# Efficacy of Fluoroquinolones Against Pathogenic Oral Bacteria

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**Abstract:** This article reviews the characteristics of the main fluoroquinolones used in dentistry (ciprofloxacin, levofloxacin and moxifloxacin), including pharmacokinetic/ pharmacodynamic parameters, susceptibility profiles of oral bacteria and clinical trials on their efficacy in dental practice. It seems that some of these antibiotics might represent a safe alternative in patients with allergy, intolerance, or lack of response to beta-lactams.

**Key Words:** Antimicrobial susceptibility, ciprofloxacin, fluoroquinolones, focal infection, levofloxacin, moxifloxacin, oral infection, oral pathogens.

## 1. GENERAL CHARACTERISTICS OF THE FLUOROQUINOLONES

The quinolones are a group of synthetic antimicrobial compounds with bactericidal action. The first member of this group used as an anti-infectious agent was nalidixic acid (1,8 naphthyridine), synthesized by George Y. Lesher in 1962 from the antimalarial agent chloroquine [1]. Since that time, numerous quinolones have been developed, with the greatest qualitative progress being made at the end of the 1970s with the synthesis of pipemidic acid, oxolinic acid, and cinoxacin, as a consequence of modifications introduced into the nucleus of the 4-quinolone molecule.

### 1.1. Chemical Structure and Classification

4-quinolone is formed of a double ring -one pyridone and the other aromatic, benzene, or another type. In order for the molecule to present bactericidal activity, the pyridone must have a nitrogen at position 1, a carboxyl group at position 3, and a carbonyl group at position 4 (Fig. (**1**)). These latter 2 radicals are necessary for interaction with bacterial DNA. The radical at position 2 must always be a hydrogen atom due to its proximity to the site of interaction. Finally, there must be a double bond between positions 2 and 3 [2].

The structural differences between the quinolones are derived from the number and positions of nitrogen atoms, the side chains, and the fluoride atoms in the structure. Their antibacterial potency and spectrum increases significantly when a fluoride atom is introduced at position 6 (fluoroquinolones). In addition, their efficacy against Gram-negative bacteria also increases if position 7 carries a piperazine group (e.g. norfloxacin, ciprofloxacin) or a methylpiperazine group (e.g., ofloxacin, levofloxacin, gatifloxacin). In addition, methyl substituents on the piperazine ring improve oral bioavailability. Compounds that have a pyrrolidine-derived double ring at position 7 (e.g. moxifloxacin) have greater activity against Gram-positive bacteria. A methoxy group at position 8 (e.g. moxifloxacin, gatifloxacin) improves activity against anaerobic microorganisms [3] (Table **1**).

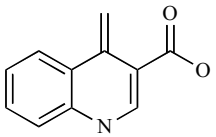


**Fig. (1).** Basic chemical structure of quinolone. Chemical name: 3 quinolinecarboxylic acid.

An expert group of the Paul Ehrlich Society for Chemotherapy has presented a classification of the fluoroquinolones (FQs) according to the antibacterial spectrum and activity and main indications (Table **2**) [4]. The first generation present greater activity than the traditional quinolones against Gram-negative organisms, including *Pseudomonas aeruginosa*, and are effective against some atypical pathogens; however, they have only moderate activity against Gram-positive organisms and practically no activity against anaerobic bacteria. These drugs only reach low concentrations in the serum and in many tissues, for which reason they are not used in systemic infections. The second-generation FQs have been widely used in clinical practice due to their excellent activity against *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and other aerobic Gram-negative bacilli. They have relatively low activity against aerobic Gram-positive cocci and are almost ineffective against anaerobic bacteria. Because of their pharmacokinetic properties, they can be used for the treatment of systemic infections. The third generation FQs are more active against Gram-positive organisms (including *Streptococcus pneumoniae*) and have a broader spectrum that includes anaerobic and atypical pathogens. In addition, they have certain pharmacokinetic advantages compared with second-generation agents, such as longer elimination half-lives and greater tissue penetration. The fourth generation FQs include compounds that are active against Gram-positive and Gram-negative microorganisms, atypical pathogens, and a large number of anaerobic organisms. From a pharmacokinetic viewpoint, these agents have the same advantages as their predecessors.

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**Table 1. Main Structural Differences Between the Quinolones**

| Structure | Activity | Quinolones |
|---|---|---|
| Fluoride atom at position 6 | Increases antibacterial potency and spectrum | Fluoroquinolones |
| Piperazine group at position 7 | Increases efficacy against Gram negative bacteria | Norfloxacin<br>Ciprofloxacin |
| Methylpiperazine group at position 7 | Increases efficacy against Gram negative bacteria | Ofloxacin<br>Levofloxacin<br>Gatifloxacin |
| A pyrrolidine-derived double ring at position 7 | Greater activity against Gram positive bacteria | Moxifloxacin |
| A methoxy group in position 8 | Improves activity against anaerobic bacteria | Moxifloxacin<br>Gatifloxacin |

