CIPROFLOXACIN

Indications

Ciprofloxacin is indicated for:

1) Topical treatment of ophthalmic conditions such as external infections of the eye and its adnexa, as well as corneal ulcers.
2) Local treatment of external otitis, in combination with hydrocortisone (only if the tympanic membrane is intact).
3) Prophylaxis of inhalational anthrax.
4) Treatment in adult patients for infections of the respiratory tract, genital tract, biliary tract, urinary tract, skin and soft tissues, musculoskeletal system, or systemic infections caused by ciprofloxacin-sensitive pathogenic microorganisms. Ciprofloxacin should not be used for self-limiting or spontaneously resolving infections, nor for mild or moderate infections unless alternative therapeutic options are unavailable or inappropriate.
5) Antimicrobial prophylaxis in adult surgical patients.
6) Selective intestinal decontamination, as well as prophylaxis and treatment of infections in immunocompromised adult patients.
7) Treatment of acute pulmonary exacerbations of cystic fibrosis caused by Pseudomonas aeruginosa in children and adolescents aged 5–17 years (AIFA).
8) Treatment of complicated urinary tract infections and pyelonephritis in children and adolescents aged 1–17 years (FDA).

Off-Label Use

1) Prophylaxis for meningococcal meningitis (Varon, 2009).

AIFA Information Note

As of October 2018, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) issued a notice, confirmed by the EMA Committee for Medicinal Products for Human Use (CHMP) and reiterated by the Italian Medicines Agency (AIFA) in April 2019. This notice recommends against the use of fluoroquinolone and quinolone antibiotics (for oral, parenteral, or inhalational administration) for mild to moderately severe infections that may resolve spontaneously (e.g., throat infections, acute bronchitis) or that could be managed with antibiotics from other therapeutic classes (e.g., acute exacerbation of chronic

bronchitis, acute bacterial rhinosinusitis, acute otitis media) (European Medicines Agency – EMA, 2018a; Italian Medicines Agency – AIFA, 2019).

In particular, fluoroquinolones and quinolones should not be used to prevent traveler's diarrhea or to manage recurrent lower urinary tract infections (i.e., infections confined to the bladder) (European Medicines Agency – EMA, 2018a). These drugs can lead to potentially long-lasting and disabling side effects affecting the muscles, bones, tendons, and nervous system (European Medicines Agency – EMA, 2018).

Dosage

Monotherapy

Below are the dosing guidelines for ciprofloxacin in various therapeutic indications.

Acute Uncomplicated Cystitis

Oral Administration.

Adults: 250–500 mg/day in two divided doses for 3 days.

Intravenous Administration:

Adults: 200 mg/day in two divided doses.

Complicated Cystitis (Empirical Therapy)

Oral Administration.

Adults: 1000–1500 mg/day in two divided doses for 5 or more days, based on the patient's clinical condition (ISF, 2009).

Intravenous Administration.

Adults: 400 mg/day in two divided doses.

Complicated Urinary Tract Infections

Oral Administration.

Adults: 500–1000 mg/day in two divided doses for 1–2 weeks.

Children (1–17 years): 10–20 mg/kg (avoid single doses >750 mg, even in patients weighing more than 51 kg) twice daily for 10–21 days.

Intravenous Administration.

Children (1–17 years): 6–10 mg/kg (avoid single doses >400 mg, even in patients weighing more than 51 kg) three times daily for 10–21 days.

Simple or Complicated Acute Pyelonephritis (Empirical Therapy)

Oral Administration.

Adults: 1000–1500 mg/day in two divided doses for 1 week; extend to 3 weeks or more in cases of abscess, multidrug-resistant organism, or chronic renal failure.

Intravenous Administration.

Adults: 800–1200 mg/day in 2–3 divided doses for 1 week; extend extend to 3 weeks or more in cases of abscess, multidrug-resistant organism, or chronic renal failure (ISF, 2009).

Pelvic Inflammatory Disease

Intravenous Administration.

Adults: 400 mg/day in two doses, combined with other antimicrobial agents (The Medical Letter, 1999).

Acute Uncomplicated Gonorrhea (Urethritis and Cervicitis)

Oral Administration.

Adults: Single dose of 250–500 mg.

Intravenous Administration.

Adults: 100 mg single dose daily for acute cases; 200 mg/day in two divided doses for chronic cases.

Chancroid (Venereal Ulcer)

Oral Administration.

Adults: 1000 mg/day in two divided doses for 3 days (The Medical Letter, 1999).

Prostatitis

Oral Administration.

Adults: 1000 mg/day in two divided doses for up to 4 weeks.

Respiratory Tract Infections

Oral Administration.

Adults: 500–1000 mg/day in two divided doses for 1–2 weeks.

Intravenous Administration:

Adults: 400–800 mg/day, depending on infection severity, in two divided doses.

Skin and Soft Tissue Infections

Oral Administration.

Adults: 1000 mg/day in two doses for 5–10 days.

Osteomyelitis

Oral Administration.

Adults: 1000 mg/day in two doses for 4–6 weeks.

Severe Bacterial Enteritis

Oral Administration.

Adults: 1000 mg/day in two divided doses for 3–7 days.

Diarrhea

Intravenous Administration.

Adults: 400 mg/day in two divided doses.

Traveler's Diarrhea

Prophylaxis (Oral Administration).

Immunocompromised adults: 500 mg daily during travel and for 2–21 days after return (The Medical Letter, 2002; 2008).

Treatment (Oral Administration).

Adults: 750 mg once daily or 1000 mg/day in two divided doses for 3 days (ISF, 2000); 1000 mg/day in two divided doses for 1–3 days (The Medical Letter, 2008).

Severe Systemic Infections by Gram-negative Bacteria

Oral Administration.

Adults: 1000–1500 mg/day in two divided doses, with duration tailored to infection and patient status.

Acute Pulmonary Exacerbation of Cystic Fibrosis Due to Pseudomonas aeruginosa

Oral Administration.

Children and adolescents (5–17 years): 40 mg/kg/day in two doses (max 1500 mg/day) for 10–14 days.

Intravenous Administration.

Children and adolescents (5–17 years): 30 mg/kg/day in three doses (max 1200 mg/day).

Severe, Potentially Life-threatening Infections (Osteomyelitis, Sepsis, Pneumonia from Streptococcus, Recurrent Infections in Cystic Fibrosis, Severe Skin/Soft Tissue Infections, or Peritonitis)

Oral Administration.

Adults: 1500 mg/day in two divided doses.

Intravenous Administration.

Adults: 1200 mg/day in three doses.

