CHAPTER IV

LITERATURE REVIEW OF DRUGS SELECTED

4.1 Norfloxacin – A Profile

Fig. 4.1.1: Chemical structure of norfloxacin

Chemical Name : 1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1H quinoline-3-carboxylic acid
Molecular Formula: C₁₆H₁₈FN₃O₃
Molecular Weight : 319.34
Description : White to pale yellow crystalline powder
Solubility : Freely soluble in glacial acetic acid, and very slightly soluble in ethanol, methanol and water.
\( p^Ka \) value : 6.22 & 8.51
Melting point : 221 °C

Pharmacology, bioavailability and pharmacokinetics:

Mechanism of action:

Norfloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division. Although human cells do not contain DNA gyrase, they do contain a topoisomerase enzyme that functions in the same manner. This mammalian enzyme is not affected by bactericidal concentrations of quinolones. It is unclear how
inhibition of DNA gyrase leads to bacterial cell death. Both rapid and slow growing organisms are inhibited by fluoroquinolones. In addition, fluoroquinolones exhibit a prolonged post-antibiotic effect (PAE). Organisms may not resume growth for 2-6 hours after exposure to norfloxacin, despite undetectable drug levels.

**Pharmacokinetics:**

Norfloxacin is administered orally and topically to the eye. Norfloxacin is widely distributed to body tissues and appears to cross the placenta. Protein binding is approximately 10-15%. Biliary concentrations of norfloxacin can be up to 10-fold higher than serum concentrations. It is not known whether the drug distributes into breast milk.

Norfloxacin is eliminated primarily through biliary and renal excretion. It is only moderately metabolized in the liver. A few of these metabolites may be active, but they are not as active as the parent compound. The plasma half-life of norfloxacin is 2.3-4 hours in adults with normal renal function. Approximately 26-32% of an oral dose is eliminated unchanged in the urine within 24 hours, 5-8% is eliminated in the urine as metabolites, and 28-30% is excreted in the bile and feces.

Following oral administration, norfloxacin oral absorption is incomplete, unlike other fluoroquinolones. Bioavailability is approximately 30-50% for norfloxacin, but 70-80% for ciprofloxacin and 95-98% for lomefloxacin. The presence of food, dairy products, or divalent/trivalent cations can further decrease bioavailability if administered simultaneously. Peak plasma concentrations are attained within 1-2 hours after oral administration. Single doses of 800, 1200, or 1600 mg administered to healthy, fasting adults results in peak serum concentrations of 2.4, 3.2, or 3.9 mcg/ml respectively.
Contraindications:

Norfloxacin is contraindicated in those with a history of tendonitis, tendon rupture and those with a hypersensitivity to fluoroquinolones. Concomitant administration with tizanidine is contraindicated.

Norfloxacin is contraindicated in patients with known quinolone hypersensitivity. Serious and sometimes fatal hypersensitivity reactions have occurred after even the initial dose of the drug. Norfloxacin should be discontinued if an allergic reaction such as a rash occurs.

All systemic fluoroquinolones should be used cautiously in patients with cardiac arrhythmias or other cardiac disease that predisposes to cardiac arrhythmias. Fluoroquinolones have the potential to cause QT prolongation and possibly torsade de pointes by blocking human cardiac potassium (K+) channel currents. Because of poor systemic bioavailability after oral administration, norfloxacin is not likely to cause QT prolongation and is almost exclusively used to treat urinary tract infections.

Systemic norfloxacin can cause CNS stimulation and exacerbate central nervous system disorders. Norfloxacin should be used with caution in patients with CNS disorders (such as seizures) or cerebrovascular disease (such as cerebral arteriosclerosis). Concomitant administration of NSAIDs and quinolones, including norfloxacin, may increase the risk of CNS stimulation and convulsive seizures. Use quinolones cautiously in patients already taking NSAIDs.

Patients receiving norfloxacin or other fluoroquinolones have experienced phototoxic reactions. Patients should avoid excessive sunlight (UV) exposure or
artificial ultraviolet light. Norfloxacin therapy should be discontinued if phototoxicity occurs.

Avoid systemic quinolones, such as norfloxacin, in patients with a history of myasthenia gravis. Quinolones may exacerbate the signs of myasthenia gravis and lead to life threatening weakness of the respiratory muscles. Serious post-marketing events, including deaths and the requirement for ventilatory support, have been associated with quinolone use in patients with myasthenia gravis.

