Fluoroquinolones

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Abstract

Fluoroquinolones are synthetic compounds, structurally related to nalidixic acid. Its mechanism of action involves inhibition of bacterial DNA-gyrase. They have a broad spectrum of activity. They are highly active against Enterobacteriaceae and also active against some strains of Pseudomonas aeruginosa and Staphylococcus sp., however recent reports indicate increasing resistance. They have poor activity against streptococci and anaerobes. These agents exhibited excellent oral absorption, good tissue distribution and are excreted primarily by way of the kidney. The incidence of adverse effects of fluoroquinolones appears to be low. The most common are gastrointestinal reactions, followed by central nervous system disorders. Hypersensitivity reactions occur occasionally. Fluoroquinolones interact with a number of other agents, with potential clinical manifestations, such as antacids, theophylline, and warfarin.

The bioavailability after oral administration allows the use of these agents without loss of efficacy, when compared with IV administration, thus reducing substantially the treatment cost.

Key words, fluoroquinolones, antimicrobials, norfloxacin, ciprofloxacin, ofloxacin, pefloxacin.

Introduction

Fluoroquinolones (6-fluor-7-piperazinilquinolone) are synthetic derivatives chemically related with the nalidixic acid (*Fig. 1*).[1]

Although the mechanism of action is not yet fully clarified, it is thought they act inhibiting DNA-gyrase, a crucial enzyme in DNA replication. [2,3]

Antimicrobial activity

Fluoroquinolones are antimicrobial agents of wide spectrum, very active against Gram (-), namely Enterobacteriaceae and Pseudomonas show less activity against Gram (+): although active against Staphylococcus aureus, its activity regarding Streptococcus is reduced. It is similarly limited the activity of fluoroquinolones against anaerobes.[2,4,5]

Pharmacokinetics

They are well absorbed after oral administration, being higher the absorption regarding the ofloxacin and to pefloxacin (*Table 1*).[1,6]

With exception to norfloxacin, penetrate well in most tissues – lungs, bladder, prostate, purulence, salivation, bones and aqueous humor – reaching tissue concentration higher than the corresponding serial ones. [1,6]

Low serum concentrations associated to a lower antimicrobial activity make that norfloxacin should only be used in urinary tract infections.

The penetration on cerebrospinal fluid is changeable increasing with inflammatory meninges. However tissue concentrations are rather inferior to the matching serum concentrations.[1,6]

Half-life although changing between different fluoroquinolones, allow an administration gap or 12 hours or above.[1,2,6]

They undergo liver metabolization in variable degrees, changing from pefloxacin which is extensively metabolized to ofloxacin which is excreted practically unaltered in the urine.

The elimination is preferentially renal although there is some biliary excretion.[1,2,6]

Recommended use

Fluoroquinolones have been widely used in clinical practice both to outpatients as inpatients. However it is necessary to be used under a rigorous criteria.[2,6,7]

Fluoroquinolones are a therapy alternative of interest in different clinical situations. However, they are only first choice agents in infections as Shigella, Salmonella spp and Campylobacter jejuni.[8]

Urinary tract infections

Although rather effective in such infections, they should be reserved for situations where pathogenic agents are involved which do not respond to conventional therapy, being first choice in urinary infections

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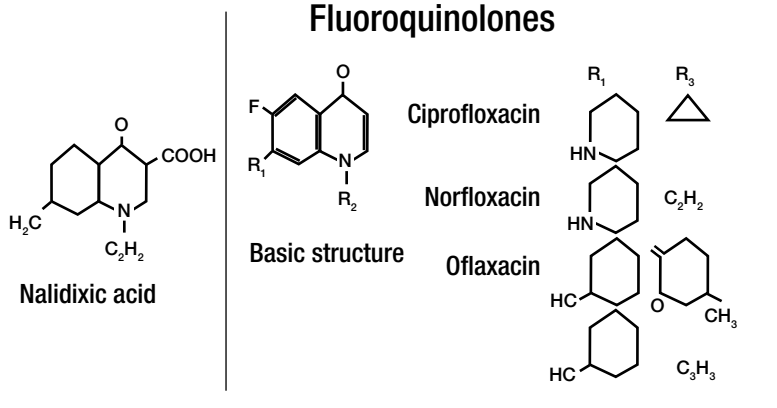

FIG. 1

to Pseudomonas aeruginosa.[8] They are agents of interest for prostatitis due to a good penetration in the prostate fluid but further studies are needed to evaluate its efficacy.[1,6,9]

