Fluoroquinolones in Ophthalmology

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Introduction

This class of drugs represents a particularly important therapeutic advance, since they have;

1. A broad antimicrobial activity
2. Are bactericidal
3. Relatively few side effects
4. Resistance does not develop rapidly

Development

The first quinolone (Nalidixic Acid) was developed in 1962 as a by-product of Chloroquine synthesis.
Cinoxacin, Pipemedic acid and Oxolinic Acid soon followed (II generation).

However their use was mainly restricted to the treatment of Urinary Tract Infections (UTI), due to their poor plasma concentration and excellent concentration in the Urinary System.

It was also observed that resistance developed rapidly, and that these were not effective against Pseudomonas Aeruginosa.

The Fluoroquinolones

Also called the fluorinated 4-quinolones (III and IV generation quinolones).

They contain a corboxylic acid moiety at the III position of the ring structure and a fluorine substituent at the VI position, Piperazine moiety at VII position.

Introduced in the 1980's and gained popularity in the 1990's.

Chemical characteristics

Piperazinyl group (at C7)

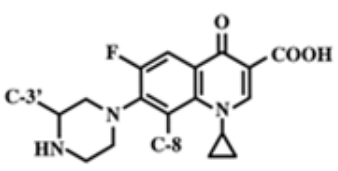
- Increases activity against Pseudomonas spp.

Fluorine atom (at C6)

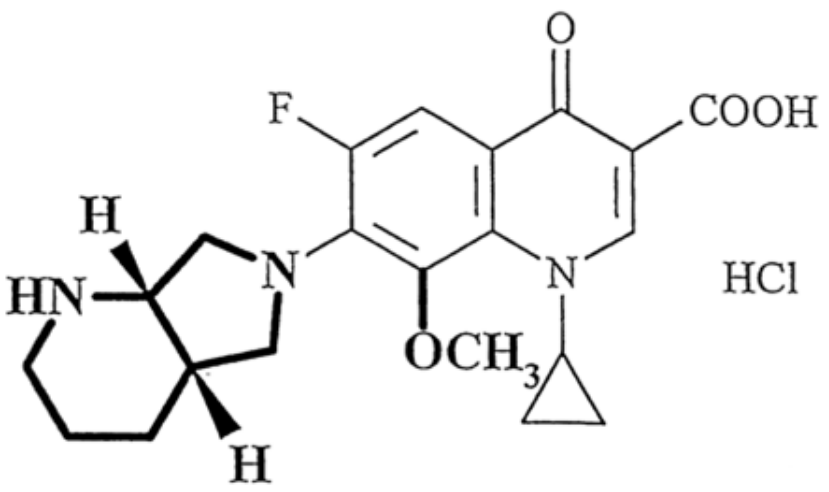
- Increases activity against some gram(+) bacteria

Carboxyl moiety (at C3)

- DNA binding



Gatifloxacin



Moxifloxacin

Drawbacks

Incompatibilities

- Large inocula (concentration dependent antibiotics as against time-dependent)
- Bivalent cations (e.g., Mg++) and other antacids -- chelation reduce bioavailability
- Alkaline pH decreases solubility (problem in urine if pH>7 with crystalluria)

Classification

Divided into 4 generations

Generation 1 = Nalidixic acid
Generation 2 = Oxolinic acid, Pipemidic acid, Cinoxacin

Generation 3 = Norfloxacin, Ciprofloxacin, Ofloxacin, Lomefloxacin, Pefloxacin, Fleroxacin, Amifloxacin, Sparfloxacin and Levofloxacin.
Generation 4 = Gatifloxacin and Moxifloxacin (developed in 1999 - introduced in 2003).

Mechanism of action

Generation 1-3 inhibit the DNA gyrase (topoisomerase II) in bacteria which causes failure in replication and cell death.

This action occurs at concentrations of 0.1 to 10 micro-grams/ml.

Why are human cells not affected?

- No DNA gyrase, but a similar type II topoisomerase which is inhibited at higher concentrations (100 to 1000 micro-grams/ml).

Generation 4 also inhibit topoisomerase IV.

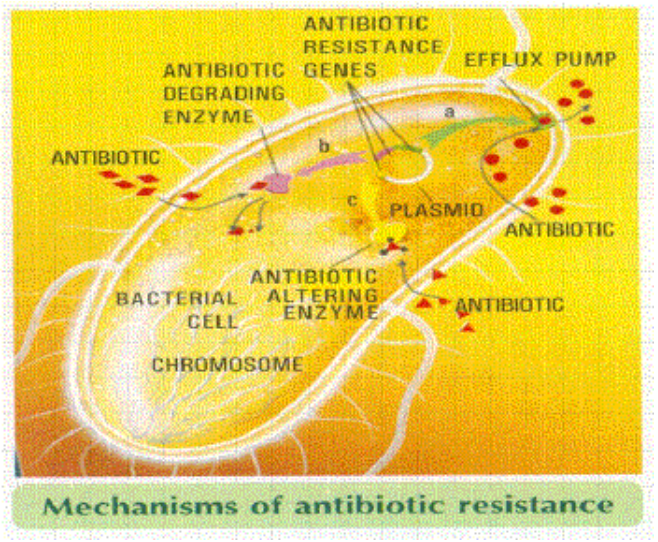
The Advantage of Gen-IV

The most apparent advantage of the IV generation lies in the fact that the drugs act by inhibiting both topoisomerases II and IV in both +ve & -ve. (Whereas the III generation were active against topo IV in gm +ve and topo II in gm -ve)

