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# Moxifloxacin and its therapeutic uses in animals: An overview

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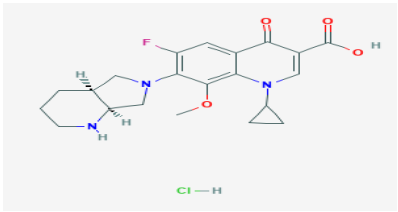
**Abstract**
Fluoroquinolones are a group of antibiotics that have increased in numbers in recent years. Their usefulness has greatly expanded with the introduction of several new quinolones having improved properties compared to older members. Moxifloxacin is a new fluoroquinolone antibiotic used to treat a number of bacterial infections in animals. It includes urinary tract infections, pneumonia, conjunctivitis, endocarditis, tuberculosis, respiratory tract infections, cellulitis, anthrax, intra-abdominal infections, endocarditis, meningitis and sinusitis. As compare to older fluoroquinolones like enrofloxacin, ciprofloxacin and levofloxacin, moxifloxacin is found highly effective, bioavailable and with less adverse effects. It is well absorbed after different routes of administration like intravenous, intramuscular and oral with an absolute bioavailability of 95% and the plasma half life is between 8.15-11.70. This review article will explain about the different uses of moxifloxacin in different disease conditions.

**Keywords:** Fluoroquinolones, moxifloxacin, uses

## Introduction
Moxifloxacin is a fourth generation fluoroquinolone with a methoxy group in the C-8 position and C-7 side chain. Moxifloxacin has *in vitro* activity similar to that of older Fluoroquinolones against Gram-negative bacteria, but shows improved activity against Gram-positive cocci, aerobic, anaerobic intracellular bacteria, as well as atypical organisms, such as Mycoplasma and Chlamydia, compared with older Fluoroquinolones. As a member of the fluoroquinolone group, moxifloxacin acts on bacterial DNA topoisomerases II and IV [1, 16, 17, 28].
Moxifloxacin was discovered in 1999 by addition of an Azabicyclo-substitution at C-7, which is associated with activity against a broad spectrum of pathogens, encompassing Gram-negative and Gram-positive bacteria [4].

## Physico-chemical properties of Moxifloxacin hydrochloride
Moxifloxacin is a new, enantiomerically pure 1-cyclopropyl-7-(2,8 diazabicyclo [4.3.0] nonane)-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3 quinoline carboxylic acid hydrochloride which has potent activity against an extensive spectrum of bacteria [36]. It is a slightly yellow to yellow crystalline substance with a molecular weight of 401.431 $g.mol^{-1}$. Its empirical formula is $C_{21}H_{24}FN_3O_4$. It is soluble in 0.1 $mol.L^{-1}$ NaOH; sparingly soluble in water and methanol and slightly soluble in 0.1 $mol.L^{-1}$ HCI, N,N-dimethylformamide and ethanol.
Moxifloxacin, also known as Bay12-8039, is a new oral 8- methoxyfluoroquinolone that has significant use in the treatment of bacterial infections of the skin. It differs from the other quinolones by having a methoxy radical at the 8-position, with an S, S-configured diazabicyclonoyl ring moiety at the 7-position and by having improved anti-bacterial activity over other similar quinolones [27]. The chemical structure of moxifloxacin hydrochloride is depicted in Figure 1.



**(Source:** PubChem Database)

**Fig 1:** General structure of Moxifloxacin hydrochloride

**Mechanism of action**

The fourth generation quinolones of which moxifloxacin is the only readily available agent have the most potent activity against gram-positive bacteria, especially against the pneumococcus, and anaerobes, and still retain their excellent activity against aerobic gram-negative pathogens. Furthermore, moxifloxacin possesses a C-8 methoxy group and a bulky side chain at C-7. The C-8 methoxy group has potent activity against both topoisomerase II (DNA gyrase) and topoisomerase IV, a capability that allows moxifloxacin to kill resting bacterial cells as well as those that are actively multiplying. This may delay or prevent the emergence of bacterial resistance to the quinolones [2].