### 1.2. Mechanism of Action and Resistance

Quinolones act on bacterial chromosomal DNA, mainly binding to certain topoisomerases and inhibiting their action [5,6]. During DNA synthesis, the topoisomerases are involved in the winding and unwinding of chromosomal DNA, and maintain the chromosomes in a supercoiled state. To date, 4 different DNA-topoisomerases have been identified in bacteria. Topoisomerases I and III are not particularly susceptible to inhibition by the quinolones, whereas topoisomerases II (DNA-Gyrase) and IV are the principal targets of these agents. Topoisomerases II and IV are both tetrameric structures composed of 2 pairs of subunits. The 4 subunits in topoisomerase II consist of 2 A monomers and 2 B monomers, which are known as "Gyr A" and "Gyr B". The A and B subunits of topoisomerase IV are encoded by the *parC* and *parE* genes. In Gram-negative bacteria, the quinolones mainly inhibit DNA-gyrase; the principal function of this enzyme is to maintain a degree of coiling of the DNA that facilitates movement towards the complexes that are formed during replication and transcription, and it also releases negative coiling in an ATP-dependent process. The quinolones interact with the amino acids of the alpha-helices close to the tyrosine of the active centre of DNA-gyrase, which is involved in DNA cleavage. In Gram-positive bacteria, the principal target is topoisomerase IV, which acts to cleave the DNA strands after each replication. This enzyme also relaxes the DNA chain [7]. An important phase in the mechanism of action of the quinolones is the formation of a quinolone-enzyme-DNA complex that contains DNA fragments. The binding of a quinolone to DNA-gyrase leads to a conformational change that is responsible for the inhibition of the DNA-gyrase complex. Topoisomerase IV forms similar complexes to those formed with the gyrase [8]. The action of the quinolones on the topoisomerases, although necessary, cannot alone explain their bactericidal action; there must therefore be subsequent events, the details of which are currently unknown.

The mechanisms of bacterial resistance to the quinolones can be grouped into 3 categories [9]:

- Chromosomal resistance, which is caused by mutations in specific segments of the genes that code for DNA-gyrase (particularly subunit A) and topoisomerase IV, giving rise to the Quinolone Resistance-Determining Re-

**Table 2. Classification of Fluoroquinolones (FQs) (Modified According to [4])**

| | | |
|---|---|---|
| First generation | Oral FQs with indications essentially limited to urinary tract infections | Norfloxacin<br>Pefloxacin |
| Second generation | FQs with broad indications for systemic use | Amifloxacin Ciprofloxacin<br>Enoxacin<br>Fleroxacin<br>Lomefloxacin<br>Ofloxacin |
| Third generation | FQs of improved activity against Gram-positive and 'atypical' pathogens | Grepafloxacin Levofloxacin Sparfloxacin<br>Temafloxacin |
| Fourth generation | FQs with improved activity against Gram-positive and 'atypical' pathogens, as well as anaerobes | Clinafloxacin Gatifloxacin<br>Gemifloxacin<br>Moxifloxacin Sitafloxacin Trovafloxacin |

gion [10]. Mutations in *gyrA* are the most common mechanism in Gram-negative organisms, whereas mutations in *parC* are more common in Gram-positive organisms.

- Resistance due to changes in the external bacterial membrane, reducing entry of the drug into the cell. These changes arise from alterations in the genes that code for the porin channels, blocking entry of the quinolone into the bacterial cell [11].
- Resistance based on expulsion of the drug from the intracellular medium into the extracellular medium by endogenous active pumps [12].

In 1994, Kaneko *et al.* [13] reported a progressive increase in resistance to FQs in strains of oral streptococci. In the year 2000, this same research group demonstrated that the strains of oral streptococci that were highly resistant to ofloxacin, ciprofloxacin, and norfloxacin presented mutations in both *gyrA* and *parC* [14].

### 1.3. Pharmacokinetic and Pharmacodynamic Properties

FQs are absorbed well after oral administration, with a bioavailability of over 50% in almost all cases, and close to 100% for some agents. The serum levels after oral administration are similar to those reached after intravenous administration, making sequential therapy possible. Maximum serum concentrations are low in the case of norfloxacin, compared with 2 to 7 mg/L reached by third and fourth generation FQs. Plasma protein binding is low, usually around 20 to 40%; binding occurs principally to albumin [15]. The plasma half-life varies between 1.5 and 17 hours. The agents are widely distributed throughout the body and have a large volume of distribution, which is frequently greater than the total body water volume, meaning that high intracellular concentrations are reached. Their concentrations in prostatic and lung tissue, bile, neutrophils, and macrophages are higher than the serum levels. The concentrations reached in the oral cavity (particularly in the gingival crevicular fluid) are similar to serum concentrations [16], and in the cerebrospinal fluid are usually below half the serum concentration. The route of excretion is principally *via* the kidneys for ofloxacin and levofloxacin, *via* non-renal pathways for moxifloxacin, and mixed in the case of norfloxacin and ciprofloxacin.

FQs can cause adverse effects, in particular affecting the gastrointestinal tract (sickness, vomiting, diarrhea and abdominal pain), central nervous system (seizures, headaches and dizziness), and glucose homeostasis dysregulation. FQs should be also used with caution in patients with a record of seizures and may cause phototoxicity, QTc interval prolongation, tendinopathy and *Clostridium difficile*-associated diarrhea [17].

FQs can present interactions with other drugs. The oral administration of products containing cations such as calcium, aluminum, magnesium, iron, or zinc, included in antacids, nutritional supplements, mineral or multivitamin supplements, or sucralfate within 2 to 4 hours after the administration of a FQ can lead to a fall of between 25% and 90% in the serum concentration of the FQ. The anticoagulant effect of warfarin and the serum concentrations of caffeine, cyclosporine, and theophylline can be increased by the concomitant administration of FQs. There is also an increase in the risk of convulsions and of central nervous system stimulation if FQs are administered concomitantly with nonsteroidal anti-inflammatory drugs. In addition, they can provoke hypoglycemia and/or hyperglycemia in patients who are receiving oral antidiabetic agents or insulin [18].

The activity of the quinolones is concentration-dependent; the quotient of the maximum serum concentration (Cmax) and minimum inhibitory concentration (MIC) is therefore of particular relevance for predicting the antimicrobial response and, thus, clinical success. Cmax/MIC should be greater than 10 in order to achieve maximum clinical efficacy and lowest selection of resistances. Another important pharmacodynamic parameter is the quotient of the area under the serum concentration-time curve (AUC) and the MIC (AUC/MIC), which should be $\geq 25$ for less severe infections or in immunocompetent hosts, and $\geq 100$ in more severe infections or in immunocompromised hosts [19].