It would therefore appear that resistance to these drugs may not occur as a spontaneous mutation at two levels at once.

A possible mechanism of drug resistance development to this generation has been postulated - resistance at the bacterial cell wall by increased eflux (remains to be seen).

Bacterial resistance



The Moxifloxacin Advantage

Moxifloxacin has a unique advantage over Gatifloxacin in having a bi-cyclic C-7 side chain;
Which reduces the ability of the bacterial cells eflux pump to flush out the antibiotic,
This increased drug stay in the bacterial cell allows for;

- Enhanced activity
- Expanded spectrum of activity
- Additional defense against resistance.

Moxifloxacin is "KING"!

- The pH value is close to tears (6.8)
- Does not need a preservative
- Topical dosage need not be increased beyond thrice a day due to increased drug stay in the bacterial cell.
- Systemic administration - Has the lowest phototoxic and CNS adverse event potential among the currently available fluoroquinolones.

Spectrum of Action

Whereas the earlier quinolones had limitations in treating only the common Gm -ve infections (and had no action against Pseudomonas sp.), the newer generations have a broad spectrum.

- Most of the common Gm +ve organisms
- Gm -ve organisms (including Pseudomonas sp)
- Chlamydia, Mycoplasma, Legionella, Brucella and Mycobacteria (including tuberculosis).
- Most anaerobes are resistant with the exception to Sparfloxacin.

Susceptible Gm +ve

Corynebacterium sp.
Micrococcus luteus
Staphylococcus (aureus, epidermidis, haemolyticus, hominis, warneri, pneumoniae)
Streptococcus viridans group.

MAINLY - CIPROFLOXACIN, OFLOXACIN, PEFLOXACIN, SPARFOXACIN, GATIFLOXACIN AND MOXIFLOXACIN.

Susceptible Gm -ve

Acinetobacter
Haemophilus influenzae and parainfluenzae
Pseudomonas, enterococci, pneumococci and E coli (CIPROFOXACIN AND NORFLOXACIN)

Other susceptible organisms

Chlamydia trachomatis (OFLOXACIN given for a few days - Azithromycin 500 mg stat (single dose) more effective and the drug of choice)

Mycobacteria and Atypical Mycobacteria (CIPROFOXACIN OR OFLOXACIN with other drugs especially in cases of HIV related tuberculosis)

Adverse Effects (Systemic)

Generally well tolerated

2-12% report nausea, abdominal discomfort, headache and dizziness.

0.2% hallucinations, delirium, and seizures (especially when given in conjuction with theophylline, NSAID's) (CIPRO AND ENOXACIN).

Very rare - rashes and photosensitivity (accentuated by biotin deficiency), Leukopenia.

Arthralgias and joint swelling in prepubertal age.

Acute hepatitis and failure

- Trovafloxacin

Photosensitivity

- Sparfloxacin
  Lomefloxacin
  Pefloxacin

Levofloxacin, Gatifloxacin, Moxifloxacin and Ofloxacin have the least phototoxic potential.

QT prolongation & arrhythmia

- Grepafoxacin
  Moxifloxacin
  Levofloxacin
  Sparfloxacin
  Gatifloxacin

Blood sugar levels

Gatifloxacin & Moxifloxacin -

- Associated with hyperglycemia in DM
- Hypoglycemia in patients taking anti-diabetic drugs (insulin and glyburide)

Drug interactions

- NSAID, theophylline, warfarin (hepatic biotransformation)
- May be given after food, but not with chelating agents - upto 8 hours after taking antacids & 1-2 hours before taking antacids.
- Antacids (aluminum, calcium,or magnesium-containing)
- Laxatives (magnesium-containing, or sucralfate or Zinc)
- Ferrous sulfate and Bismuth salicylate

