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Moxifloxacin

In Uncomplicated Skin and Skin Structure Infections

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Contents

Abstract

▲ Moxifloxacin is a fluoroquinolone antibacterial agent which attains good penetration into peripheral tissues and inflammatory fluids. The drug shows good *in vitro* activity against staphylococci and streptococci. Moxifloxacin is therefore a suitable option for the treatment of uncomplicated skin and skin structure infections of bacterial origin.

▲ In clinical trials, moxifloxacin was as effective as cephalexin in the treatment of uncomplicated skin and skin structure infections in patients aged ≥18 years. Moxifloxacin 400mg once daily or cephalexin 500mg three times daily for 7 days both resulted in clinical resolution in 84% of patients during a double-blind, randomised trial in 401 patients (intent-to-treat). The main infectious agent in this study was *Staphylococcus aureus*. Similar results were obtained in two other randomised, double-blind trials published as abstracts.

▲ The bioavailability of moxifloxacin is substantially reduced by coadministration with antacids or iron preparations. Moxifloxacin, however, does not show pharmacokinetic interaction with theophylline or warfarin. Dosage adjustments are not required in patients with renal impairment or in patients with mild to moderate hepatic insufficiency.

▲ The most common adverse events reported during moxifloxacin treatment are gastrointestinal disturbances. The potential for photosensitivity reactions during moxifloxacin treatment is low.

Features and properties of moxifloxacin	
New indication	
Uncomplicated skin and skin structure infections	
Mechanism of action	
Bacterial DNA gyrase / topoisomerase inhibitor	
Pharmacokinetics (single oral dose 400mg)	
C_{max}	3.1 mg/L
AUC	36.1 mg • h/L
Route of elimination	Biliary/faecal, metabolic (glucuronide and sulfate conjugation)
Elimination half-life	11.5 - 15.6h
Dosage and administration	
Route of administration	oral or intravenous infusion
Dosage	400 mg/day for 7 days
No dosage adjustment is required in patients with impaired kidney function or hepatic insufficiency	
Drug interactions	
Drugs decreasing moxifloxacin absorption	Antacids, iron preparations
Drugs with no moxifloxacin interaction	Theophylline, ranitidine, probenecid, warfarin, oral contraceptives, itraconazole
Adverse events	
Most frequent	Gastrointestinal disturbances

1. Introduction

Moxifloxacin is an 8-methoxy fluoroquinolone antibacterial agent that is approved for the treatment of bacterial infections of the respiratory tract including sinusitis, community acquired pneumonia and acute exacerbations of chronic bronchitis. The use of the drug in these indications has been extensively reviewed in *Drugs*.[1] Moxifloxacin was recently approved for use in uncomplicated skin and skin structure infections, which forms the basis for the present review. Uncomplicated bacterial infections of the skin and skin structures predominantly involve *Staphylococcus aureus* and *Streptococcus pyogenes* (group A streptococci).[2,3]

2. Antibacterial Activity

Moxifloxacin is a fluoroquinolone antibacterial agent. The drug inhibits growth of susceptible bacteria by inhibiting bacterial DNA topoisomerases, which are involved in bacterial DNA replication, transcription, repair and recombination.[4] Moxifloxacin is active against a broad range of bacteria, including Gram-positive, Gram-negative and atypical respiratory pathogens. The *in vitro* antibacterial properties of moxifloxacin have been extensively reviewed in *Drugs*.[1] This profile presents a brief overview of the *in vitro* antibacterial activity of moxifloxacin against bacteria most frequently found in uncomplicated skin and skin structure infections.[3] Antibacterial activity refers to minimum inhibitory concentrations (MICs) determined using National Committee for Clinical Laboratory Standards (NCCLS) approved broth or agar dilution techniques.[5-8] MIC_{90} values are the minimum concentration of a given drug required to inhibit the growth of 90% of strains of a given species.

• The proposed MIC breakpoint values for moxifloxacin indicative of susceptibility, intermediate susceptibility and resistance, respectively are ≤2, 4 and ≥8 mg/L for *Staphylococcus* species and ≤1, 2 and ≥4 mg/L for *Streptococcus* species.[4] Confirmed (NCCLS) breakpoint values for ciprofloxacin are: susceptible ≤1 mg/L, intermediate 2 mg/L and resistant ≥4 mg/L for *S. aureus*.[9] NCCLS guidelines do not provide ciprofloxacin breakpoint values for streptococci.[9]

Gram-Positive Cocci

Staphylococci

• As presented in figure 1a, methicillin-susceptible *S. aureus* (MSSA) isolates are susceptible to moxifloxacin *in vitro* (MIC_{90} 0.06 mg/L).[10] Methicillin-resistant *S. aureus* (MRSA) isolates tested, however, showed a MIC_{90} value of 1 mg/L. MIC_{90} values for ciprofloxacin against these isolates were 0.5 mg/L for MSSA and >16 mg/L for MRSA.