Moxifloxacin have 2 enzyme targets, DNA gyrase and topoisomerase IV, in the bacterial cell; both of these targets are essential for bacterial DNA replication. DNA gyrase is a tetramer composed of 2 GyrA and 2 GyrB subunits. Topoisomerase IV is similarly structured and is composed of 2 ParC and 2 ParE subunits, which are also known as GrlA and GrlB, respectively, in *Staphylococcus aureus*. ParC is homologous to GyrA, and ParE is homologous to GyrB. DNA gyrase is the only bacterial enzyme that introduces negative superhelical twists into DNA. Negatively supertwisted DNA is important for initiation of DNA replication. DNA gyrase also facilitates DNA replication by removing positive superhelical twists that accumulate ahead of the replication fork or as a result of the transcription of certain genes. Topoisomerase IV acts in the terminal stages of DNA replication, allowing for the separation of interlinked daughter chromosomes so that segregation into daughter cells can occur. Moxifloxacin inhibit these enzymes by stabilizing either the DNA–DNA gyrase complex or the DNA–topoisomerase IV complex. The stabilized DNA–DNA gyrase complex blocks movement of the replication fork, causing formerly reversible DNA-enzyme complexes to become irreversible. Damage to DNA and the generation of DNA strand breaks then trigger a set of events, as yet poorly defined, that follow the rapid inhibition of DNA synthesis and result in eventual cell death [20].

**Antimicrobial spectrum**

Moxifloxacin is a broad-spectrum synthetic antimicrobial agent with excellent Gram-positive activity and good Gram-negative activity (Parish *et al.*, 2001). It exhibits concentration-dependent activity against both Gram-positive and Gram-negative bacteria [12].

Moxifloxacin, have *in vitro* potency against a broad spectrum of anaerobic bacteria and appear to have the potential to treat mixed aerobic and anaerobic infections [34]. It is also found active against *Leuconostoc* and *Rhodococcus* species [23].

The antimicrobial spectrum of moxifloxacin includes gram-positive cocci and anaerobic bacteria that may be resistant to other quinolones. Because other veterinary fluoroquinolones are preferred for initial use (enrofloxacin, orbifloxacin, danofloxacin, and marbofloxacin), moxifloxacin use is not common [26].

Moxifloxacin is two to sixteen fold more active than ciprofloxacin and ofloxacin against non-fermenting bacteria (except *Pseudomonas spp*. and *Burkholderia cepacia*), staphylococci, streptococci, enterococci and anaerobes, but only half as active as ciprofloxacin against enterobacteriacae. Moxifloxacin is also more active than ciprofloxacin against *Chlamydia trochamatis* and *Chlamydia pneumonia* and mycoplasmas [37].

Compared with ciprofloxacin and levofloxacin, moxifloxacin have greater *in vitro* activity against *S. aureus* and some Enterococcus strains. Moxifloxacin, have exceptional activity against intracellular respiratory pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* [25].

The MICs ($\mu g.ml^{-1}$) of moxifloxacin, as reported by several workers, against various pathogenic microbes are presented in Table 1. The Clinical and Laboratory Standards Institute (CLSI), USA and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), Sweden (EU), MICs ($\mu g.ml^{-1}$) and PK-PD breakpoint of moxifloxacin against pathogenic microbes have been tabulated in Table 2.