Typhoid Fever

Oral Administration.

Adults: 1000 mg/day in two doses for 10 days.

Inhalational Anthrax

Oral Administration.

Adults: 1000 mg/day in two divided doses for 60 days; 28 days if anthrax vaccine available.

Children: 20–30 mg/kg/day in two divided doses for 60 days; 28 days with vaccine (The Medical Letter, 2001).

Intravenous Administration.

Adults: 800 mg/day in two doses for 60 days.

Children: 20 mg/kg/day in two doses (max 800 mg/day) for 60 days.

Genitourinary Surgical Prophylaxis

Oral Administration.

High-risk adults positive or unavailable urine culture, preoperative catheter, transrectal prostate biopsy): 500 mg.

Intravenous Administration.

High-risk adults (positive or unavailable urine culture, preoperative catheter, transrectal prostate biopsy): 400 mg (The Medical Letter, 2001).

Meningitis Prophylaxis

Oral Administration.

Adults: 500 mg single dose (Doctor, 2003).

Corneal Ulcers

Topical Administration.

Adults and children (>1 year): 2 drops of eye drops (containing 3 mg/ml ciprofloxacin) every 15 minutes for the first 6 hours, then every 30 minutes for the rest of the first day, every hour on the second day, and every 4 hours thereafter. Alternatively, apply a dose (approximately 1.25 cm) of ointment (containing 3 mg/g of ciprofloxacin) into the conjunctival sac, 12–24 times per day (i.e., every 1–2 hours) during the first 2 days of treatment, then 6 times per day (every 4 hours) for the subsequent 12 days, including nighttime applications.

Ocular Infections

Topical Administration.

Adults and children (>1 year): 1–2 drops of eye drops (containing 3 mg/ml ciprofloxacin) 6 times/day (every 2 hours, only during the day) for the first 2 days, then 3 times/day (every 4 hours, only during the day) as infection resolves. Alternatively, apply a dose (1.25 cm) of ointment (containing 3 mg/g ciprofloxacin) into the conjunctival sac 3 times/day for the first 2 days of treatment, then twice daily for 5 days.

Special patient populations

Elderly Patients

Dosing adjustments may be necessary based on infection severity and renal function, assessed via creatinine clearance.

Renal Impairment

Adjustments depend on renal function level.

Mild impairment (creatinine clearance: 31–60 ml/min/1.73 m^2, serum creatinine between 120 and 170 mcmol or 1.4-1.9 mg/dl): max 800 mg/day (IV) or 1000 mg/day (oral).

Moderate to severe impairment (creatinine clearance <30 ml/min/1.73 m², serum creatinine >175 mcmol or >2.0 mg/dl): max 400 mg/day (IV) or 500 mg/day (oral; can be increased to 750 mg/day in severe infections). However, the intervals between administrations do not change.

Administer ciprofloxacin post-hemodialysis.

In peritonitis in patients on continuous ambulatory peritoneal dialysis, based on limited clinical experience with this indication, add 50 mg ciprofloxacin per liter of dialysate every 6 hours.

Hepatic Impairment

Dose adjustment may be necessary only for severe hepatic impairment.

Combinations

Otological Preparations

Ciprofloxacin plus Hydrocortisone

Topical administration.

Adults and children (>2 years): 6 drops of suspension/day (containing 2 mg/ml ciprofloxacin and 10 mg/ml hydrocortisone) in two doses for 1 week.

Contraindications

Contraindications for ciprofloxacin use:

2) Hypersensitivity to ciprofloxacin or other quinolones (risk of cross-sensitivity);
3) History of tendon disorders related to fluoroquinolones (increased risk of tendon injuries with ciprofloxacin use);
4) Pediatric and adolescent patients, except for approved indications (potential risk of arthropathy);
5) Pregnancy (in vivo studies have shown maternal quinolone exposure may lead to fetal cartilage damage);
6) Breastfeeding (quinolones are excreted in breast milk).

Warnings

Duration of Therapy: The duration of antibiotic treatment depends on the severity of the condition and its clinical and bacteriological progression. It is recommended to continue ciprofloxacin therapy for at least two days after symptom resolution. On average: 1 day for uncomplicated acute gonorrhea and cystitis; up to 7 days for renal, urinary tract, and abdominal cavity infections; for the full neutropenic phase in immunocompromised patients; up to 2 months for osteomyelitis; and for 7–14 days in other infections. In streptococcal infections, treatment should continue for at least 10 days due to the risk of late complications. Chlamydia infections should also be treated for a minimum of 10 days.

Tendinopathy: The America agency responsible for drugs, The Food and Drug Administration (FDA), has added a warning to fluoroquinolone drug labels regarding potential tendon damage (oral, parenteral, inhaled). In October 2018, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) issued a restriction on fluoroquinolone and quinolone use due to the potential long-term and disabling musculoskeletal effects, albeit rare (European Medicines Agency - EMA, 2018). This was reinforced in November by the Committee for Medicinal Products for Human Use (CHMP) (European Medicines Agency - EMA, 2018a). Tendonitis or tendon rupture may rarely occur with systemic fluoroquinolones, during or months after treatment. Tendon damage related to fluoroquinolone therapy is rare; the estimated incidence in the general population is 0.14-0.40%. Tendon damage risk is higher in patients >60 years or those on corticosteroids. Incidence can reach 15% in organ transplant recipients (Muzi et al., 2007). High-intensity physical activity, renal insufficiency, and prior tendon disorders such as rheumatoid arthritis also increase this risk. Tendinitis and tendon rupture have, however, also been reported in patients without the above-mentioned risk factors.

A case-control study conducted in Italy on 22,194 cases of non-traumatic tendinitis and 104,906 controls found that the use of fluoroquinolones was significantly associated with various tendon disorders, tendon rupture and Achilles tendon rupture. Achilles tendon rupture occurred following treatment with fluoroquinolones in 1 of 5989 patients of any age and in 1 of 1638 patients aged > 60 years (Corrao et al., 2006).

Ciprofloxacin should be discontinued immediately if a patient experiences pain, swelling, or tendon rupture, and an alternative antibiotic should be considered.

Hypersensitivity: Rare hypersensitivity reactions, sometimes after the first dose, may occur and can progress to anaphylactic shock. Ciprofloxacin should be discontinued immediately in such cases, and medical assistance should be sought (e.g., anti-shock therapy).

Hepatic Adverse Reactions: Hepatic necrosis and potentially fatal hepatic failure have been reported with ciprofloxacin use. Signs or symptoms of liver disorders (e.g., anorexia, jaundice, dark urine, itching, abdominal tenderness) require immediate discontinuation and medical consultation.