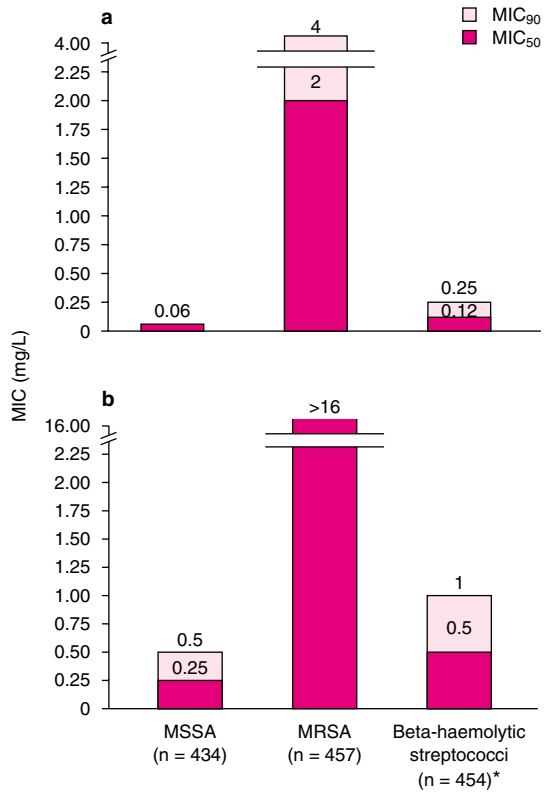

Fig. 1. *In vitro* activity of moxifloxacin (a) and ciprofloxacin (b) against *Staphylococcus aureus* and β-haemolytic streptococci isolates from Europe (14 countries), Israel and South Africa.[10] **MIC_{90}** = minimum concentration required to inhibit the growth of 90% of strains; **MIC_{50}** = minimum concentration required to inhibit the growth of 50% of strains; **MRSA** = methicillin-resistant *S. aureus*; **MSSA** = methicillin-susceptible *S. aureus*. * Includes 181 group A streptococci (*Streptococcus pyogenes*), 210 group B, 18 group C, and 45 group G strains.

These values were obtained using clinical isolates from Europe (14 countries), Israel and South Africa.[10]

• The MIC_{90} for moxifloxacin against 189 MRSA isolates resistant to ciprofloxacin was 2 mg/L (international study).[11] For 16 methicillin-susceptible, but ciprofloxacin-resistant, strains of *S. aureus* a MIC_{90} of 1 mg/L has been reported.[11] The MIC_{90} value of moxifloxacin against 53 ciprofloxacin-resistant *S. aureus* isolates from the US was 4 mg/L; of these isolates, 68% were susceptible to moxifloxacin and 47% were susceptible to ciprofloxacin.[12]

Streptococci

• Moxifloxacin shows good *in vitro* activity against β-haemolytic streptococci in general, as demonstrated by the previously mentioned international study [figure 1, MIC_{90} 0.25 mg/L for all 454 strains tested; 181 Group A streptococci (*S. pyogenes*), 210 group B, 18 group C, and 45 group G strains]. The MIC_{90} value for ciprofloxacin against these isolates was 1 mg/L.[10]

• In a study of 30 clinical isolates of *S. pyogenes* obtained in the US, the MIC_{90} value was 0.25 mg/L for moxifloxacin and 0.5 mg/L for ciprofloxacin.[13]

Bactericidal Activity and Postantibiotic Effects

• In time-kill assays, moxifloxacin showed bactericidal effects (2 to 3 $\log_{10}$ decrease in colony forming units per ml) against *S. aureus* [14,15] and *S. pyogenes*[15] at concentrations of 2 to 10 × MIC.