### 1.4. Clinical Indications

FQs are recommended for the treatment of a wide variety of infections, both in the hospital setting and in the community. They are used successfully in infections of the urinary tract, sexually transmitted diseases, gastrointestinal and abdominal infections, bone infections such as chronic osteomyelitis, respiratory tract infections, and serious systemic infections [20].

To date, oral infections have not been included among the clinical indications of FQs. However, in recent years, drugs from all generations of the FQs have often been prescribed empirically in the dental setting. Norfloxacin, a first-generation FQ, was tested against pathogens associated with periodontitis [21]. Ciprofloxacin stands out among the second-generation drugs, although others such as ofloxacin and lomefloxacin have also been evaluated against periodontal pathogens [22-24], the bacterial flora of periapical abscesses [25], and in root cysts [26]. Levofloxacin is the third generation FQ that has been studied most extensively on the oral flora, though moxifloxacin is certainly the agent that shows greatest evidence of microbiological and clinical efficacy in the context of dental infection.

This article reviews the characteristics of the main FQs used in dental practice, including their pharmacokinetic/pharmacodynamic parameters, and presents an overview of the susceptibility profiles of oral bacteria and resistance mechanisms. The final section deals with clinical trials on the usefulness of FQs in the treatment of oral infections and as prophylactic drugs to prevent focal infections of oral origin.

## 2. FLUOROQUINOLONES USED IN DENTAL PRACTICE

### 2.1. Ciprofloxacin

#### *Overview*

Ciprofloxacin (CPF) is a second generation FQ first synthesized in 1981. It is a monofluorinated benzopyridone with a piperazine group at position 7 and a cyclopropyl ring at

position 1; its chemical formula is 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (Fig. (**2**)).

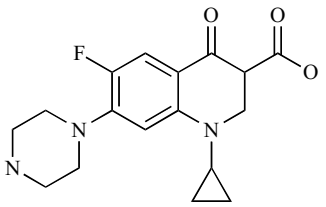

**Fig. (2).** Ciprofloxacin. Chemical name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3 quinolinecarboxylic acid.

It is one of the most commonly prescribed antimicrobial agents in the world; for example, in Spain, it was the fifth most used antibiotic in the year 2000 [27]. Like other FQs, CPF blocks chromosome replication and interferes with cell division and gene expression [28]. It is the most powerful second-generation FQ against Gram-negative organisms and has better activity against *Pseudomonas aeruginosa*. It has limited activity against Gram-positive cocci, particularly those resistant to methicillin, and has hardly any activity against anaerobic organisms [29]. The accumulation of several bacterial mutations (affecting DNA-gyrase and bacterial permeability) has been associated with the development of very high CPF MICs in isolates of *Staphylococcus aureus, Enterobacteriaceae* spp. and *Pseudomonas aeruginosa* [30].

Significant untoward reactions are uncommon; the most frequent being gastrointestinal tract disturbances (approximately 3%) and rashes (<1%). Central nervous system disturbances have been reported in 1% of patients [31].

Its therapeutic applications include skin and soft tissue, lower respiratory tract, and urinary tract infections, as well as intestinal, gynecologic, otorhinolaryngological, and ophthalmologic infections, bacteremia, sexually transmitted diseases, and typhoid fever [32]. It is also indicated in bone and joint infections and constitutes one of the best therapeutic options for the treatment of chronic osteomyelitis [33, 34].

### *Pharmacokinetic and Pharmacodynamic Properties*

CPF is available for parenteral and oral administration and stands out for its excellent tolerance, although its oral bioavailability is relatively low and irregular (bioavailability, 70-75%). The drug is widely distributed in body water, with high concentrations in most tissues and in phagocytic cells similar to those in plasma [31]. At therapeutic doses, the drug appears in saliva at or below the levels achieved in serum [35]. The terminal half-life ranges between 3 and 4 h. Maximal serum concentrations are reached 0.5 to 1 h after dosing. The proportion of the relative amount of metabolites to the total amount of drug excreted in urine increased from 29.7% after intravenous administration to 42.7% after oral dosing, indicating a first-pass effect of the liver. High total and renal clearances suggest additional elimination pathways, such as tubular secretion, metabolism, or biliary excretion [36].

The ability of CPF to reach the periodontal tissues through the gingival crevicular fluid (GCF) has been analyzed in clinical studies, which have demonstrated higher levels of the drug in the GCF than in the serum after the oral administration of CPF to periodontally healthy subjects [37, 38] and to patients with chronic periodontitis [37,39,40]. Tozum *et al.* [39] suggested that the polymorphonuclear cells (PMNs), which are present in large numbers at sites of infection, may help to transport the drug into the gingival crevice. The uptake process of the PMNs is so efficient that FQ levels inside these cells are usually 4- to 8-fold higher than the levels in the extracellular medium [40]. CPF retains its bactericidal activity inside PMNs, and enhances intracellular killing of susceptible bacteria [41-43]. Since periodontally healthy subjects also exhibited relatively high levels of CPF in the GCF [36], other mechanisms appear to be involved. Lavda *et al.* [38] suggested that fibroblasts serve as a reservoir of CPF in the gingival connective tissue and that they could contribute to the relatively high levels reached in the GCF.

The increased availability in GCF is of considerable clinical relevance as it enhances its bactericidal effects against susceptible subgingival microorganisms. Cacchillo and Walters [43] demonstrated that PMNs loaded with CPF maintained therapeutic levels of the agent and killed *Aggregatibacter actinomycetemcomitans* more rapidly than did unloaded PMNs.

### *Susceptibility Profile of Oral Pathogens*

It has been shown that CPF presents marked activity against *Aggregatibacter actinomycetemcomitans*, enteric rods, and *Pseudomonas* spp. associated with advanced adult periodontitis [43-46].