CNS Adverse Reactions: Adverse CNS effects may occur following the first systemic or inhaled dose, and in rare cases, depression and psychosis can induce self-harming behaviors. In July 2018, the FDA updated the risk/benefit assessment for fluoroquinolones, citing potential neuropsychiatric risks, including cognitive disorders, delirium, nervousness, agitation, and disorientation (Food and Drug Administration - FDA, 2018). In October, the EMA issued a restriction on fluoroquinolone use for similar reasons (European Medicines Agency - EMA, 2018, 2018a). Treatment should be stopped if such reactions occur.

Hypoglycemia: Severe hypoglycemia has been reported with fluoroquinolones, especially in elderly patients or those with diabetes, renal insufficiency, or concurrent hypoglycemic agents or insulin. Symptoms of significant glucose reduction (e.g., confusion, dizziness, headache, sweating) warrant discontinuation of ciprofloxacin and, if feasible, a switch to an antibiotic from another class (Food and Drug Administration - FDA, 2018).

Epilepsy and CNS Disorders: Patients with epilepsy or other CNS lesions (e.g., reduced seizure threshold, seizure history, stroke) should use ciprofloxacin only after a careful risk/benefit assessment due to increased risk of CNS adverse effects.

Cardiac Disorders: Ciprofloxacin has rarely been associated with QT interval prolongation. Caution is advised in patients with a predisposition to torsades de pointes arrhythmias.

Aortic Aneurysm and Dissection: Epidemiologic and preclinical studies have shown an association between fluoroquinolones and an increased risk of aortic aneurysm and dissection (Pasternak et al., 2018; LeMaire et al., 2018; Daneman et al., 2015, Lee et al., 2015). This is believed to be a class effect as already observed for tendon lesions. Aortic aneurysm and dissection are rare events, with an incidence of 3-30 cases per 100,000 people per year. Factors that increase the risk include: family history of aneurysm, pre-existing aortic aneurysm or aortic dissection, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension and atherosclerosis. Patients with risk factors for aortic aneurysm and dissection, particularly if elderly, should be carefully evaluated before prescribing ciprofloxacin, considering alternative treatments when possible (Agenzia Italiana del farmaco - AIFA, 2018).

Hydration: Crystalluria has been reported with ciprofloxacin; patients should be well hydrated to avoid this effect, and excessive urinary alkalinity should be avoided.

Glucose-6-Phosphate Dehydrogenase Deficiency: Patients with this deficiency or related family history are predisposed to hemolytic reactions with quinolones; ciprofloxacin should be used with caution in such patients.

Photosensitivity: Ciprofloxacin and other fluoroquinolones may cause photosensitivity. Patients should avoid unnecessary sun exposure and UV radiation. If sun exposure is unavoidable, sunscreen should be used, and treatment should be stopped if photosensitivity occurs.

Injection Site Reactions: Local reactions at injection sites are possible if infusion time is ≤30 minutes or if small hand veins are used. These reactions typically resolve post-infusion.

Myasthenia Gravis: Ciprofloxacin can worsen symptoms of myasthenia gravis. Discontinuation of treatment should be considered if symptoms worsen.

Tuberculosis: Ciprofloxacin's activity against Mycobacterium tuberculosis may yield false-negative cultures if samples are taken during ciprofloxacin treatment.

Severe Infections: For severe infections (e.g., sepsis), ciprofloxacin should be combined with an appropriate antimicrobial. Ciprofloxacin monotherapy is only appropriate if pathogens sensitive to ciprofloxacin have been confirmed or suspected based on clinical context.

Syphilis: Ciprofloxacin is ineffective for syphilis treatment. Antimicrobial agents used in high doses for short periods in the treatment of gonorrhea may mask or delay the incubation symptoms of syphilis. Patients treated with ciprofloxacin for gonorrhea should undergo syphilis testing at diagnosis and again 3 months post-treatment.

Mumps: Ciprofloxacin is not recommended for uncomplicated acute mumps (penicillinase-resistant penicillin or a cephalosporin is preferred).

Pneumonia: Ciprofloxacin is not recommended as a first-line treatment for pneumococcal pneumonia (Carbon, 1993).

Pseudomembranous Colitis: Severe or persistent diarrhea during or post-treatment with ciprofloxacin may indicate pseudomembranous colitis (this infection can be life-threatening). Ciprofloxacin should be stopped, and appropriate treatment initiated.

CYP450 Metabolism: Fluoroquinolones may competitively inhibit CYP3A and CYP1A-mediated biotransformation, increasing co-administered drugs' plasma levels and potential side effects (McLellan et al., 1996). Monitoring for overdose symptoms is advised for patients on drugs metabolized by these enzymes.

Corticosteroids: Concomitant corticosteroid use increases tendon rupture risk, and combination therapy is discouraged (European Medicines Agency - EMA, 2018, 2018a).

Barbiturates: Cardiovascular function should be monitored if intravenous ciprofloxacin is given with barbiturate anesthetics.

Theophylline: Concurrent theophylline administration may elevate plasma levels, potentially leading to life-threatening theophylline-induced side effects. Theophylline levels should be monitored, and dosage adjusted if necessary.

Cyclosporine: Temporary serum creatinine increases have been reported with cyclosporine and ciprofloxacin co-administration. Creatinine levels should be checked biweekly.

Methotrexate: Ciprofloxacin may inhibit methotrexate's renal tubular transport, increasing plasma levels and toxicity risk. Close monitoring is advised if co-administration is necessary.

Alkalinizing Drugs: Patients should be monitored for crystalluria or nephrotoxicity.

Sucralfate, Antacids, and Mineral Supplements: Avoid simultaneous administration with ciprofloxacin. Administer ciprofloxacin 1–2 hours before or 3–4 hours after these products.

Benzalkonium Chloride: Fluoroquinolone eye drops containing benzalkonium chloride should not be used with extended wear contact lenses. Benzalkonium chloride tends to concentrate in the lens, damaging the eye once the lenses are put back in.

Sodium: Some ciprofloxacin infusion solutions contain sodium, which should be considered for patients on sodium-restricted diets.

Glucose: some ciprofloxacin intravenous formulations contain glucose, which should be considered for diabetic patients.

Incompatibility: Ciprofloxacin is incompatible with sodium heparin, flucloxacillin, amoxicillin, amoxicillin/clavulanic acid, and aminophylline.

Attention Capacity: Caution is advised in activities requiring alertness and coordination, as ciprofloxacin may impair attention.