• Moxifloxacin showed a postantibiotic effect (PAE) of 1.4 to 2.7 hours at 4 × MIC against *S. aureus*. At 1 × MIC, the PAE ranged from 0.7 to 1.8 hours.[15,16]

• Exposure of *S. aureus* strains to fluctuating moxifloxacin concentrations (simulating therapeutic human serum concentrations) resulted in at least 3 $\log_{10}$ kill (99.9 %) within 5 hours.[15,17,18]

Resistance

• As reviewed in detail in *Drugs*,[1] proposed mechanisms for resistance to fluoroquinolones include mutations in genes encoding for DNA gyrase (*gyrA* and *gyrB*), DNA topoisomerase IV (*parC* and *parE*) and in a gene (*norA*) encoding for an efflux pump which reduces fluoroquinolone accumulation in bacteria. High-level resistance results from multiple resistance mechanisms.[1]

• The gyrase inhibitory activity of moxifloxacin appears to be less affected by genetic mutations than that of three other fluoroquinolones in *Escherichia coli*.[19] A double mutation in the gene encoding for DNA gyrase (*gyrA*) resulted in IC_{50} (concentration at which the enzyme is inhibited by 50%) values of ≥1500 mg/L for ciprofloxacin, sparfloxacin and norfloxacin, whereas those of moxifloxacin and clinafloxacin were 37.6 and 2.78 mg/L, respectively. Single mutations in *gyrA* had little or no effect on IC_{50} values for any of the fluoroquinolones.[19]

• Of five fluoroquinolones tested, moxifloxacin was the least affected by mutations in *gyrA*, *gyrB*, *parC* or *parE* in *S. aureus* strains (n = 116).[20] The rank order of MICs for these isolates was moxifloxacin < sparfloxacin < levofloxacin < ofloxacin < ciprofloxacin.[20]

• A study performed using 102 clinical *S. aureus* isolates suggests that the activity of the hydrophobic drugs moxifloxacin and sparfloxacin is less affected by the multi-drug efflux transporter *norA* than that of ciprofloxacin.[21] Inhibition of the *norA* efflux pump with reserpine (allowing drug accumulation) resulted in a 1- to 4-fold reduction in MIC for ciprofloxacin and in a 1- to 2-fold MIC reduction for moxifloxacin and sparfloxacin.[21]

3. Pharmacokinetic Profile

The pharmacokinetic profile of moxifloxacin has been extensively reviewed in *Drugs*.[1] A brief overview is presented here. Pharmacokinetic data reviewed in the following paragraphs are focused on the distribution of moxifloxacin to skin and skin structures. Generally, available studies suggest that moxifloxacin is rapidly absorbed and penetrates peripheral tissues and inflammatory fluid well.[22,23]

Absorption and Distribution

• The absolute bioavailability of moxifloxacin after a single 400mg oral dose was 86% (geometric mean) in 12 healthy volunteers.[24] The pharmacokinetics of moxifloxacin are not markedly affected when the drug is taken with food; the drug can therefore be given with or without food (see section 6).[25] Moreover, dairy products do not affect the absorption of moxifloxacin.[26]

• The mean area under the concentration-time curve (AUC) determined in plasma after a single oral moxifloxacin dose (400mg) was 36.1 mg • h/L in 372 healthy volunteers. The mean peak plasma concentration (C_{max}) was 3.1 mg/L.[4]

• During a randomised, nonblind crossover (washout at least 1 week) study in 12 healthy volunteers, the AUC_{12h} value for plasma, cantharides-induced skin blister fluid and subcutis (microdialysis, i.e. unbound fraction) were 19.8, 12.3 and 8.0 mg • h/L after a single oral dose (400mg). C_{max} values in these compartments were 3.2, 1.6 and 0.9 mg/L, respectively.[22]

• In seven healthy volunteers, a single oral dose (400mg) of moxifloxacin resulted in an AUC_{∞} of 45.5 and 40.3 mg • h/L and a C_{max} of 5 and 2.6 mg/L for plasma and skin blister fluid, respectively. The average penetration into skin blister fluid was 83.5%.[23]

Metabolism and Elimination

• The elimination half-life of a single 400mg dose of moxifloxacin in 372 healthy volunteers was 11.5 to 15.6h.[4] Moxifloxacin is metabolised via glucuronide and sulphate conjugation.[24] The drug is mainly excreted in faeces (sulphate conjugate) and urine (glucuronide conjugate).[24] About 35% of the administered dose was found in urine and about 61% in faeces.[24]

• The cytochrome P450 (CYP) system is not involved in the metabolism of moxifloxacin.[4,24,27]