Sexually transmitted diseases

All fluoroquinolones may be an alternative to ceftriaxone in the treatment of infections by N. gonorrhea (eg., allergy to beta-lactamas).[8] In what refers to infections by C. trachomatis, ofloxacin seems to be, within this group, the most active, being an alternative to tetracycline or erythromycin. Once that in gonococcus infections Chlamydia is often present, if the therapeutic alternative is considered for a fluoroquinolone, this would be preferentially the ofloxacin. [2,6,10] The ciprofloxacin had an important role in the treatment of chancroid, but equally as a second choice agent.[6,8]

Respiratory infections

The fluoroquinolones are not drugs of choice in community acquired pneumonia where the S. pneumoniae is still the most common causal agent.[6,11]

They should not be used in aspiration pneumonia once they have a limited activity against anaerobes.[2,6]

They can be a therapy alternative in Gram (-) infections of the lower airways tract. However it has been referred some therapeutic failures in Pseudomonas aeruginosa infections, namely regarding the ciprofloxacin which is within these antimicrobial the most active against this microorganism.[2,6,12]

They have been used in oral therapy (usually in combined therapy) in pneumonia associated to cystic fibrosis. However, the appearance of resistance, namely related to Pseudomonas, come to question the use of these drugs in this situation once that we are before a long term treatment.[1,2,6,13]

Due to the high concentrations obtained in the phagocytes cytosol, fluoroquinolones can have some interest in intracellular infections, and within these, in the field of respiratory infections they can be useful in more severe conditions of pneumonia by Legionella. They may in such cases be used in combination with erythromycin or in situations where the association erythromycin more rifampicin is not recommended.[2,6,14,15]

Ofloxacin and ciprofloxacin may in the future be important in the treatment of infections by Mycobacterium especially regarding multi-resistant strains (always in association).[6,15]

Ciprofloxacin in association with clarithromycin is referred as a first choice agent in the treatment of infections by Mycobacterium avium complex.[8]

Gastrointestinal tract infections

The high degree of activity against Enterobacteriaceae and the high concentration obtained in the intestinal lumen,

TABLE I

Pharmacokinetics – Dosage (mg)

	CIP	NOR	OFL	PEF
	200 IV 500 oral	400 oral	200 IV 400 oral	400 IV 400 oral
Bioavailability (%)	60-80%	35-45%	65-95%	90-100%
Vd(L)	165-307	>100	86-102	110-134
T ½ (h)	3-6	3-7	5-7	6-14
Prot. Liaison (%)	20-35	14	25	20-30
Elimination Renal (%) Fecal (%)	60-75 30-45 ? 17-35	?? – 30 28	73-82 80-90 3 4	? – 31-59 ? ?

TABLE II

Interactions

Drug	Fluoroquinolones	Effect	Recommendations
Anti-acids (Al/Mg/Ca) (?)Sucralphate (Al) Diuretic Sup. (Fe.Zn)	?? Oflox Ciprof ??	Absorption ↓ (????)	Administer 2-4 hours after quinolone
Theophylline	? ? ? ?	Serial concentrations Theophylline ↑ ? (by inhibition liver metabolism) O8, ????	Monitor theophylline serum concentration
Warfarin	? ? ? ?	??	??????????
NSAIDs	?	??	Surveillance Avoid simultaneous use in patients with seizures history

associated to a long half-life time of elimination, make the fluoroquinolones important drugs in the treatment of enteric bacterial infections.

They are drugs of choice in diarrhea by Shigella, Salmonella spp and Campylobacter jejuni.[2,6,8,16]

It is not usually recommended the empirical therapy of acute diarrhea. However, in infectious diarrhea the fluoroquinolones may be effective as often Enterobacteriaceae are involved. However it is necessary to weigh the risk/benefit due to the increase on resistances that has been verified regarding Campylobacter jejuni. [16-17] The selective suppression of fluoroquinolones in the intestinal flora, associated to the fact of still being relatively reduced the resistance to Enterobacteriaceae, induces the question on the role of such antimicrobial agents in the prophylaxis of Gram (-) infections in granulocytopenia patients. The results lead us once again to a binomial: if on one hand they seem to prevent effectively infections by Gram (-), on the other they seem to increase resistance to Gram (+) making patients more susceptible to these microorganisms.[16-18] The degree in which resistance emerges over time, will define which is the place of fluoroquinolones in this situation.

Soft tissue infections

Fluoroquinolones are not a first choice and their efficacy in these situations depends on the causal agent.

Streptococcus, as well as anaerobes often involved, are not very sensitive being more easily treated with other more specific agents. In Gram (-) infections, for instances in surgical lesions, where Enterobacteriaceae are often involved, fluoroquinolones may be of interest, once that besides a good activity facing these bacteria, allow an oral administration. Regarding Staphylococcus infections, also rather frequent, although there is activity against such microorganism, resistances will increase gradually.[1,2,6]

Bones and joints infections

As happens in most situations mentioned previously, fluoroquinolones are not a first choice.