Renal Insufficiency: Dosage adjustment is required for renal impairment.

Hepatic Insufficiency: Generally, no dosage adjustment is needed for hepatic impairment.

Elderly: Increased risk of tendinopathy and tendon rupture. Ciprofloxacin should not be administered at intervals shorter than 12 hours to minimize accumulation risk (Vance-Bryan et al., 1990).

Pediatrics: Ciprofloxacin should be used in pediatric patients <18 years only for registered indications due to the risk of weight-bearing joint arthropathy observed in immature animals.

Pregnancy: Quinolones should be avoided in pregnant women due to observed arthropathy in animal studies, with safer alternatives available.

Lactation: Ciprofloxacin is contraindicated during breastfeeding, as therapeutic doses are excreted into breast milk at levels potentially affecting the infant.

Interactions

Garlic: In an animal model of chronic bacterial prostatitis, garlic exhibited a synergistic effect with ciprofloxacin; the combination of garlic and ciprofloxacin led to a significant reduction in bacterial growth and improved prostatic inflammation compared to ciprofloxacin alone (Sohn et al., 2009).

Aminoglycosides: Demonstrates a synergistic effect against certain strains of Enterobacteriaceae and *P. aeruginosa* (Haller, 1985).

Anticoagulants: Ciprofloxacin can potentiate the anticoagulant effects of coumarins, thereby increasing the risk of bleeding (Penning-van Beest et al., 2008).

Antimalarials: Some fluoroquinolones and antimalarial drugs may prolong the QT interval (Owens, Nolin, 2006); concurrent use is therefore discouraged to avoid cardiac arrhythmias.

Azlocillin, Mezlocillin: Subtherapeutic doses increase the therapeutic activity of ciprofloxacin against *P. aeruginosa* and *E. coli* (Haller, 1986).

Banana: Pharmacokinetic parameters (serum concentration, AUC or Area Under the Curve, peak concentration, elimination rate) and the antimicrobial activity of ciprofloxacin are significantly reduced when administered with unripe banana pulp. This effect is likely due to the formation of complexes between ciprofloxacin and multivalent cations in the fruit, which decrease absorption and thus bioavailability of the antibiotic (Sv et al., 2003).

Benzodiazepines: Benzodiazepine premedication does not alter ciprofloxacin levels; however, a 7-day pretreatment with ciprofloxacin significantly reduced the clearance of a single intravenous dose of diazepam and prolonged its half-life in healthy volunteers (Kamali et al., 1993).

BM-Test-7 (urinary glucose test): Ciprofloxacin may yield false-positive results.

Byakkokaninjinto: This kampo preparation (a Japanese variant of traditional Chinese medicine based on herbal practices), composed of five components (Anemarrhena asphodeloides rhizome, ginseng root, licorice root, rice grains, fibrous gypsum) (Kimura et al., 1999), contains several metal cations. It reduces ciprofloxacin bioavailability without affecting renal excretion by decreasing gastrointestinal absorption of the antibiotic via insoluble chelate formation with calcium (Ohnishi et al., 2009).

Caffeine: Ciprofloxacin inhibits hepatic metabolism of caffeine, increasing its plasma concentration (Marchbanks, 1993).

Cyclosporine: Co-administration of cyclosporine and quinolones can result in synergistic nephrotoxicity (Avent et al., 1988).

Chloroquine: Co-administration with ciprofloxacin increases cumulative urinary concentration and excretion rate of the antibiotic (Ilo et al., 2008).

Clozapine: Ciprofloxacin inhibits CYP1A2 and CYP3A4 enzymes, resulting in delayed metabolism and elevated plasma concentrations of clozapine, which can cause adverse effects (Brouwers et al., 2009).

Oral Contraceptives: Ciprofloxacin (500 mg twice daily for 7 days) does not reduce the efficacy of co-administered oral contraceptives (Maggiolo et al., 1991).

Corticosteroids: An increased risk of tendon damage has been observed with fluoroquinolones combined with corticosteroids; co-administration is not recommended (European Medicines Agency – EMA, 2018, 2018a).

Dairy Products: Reduces ciprofloxacin absorption; this effect is attributed not only to ciprofloxacin-calcium complexation but also to the adsorption of the antibiotic on casein surfaces, reducing the absorbable drug quantity (Pápai et al., 2010).

Diclofenac: Co-administration of oral ciprofloxacin and diclofenac increases AUC and peak concentration of the antibiotic while reducing its peak time and total clearance (Iqbal et al., 2009).

Duloxetine: Ciprofloxacin can inhibit duloxetine metabolism, potentially increasing plasma concentrations of the antidepressant; concurrent use should be avoided.

NSAIDs, Foscarnet: Convulsant activity of fluoroquinolones may be enhanced by concurrent administration of NSAIDs (Kim et al., 2009) or foscarnet (Fan-Harvard et al., 1994).

Phenazopyridine: Co-administration with ciprofloxacin increases the antibiotic's bioavailability, particularly the AUC and duration in the body, which may be useful in treating urinary infections where phenazopyridine is often prescribed to alleviate symptoms (Marcelín-Jiménez et al., 2006).

Phenytoin: Clinical and experimental evidence shows that concurrent administration of quinolones in patients treated with phenytoin may reduce serum concentrations, potentially triggering seizures in treated epilepsy (Job et al., 1994).

Glyburide: A case of prolonged hypoglycemia in a diabetic patient on glyburide was reported following ciprofloxacin administration, likely due to complex, multifactorial interactions (Lin et al., 2004).

Indirubin: Enhances ciprofloxacin efficacy against *Staphylococcus aureus* by four-fold MIC reduction, likely through inhibition of the efflux pump mechanism responsible for antibiotic resistance (Ponnusamy et al., 2010).

Ketoconazole, Itraconazole: Increase peak concentration, half-life, mean residence time, and AUC of ciprofloxacin, with no effect on peak time but reduced clearance via renal excretion inhibition (Abou-Auda et al., 2008).

Lanthanum Carbonate: Significantly reduces systemic exposure to orally administered ciprofloxacin, with reductions in AUC, peak concentration, and 24-hour urinary excretion by 54%, 56%, and 52%, respectively (How et al., 2007).

Methadone: Ciprofloxacin administration in a patient with over six years on methadone resulted in profound sedation, confusion, and respiratory depression,

likely due to CYP1A2 and CYP3A4 inhibition, key enzymes in methadone metabolism (Herrlin et al., 2000).

Metoclopramide: By accelerating gastric emptying, metoclopramide can reduce the time to peak concentration of ciprofloxacin.