**Table 1:** MIC ($\mu g.ml^{-1}$) of moxifloxacin against pathogenic microbes

| Pathogen | $MIC_{50}$ ($\mu g.ml^{-1}$) | $MIC_{90}$ ($\mu g.ml^{-1}$) | References |
|---|---|---|---|
| **Gram-positive organisms** | | | |
| *Clostridium clostridiiforme* | 8.0 | 8.0 | Stein and Goldstein, 2006 [34] |
| *Clostridium perfringens* | 0.5 | 0.5 | Stein and Goldstein, 2006 [34] |
| *Enterococcus faecium* | - | 1-4 | Saravolatz and Leggett, 2003 [31] |
| *Enterococcus faecalis* | - | 1.0 | Saravolatz and Leggett, 2003 [31] |
| *Peptostreptococcus micros* | 0.25 | 0.5 | Stein and Goldstein, 2006 [34] |
| *Staphylococcus aureus* | 0.032 | 0.252 | Sueke *et al.*, 2010 [35] |
| Methicillin-resistant *S. aureus* | - | 4.0 | Saravolatz and Leggett, 2003 [31] |
| *Mycobacterium intracellulare* | 0.5 | 4.0 | Fang *et al.*, 2017 [15] |
| *Mycobacterium avium* | 0.5 | 1.0 | Fang *et al.*, 2017 [15] |
| *Mycobacterium abscessus* | 4.0 | 8.0 | Fang *et al.*, 2017 [15] |
| *Mycobacterium gordonae* | 0.5 | 4.0 | Fang *et al.*, 2017 [15] |
| *Staphylococcus epidermis* | - | 0.13 | Saravolatz and Leggett, 2003 [31] |
| *Streptococcus pyogenes* | - | 0.25 | Saravolatz and Leggett, 2003 [31] |
| **Gram-negative organism** | | | |
| *Bacteroides distasonis* | 0.5 | 8.0 | Stein and Goldstein, 2006 [34] |
| *Bacteroides fragilis* | 0.5 | 2.0 | Stein and Goldstein, 2006 [34] |
| *Bacteroides tectum* | 0.06 | 0.125 | Stein and Goldstein, 2006 [34] |
| *Bacteroides thetaiotaomicron* | 1.0 | 4.0 | Stein and Goldstein, 2006 [34] |
| *Burkholderia cepacia* | - | 256 | Saravolatz and Leggett, 2003 [31] |
| *Campylobacter jejuni* | - | 0.125 | Saravolatz and Leggett, 2003 [31] |
| *Enterobacteriaceae* | 0.064 | 0.250 | Sueke *et al.*, 2010 [35] |
| *Enterobacter cloacae* | - | 0.06 | Saravolatz and Leggett, 2003 [31] |

| | | | |
|---|---|---|---|
| *Escherichia coli* | 0.03 | 0.06 | Edmiston *et al.*, 2004 [13] |
| *Fusobacterium nucleatum* | 0.125 | 0.25 | Stein and Goldstein, 2006 [34] |
| *Helicobacter pylori* | - | 0.125 | Saravolatz and Leggett, 2003 [31] |
| *Klebsiella pneumonia* | 0.094 | >32 | Grillon *et al.*, 2016 [19] |
| *Legionella pneumophila* | - | 0.015 | Saravolatz and Leggett, 2003 [31]; Ball, 2000 [6] |
| *Moraxella catarrhalis* | - | 0.03 | Saravolatz and Leggett, 2003 [31] |
| *Neisseria gonorrhoeae* | - | 0.016 | Saravolatz and Leggett, 2003 [31] |
| *Porphyromonas saccharolytica* | 0.5 | 0.5 | Stein and Goldstein, 2006 [34] |
| *Prevotella melaninogenica* | 0.5 | 1.0 | Stein and Goldstein, 2006 [34] |
| *Prevotella intermedia* | 0.25 | 0.5 | Stein and Goldstein, 2006 [34] |
| *Pseudomonas aeruginosa* | 1.5 | >32 | Grillon *et al.*, 2016 [19] |
| *Salmonella* species | - | 0.13 | Saravolatz and Leggett, 2003 [31] |
| *Serratia marcescens* | - | 8 | Saravolatz and Leggett, 2003 [31] |
| *Stenotrophomonas maltophilia* | 0.75 | 6 | Grillon *et al.*, 2016 [19] |
| **Atypical bacteria** | | | |
| *Mycoplasma pneumonia* | - | 0.06-0.12 | Saravolatz and Leggett, 2003 [31]; Ball, 2000 [6] |
| *Chlamydia pneumonia* | - | 0.06-1 | Ball, 2000 [6] |
| *Chlamydia trachomatis* | - | 0.03-0.125 | Saravolatz and Leggett, 2003 [31] |