In 1999, Eick *et al.* [47] defined the susceptibility to CPF of obligate and facultative anaerobic bacteria obtained from samples of subgingival plaque from patients with progressive periodontitis. In contrast to the anaerobic spp., *Aggregatibacter actinomycetemcomitans* and *Eikenella corrodens* - both important species in cases of periodontitis- were susceptible to CPF, with a MIC range of 0.125 to 0.5 mg/L for both organisms, with no cases of resistance. In agreement with this finding, Müller *et al.* [46] confirmed that strains of *Aggregatibacter actinomycetemcomitans* isolated from patients with gingivitis or periodontitis were highly susceptible to CPF, with a $MIC_{90}$ of 0.006 mg/L, a figure slightly lower than that obtained in previous studies, such as the ones by Pavicic *et al.* [48] ($MIC_{90}$, 0.010 mg/L) and Pajukanta *et al.* [49] ($MIC_{90}$, 0.015 mg/L). In a study performed in Spanish and Dutch patients with periodontal disease [50], strains of *Aggregatibacter actinomycetemcomitans* resistant to CPF were isolated from Spanish patients, and presented an MIC in the range 0.001 to 32 mg/L and a percentage of resistance of 10%. In the case of strains of *Aggregatibacter actinomycetemcomitans* from Dutch patients, 100% were susceptible to CPF (MIC range, 0.001-0.094 mg/L).

In 2004, Eick *et al.* [51] defined the susceptibility of strains of *Porphyromonas gingivalis* to CPF, finding an MIC range of 0.064 to 0.25 mg/L. The results published by van Winkelhoff *et al.* [50] showed that 100% of strains of *Porphyromonas gingivalis*, *Prevotella intermedia*, *Micromonas micros*, and *Fusobacterium nucleatum* obtained from samples from patients with destructive periodontitis were suscep-

tible to CPF, presenting the following MIC ranges (mg/L): 0.15-0.75, 0.001-0.64, 0.001-0.94, and 0.001-1, respectively.

In a series of blood culture isolates of viridans group streptococci (a very common microorganism in the oral environment) from across Canada, the percentage of resistance to CPF was 8% (MIC ≥ 4 mg/L) [52,53].

### *Clinical Efficacy in Dental Practice*

CPF figures in the list of antibiotics commonly used in the treatment of dental infections [54]. Initially, this antibiotic was used in combination with metronidazole to treat mixed infections of anaerobic bacteria, enteric rods, and *Aggregatibacter actinomycetemcomitans* [48].

Soleymani Sahyesteh *et al.* [55] studied the efficacy of systemic CPF to eradicate *Aggregatibacter actinomycetemcomitans* from the subgingival region in patients with aggressive periodontitis. In this randomized, controlled clinical trial, the administration of CPF (500 mg twice a day for 10 days) was compared with the combination of amoxicillin (500 mg 3 times a day for 7 days) plus metronidazole (250 mg 3 times a day for 7 days). CPF eliminated *Aggregatibacter actinomycetemcomitans* from 91.7% of positive sites and amoxicillin plus metronidazole eliminated this microorganism from 81.3% of positive sites; there was no statistically significant difference between these results.

Tezel *et al.* [40] measured the effects of the administration of CPF (500 mg 3 times a day for 7 days) as adjuvant treatment in patients with chronic gingivitis and chronic periodontitis, evaluating a series of clinical parameters (gingival index, plaque index, and clinical attachment levels). Analysis of the results demonstrated that the administration of CPF did not have any positive or statistically significant effect on the clinical parameters of subjects with gingivitis. These authors stress the need for long-term studies to assess the effects of CPF on clinical parameters [40] (Table **3**).

## 2.2. Levofloxacin

### *Overview*

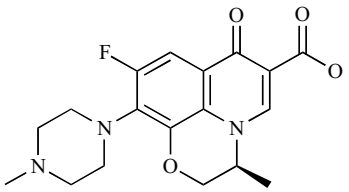


**Fig. (3).** Levofloxacin. Chemical name: 7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (3S)-.

Levofloxacin (LVF) is an active enantiomer of ofloxacin, belonging to the third-generation FQs. Its chemical formula is 7H-Pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, (3S)- (Fig. (**3**)). This broad spectrum antibiotic is

**Table 3. Susceptibility Profiles of Oral Bacteria and Clinical Trials on the Efficacy in Dental Practice for Ciprofloxacin**

| | **Bacteria** | **MIC Range (mg/l)** | **$MIC_{90}$ (mg/l)** | **References** |
|---|---|---|---|---|
| **Susceptibility profile of oral bacteria** | *Aggregatibacter Actinomycetemcomitans* | 0.125-0.5<br>-<br>-<br>-<br>0.001-32 | -<br>0.006<br>0.010<br>0.015<br>- | Eick *et al*. 1999 [47]<br>Müller *et al*. 2002 [46]<br>Pavicic *et al*. 1992 [48]<br>Pajukanta *et al*. 1993 [49]<br>van Winkelhoff *et al*. 2005 [50] |
| | *Eikenella corrodens* | 0.125-0.5 | - | Eick *et al*. 1999 [47] |
| | *Porphyromonas gingivalis* | 0.064-0.25<br>0.15-0.75 | - | Eick *et al*. 2004 [51]<br>van Winkelhoff *et al*. 2005 [50] |
| | *Prevotella intermedia* | 0.001-0.64 | - | van Winkelhoff *et al*. 2005 [50] |
| | *Micromonas micros* | 0.001-0.94 | - | van Winkelhoff *et al*. 2005 [50] |
| | *Fussobacterium nucleatum* | 0.001-1 | - | van Winkelhoff et al. 2005 [50] |
| | *Streptococcus viridans* | - | >4 | De Azavedo *et al*. 1999 [52]<br>Gershon *et al*. 2000 [53] |
| | **Antibiotic Regimen** | **Indication** | **Outcomes** | **References** |
| **Clinical efficacy in dental practice** | Ciprofloxacin *versus* amoxicillin plus metronidazole | Periodontitis | Both similar results | Soleymani *et al*. 2004 [55] |
| | Ciprofloxacin | Gingivitis<br>Periodontitis | No effects on gingivitis | Tezel *et al*. 2005 [40] |

active against a large number of Gram-negative bacteria and shows improved activity against Gram-positive microorganisms, particularly respiratory pathogens. As with other quinolones, it acts by inhibiting the enzyme DNA-gyrase [56].