Disturbances of blood glucose have been reported in patients with diabetes mellitus who were receiving an oral hypoglycemic agent or insulin concomitantly with quinolone antibiotics, such as systemic norfloxacin. Careful monitoring of blood glucose is recommended. Patients with diabetes may also be at an increased risk of developing detachment of the retina\(^5\).

**Dosage and administration**

Ailments such as typhoid fever caused by Salmonella typhi, uncomplicated urinary tract infection (UTI), including cystitis, due to Escherichia coli, Klebsiella pneumoniae, or Proteus mirabilis and traveler's diarrhea are being treated with the usual doses of 15 mg/kg/day PO given in two divided doses for 5-7 days\(^6\), 400 mg PO every 12 hours for 3 days and 400 mg PO every 12 hours up to 3 days\(^7\) respectively. The Penultimate doses are only for adults.

To treat bacterial conjunctivitis, the usual dose for adults and children is instill one drop of 0.3% solution in affected eye four times daily for up to 7 days. For severe infections instill 1-2 drops every 2 hours for the first day.
Adverse effects:

Joint and tendon problems, as seen with all drugs within this class, have been associated with norfloxacin. In 1989 Jeandel et al comments on arthritis being induced by norfloxacin. Within the cases of tendinopathy reported to the FDA from 1987 to 1997, more reports of ruptures and tendonitis were associated with norfloxacin, than any other fluoroquinolone in use at that time. Norfloxacin-induced hepatitis, and acute pancreatitis has also been linked to norfloxacin.

Serious visual complications have also been reported to occur with ophthalmic fluoroquinolone therapy, which may also occur with norfloxacin eye drops, especially corneal perforation, but also evisceration and enucleation. This increased incidents of corneal perforation may be due to fluoroquinolones causing alterations in stromal collagen, leading to a reduction in tectonic strength.

Storage: Store at 25°C; excursions permitted to 15-30°C, protected from light and moisture.
4.2 Ciprofloxacin HCl – A Profile

![Chemical structure of ciprofloxacin HCl]

**Fig. 4.2.1: Chemical structure of ciprofloxacin HCl**

Chemical Name : 3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, monohydrochloride, monohydrate.

Molecular Formula : C₁₇H₁₈FN₃O₃·HCl·H₂O

Molecular Weight : 385.82

Description : Faintly yellowish to light yellow crystalline substance

Solubility : in water: 3.5g/dL

  in methanol: 0.21g/dL

  in acetic acid: 0.14g/dL

  in ethanol: 0.016g/dL

Soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in acetone, in ethyl acetate and in methylene chloride.

pKᵣ value : 6.2 & 8.59

Melting point : 318-320°C
Pharmacology, bioavailability and pharmacokinetics

Mechanism of action:

Ciprofloxacin is a broad-spectrum antibiotic active against both Gram positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV \(^1\), enzymes necessary to separate bacterial DNA, thereby inhibiting cell division.

Pharmacokinetics:

Ciprofloxacin is administered orally as extended-release tablets, immediate-release tablets, oral suspension, and intravenously as an infusion. Ciprofloxacin is also administered via the ophthalmic and otic routes. Plasma protein binding of ciprofloxacin is low (20-40%) and the antibiotic is widely distributed into most tissues. Penetration into CSF is minimal when meninges are not inflamed. Concentrations higher than serum are achieved in bile, lungs, kidney, liver, gallbladder, uterus, seminal fluid, prostate tissue, tonsils, endometrium, fallopian tubes and ovaries.

Following oral administration of immediate-release tablets or suspension, ciprofloxacin hydrochloride is rapidly absorbed from the GI tract and undergoes minimal first-pass metabolism; in healthy, fasting adults, 50-85% (mean: 70%) of a dose is absorbed. Peak serum concentrations ranging from 1.6-2.9 mcg/ml are reached in 0.5-2.3 hours after a 500 mg oral dose. When ciprofloxacin immediate-release tablets are given with food, the time to peak concentration is delayed (e.g., 2 hours after dosing rather than 1 hour); there is no delay when ciprofloxacin suspension is given with food. The overall absorption of ciprofloxacin from immediate-release tablets or suspension is not substantially affected by food. Mean concentrations 12 hours after oral dosing with 250
mg, 500 mg, or 750 mg immediate-release tablets are 0.1, 0.2 and 0.4 mcg/ml, respectively.

**Contraindications:**

All fluoroquinolones, including systemic ciprofloxacin, should be used cautiously in patients with cardiac arrhythmias or other cardiac disease that predisposes to cardiac arrhythmias. Fluoroquinolones have the potential to cause QT prolongation and possibly torsade de pointes by blocking human cardiac potassium (K+) channel currents\textsuperscript{2,3}.