Precautions

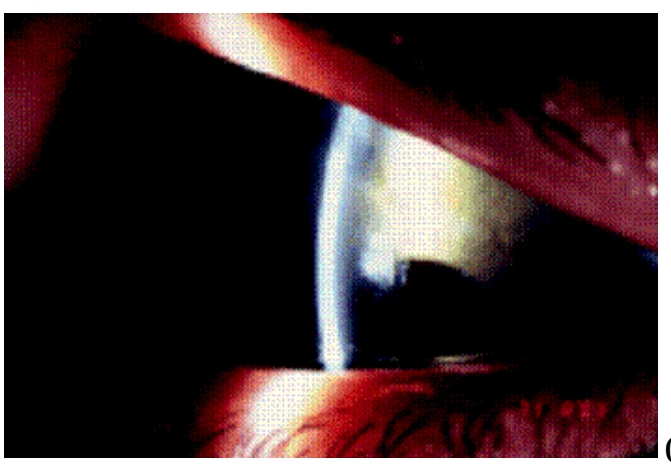
- History of hypersensitivity to the quinolones (Steven Johnson's type syndrome may occur).
- For systemic administration - hepatic and renal impairment needs to be considered.
- Achilles tendinitis and tendon rupture reported 2-42 days after systemic administration.
- Contraindicated in pts. with history of convulsions.
- Pregnancy category C - NOT to be given to pregnant mothers, lactating mothers (Adequate animal studies, inadequate human studies).

Ocular Adverse Reactions

1-6% of the patients report some of the following:

- conjunctival chemosis and inflammation
- reduced visual acuity (cause not known)
- dry eye, keratitis, ocular discomfort
- ocular pain, pruritis
- subconjunctival hemorrhage and tearing.
- Crystaline corneal deposits (Ciprofoxacin, Sparfloxacin, Norfloxacin, Ofloxacin and Gatifloxacin).

Ofloxacin in Cornea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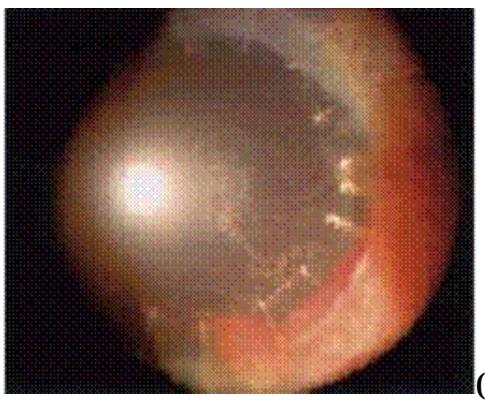
Sparfloxacin in Cornea

 **(from IJO, Dr Nikhil Gokhale)**

Corneal deposits implications

- Deposits occur at the superficial to mid-stromal level
- Usually occur whenever there is a break in the epithelium
- Cause delayed re-epithelization, therefore delayed wound healing
- Permanent.

Indications

Acute susceptible bacterial infections with or without breach in the epithelium.

Chronic susceptible bacterial infections - Chlamydia trachomatis

Prophylaxis - pre-surgical - administered topically 2-3 times before surgery (pre-surgical povidone iodine irrigation of the conjuctiva, cul-de-sacs, and painting of the lid margins is a must). (OFLOXACIN, GATIFLOXACIN AND MOXIFLOXACIN).

Gatifloxacin Vs Moxifloxacin

pH

- Moxifloxacin 0.5% has a pH of 6.8
- Gatifloxacin 0.3% has a pH of 6.0

Inference:

- Moxifloxacin being closer to neutral pH has a negligible chance of precipitation
- Also, Moxifloxacin has a higher solubility than Gatifloxacin at neutral pH

Penetration into the Aqueous

- Moxifloxacin achieves a concentration of 1.86 µg/ml
- Gatifloxacin achieves a concentration of 0.94 µg/ml

Due to the above fact - the Cmax is 10x the MIC, therefore the chances of mutation and resistance reduce significantly
No other anti-bacterial a Cmax that is 10x the MIC.

Why the better penetration?

Moxifloxacin is more soluble at neutral pH than Gatifloxacin
Moxifloxacin has a concentration of 0.5% as compared to 0.3% of Gatifloxacin
Moxifloxacin has a bi-phasic characteristic in penetration.

Preservatives

Moxifloxacin is preservative-free
Gatifloxacin has BAC (0.005%)

Advantage

Moxifloxacin maintains health and integrity of the corneal surface and thus has no effect on ulcer or wound healing

Disadvantage

The likelyhood of drug contamination with yeasts and amoeba increases (bottle tip handling)

Dosage

Moxifloxacin is recommended 3 times a day for 4 days in Acute Bacterial Conjunctivitis

Gatifloxacin is recommended 2 hourly initially and then 4 times a day (Patient compliance?)

Adverse reactions

The chances of conjunctival erythema are more with Moxifloxacin (p = .0005)
Reduction in pupil size with moxifloxacin (p = .001) (prostaglandin release)
5-10% cases on Gatifoxacin may develop keratitis and papillary conjunctivitis
All other systemic and topical adverse effects are similar
One case of Fatal Anaphylaxis has been reported with intra-venous Gatifloxacin