LVF can cause adverse effects affecting the gastrointestinal tract (sickness, vomiting and diarrhea). Skin reactions (rash, pruritus and erythema) are observed in 0.1-1% of patients. Phototoxicity and central nervous system disturbances are unusual, but chondro-toxicity is as common as with other FQS [56].

LVF has been approved for use in the treatment of both uncomplicated and complicated urinary tract infections (including pyelonephritis and chronic bacterial prostatitis), skin and skin structure infections, acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia (including those due to penicillin-resistant or multidrug-resistant *Streptococcus pneumoniae*), and nosocomial pneumonia [20].

***Pharmacokinetic and Pharmacodynamic Properties***

Of interest in its pharmacokinetic profile is its rapid absorption after oral administration, with a bioavailability of close to 99%, a very large volume of distribution (approximately 1.1 L/kg) [57], and an elimination half-life of 6 to 8 hours. It is mainly excreted *via* the kidney (>85%) [58]. These characteristics make it possible to administer the drug in a single daily dose, whether intravenously or orally [59].

According to studies that have applied the concepts of pharmacokinetics and pharmacodynamics in dentistry, and analysed different antibiotics used for the 5 most prevalent bacteria isolated in dental infections (V*iridans group streptococci*, *Peptostreptococcus* spp., *Prevotella intermedia*, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*), LVF (500mg/24 horas) showed activity against *Peptoestreptococcus spp.* and *Porphyromonas gingivalis*, with a rate AUC/CIM > 25 in all analyzed isolates [16].

***Susceptibility Profile of Oral Pathogens***

In the literature there are reports of the susceptibility to LVF of numerous oral pathogens isolated from purulent collections caused by dental-alveolar infections, periodontitis, or pericoronaritis [60-63].

It has been shown that only 56% of penicillin G-susceptible *Streptococcus viridans* strains were susceptible to LVF, and that this rate was significantly lower among penicillin G-resistant strains of *Streptococcus viridans* (25%); in both cases, the $MIC_{90}$ values were high ($MIC_{90}$, 8 mg/L) [60]. However, in later studies, higher levels of susceptibility (≥92%) were observed for Gram-positive cocci, including *Streptococcus viridans* [62,64]. High levels of susceptibility to LVF were also found for *Peptostreptococcus* spp. (≥96%), with low $MIC_{90}$ values (1 mg/L), with the exception of penicillin G-resistant strains, in which the $MIC_{90}$ was 8 mg/L [60]. Similarly, other Gram-positive cocci (e.g. *Gemella* spp.) showed a susceptibility of 100%, with low $MIC_{90}$ values (2 mg/L) [62].

Eguchi *et al.* [65] analyzed the susceptibility of periodontopathic bacteria (standard strains and clinical isolates) to LVF and other FQs. LVF showed excellent activity against *Ekinella corrodens* and *Aggregatibacter actinomycetemcomitans*.

According to Kuriyama *et al.* [60,61,63], antimicrobial susceptibility to LVF of the Gram-negative, obligate anerobes, *Prevotella* spp., *Porphyromonas* spp., and *Fusobacterium* spp. is very variable. The susceptibility rate for *Prevotella* spp. was greater than 80%, although the $MIC_{90}$ values were very high (between ≤32 and ≤64 mg/L) [61,63]; this result agrees with the 83% obtained by other authors in strains isolated from periodontal infections [66]. In the case of *Porphyromonas* spp., the susceptibility rate varied between 91% and 77.7%, and the $MIC_{90}$ between 1 and 16 mg/L [60, 61].

With respect to *Fusobacterium* spp., the results published show mean $MIC_{90}$ values less than or equal to 4 mg/L and susceptibility rates equal to or greater than 70% [60,61,63]. Other authors obtained a susceptibility of 100% in strains of *Fusobacterium nucleatum* isolated from periodontal infections in a selected area of southern Italy [66].

***Clinical Efficacy in Dental Practice***

To our knowledge, there are no publications to date of any comparative clinical studies between LVF and other antibiotics commonly used in the management of dental infections (Table **4**).

**2.3. Moxifloxacin**

***Overview***

Moxifloxacin (MXF) is a fourth-generation FQ that has a methoxy group at position 8 (Fig. (**4**)) [67]. It has a broad antibacterial spectrum that includes typical, atypical, and intracellular respiratory pathogens, Gram-negative organisms, and obligate anaerobic bacteria [68]. It is also active against microorganisms resistant to penicillins, macrolides, tetracyclines, trimethoprim-sulfamethoxazole, and some quinolones [69].