Systemic quinolones, including ciprofloxacin, should be used with caution in patients with CNS disorders (such as seizures) or cerebrovascular disease (such as cerebral arteriosclerosis) that may predispose to seizures or lower the seizure threshold or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain Drug therapy, renal impairment).

Patients receiving systemic ciprofloxacin and other fluoroquinolones have experienced phototoxic reactions\textsuperscript{4}. Moderate to severe photosensitivity/phototoxicity reactions can occur after being exposed to direct or indirect sunlight or to artificial ultraviolet light (e.g., sunlamps) during or after treatment with ciprofloxacin.

Avoid systemic quinolones, like ciprofloxacin, in patients with a history of myasthenia gravis. Quinolones may exacerbate the signs of myasthenia gravis and lead to life threatening weakness of the respiratory muscles. Serious post-marketing events, including deaths and the requirement for ventilatory support, have been associated with quinolone use in patients with myasthenia gravis.

Disturbances of blood glucose have been reported in patients with diabetes mellitus who were receiving an oral hypoglycemic agent or insulin concomitantly with
systemic quinolone antibiotics, like ciprofloxacin. Careful monitoring of blood glucose is recommended. Patients with diabetes may also be at an increased risk of developing detachment of the retina.5

**Dosage and administration**

Ailments such as typhoid fever caused by Salmonella typhi, uncomplicated urinary tract infection (UTI), including cystitis, due to Escherichia coli, Proteus mirabilis, E. faecalis, or S. saprophyticus and traveler's diarrhea are being treated with the usual doses of 15 mg/kg/day PO given in two divided doses for 5-7 days, 400 mg PO every 12 hours for 3 days and 500 mg PO every 12 hours up to 3 days respectively. The Penultimate doses are only for adults.

To treat bacterial conjunctivitis, the usual dose for adults and children is instill one drop of 0.3% solution in affected eye four times daily for up to 7 days. For severe infections instill 1-2 drops every 2 hours for the first day.

For the treatment of severe and/or complicated infections:

*Intravenous dosage:*

**Adults:** 400 mg IV every 8 hours. Duration of therapy is 7-14 days for skin and skin structure infections. Bone and joint infections may require therapy for 4-6 weeks or longer

**Children:** 15-20 mg/kg/day IV divided every 12 hours, depending on the severity of the infection.

*Oral dosage:*

**Adults:** 750 mg PO every 12 hours. Duration of therapy is 7-14 days for skin and skin structure infections. Bone and joint infections may require therapy for 4-6 weeks or
longer.

*Children:* 20-30 mg/kg/day PO divided every 12 hours, depending on the severity of the infection. Maximum dose is 1.5 g/day.

**Adverse effects:**

The serious adverse effects that may occur as a result of ciprofloxacin therapy include irreversible peripheral neuropathy\(^{17}\), spontaneous tendon rupture and tendonitis, acute liver failure or serious liver injury (hepatitis)\(^{18,19}\), QTc prolongation/torsades de pointes, toxic epidermal necrolysis (TEN)\(^{20,21}\), and Stevens–Johnson syndrome, severe central nervous system disorders (CNS) and Clostridium difficile associated disease (CDAD: pseudomembranous colitis)\(^{22}\) as well as photosensitivity/phototoxicity reactions. Psychotic reactions and confusional states, acute pancreatitis\(^{23}\), bone marrow depression, interstitial nephritis and hemolytic anemia may also occur during ciprofloxacin therapy \(^{24,25}\). Additional serious adverse reactions include temporary, as well as permanent, loss of vision \(^{26,27}\), irreversible double vision \(^{28}\), drug induced psychosis \(^{29,30}\) and chorea (involuntary muscle movements) \(^{31}\), impaired color vision, exanthema, abdominal pain, malaise, drug fever, dysaesthesia and eosinophilia \(^{17}\). Pseudotumor cerebri, commonly known as idiopathic intracranial hypertension (IIH), (also referred to as increased intracranial pressure), has been reported to occur as a serious adverse reaction to ciprofloxacin\(^{32}\).

**Storage:** Preserve in tight, light-resistant containers. Store at 25°C, excursions permitted between 15°C and 30°C.
REFERENCES


32. Winrow AP; Supramaniam Benign intracranial hypertension after ciprofloxacin administration. Archives of Disease in Childhood. (1990), 65 (10): 1165-1166.