Methotrexate: Ciprofloxacin may delay the elimination of methotrexate, potentially increasing its toxicity (Dalle et al., 2002).

Mexiletine: Concurrent administration of ciprofloxacin and mexiletine may lead to elevated mexiletine concentrations due to reduced clearance (Labbé, Turgeon, 1999).

Omeprazole: Omeprazole does not influence the pharmacokinetic plasma or urinary parameters of an extended-release oral formulation of ciprofloxacin (Washington et al., 2006).

Opioids: Concentrated dry opium extract appears to reduce the plasma peak of ciprofloxacin. Premedication with opioid analgesics in surgical settings may decrease ciprofloxacin plasma concentrations.

Pentamidine: Both pentamidine and certain fluoroquinolones can prolong the QT interval (Owens, 2004); therefore, concomitant use of these drugs may increase the risk of arrhythmias.

Pentoxifylline: Co-administration of ciprofloxacin with the primary active metabolite of pentoxifylline (rapidly converted to pentoxifylline in vivo) significantly raises serum concentrations of both pentoxifylline and its active metabolite. This combination could be exploited to enhance the pharmacological effects of pentoxifylline (Raoul et al., 2007).

Didanosine preparations containing cations: Ciprofloxacin bioavailability is reduced when co-administered with didanosine formulations containing cations (Sahai et al., 1993).

Procainamide, N-acetylprocainamide: Ciprofloxacin significantly decreases the renal clearance of these compounds (Bauer et al., 2005).

Probenecid: Probenecid reduces renal tubular secretion of ciprofloxacin and its metabolite desethylene-ciprofloxacin (M1), likely through a competitive mechanism (Landersdorfer et al., 2010).

Strontium ranelate: Cations reduce quinolone absorption, thus concurrent use of strontium ranelate during ciprofloxacin antibiotic therapy is not recommended.

Ropinirole: Ciprofloxacin increases plasma concentration of ropinirole by inhibiting its metabolism (Kaye, Nicholls, 2000).

Ropivacaine: Ciprofloxacin reduces the mean clearance of ropivacaine by inhibiting CYP1A2-mediated formation of its 3-hydroxy derivative and increases the formation of (S)-2,6-pipecoloxylidide via CYP3A4. There is substantial interindividual variability in these interactions, potentially leading to toxic effects in certain individuals receiving both drugs concurrently (Jokinen et al., 2003).

Sevelamer: Co-administration of sevelamer reduces ciprofloxacin bioavailability (Kays et al., 2003).

Sildenafil: Ciprofloxacin significantly increases sildenafil bioavailability, likely due to inhibitory effects on CYP3A4. Dose adjustment of sildenafil may be necessary when co-administered with ciprofloxacin (Hedaya et al., 2006).

Simvastatin: A case of rhabdomyolysis has been reported following the addition of ciprofloxacin to chronic simvastatin therapy. As ciprofloxacin is a weak CYP3A4 inhibitor, other mechanisms involving drug efflux transporters, such as ATP-binding cassette (ABC) proteins, may be implicated in this interaction (Sawant, 2009).

Fruit juices: Ciprofloxacin absorption may be reduced by concomitant ingestion of fruit juices containing calcium carbonate and grapes; thus, ciprofloxacin should not be taken with such beverages to avoid the risk of therapeutic failure due to subtherapeutic drug levels in systemic circulation (Akinleye et al., 2007).

Sucralfate, antacids containing aluminum or magnesium, calcium-, iron-, zinc-containing preparations: reduce ciprofloxacin absorption likely due to chelation (Deppermann, Lode, 1993; Polk, 1989).

Theophylline: Ciprofloxacin may inhibit hepatic metabolism of theophylline, increasing plasma concentration (up to 114% in the elderly), reducing clearance (up to 56-64% in the elderly), and potentially increasing central nervous system toxicity (seizures).

Tizanidine: Ciprofloxacin consistently increases plasma concentrations of tizanidine, dangerously potentiating its hypotensive and sedative effects, mainly by inhibiting its CYP1A2-mediated metabolism (Granfors et al., 2004).

Triclosan: Triclosan weakens the survival ability of bacterial cells associated in biofilms when exposed to ciprofloxacin, likely by enhancing the antibiotic's permeability or activity (Tabak et al., 2009).

Warfarin: Quinolones can increase prothrombin time. Co-administration of warfarin and extended-release ciprofloxacin formulations does not result in significant pharmacokinetic or pharmacodynamic interactions, with only a slight increase in R-warfarin half-life, not considered clinically significant (52.6 hours vs 50.1 hours; p=0,029) (Washington et al., 2007).

Zolmitriptan: Quinolones may inhibit zolmitriptan metabolism; dose adjustment is recommended if necessary.

Side effects

Side effects occur in approximately 4-10% of patients, leading to treatment discontinuation in 1.5% of cases. In 2008, six suspected adverse reactions (one of which was serious) to ciprofloxacin were reported in adolescents aged 12 to 17 years (BIF, 2009).

In July 2018, the U.S. Food and Drug Administration (FDA) published the findings of an internal review of the fluoroquinolone class, which revealed a class-wide risk of severe hypoglycemia (including coma) and neuropsychiatric disorders (attention disorders, memory impairment, delirium, nervousness, agitation, and disorientation). The drugs included in the review were ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin. Data analyzed were drawn from the literature and the FDA Adverse Event Reporting System (FAERS), covering the period from 1987 to 2017 (Food and Drug Administration - FDA, 2018).

Cardiovascular: (uncommon) palpitations; (very rare) transient loss of consciousness (syncope), peripheral edema, flushing, tachycardia, hypertension; (parenteral administration) phlebitis, thrombophlebitis; aortic aneurysm and dissection.

Rare cases of QT interval prolongation, ventricular arrhythmia, and torsades de pointes (a type of ventricular tachycardia) have been reported, as well as isolated cases of stroke (Adverse Drug Reaction Bulletin, 2000) and hemorrhagic vasculitis (van den Berg et al., 2010).

Systemic and inhaled administration of fluoroquinolones has been associated with an increased risk of aortic aneurysm and dissection, particularly in elderly patients (Agenzia Italiana del Farmaco - AIFA, 2018; Pasternak et al., 2018; Daneman et al., 2015; Lee et al., 2015).