• The pharmacokinetics of moxifloxacin are unlikely to be significantly affected by renal impairment; no dosage adjustments are required in these patients (see section 6).[28] Moreover, the effects of mild to moderate hepatic insufficiency on moxifloxacin do not warrant dosage adjustments in patients with this condition (see section 6). The pharmacokinetics of moxifloxacin in patients with severe hepatic insufficiency have not been studied.[4]

Drug-Drug Interactions

• The bioavailability of moxifloxacin is substantially (23 to 60% reduction in AUC) affected by coadministration with aluminium/magnesium-containing antacids or iron preparations (See section 6).[29-31] The extent of moxifloxacin absorption is not affected by calcium, although the absorption rate is slightly reduced.[32]

• As the cytochrome P450 system is not involved in moxifloxacin metabolism,[4,24,27] the drug has low potential for metabolic drug-drug interactions with agents metabolised by CYPs. No clinically significant pharmacokinetic drug-drug interactions have been reported after concomitant administration of moxifloxacin with warfarin,[27] theophylline,[33] digoxin,[27] glyburide,[27] ranitidine,[29] oral contraceptives,[27] morphine[34] or probenecid.[35]

4. Therapeutic Trials

The results of a small randomised pilot study[36] suggest that once daily moxifloxacin 400mg is as effective as cephalexin 500mg three times daily in the treatment of patients with uncomplicated skin and skin structure infections. Hence, larger studies were conducted to confirm these preliminary findings.[37,38] Antibacterial drugs were administered orally during all trials.

• Oral moxifloxacin was as effective as cephalexin in the treatment of uncomplicated skin infections in adults. During a double-blind, randomised, multicentre trial, patients received either oral moxifloxacin (400mg once daily for 7 days) or cephalexin (500mg 3 times daily for 7 days). The clinical response (primary outcome) assessed 7 to 21 days after treatment is presented in figure 2 (intent-to-treat analysis, n = 401). Based on these results, the null-hypothesis that the cephalexin group

had a resolution rate at least 10% higher than that of the moxifloxacin group was rejected. Clinical failure was documented in ≤10% of patients in the intent-to-treat population.[37]

• The main specific infections during this trial were trauma, cellulitis and impetigo. About 70% of infections were spontaneous, and approximately 30% followed a wound. The main infectious agent in microbiologically evaluable patients (n = 125) was *S. aureus* (78% of 137 isolates). Other Gram-positive cocci were *S. pyogenes*, *S. agalactiae* and non-group A or B streptococci. The eradication rates for *S. aureus* in microbiologically evaluable patients were comparable for moxifloxacin and cephalexin, i.e. 92 and 93%. The eradication rates for the less frequently encountered bacteria were 2 out of 2 and 3 out of 4, respectively, for *S. pyogenes*, 6 out of 7 and 4 out of 5 for *S. agalactiae* and 1 out of 1 and 2 out of 2 for non group A or B streptococci. [37]

• Patients enrolled in this trial were ≥18 years of age. Inclusion criteria were fever (>38°C), oedema, erythema, purulent exudate, local pain or local warmth. A pretreatment specimen from the site of infection was required within 24 hours of inclusion into the study. Patients were excluded if they had serious mixed infections (diabetic foot infections, decubitus ulcers or postsurgical infections). Further exclusion criteria were skin and skin structure infections present for more than 7 days and antimicrobial therapy up to the day of enrolment (topical or systemic). Patients with neutropenia (neutrophil count <1000/μl), a CD4 count <200/μl or other conditions associated with a significantly compromised host defence were also excluded from the trial. Furthermore, patients with suspected underlying osteomyelitis or *Pseudomonas aeruginosa* infections were excluded. Lastly, patients with known significant renal insufficiency, liver impairment, prolonged QT_c intervals or patients that were receiving QT_c interval-prolonging antiarrhythmic drugs or other agents known to cause an increased QT_c interval did not qualify for inclusion.[37]

