Reviews/Evaluations

Fluroquinolone Drug Class Review

Introduction

Fluoroquinolones are broad-spectrum antibiotics with concentration dependent bactericidal activity. The mechanism by which they exert this effect is by binding to and inhibiting topoisomerase II (DNA-gyrase) and topoisomerase IV. These bacterial enzymes are responsible for the coiling and uncoiling of DNA, which is needed for bacterial cell repair and replication.(1)

Fluoroquinolone Classification System (2-12)

Brand	Generic	Manufacturer	Generation	Microbiology	General Indications
NegGram	Nalidixic acid	Sanofi-synthelabo	1st	Gram Negative but not pseudomonas	Uncomplicated UTIs
Noroxin	Norfloxacin	Merck	2nd	As above but including pseudomonas. Some gram + including *s.aureus*. Not strep pneumoniae. Atypical including chlamydia, mycoplasma and legionella.	UTIs, Pyelonephritis, STD, Prostatitis, Skin and soft tissue infections
Maxaquin	Lomefloxacin	Searle	2nd		
Floxin	Ofloxacin	Ortho-McNeil	2nd		
Cipro	Ciprofloxacin	Bayer	2nd		
Levaquin	Levofloxacin	Ortho-McNeil	3rd	Same as above +expanded gram — including pen sensitive and resistant *s. pneumoniae*. More so with Tequin and Avelox	Acute exacerbations of chronic bronchitis and community acquired pneumoniae
Zagam	Sparfloxacin	Rhone-poulenc Rorer	3rd		
Tequin	Gatifloxacin	Bristol-Myers Squibb	3rd		
Avelox	Moxifloxacin	Bayer	3rd		
Trovan	Trovafloxacin	Pfizer	4th	Same as above plus broad anaerobic coverage	As above except UTIs and pyelonephritis. Plus intra-abdominal infections, PID and nosocomial pneumonia

The classification of the fluoroquinolones is somewhat informal and unstandardized, but it does serve a clinical purpose to classify them by their spectrum of action and indication. Often gatifloxacin and Moxifloxacin are put into the 4th generation category, which would make trovafloxacin 5th generation. The later generations of fluoroquinolones underwent structural

changes in order to improve their half-life, spectrum of activity and potential for less resistance. The addition of a methoxy- group in the R8 position (gatifloxacin and moxifloxacin) increases the binding affinity for topoisomerase II and IV, which increases the activity against *Streptococcus pneumoniae* and helps prevent resistance to all susceptible bacteria. A fluorine in the R8 position increases the potential for phototoxicity (Lomefloxacin, Sparfloxacin).(1,12-13)

Pharmacological Principles (2-12)

The maximum concentration (Cmax) is important because the fluoroquinolones' effectiveness is concentration-dependent. It has been shown that in order for bacteria to be highly susceptible to the fluoroquinolones and prevent resistant mutants, the Cmax must be 10 times that of the MIC when treating gram-positive bacteria. To calculate it another way, for gram-negative organisms the AUC-to-MIC ratio desired is greater than 125; for gram-positive organisms the AUC-to-MIC ratio should be at least 30.(14) Adjustment is required for ciprofloxacin, gatifloxacin, levofloxacin, ofloxacin and sparfloxacin when creatinine clearance is less than 50ml/min. Noroxin adjustment is required when creatinine clearance is less than 30 ml/min.

Pharmacokinetics of Fluoroquinolones

Drug By Brand Name	Orally Absorbed	Cmax (Mg/dl)	T ½ (hrs)	Regards to food	Protein bound	Elimination Path	Dosage forms
Norfloxacin	30-40%	1.5	3.5	Empty stomach	10-15%	Biliary and renal	Oral
Ciprofloxacin	70%	2.4	4	Empty stomach	20-40%	Renal 66% Hepatic 33%	Oral IV
Ofloxacin	98%	2.9	4.5	Not studied	32%	Renal	Oral; IV Ophthalmic
Lomefloxacin	>95%		8	Empty stomach	10%	Renal, 65% unchanged in urine	Oral
Levofloxacin	99%	5.7	6-8	No effect	24-38%	Renal, 87% unchanged in urine	Oral IV
Sparfloxacin			16-30	No effect	45%	Hepatic glucuronidation	Oral
Moxifloxacin	90%	4.5	12	No effect	50%	Renal, 45% excreted unchanged in urine; Hepatic conjugation	Oral
Gatifloxacin	96%	3.8	7.8	No effect	20%	Renal, 70% unchanged in urine	Oral IV
Trovafloxacin	88%	2.1	9.6	No effect	76%	Conjugation; 43% unchanged in feces	Oral IV

Drug Interactions (2-12)

This section highlights some of the more significant drug interactions. It is not an inclusive list.