Central Nervous System: (common) tremors, dizziness, headache; (very rare, including isolated reports) sweating, paresthesia (sensitivity alteration characterized by numbness, tingling), ataxia (lack of muscle coordination), increased intracranial pressure, orofacial dyskinesia (abnormal movement of lips, tongue, jaw); seizures, more common in patients with renal impairment or other electrolyte imbalances (Kushner et al., 2001); a case of hemiballism (a hyperkinetic syndrome characterized by large, violent movements of one side of the body, often involving proximal muscles) has been reported in a patient with liver cirrhosis (Kim et al., 2009).

Dermatologic: (common) skin reactions (itching, rash, drug fever); (very rare) hemorrhagic blisters, petechiae (pinpoint skin hemorrhages), crusted papules indicating vascular involvement (vasculitis), erythema nodosum, severe erythema multiforme (Stevens-Johnson syndrome), urticaria, Lyell’s syndrome (epidermal necrolysis), photosensitivity.

Gastrointestinal: (common) digestive disorders, loss of appetite, nausea, vomiting, diarrhea, abdominal pain, flatulence; (rare) pseudomembranous colitis (colitis associated with antibiotic use). A case of hemorrhagic segmental colitis has been reported (Boesler et al., 2009).

Hematologic: (uncommon) anemia, thrombocytopenia, eosinophilia, leukopenia, granulocytopenia, epistaxis; (very rare) hemolytic anemia, pancytopenia (reduction of white blood cells, red blood cells, and platelets below normal values), leukocytosis, thrombocytosis, agranulocytosis, prothrombin alterations.

Hepatobiliary: (very rare) pancreatitis; increases in liver enzymes (transaminases, alkaline phosphatase) and bilirubin, cholestatic jaundice (bile duct obstruction), more frequently in patients with pre-existing liver damage; hepatitis and hepatic necrosis up to potentially fatal liver failure.

Metabolic: blood glucose alterations (hyper/hypoglycemia); severe hypoglycemia (including coma). In the FDA's internal review, published in July 2018, 67 cases of hypoglycemic coma were reported, the majority of which were in patients with risk factors for hypoglycemia. Of these, 20 cases were reported in non-diabetic patients not on hypoglycemic medications, including insulin; hypoglycemia was fatal in 13 patients and resulted in permanent damage in 9. Twelve cases were attributed to ciprofloxacin (levofloxacin: 44; moxifloxacin: 9; ofloxacin: 2) (Food and Drug Administration - FDA, 2018).

Musculoskeletal: (uncommon) joint swelling and arthralgia; (very rare, including isolated reports) tenosynovitis (inflammation of the tendon sheath), muscle pain, tendinitis and tendon rupture, exacerbation of myasthenia symptoms; a case of rhabdomyolysis following interaction with simvastatin has been reported (Sawant, 2009).

Ophthalmic: deposition of a white precipitate on the ocular surface (reversible with dose reduction or drug discontinuation), photophobia, corneal staining, allergic reactions; (very rare) visual disturbances such as diplopia (double vision) or chromatopsia (distorted color perception).

Otological: (very rare) transient hearing loss (particularly high-frequency hearing), tinnitus.

Psychiatric: (common) confusion, fatigue, agitation; (very rare, including isolated reports) nightmares, insomnia, anxiety, hallucinations, distress, depression, psychotic reactions (potentially leading to self-harm); (post-marketing) attention disorders, memory disorders, delirium, nervousness, and disorientation (Food and Drug Administration - FDA, 2018; European Medicines Agency - EMA, 2018).

Respiratory: (uncommon) dyspnea, hiccups, pulmonary embolism, pulmonary edema, hemoptysis.

Sensory Organs: dysgeusia (altered taste perception) and dysosmia (altered smell perception), with possible loss of the sense of smell, typically resolving upon therapy cessation.

Systemic: infections and infestations; allergic reactions manifesting as vasculitis, anaphylaxis, toxic epidermal necrolysis; (very rare) asthenia.

Urological: (very rare, including isolated reports) transient renal function alterations (up to temporary renal failure), crystals or blood in urine, transient elevation in serum creatinine or urea, interstitial nephritis; a case of bilateral hydronephrosis from ciprofloxacin-induced crystalluria and stones has been reported (Chopra et al., 2000).

Toxicity

Overdose: Following the ingestion of excessive doses of ciprofloxacin, patients may experience seizures, dizziness, tremors, headaches, mental confusion, fatigue, hallucinations, gastrointestinal disturbances, hepatic and renal abnormalities, crystalluria, hematuria, QT interval prolongation, and reversible renal damage (in cases of acute and extreme overdose). In case of overdose, gastric lavage or the administration of activated charcoal and antacids containing calcium or magnesium may be appropriate to reduce ciprofloxacin absorption. The patient should be closely monitored and provided with both symptomatic and supportive treatment; renal function should be monitored, and the patient should be hydrated to prevent the deposition of crystals in the urine. Hemodialysis or peritoneal dialysis can remove only a minimal amount of the drug (<10%).

Chronic toxicity: In sub-acute (4 weeks), sub-chronic (3 months), and chronic (6 months) tolerability studies, ciprofloxacin was generally well tolerated; however, in some animal species, pseudo-allergic reactions due to histamine release, crystal deposition in urine, and tubular renal alterations were observed. Renal damage is not due to a primary toxic action of the drug on renal tissue but rather to the precipitation of crystals (composed of ciprofloxacin, magnesium, and proteins) within the renal tubules. Some quinolones have caused alterations (of varying severity, depending on age, animal species, and dosage) in the weight-bearing joints of immature animals, observable even months after treatment; however, the damage may be mitigated by unloading the joints. Although ciprofloxacin binds to the retina, in vivo studies have demonstrated that it does not cause any damage to this organ.

Carcinogenicity: In vivo studies have shown no evidence of ciprofloxacin carcinogenicity.

Mutagenicity: In vivo studies have not demonstrated any significant mutagenic activity of ciprofloxacin.

Reproductive toxicity: Ciprofloxacin is classified in teratogenic risk category C (drugs for which animal studies have shown harmful effects on the fetus, including teratogenic or lethal effects, and for which there are no controlled studies in women, or no studies are available for either humans or animals). The drug should only be administered if the potential benefit justifies the potential risk to the fetus. In vivo, quinolones cause joint damage in immature animals and their fetuses; however, in humans, their use during the first trimester of pregnancy has not been associated with fetal harm (Schaefer et al., 1996; Loebstein et al., 1998). At doses typically used in clinical practice, the teratogenic risk associated with quinolone use is likely low; however, given the limited data available, their absolute safety cannot be confirmed with certainty (Friedman, Polifka, 2000), and thus their use during pregnancy is contraindicated, except in exceptional cases (e.g., severe infection that cannot be treated with other antimicrobial agents) (Garbis et al., 2001).