As they have a good bone penetration, they are drugs of interest in osteomyelitis by Enterobacteriaceae. Similarly to what happens with soft tissues, they can be an alternative in infections by Staphylococcus, especially as they enable an oral administration with a therapeutic efficacy similar to the one achieved after endovenous administration, what is important in these situations requiring a long term treatment. However, one must reflect upon the emergence of developed resistance even during treatment.[1,2,6]

CNS Infections

These antimicrobial agents are not indicated in CNS infections by two reasons:

the concentration obtained in tissues change, being always lower that the matching serial concentration

they have a limited activity against some pathogenic agents potentially involved: Streptococcus

TABLE II

Posology

Fluoroquinolone	Adult	Decreased renal function
Norfloxacin	Oral Route 200-400 mg 12h-12h	Clor 0-30 Oral route 400mg/day
Ciprofloxacin	Oral Route 250-750 mg 12h – 12h IV 200 – 400 mg 12h – 12 h	Clor 30-80 Oral route 250-500 mg 12/12h IV usual dose Clor 5-30 Oral Route 250-500 mg 18/18h IV 200-400 mg 18/24h
Ofloxacin	Oral Route and Intravenous 200-400 mg 12h/12h	Clor 10-50 Usual dose 24/24h Clor -19 ½ usual dose 24/24 hours
??	Oral Route and Intravenous 400 mg – 12h / 12h	Usual dose

*in severe liver failure is recommended the dosage adjustment.

(important in meningitis) and anaerobes (important in cerebral abscesses).[2,6]

Prophylaxis in surgery

Similarly to what happens with other wide spectrum antimicrobial, fluoroquinolones should not be used in surgical prophylaxis due to the possibility of colonizing the patient and/or increased risk of emergence of reinfection with resistant bacteria.[6,19]

Side effects

Fluoroquinolones are usually safe drugs and in general well tolerated.

The most common secondary effects are the gastrointestinal (nausea and vomiting), and at CNS level (dizziness and headaches). Some cases of seizures have also been reported in elderly patients and/or with a previous history of epilepsy or other CNS lesions.

Other secondary effects, although rarer, are the hypersensitivity (rash, photosensitivity and anaphylactic reaction), liver, haematologic, renal and cardiovascular changes.

Lesions have been referred at the level of joint cartilages, reason why these drugs are not recommended in children, pregnant and breastfeeding women.[2,5,6,20]

Interactions

It is perfectly documented that fluoroquinolones can interact with other important drugs in clinical practice (Table 2).

Anti-acids and other drugs containing divalent ions reduce substantially fluoroquinolones absorption, probably by the formation of chelate, reason why they should be administered 2 to 4 hours after the fluoroquinolone administration.

One of the interactions of higher clinical significance it is verified with theophylline, possibly due to an inhibition of its metabolism at the P450 cytochrome, resulting in an increase in the serial concentrations of theophylline, being necessary to make its monitoring and dosage adjustment. However, this interaction it is not verified with the ofloxacin in normal dosages due to the fact that is the only fluoroquinolone that practically does not undergo a liver metabolization. Being necessary the simultaneous administration of theophylline and one fluoroquinolone, ofloxacin will be the choice.

Another marked interaction it is verified with warfarin, having an increase of prothrombin time, although its mechanism is not clear yet. Probably it will be by competition to the place of link to albumin or due to a reduction on the warfarin liver metabolism. Other interaction although not very well documented, it is verified with non-steroid anti-inflammatory drugs, increasing the risk of potentiating the side effects at CNS level and subsequently the risk of seizures.[2,6,21]

Dosage and administration

Table 3 has a description of the usual posology for adults.

In kidney failure is necessary to make an adjustment of dosage for all fluoroquinolones with exception of perfloxacin, that suffering a full hepatic metabolization only needs a reduction of dosage in a severe liver failure.[2,4]

All fluoroquinolones may be administered through oral and endovenous routes, except norfloxacin only administered orally.

Bioavailability of these drugs enables its oral administration without loss of therapeutical efficacy, making this route the one of choice.[2,4,5,6]

Conclusions

Fluoroquinolonas are safe drugs, being a good therapy alternative in several clinical situations, essentially because they enable an oral administration with equal efficacy to endovenous administration.

As it happens regarding all antimicrobial agents, the therapy option should be pondered, bearing in mind:

• The ratio risk/benefit, namely regarding the resistance emergence that has significantly increased with its high cost.

• The ratio cost/benefit particularly in endovenous therapy. ■

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