ANTACIDS AND OTHER MINERAL CONTAINING COMPOUNDS: This is a class effect for the fluoroquinolones. When taken in conjunction with cations such as aluminum, magnesium, calcium, iron and zinc their absorption is severely impaired. Ciprofloxacin absorption has been shown to be 90% less absorbed.

NSAIDS: When NSAIDs are taken with the fluoroquinolones, CNS side effects (insomnia, nervousness and seizures) are increased. It is thought this action is due to the displacement of GABA from its receptor.

THEOPHYLLINE: The fluoroquinolones differ in the amount of which they impair the elimination of Theophylline and other Methylxanthines. The mechanism is thought to involve the cytochrome p450 1A2 enzyme. Ciprofloxacin, by reducing metabolism by 30%, can increase theophylline serum levels by 20%to 90%. Norfloxacin, ofloxacin, levofloxacin, lomefloxacin, sparfloxacin and trovafloxacin show no significant increase in theophylline levels.

WARFARIN: Many of the fluoroquinolones have been associated with an increasing in PT/INR when patients are taking warfarin. This is a serious reaction and patients on warfarin should be monitored when prescribed a fluoroquinolone.

ALKALYZING AGENTS: Agents that alkalyze the urine may cause crystaluria. In order to aid the prevention of this occurrence every patients should be instructed to drink plenty of fluids while taking any fluoroquinolone.

Side Effects (2-15)

ACHILLES TENDONITIS: Both the older and newer fluoroquinolones have been associated with arthropathy in weight bearing joints. Studies have shown erosion and permanent lesions of the cartilage due to quinolone use in animals. Although Achilles tendon rupture has been the most common injury with over 200 cases reported other joints may also be affected. Injury has been noted up to 90 days out after completion of therapy. Due to the affect on cartilage, fluoroquinolones are contraindicated in pregnant or nursing mothers and children under the age of 18.(15)

CARDIAC: QT prolongation is thought to be due to a halogen substitution at the number 8 position. Moxifloxacin's prescribing information warns against its use in patients: taking other drugs that may cause QT prolongation, taking anti-arrhythmics, or have hypokalemia. Similar warnings are also present for gatifloxacin and sparfloxacin although there is not a halogen in the R8 position. Torsades de pointes was associated with ciprofloxacin less than levofloxacin or gatifloxacin. Occurrence rates are 0.3, 5.4 and 27 respectively per 10 million prescriptions, which was significant. Levofloxacin and gatifloxacin should be used with caution in-patient with risk of QT prolongation.

GASTROINTESTINAL: With all of the fluoroquinolones the most common side effects are nausea, vomiting and diarrhea, with an occurrence rate ranging from 3% to 17%.(15,18,23)

CNS: Effects such as insomnia, dizziness, and anxiety have been reported in 0.9% to 11% of patients. Seizures are a rare occurrence but have been increasingly reported when used with theophylline or with NSAIDs. The occurrence frequency has been reported with trovafloxacin > norfloxacin > sparfloxacin > ciprofloxacin > ofloxacin > levofloxacin (14) Norfloxacin has been associated with convulsions which may lead to an increase in intracranial pressure.

CRYSTALURIA: Crystaluria has been associated with the fluoroquinolones, except levofloxacin, gatifloxacin, moxifloxacin and trovafloxacin. Patients should be instructed to drink plenty of water to avoid this occurrence.(15,23,18)

LIVER TOXICITY: In an 18-month post approval follow up study by the FDA for trovafloxacin 140 cases of liver toxicity were found. Due to these findings trovafloxacin's use is limited to hospitalized patients with life or limb threatening diseases.(8)

PHOTOTOXICITY: Phototoxicity has been reported and most likely to occur in ciprofloxacin, lomefloxacin and norfloxacin.

Approved Indications for the Fluoroquinolones (2-12)

	Norfloxacin	Ciprofloxacin	Ofloxacin	Lomefloxacin	Levofloxacin	Sparfloxacin	Moxifloxacin	Gatifloxacin
UTI	X	X	X	X	X			X
UTI (complicated)		X	X					X
Prostatis	X	X	X					
STD's	X	X	X					X
Infectious Diarrhea		X						
Conjunctivitis			X					
Acute Sinusitis		X			X		X	X
AEOCB		X	X	X	X	X	X	X
CAP		X *	X		X	X	X	X
Intra-abdominal		X						
Skin and Skin Structure		X	X		X			
Bone and joint		X						
Typhoid fever		X						
Nosocomial Pneumonia		I.V. Form						

* non-pneumococcal, AEOCB = acute exacerbations of chronic bronchitis, CAP = community acquired pneumonia.
Trovafloxacin is not discussed in this table due to its limited use in the clinical setting.