**Table 2:** CLSI and EUCAST MIC (µg.ml$^{-1}$) and PK-PD breakpoint of moxifloxacin against pathogenic microbes

| Pathogen | MIC(µg.ml$^{-1}$) | | | References |
|---|---|---|---|---|
| | Susceptible | Intermediate | Resistant | |
| *Staphylococcus species* | ≤ 0.5 | 1 | ≥ 2 | CLSI, 2018 [10] |
| | < 0.25 | - | > 0.25 | EUCAST, 2018 [14] |
| *Haemophilus influenza* | ≤ 1 | - | - | CLSI, 2016 [9] |
| | < 0.125 | - | > 0.125 | EUCAST, 2018 [14] |
| *Streptococcus pneumoniae* | ≤ 1 | 2 | ≥ 4 | CLSI, 2018 [11] |
| | < 0.5 | - | > 0.5 | EUCAST, 2018 [14] |
| *Clostridium difficile* | ≤ 2 | 4 | ≥ 8 | CLSI, 2012 [8] |
| PK-PD (Non species related breakpoints) | < 0.25 | - | > 0.25 | EUCAST, 2018 [14] |

**Bacterial resistance**

Bacterial resistance to quinolones or Fluoroquinolones is usually accomplished by interference with bacterial DNA metabolism mediated by mutations in bacterial DNA gyrase (gyr A and gyr B) and topoisomerase IV (par C and par E) genes, as well as by active efflux. These mutations prevent antimicrobial agents from binding to their topoisomerase targets and carrying out their antimicrobial activity [21]. Resistance mediated by plasmids also occurs, but it is found less frequent [18].

Fluoroquinolones have been extensively used in veterinary medicine and humans due to their effectiveness against both Gram-positive and Gram-negative bacteria. Despite prescribing guidelines now recommending reserving Fluoroquinolones use, resistance continues to rise and is a major problem encountered in the clinical setting. The percentage of *E. coli* isolates in the UK resistant to Fluoroquinolones rose from 6 to 20 per cent from 2001 to 2006 and remained at about 17 per cent for the rest of the decade. Similar rises have been seen in other species of microorganisms; for example, the proportion of fluoroquinolone-resistant *Klebsiella pneumoniae* isolates in Italy has consistently increased yearly, with an almost fivefold increase from 11 per cent in 2005 to 50 per cent in 2012 [29].

Resistance to ciprofloxacin in pneumococci occurred rapidly and when moxifloxacin was introduced prescribing patterns shifted to this newer, more effective drug that target GyrA and ParC with equal affinity in this species. This (dual-targeting) property of moxifloxacin allowed it to be effective against ciprofloxacin-resistant *S. pneumoniae*. Before the use of moxifloxacin, the vast majority of fluoroquinolone-resistant *S. pneumoniae* had parC mutations. The increased use of moxifloxacin changed the selection pressures on *S. pneumoniae* and there has been a consequent increase in the proportion of isolates with both par C and Gyr A mutations [29].

**Therapeutic uses**

Moxifloxacin is a fourth generation fluoroquinolone that has been shown to be effective against Gram-positive, Gram-negative, and atypical strains, as well as multi-drug resistant *Streptococcus pneumoniae.* Moxifloxacin is used for pneumonia, bronchitis, sinusitis, otitis-media, in which efficacy is comparable to β-lactam antibiotics [38].