LD50: Following oral administration, approximately 5000 mg/kg (in mice and rats), 2500 mg/kg (in rabbits); following intravenous administration, approximately 290 mg/kg (in mice), 145 mg/kg (in rats), 125 mg/kg (in rabbits), and 250 mg/kg (in dogs).

Pharmacology

Ciprofloxacin is a fluoroquinolone antibiotic, structurally related to nalidixic acid but differentiated by substitutions at the N1 and C7 positions of the quinolone nucleus.

Ciprofloxacin exerts both a direct action on the bacterial cell and an indirect action that impairs bacterial virulence. The direct action involves inhibition of DNA gyrase (topoisomerase II), leading to blockage of DNA supercoiling and repair in bacterial cells. The indirect action results from alterations in regulatory systems that control cell morphology and adhesion, production of extracellular enzymes, and maintenance of plasmid units.

The indirect action of the antibiotic on the bacterial cell manifests, in vitro, at concentrations below the minimum inhibitory concentration (MIC) (Sosstein, Burnham, 1993).

Ciprofloxacin demonstrates selectivity for topoisomerase II, being active on the human enzyme at concentrations 100 times higher than those required to inhibit bacterial growth. In vitro, at high concentrations, it also appears capable of inhibiting mitochondrial topoisomerase II (Lawrence et al., 1993).

The antibiotic has a broad spectrum of activity encompassing Gram-negative, Gram-positive, and anaerobic bacteria.

Ciprofloxacin appears to be four times more potent than other fluorinated analogs (norfloxacin, ofloxacin, enoxacin) (Tanimura et al., 1986). Unlike norfloxacin, it is more active against Chlamydia, Mycoplasma, and certain mycobacterial species (Furet, Pechere, 1991).

Gram-negative Bacteria: Highly active (MIC90 ≤1 mg/mL) against Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Haemophilus influenzae, Proteus spp., Morganella morganii, Serratia spp., Citrobacter spp., Acinetobacter spp., Pseudomonas aeruginosa, Neisseria meningitidis, and Neisseria gonorrhoeae. Active (MIC90: 4 mg/mL) against Providencia spp., Pseudomonas spp. (Terp, Rybay, 1987).

Gram-positive Bacteria: Active (MIC90 <2 mg/mL) against Staphylococcus aureus, Staphylococcus epidermidis, and streptococci (excluding penicillin-resistant strains), as well as cocci resistant to co-trimoxazole, ampicillin, mezlocillin, gentamicin, and ceftazidime (Klietmann et al., 1987).

Effective against Salmonella spp., Shigella spp. (MIC90: 0.020 mg/mL); Campylobacter spp. (MIC90: 0.5 mg/mL); less active against anaerobic bacteria (Clostridium spp. MIC90: 1 mg/mL; Clostridium difficile MIC90: 16 mg/mL; Bacteroides spp. MIC90: 16 mg/mL; Bacteroides fragilis MIC90: 8 mg/mL).

An MIC90 of 4 mg/mL inhibits 99% of Gram-positive strains, 98.5% of Gram-negative strains, and 85% of anaerobes (Klietmann et al., 1987).

The antibiotic appears active against infections caused by Mycobacterium tuberculosis and Mycobacterium avium intracellular (Kehana, Spino, 1991).

It is effective in necrotizing otitis externa (symptom resolution in 90% of patients) and urethral or rectal gonorrhea, even in cases with penicillinase-producing N. gonorrhoeae strains.

Ciprofloxacin appears capable of eradicating the carrier state of Neisseria meningitidis, including in rifampicin non-responders (97% of patients).

Urinary Tract Infections

Ciprofloxacin is as effective as co-trimoxazole in bacterial eradication and more effective than trimethoprim (follow-up at 5–10 days: 94% vs. 75%; follow-up at 4 weeks: 75% vs. 44%) (Newsom et al., 1986).

In treating uncomplicated urinary tract infections, ciprofloxacin achieves bacterial eradication in 80% of treated patients. In cases of complicated infections (e.g., P. aeruginosa), it provides complete clinical response in 85-95% of patients (Fass, 1987); response is greater in patients under 65 years (98% vs. 88%).

For cystitis, ciprofloxacin, norfloxacin, and ofloxacin are effective, with only 5% of infecting organisms displaying resistance (Winstanley et al., 1997). To prevent increased resistance, these antibiotics should be restricted to complicated infections or cases with pathogens unresponsive to other antimicrobials (DTB, 1998).

Ciprofloxacin is also effective in patients unresponsive to co-trimoxazole and in both acute and chronic prostatitis (100% response rate).

Preoperative Prophylaxis

Postoperative infection rates are similar between ciprofloxacin and cefotaxime (6% vs. 8%), but lower with ciprofloxacin after three weeks of follow-up (8% vs. 16%) (Cox, 1989).

Administered prophylactically in urogenital surgery, ciprofloxacin reduces postoperative infection incidence (40% treated vs. 11% placebo); short-term administration is effective in the absence of preoperative infection (infections in 3.4% of treated vs. 19.4% untreated patients), while long-term administration is effective in the presence of preoperative infection (8.8% treated vs. 86.6% untreated patients) (Grabe et al., 1987).

Respiratory Infections

Ciprofloxacin shows therapeutic activity comparable to ceftriaxone, cefamandole, ceftazidime, and amoxicillin.

In chronic pulmonary disease exacerbations, it shows comparable therapeutic efficacy to trimethoprim-sulfamethoxazole (92.6% vs. 97.4%), with lower bacterial resistance rates (1.8% vs. 25%) (Grossman et al., 1994).

It is effective in achieving complete symptom remission in lower respiratory infections (85% of patients; bacterial eradication 66–93%), in cystic fibrosis caused by P. aeruginosa (80% of patients), and in drug-resistant chronic bronchopneumopathies. Fluoroquinolones are first-line antibiotics for treating bronchiectasis exacerbations (minimum therapy duration: 7–10 days) (Doctor, 2002).

Relapses have been reported with ciprofloxacin in respiratory infections (Thys et al., 1991).

Ocular Infections

Ciprofloxacin is more effective than ofloxacin against P. aeruginosa but less effective against C. trachomatis (Drug Ther. Bull., 1994). It shows similar efficacy to tobramycin and chloramphenicol for bacterial conjunctivitis and to cefazolin/gentamicin or tobramycin for keratitis (Drug Ther. Bull., 1994).

Skin and Soft Tissue Infections

Ciprofloxacin shows limited efficacy in skin and soft tissue infections, and its use in Staphylococcus aureus infections is associated with high resistance (14–90%) (Shalit et al., 1989).