As with other quinolones, MXF exerts its bactericidal activity by binding to and blocking bacterial topoisomerases (II and IV). Topoisomerase II constitutes the preferential target when MXF acts on Gram-negative microorganisms, whereas it inhibits both topoisomerases in Gram-positive microorganisms. This "double target" mechanism of MXF in Gram-positive bacteria contrasts with the "single target" mechanism of the majority of the FQs [70]. It appears that the C-8-methoxy moiety of the molecule contributes to this activity and reduces the selection of resistant mutants among Gram-positive bacteria, in comparison with the C-8-H moiety. The massive presence of the bicycloamine substituent at position 7 impedes the active efflux associated with genes *norA* and *pmrA* expressed by certain Gram-positive bacteria [71]. The mechanisms of resistance that inactivate penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines do not interfere with the antibacterial activity of MXF. Other mechanisms of resistance such as changes in permeability (common in *Pseudomonas aeruginosa*) and the efflux mechanisms can also alter susceptibility to MXF [72]. *In vitro* resistance to MXF is acquired as a gradual process through mutations at target sites on topoisomerases II and IV

**Table 4. Susceptibility Profiles of Oral Bacteria and Clinical Trials on the Efficacy in Dental Practice for Levofloxacin**

| | Bacteria | MIC Range (mg/l) | $MIC_{90}$ (mg/l) | References |
|---|---|---|---|---|
| **Susceptibility profile of oral bacteria** | *Streptococcus viridans* | - | 8 | Kuriyama *et al.* 2000 [60] |
| | *Peptostreptococcus spp.* | - | 1 | Kuriyama *et al.* 2000 [60] |
| | *Gemella spp.* | - | 2 | Kuriyama *et al.* 2002 [62] |
| | *Prevotella spp.* | - | <32<br><64 | Kuriyama *et al.* 2001 [61]<br>Kuriyama *et al.* 2007 [63] |
| | *Porphyromonas spp.* | - | 1<br>16 | Kuriyama *et al.* 2000 [60]<br>Kuriyama *et al.* 2001 [61] |
| | *Fusobacterium spp.* | - | <4 | Kuriyama *et al.* 2000, 2001, 2007 [60, 61, 63] |
| ***Clinical efficacy in dental practice*** | *There are no published references* | | | |

and on DNA-gyrase. Cross-resistance has been reported between MXF and other FQs; however, some Gram-positive bacteria can be resistant to other quinolones but sensitive to MXF [73].

MXF is indicated in adults for the treatment of acute exacerbations of chronic bronchitis, community-acquired pneumonia except for severe pneumonia, acute bacterial sinusitis, and infections of the skin and soft tissues [20].

### *Pharmacokinetic and Pharmacodynamic Properties*

MXF has suitable pharmacokinetic properties, characterized by a high bioavailability, long half-life, and excellent penetration of body fluids and tissues [74], including the interstitial fluids, lungs (particularly the alveolar macrophages), and saliva [75]. Concentrations in saliva and capillary plasma closely reflect or are even higher than the corresponding concentrations in venous plasma [76,46]. It has been demonstrated that the concentration of MXF in the gingival fluid is similar to or higher than the serum concentration [77]. Tissue penetration into compact and spongy bone is also evident, and higher concentrations are reached in these tissues than in the plasma [78]. As other quinolones, it may also become concentrated at the site of infection as it penetrates PMNs and epithelial cells [79].

The most common adverse effects of MXF are disorders of the gastrointestinal tract and central nervous system; they are usually transitory and of moderate intensity [80]. MXF should be administered with caution in patients with QTc interval prolongation. In contrast to other quinolones, MXF is not metabolized by the cytochrome P450 system, thus reducing the risk of drug interactions; this agent is therefore a therapeutic option in diabetic patients, the elderly, patients with renal dysfunction, and those with mild or moderate liver dysfunction [80]. In addition, it is usually well tolerated by patients with a history of intolerance to beta-lactam antibiotics [81].

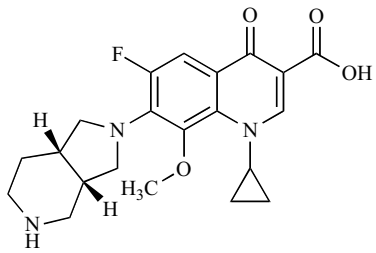


**Fig. (4).** Moxifloxacin. Chemical name: (1'S,6'S)-1-Cyclopropyl-7-(2,8-diazabicyclo[4.3.0]non-8-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

The pharmacodynamic properties are also suitable. It is bactericidal at concentrations of 2-4 times the MIC [82] and, at a dose of 400 mg/24 hours showed appropriate efficacy indices (AUC/MIC > 25) against the microorganisms most commonly implicated in dental infections including Viridans group streptococci, *Peptostreptococcus* spp., *Prevotella intermedia*, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, presenting AUC/CIM ranges: 72.3, 289, 36.2, 72.3 and 144, respectively [16].

### *Susceptibility Profile of Oral Pathogens*

In 2002, Sobottka *et al.* [83] found that the most prevalent bacteria isolated from dental abscesses were various viridans group streptococci and *Prevotella* spp., and that MXF presented high *in vitro* activity against both microorganisms (100% and 97%, respectively, of the isolates were susceptible to MXF). The $MIC_{90}$ of MXF in the viridans group streptococci was 0.5 mg/L (range, 0.064-0.5 mg/L), and that of the *Prevotella* spp. was 1 mg/L (range, 0.032-2 mg/L). In agreement with these results, Warnke *et al.* [84], after examining the spectrum of oral pathogens found in dental abscesses, confirmed that the most prevalent bacteria were *Streptococcus viridans*, accounting for 54% of the aerobic/facultative anaerobic bacteria, and *Prevotella* spp.,

which made up 53% of the anaerobic organisms. That study reported a susceptibility to MXF of over 99% for aerobes/ facultative anaerobes and 96% for obligate anaerobes, with $MIC_{90}$ values of 0.38 mg/L and 1 mg/L, respectively.

In 2004, Tomás *et al.* [85] evaluated the *in vitro* activity of MXF against *Streptococcus* spp. isolated from peripheral blood cultures following dental extractions, finding an $MIC_{90}$ for MXF of 0.125 mg/L in all the bacterial isolates, confirming the *in vitro* efficacy of MXF against oral streptococci observed in previous studies [83]. In agreement with these results, Limeres *et al.* [86] found that 100% of viridans group streptococci from dental abscesses were susceptible to MXF, with low $MIC_{90}$ values in all isolates ($MIC_{90}$, 0.190 mg/L).