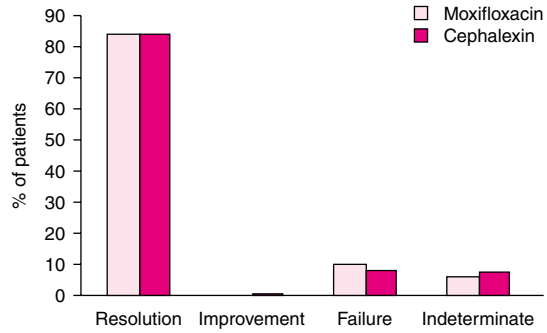

Fig. 2. Clinical response to moxifloxacin (400mg once daily for 7 days) compared with cephalexin (500mg 3 times daily for 7 days) 7 to 21 days after the end of treatment in patients with uncomplicated infections of the skin. Intent-to-treat values from 401 patients receiving at least one dose of the test drugs during a randomised, double-blind, multicentre trial.[37]

• Similar results were obtained during a double-blind, multicentre trial (published as an abstract). Adult patients with mild to moderate uncomplicated skin and skin structure infections (inclusion/exclusion criteria not specified) were randomised to receive either moxifloxacin (400mg once daily) or cephalexin (500mg 3 times daily) with or without metronidazole (400mg 3 times daily, % of patients not stated) for 5 to 14 days. Clinical resolution (not defined) was achieved in 92.7% of 191 evaluable patients for moxifloxacin and in 92.8% of 194 of those receiving cephalexin. Bacteriological success (not defined) was accomplished in 89% of 100 and 93.8% of 105 bacteriologically evaluable patients treated with moxifloxacin and cephalexin, respectively. The predominant infectious agents were *S. aureus* and *Streptococcus* spp. The eradication rates for *S. aureus* were 91.7 and 89.3% for moxifloxacin and cephalexin.[38]

5. Tolerability

The tolerability profile of moxifloxacin has been reviewed previously in *Drugs*.[1] In this article, a brief overview of the adverse events most frequently reported during moxifloxacin treatment is presented.

• Data from 7900 patients (with various types of infections) treated with moxifloxacin (of which at least 6700 patients received 400 mg/day) show that adverse events associated with this drug are mostly mild or moderate. Only 3.6% of patients discontinued treatment with oral moxifloxacin because of a drug-related adverse events (compared with 5.7% of patients treated with intravenous moxifloxacin followed by the oral formulation).[4] The most frequently observed adverse events were nausea (7%), diarrhoea (6%) and dizziness (3%).[4]

• Some quinolones are associated with QT_c interval prolongation. Moxifloxacin treatment resulted in a small and clinically insignificant QT_c interval prolongation in 465 of 787 patients from whom baseline and during-treatment ECG data were recorded. Using a worldwide data pool, an average QT_c interval prolongation of approximately 6 msec was observed during moxifloxacin treatment.[39]

• The incidence of photosensitivity reactions during moxifloxacin treatment is low. Photosensitivity, recorded as an adverse event, occurred in 4 of 5189 patients treated with moxifloxacin. During controlled trials, 1 of 4564 patients receiving moxifloxacin and 2 of 3689 patients receiving comparator medications experienced mild drug-related photosensitivity events.[39]

6. Dosage and Administration

• In the US, moxifloxacin (both as oral and intravenous formulation) is approved for the treatment of uncomplicated skin and skin structure infections caused by *S. aureus* or *S. pyogenes* in patients ≥18 years of age.[4]

• For the treatment of uncomplicated skin and skin structure infections, moxifloxacin is administered at a dosage of 400 mg/day (orally or intravenously) for 7 days.[4] Oral doses of moxifloxacin should be given at least 4 hours before or 8 hours after antacids containing magnesium or aluminium, as well as sucralfate. Similar precautions are required for patients taking moxifloxacin whilst receiving metal cations such as iron, multivitamin preparations with zinc or didanosine buffered tablets or the paediatric powder for oral solution.[4] The drug, however, can be taken with or without food.[4]

• Dosage adjustments are not required in patients with renal impairment or in patients with mild to moderate hepatic insufficiency (see section on Metabolism and Elimination).[4]

• Moxifloxacin is not recommended for use in children or in pregnant women.[4]

• Because of the possibility of synergistic QT_c interval prolongation with moxifloxacin (see section 5), class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic drugs should not be coadministered with moxifloxacin.[4]

7. Moxifloxacin: Current Status in the Treatment of Uncomplicated Skin and Skin Structure Infections of Bacterial Origin

Moxifloxacin (oral and intravenous infusion) has recently been approved for the treatment of uncomplicated skin and skin structure infections in patients ≥18 years of age in the US. In two well designed trials (of which one is fully published), moxifloxacin was as effective as cephalexin in the treatment of uncomplicated skin and skin structure infections.

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