It has the highest potency against *Staphylococcus aureus, Staphylococcus epidermidis* and also possess large volume distribution, low plasma protein binding and relatively low MICs against susceptible target microorganisms. Moxifloxacin is highly effective against *Mycobacterium leprae* used for treatment of leprosy, it significantly kill microorganisms upto 81 to 91 per cent. The drug thus seems to be extremely useful in a variety of infections including those of urinary tract, respiratory tract, soft tissues, bones and joints [3].

Moxifloxacin has demonstrated a faster resolution of symptoms in community-acquired pneumonia and exacerbations of chronic bronchitis patients compared with first-line therapy together with excellent eradication rates. The use of moxifloxacin as first-line therapy for moderate to severe respiratory infections in the community and the hospital has been recognized in international guidelines [24].

Moxifloxacin received approval from the US Food and Drug Administration for the treatment of complicated skin or skin-structure infections and complicated intra-abdominal infections [7, 34].

The *in vitro* activity of moxifloxacin has been studied against anaerobic bacteria isolated from odontogenic abscesses and periodontal infections. The $MIC_{90}$s were < 0.5 µg.ml$^{-1}$ for

anaerobic isolates from periodontal infections, which included *Porphyromonas gingivalis, Prevotella* species, *Actinomyces* species, *Fusobacterium nucleatum,* and *Peptostreptococcus* species [34].

Moxifloxacin achieved similar clinical success rates against all anaerobes, including those isolated from patients infected with *B. fragilis* (158 [82.7 per cent] of 191 patients), *B. thetaiotaomicron* (74 [82.2 per cent] of 90 patients), and *Clostridium* spp. (37 [80.4 per cent] of 46 patients). The overall results showed that 86 per cent (303/363) of all *B. fragilis* group isolates and 417/450 isolates of all other anaerobic genera and species, including *Fusobacterium*, *Prevotella*, *Porphyromonas*, *C. perfringens*, *Eubacterium*, and *Peptostreptococcus* spp., were susceptible to < 2 $\mu g.ml^{-1}$ of moxifloxacin [7].

Schaumann *et al*., (2004) studied the efficacy of moxifloxacin in a murine bacteremic model. After intravenous infection of mice with different strains of *B. fragilis* along with a susceptible strain of *E. coli*, survival rates and bacterial contents of organs were recorded following 3 days of treatment with moxifloxacin or imipenem. The MICs of moxifloxacin for the isolates of *B. fragilis* were < 0.5 $\mu g.ml^{-1}$ for 3 isolates and > 32 $\mu g.ml^{-1}$ for 1 isolate. Overall, mice treated with either drug showed similar improved survival, compared with controls. However, higher colony counts of *B. fragilis* could be recovered from the liver in surviving animals infected with the high-MIC strain of *B. fragilis* following treatment with moxifloxacin [32, 34].

In a prospective, randomized, double-blind trial, moxifloxacin (400 mg once daily) was compared with piperacillin-tazobactam followed by amoxicillin-clavulanate in 617 adult in patients with complicated skin and skin-structure infections. An abscess was documented in 30 per cent of patients in each group. The rates of bacteriological eradication of anaerobes, such as *Peptostreptococcus, Bacteroides,* and *Prevotella* species, were 60 per cent, 100 per cent, and 64 per cent, respectively, with moxifloxacin. In a prospective, double-blind, randomized study, moxifloxacin was compared with Piperacillin-Tazobactam in 681 patients with complicated intra-abdominal infections. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of these patients was 6, and the majority of infections were complicated appendicitis. Overall, clinical cure rates were similar for moxifloxacin (80 per cent) and piperacillin-tazobactam (78 per cent), as were bacteriological eradication rates, at 78 per cent and 77 per cent, respectively. Against anaerobes, moxifloxacin had eradication rates of 85 per cent for *B. fragilis*, 81 per cent for *B. thetaiotaomicron*, 85 per cent for *B. uniformis*, and 75 per cent for *Peptostreptococcus* species [34].