Milazzo *et al.* [87] demonstrated that the great majority of anaerobes associated with periodontal infections are inhibited *in vitro* by MXF at concentrations easily achieved by therapeutic regimens. MXF presents a high activity against *Bacteroides* spp., *Prevotella* spp., and *Fusobacterium* spp. ($MIC_{90}$ range, 0.12-0.5 mg/L). Subsequently, Tomás *et al.* [88] confirmed that MXF was active against all genera of obligate anaerobes of oral origin isolated from saliva samples from subjects with healthy periodontal tissues or with untreated, moderate-severe chronic periodontal disease; apart from *Bacteroides* spp., 94% of cultures were inhibited by a MXF concentration of 4 mg/L (this is the mean plasma concentration reached after the administration of a single oral dose of 400 mg of MXF). In agreement with these results, Ackerman *et al.* [89] reported that MXF presented high levels of activity against the obligate anaerobic pathogens of greater clinical relevance, after finding that 97% of 292 isolates analyzed were inhibited by a concentration of 4 mg/L.

With regard to pathogenic periodontal bacteria, Müller *et al.* [46] demonstrated that strains of *Aggregatibacter actinomycetemcomitans* isolated from patients with gingivitis and periodontitis were highly susceptible to MXF ($MIC_{90}$ range, 0.006-0.032 mg/L). Eick *et al.* [51] demonstrated that MXF presented a high *in vitro* activity against *Porphyromonas gingivalis*, an anaerobic Gram-negative bacterium implicated in the pathogenesis of periodontitis ($MIC_{90}$ range, 0.006-0.032 mg/L). DNA-gyrase is the primary target of FQs in *Porphyromonas gingivalis*; in terms of the concentrations that can be achieved in gingival fluid and the MIC values, MXF could prevent the onset of resistance and may be an alternative in the antibiotic treatment of *Porphyromonas gingivalis*-associated periodontitis. Eick *et al.* [77] analyzed the efficacy of MXF against a single strain of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* grown in an artificial biofilm, and found 1-fold MIC was sufficient for elimination of these microorganisms. However, in this experiment, only the 50-fold MIC completely eradicated a strain of *Streptococcus constellatus*.

LeCorn *et al.* [90] evaluated the *in vitro* activity of MXF against oral *Actinomyces* spp. (*neaslundii*, *gerencseriae*, *israelii*, *viscosus*, and *odontolyticus*) associated with endodontal infections, finding an $MIC_{90}$ of 0.38 mg/L (range, 0.094-0.75 mg/L).

MXF is associated with a considerably lower risk of selection of resistant mutants than other FQs [91]. Less than 2% of isolates of viridans group streptococci from normal oral flora were resistant to MXF [92]. The NCCLS-defined breakpoints for MXF were equal to or greater than 2 mg/L for non-susceptibility and equal to or greater than 4 mg/L for resistance (breakpoints given for *Streptococcus pneumoniae*). MXF showed good activity against viridans streptococci, with 90% inhibition at MICs of 2 and 0.25 mg/L, respectively. Resistance to these agents was detected only in 3 *Streptococcus oralis* isolates, which had MICs of 4 mg/L. Mechanisms involved in quinolone resistance in viridans streptococci include mutations primarily in *parC*, but also in *parE* and *gyrA* genes, and enhanced drug efflux [93,94].

### *Clinical Efficacy in Dental Practice*

In a clinical trial with 80 patients with submucous dental abscesses, the clinical efficacy of MXF (400 mg once a day for 5 days) was compared with amoxicillin-clavulanic acid (500/125 mg every 8 hours for 7 days) [95]. After completing the treatment period, both pharmacological options were equally effective, with no statistically significant differences in any of the clinical variables analyzed (pain, reddening, swelling, cellulitis, and fistula). The degree of adherence to treatment was better among the patients treated with MXF. Both antibiotics were well tolerated. The prevalence of undesirable effects was similar in the 2 groups, all were of mild intensity, and treatment did not have to be interrupted in any patient. In consequence, this clinical study demonstrated the *in vivo* efficacy of MXF for the treatment of submucous dental abscesses, confirming its penetration into oral tissues.

Guentch *et al.* [96] evaluated the efficacy of MXF in the treatment of severe chronic periodontitis. This multicenter, prospective, randomized clinical trial, was designed with 3 patient groups: one received treatment exclusively with scaling and root planing (control group); the second group received MXF (400 mg once a day for 7 days) in addition to scaling and root planing; and the third group received adjuvant therapy with doxycycline (200 mg on the first day followed by 100 mg per day for 9 days). Although the 3 groups presented a significant improvement in the clinical parameters evaluated, the reduction in the probing depth at 6 and 12 months was significantly greater in the MXF group compared with either of the other 2 groups. In addition, reductions in the inflammatory parameters evaluated and in the bacterial load compared to baseline were only observed in the MXF group. In consequence, these authors [96] suggested that MXF could be considered an alternative adjunctive treatment to nonsurgical periodontal treatment in patients with severe chronic periodontitis.