In treating pressure ulcers, ciprofloxacin results in a higher clinical and bacterial eradication response compared to cefotaxime (88% vs. 69%).

Anthrax

For anthrax post-exposure prophylaxis, ciprofloxacin shows similar efficacy to doxycycline. In a study, a group of monkeys (n=60) was exposed to inhaled spores of Bacillus anthracis and subsequently randomized to receive an antibiotic (ciprofloxacin, doxycycline, or penicillin G), a placebo (saline solution), or two doses of anthrax vaccine. Following treatment, the mortality due to infection was as follows: none in the group treated with doxycycline and vaccine (n=9); one in the ciprofloxacin group (n=9); one in the doxycycline group (n=10); three in the penicillin G procaine group (n=10); eight in the group receiving only the vaccine (n=10); and nine in the placebo group (n=10) (Friedlander et al., 1993).

Diarrhea

Ciprofloxacin is effective for acute diarrhea caused by E. coli, Salmonella, Shigella, Campylobacter, and Aeromonas (90% of patients); relapse rates were observed with Campylobacter and Salmonella infections (20–25%) (Nethwani, Wood, 1992).

In severe acute diarrhea, quinolones are frequently used in developed countries; for gastroenteritis of unknown origin, ciprofloxacin and norfloxacin reduce symptom duration by 24–36 hours (ISF, 2000).

For traveler’s diarrhea, a short course (1–3 days) of a fluoroquinolone like ciprofloxacin is recommended only in moderate or severe cases, persisting beyond three days, with bloody stools or fever (Dupont, 2006).

Typhoid Fever

Ciprofloxacin provides complete clinical response (100%) in typhoid fever without recurrences or chronic carrier status; it is effective in eradicating the carrier state in chronic typhoid carriers (Nethwani, Wood, 1992).

Osteomyelitis

Ciprofloxacin is effective in treating osteomyelitis caused by both Gram-negative (80%) and Gram-positive bacteria (75–90%), with the exception of Staphylococcus aureus.

Antitumor Activity

Due to its bactericidal mechanism of action, specifically the inhibition of topoisomerase II, an enzyme responsible for alterations in the three-dimensional structure of DNA during replication, transcription, and chromatin condensation, ciprofloxacin can induce cell cycle arrest and apoptosis in cancer cells. Its efficacy has been confirmed in several in vitro studies conducted on tumor cell lines, and it is particularly high against non-small cell lung cancer, attributed to the accumulation of ciprofloxacin in the lung following intravenous administration (Kloskowski et al., 2010).

Resistance

Resistance to ciprofloxacin likely stems from mutations in topoisomerase II or alterations in cell membrane permeability (Hooper, Wolfson, 1991). Cross-resistance among quinolones is possible.

Most anaerobic bacteria are resistant to ciprofloxacin (Terp, Rybak, 1987). Resistance also appears in *Chlamydia trachomatis*, *Pseudomonas cepacia*, *Pseudomonas maltophilia*, some strains of *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (especially methicillin-resistant strains).

Resistance to P. aeruginosa and S. aureus appears to be reduced, in vitro, by drugs that can increase cell permeability (such as sodium deoxycholate, tobramycin, amiloride, sulfonamides, and para-aminobenzoic acid) (Michael et al., 1993).

The resistance of Campylobacter spp. to fluoroquinolones has been prevalent since the early 1980s; more recently, strains of Salmonella exhibiting decreased sensitivity to fluoroquinolones have been isolated during episodes of bacteremia (ISF, 2000).

Pharmacokinetics

After oral administration, ciprofloxacin is absorbed from the gastrointestinal tract. The presence of food in the stomach tends to delay the plasma peak.

Bioavailability: 60-70%.

Peak plasma concentration: 1.18 mg/L (250 mg dose); 2.15 mg/L (500 mg dose); 2.71 mg/L (750 mg dose).

Time to peak plasma concentration: 1-2 hours.

Bioavailability increases in elderly patients compared to younger patients (72% vs. 58%), resulting in higher values for both plasma peak and AUC (increase from 30% to 140%) in patients over 64 years, following both single and multiple doses (Ljungberg, Nilsson-Ehle, 1989).

After intravenous administration, the peak plasma concentration is 4.28 mg/L (200 mg dose).

Serum protein binding: 20-40%.

Steady-state volume of distribution (Vd): 1.7-5.0 L/kg.

Ciprofloxacin is distributed to lung tissue, bronchial mucosa, pleural exudate, and sputum at concentrations exceeding the MIC for many pathogens.

Therapeutic fluoroquinolone concentrations are achieved in the liver, gallbladder, bile (with concentrations reaching 10 times plasma levels), and pancreatic fluid; in the pelvis (1.3-3.7 times plasma concentration); in prostate tissue (2-10 times plasma concentration); in bone; peritoneal fluid; in the eye, specifically the anterior chamber and aqueous humor; and in cerebrospinal fluid.

Ciprofloxacin concentrations in cerebrospinal fluid are adequate for treating Enterobacter meningitis but not for infections caused by Pseudomonas or Staphylococcus species (Vance-Bryan et al., 1990).

Ciprofloxacin crosses the placenta and is excreted in breast milk.

Ciprofloxacin is metabolized into desethylene-ciprofloxacin, sulfo-ciprofloxacin (the primary metabolite in feces), oxo-ciprofloxacin (the primary metabolite in urine), and formyl-ciprofloxacin.

Half-life: 3-4 hours, which tends to increase in elderly patients.

Clearance: 26.6-86 L/h.

Renal clearance: 14.7-28.6 L/h, representing approximately 60-70% of total clearance.

Clearance values tend to decrease in elderly patients.

Ciprofloxacin undergoes renal excretion (glomerular filtration and tubular secretion) and, for about one-third, hepatic and fecal excretion.

The drug is almost completely eliminated within 24 hours: approximately 40-50% of the oral dose and 70% of the intravenous dose are excreted in urine in unchanged form, and about 15% and 10%, respectively, as metabolites. Approximately 20-35% of the oral dose and 15% of the intravenous dose are excreted in feces within 5 days.

Pharmacokinetic parameters vary in cases of renal insufficiency, leading to increased half-life (up to double), peak plasma concentration, and AUC values (Vance-Bryan et al., 1990).

Dialysis removes less than 2% of the drug from plasma in 4 hours.

Classification

Chemical formula

$C_{17}H_{18}FN_3O_3$

Molecular weight

331.35

Atc code

J01MA02

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