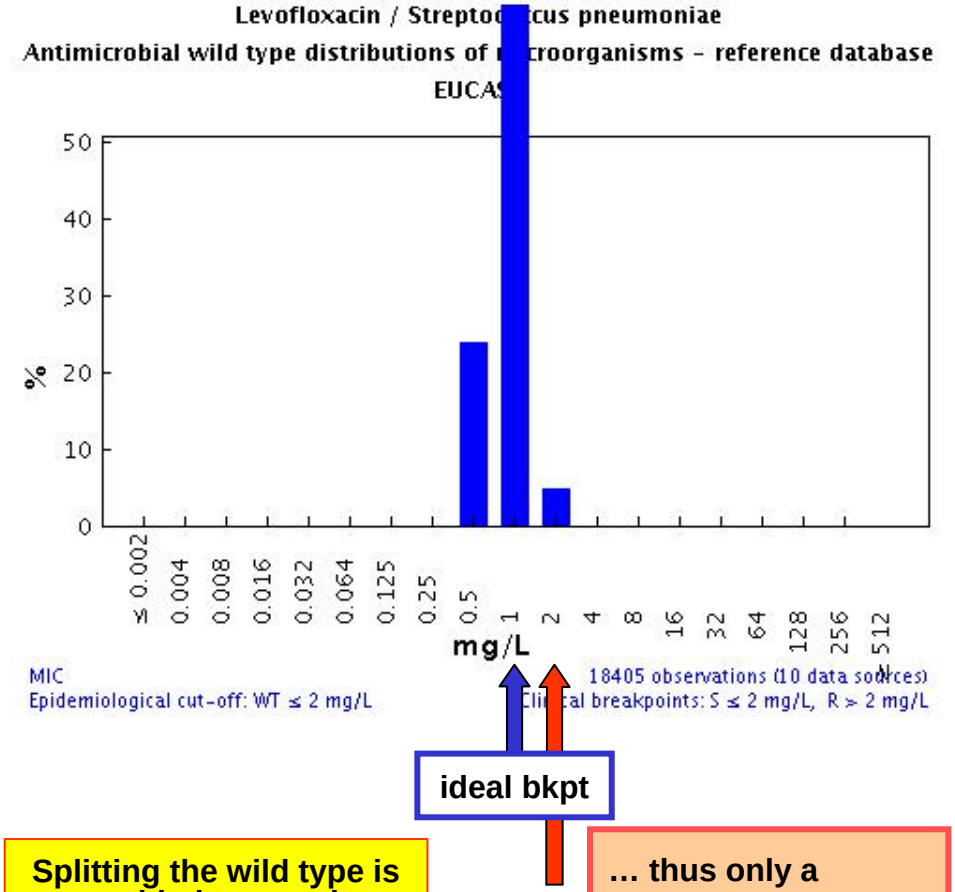
EUCAST Breakpoint setting for levofloxacin
(from EUCAST web site)

PK/PD approach for efficacy
(f AUC/MIC > 35)
with Monte Carlo simulation



"Minimum requirement for S-category" is that the highest MIC value of the wild type MIC-distribution is consistent with the MIC derived from the PK/PD index needed for optimal efficacy based on free drug".

S = 1 mg/L



Splitting the wild type is avoided to permit reproducible susceptibility testing !

… thus only a breakpoint of 2 mg/L was acceptable with a footnote that this was based on high dose therapy.