The impact of the prophylactic administration of MXF on oral function and quality of life after the extraction of third molars has also been evaluated [97]. This was investigated in a prospective, randomized, controlled, double-blind clinical study with 100 patients who underwent extraction of impacted inferior third molars. Half of the patients received MXF (400 mg once a day for 5 days), and the remaining 50 were treated with amoxicillin-clavulanic acid (500/125 mg every 8 hours for 7 days). The most common undesirable effects related to the administration of MXF and amoxicillin-clavulanic acid were headache and diarrhea, respectively. Less discomfort on mastication was observed on days 3 to 7

after the operation in the MXF group than in the amoxicillin-clavulanic acid group. The percentage of patients who tolerated a diet of normal consistency on days 5 to 7 of follow-up was significantly higher after the administration of MXF than after amoxicillin-clavulanic acid. Patients receiving amoxicillin-clavulanic acid referred greater discomfort when performing oral hygiene than those who received MXF. The percentage of patients returning to work during the first 4 days after the operation was significantly higher among those receiving MXF. In consequence, the authors indicated that MXF shortens the postoperative recovery period in terms of oral function and time off work.

In the context of prophylaxis of focal infection of oral origin, the efficacy of MXF was evaluated in the prevention of bacteremia following dental extraction [98]. This was a prospective, randomized, double-blind clinical trial with the participation of 221 patients undergoing dental extraction under general anesthesia. The patients were divided into 3 groups, each receiving one of the following antibiotic regimens 1 to 2 hours before anesthetic induction: MXF (400 mg); amoxicillin (2 g); or clindamycin (600 mg). A control group was formed of patients who did not receive antibiotic prophylaxis. Statistically significant differences were observed in the percentages of positive blood cultures between the control group and the amoxicillin and MXF groups (47.8% *vs*. 17.5% and 25.5%, respectively), but not with respect to the clindamycin group (47.8% *vs*. 50%, respectively). Statistically significant differences were also observed in the proportion of polymicrobial blood cultures between the control group and MXF and amoxicillin groups (29% *vs*. 14.8% and 0%, respectively), but not with respect to the clindamycin group (29% *vs*. 31.7%). In consequence, the prophylactic administration of MXF or amoxicillin showed high efficacy in the reduction of the prevalence and duration of bacteremia secondary to dental extractions (Table **5**).

**Table 5. Susceptibility Profiles of Oral Bacteria and Clinical Trials on the Efficacy in Dental Practice for Moxifloxacin**

| | **Bacteria** | **MIC Range (mg/l)** | **$MIC_{90}$ (mg/l)** | **References** |
|---|---|---|---|---|
| **Susceptibility profile of oral bacteria** | *Streptococcus spp.* | 0.064-05 | 0.5 | Sobottka *et al.* 2002 [83] |
| | | - | 0.38 | Warnke *et al.* 2008 [84] |
| | | - | 0.125 | Tomás *et al.* 2004 [85] |
| | | - | 0.190 | Limeres *et al.* 2005 [86] |
| | *Prevotella spp.* | 0.032-2 | 1 | Sobottka *et al.* 2002 [83] |
| | | - | 1 | Warnke *et al.* 2008 [84] |
| | | 0.12-0.5 | - | Milazzo *et al.* 2002 [87] |
| | *Aggregatibacter Actinomycetem-comitans* | 0.006-0.032 | - | Müller *et al*. 2002 [46] |
| | *Porphyromonas gingivalis* | 0.006-0.032 | - | Eick *et al.* 2004 [51] |
| | *Actinomyces spp.* | 0.094-0.75 | 0.38 | LeCorn *et al.* 2007 [90] |
| | *Bacteroides spp.* | 0.12-0.5 | - | Milazzo *et al.* 2002 [87] |
| | *Fusobacterium spp.* | 0.12-0.5 | - | Milazzo *et al.* 2002 [87] |
| | **Antibiotic Regimen** | **Indications** | **Outcomes** | **References** |
| **Clinical efficacy in dental practice** | Moxifloxacin *versus* Amoxicillin plus clavulanic acid | Dental abscesses | Both similiar results | Limeres *et al.* 2006 [95] |
| | Moxifloxacin *versus* Doxycicline *versus* Control | Chronic periodontitis | Moxifloxacin was the most effective | Guentch *et al.* 2008 [96] |
| | Moxifloxacin *versus* Amoxicillin plus clavulanic acid | Prophylaxis following third molar extractions | Moxifloxacin shortens the postoperative period | Limeres *et al.* 2009 [97] |
| | *Moxifloxacin versus Amoxicillin versus Clindamycin versus Control* | *Prophylaxis of bacteremia following dental extractions* | *Moxifloxacin and Amoxicillin were the most effective* | Diz *et al.* 2006 [98] |

## CONCLUSIONS

The synthesis of new FQs provides us with broad spectrum antibiotics with suitable pharmacokinetic and pharmacodynamic properties. Numerous *in vitro* studies have demonstrated that some of these FQs, such as CPF, LVF, and MXF, show excellent activity against oral pathogens. To date, oral infections have not been included among the indications of the FQs, and they have often been prescribed empirically in the dental setting. Very few clinical trials have been published on the clinical efficacy of FQs in the treatment of severe periodontal disease or dental abscesses, or for prophylaxis against focal infection. It seems, however, that some of these antibiotics could be useful alternatives when beta-lactams are contraindicated, although appropriate use is essential if this group of agents is to remain clinically useful. The results of this review underline the need for rigorous clinical trials to evaluate the effects of FQs on clinical parameters.

## ABBREVIATIONS

| | | |
|---|---|---|
| Amox. | = | Amoxicilina |
| AUC | = | Area under the plasma concentration time curve |
| $C_{max}$ | = | Maximum serum concentration |
| CPF | = | Ciprofloxacin |
| FQs | = | Fluoroquinolones |
| GCF | = | Gingival Crevicular Fluid |
| LVF | = | Levofloxacin |
| MIC | = | Minimum inhibitory concentrations |
| $MIC_{90}$ | = | Minimum concentration that inhibits the growth of 90% of the bacterial population. |
| MXF | = | Moxifloxacin |
| NCCLS | = | National Committee on Clinical Laboratory Standards |
| PMNs | = | Polymorphonuclear cells |
| spp. | = | species |

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