Moxifloxacin is available for oral or intravenous administration. Both formulations are indicated for the treatment of adults with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, nosocomial pneumonia or uncomplicated skin and skin structure infections. Moxifloxacin is also used as second line antituberculous agents and should be reserved for the treatment of resistant tuberculosis. It is the most potent fluoroquinolone against *Mycobacterium tuberculosis* [5, 7, 25, 31, 33, 38].

Currently, three fluoroquinolones (moxifloxacin, gatifloxacin, and levofloxacin) are used frequently as treatment for respiratory infections. Of these, moxifloxacin is the most potent against the pneumococcus whether they are penicillin sensitive or resistant. Moxifloxacin is twice as potent as gatifloxacin, which has excellent antipneumococcal activity, whereas levofloxacin is 4 to 8 times less active. The use of levofloxacin to treat pneumococcal infection is more likely to lead to quinolone resistance as compared with moxifloxacin or gatifloxacin [2].

*In vitro*, moxifloxacin has a better activity towards anaerobes (including *Porphyromonas gingivalis*) than ofloxacin and ciprofloxacin. *In vivo*, it shows superiority over doxycycline in systemic application and seems to be able to reduce pocket depths when applied topically [39].

Moxifloxacin was developed primarily for the treatment of community acquired pneumonia and upper respiratory tract infections. It is also used for the treatment of hospital acquired infections and also to be considered a drug of last remedy when all other drugs are failed (Kondaiah *et al.*, 2017). In case of humans, moxifloxacin is mainly used to treat respiratory tract infections, cellulitis, anthrax, intra-abdominal infections, endocarditis, meningitis and tuberculosis [30].

**Adverse effects**

The most common side effects of moxifloxacin reported are gastrointestinal disturbance with nausea (4–8 per cent of patients), vomiting (2 per cent), diarrhoea (4–5 per cent) and abdominal pain (2 per cent). CNS side effects occur at a rate of 2–4 per cent, manifested as headache (2–4 per cent of patients), dizziness (2–3 per cent) and other symptoms (1 per cent), including confusion, agitation, insomnia, depression, somnolence, vertigo, light-headedness, and tremors. Moxifloxacin displace g-aminobutyric acid (GABA) or compete with GABA binding at the receptor sites within the CNS. Substitution of 7-piperazinyl– or 7-pyrrolidinyl–containing compound, like moxifloxacin, is associated with reduced seizure-causing potential. Administration of nonsteroidal anti-inflammatory drugs concurrently with certain quinolones has been linked to an increase in the possibility of seizures. Phototoxicity occurs rarely, and experience reported to date suggests that, for moxifloxacin, phototoxic adverse events occur at a lower rate than with widely used Fluoroquinolones, such as ciprofloxacin and levofloxacin [31, 38].

In contrast to some other Fluoroquinolones, moxifloxacin appears to have a low propensity for causing phototoxic and CNS excitatory effects but the most common adverse events caused by moxifloxacin are gastrointestinal disturbances [5].

Moxifloxacin should not be given to patients predisposed to seizures and to those receiving Proarrhythmic drugs, because it can prolong Q-T interval. It is also not good to treat urinary tract infections [38].

Moxifloxacin in high concentrations may cause CNS toxicity, especially in animals with renal failure. Moxifloxacin may cause arthropathy in young animals. Dogs are most sensitive at 4 to 28 weeks of age. Large, rapidly growing dogs are the most susceptible. In horses, moxifloxacin at high doses causes diarrhoea and is not recommended for routine use [26].

**Conclusion**

Moxifloxacin is a new generation fluoroquinolone. It is used in animals and also in humans to treat several conditions and diseases. In emergency cases, where other drugs are found failure or resistant to microorganisms, moxifloxacin is found useful and very effective. So to avoid antimicrobial resistance to moxifloxacin its use should be in limit and according to dose.

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