Resistance (14-16)

Resistance develops to fluoroquinolones due to three possible mechanisms; alterations in topoisomerase enzymes, decreased permeability and efflux mechanisms. No quinolone-degrading enzyme has been identified. Resistance patterns have been show in strains of *Escherichia coli, Klebsiella pneumoniae; Pseudomonas aeruginosa; Chlamydia trachomatis* and *Mycoplasma pneumoniae; Campylobacter jejuni; Burkholderia cepacia; Stenotrophomonas maltophilia; Neisseria gonorrhoeae; Staphylococcus aureus* (especially oxacillin-resistant strains); *Enterococcus faecium*; and *Streptococcus pneumoniae*. Resistance to one quinolone usually confers resistance to the entire class. It has been shown that when there is a methyl or

methoxy group in position number eight the topoisomerase enzymes must undergo mutations in two sights for there to be an effect on binding affinity.(23)

Treatment Recommendations (2-12,20,23)

ACUTE SINUSITIS: Acute sinusitis is often due to allergic or viral conditions. Due to this, antibiotic therapy should be implemented in patients who have received analgesics and decongestants for 7 days, who have facial pain and purulent discharge. In this case fluoroquinolones are second line agents. If the infection is severe levofloxacin, moxifloxacin and gatifloxacin should be used.

LOWER RESPIRATORY TRACT INFECTIONS: For treatment of mild/moderate cases of acute exacerbations of chronic bronchitis (AECB), antimicrobial treatment is controversial. For the treatment of severe cases of AECB it is recommended that the fluoroquinolones with enhanced activity against resistant *S. pneumoniae* be used (levofloxacin, sparfloxacin, trovafloxacin, gatifloxacin, moxifloxacin). Several other first line agents exist: azithromycin or clarithromycin, oral cephlosporins, or amoxicillin/clavulanate. For non-hospitalized patients with community acquired pneumonia (CAP) due to S. pneumoniae, H. influenza, M. catarrhalis, S. aureus, mycoplasma, and chlamydia, fluoroquinolones with a greater affect against S. pneumoniae are recommended (levofloxacin, sparfloxacin, gatifloxacin, moxifloxin) as second line agents. First line treatment for this condition is usually azithromycin, or clarithromycin. Other second line agents are oral cephlosporins, amoxicillin/clavulanate or doxycycline. However, in hospitalized patients with CAP, the fluoroquinolones are first line agents. Ciprofloxacin along with piperacillin/tazobactam is indicated as a first line treatment for nosocomial pneumoniae.

INFECTIOUS DIARRHEA: Cipro can be used for infectious diarrhea due to *shigella, salmonella, C jejuni, E.coli, c. difficile*, or *E. histolytica*. If recent antibiotic therapy has been noted, and *c. difficile* toxin colitis is possible, either metronidazole or vancomycin should be used in conjunction with ciprofloxacin. A second line alternative in infectious diarrhea is TMP/SMX DS.

UTI: Urinary tract infections are most commonly due to *E. coli*. This organism has a resistance rate to SMX/TMP of 18%. This has made the fluoroquinolones the first line treatment in empiric treatment of UTIs much of the time. The fluoroquinolones also possess a broader spectrum than SMX/TMP.(19) The Infectious Disease Society of America still recommends SMX/TMP as a first line agent in uncomplicated UTIs. In a cost minimization analysis study it was determined that empirical treatment of UTI with a fluoroquinolone first line was more cost effective when the rate of bacterial resistance to SMX/TMP was 22%.(21)

SEXUALLY TRANSMITTED DISEASES (STDs): Either doxycycline or azithromycin are used as first line agents in *chlamydia*. Either a fluoroquinolone (ofloxacin) or erythromycin base can be used as a second line agent. For STDs due to N. gonorrhea either cephlosporins, ciprofloxin or ofloxacin are first line agents. It is estimated that 50% of patients with *N. gonorrhea* infection are also infected with *C. trachomatis*. Emperic treatment should therefore be aimed at both by adding either doxycycline or azithromycin to a fluoroquinolone or cephlosporins.

PROSTATITIS: Prostatitis due to *enterobacteriacae* may be treated with the fluoroquinolones as a first line agent. Other first line alternatives are SMX/TMP, or ceftriaxone + doxycycline.

Indications, Dose & Cost for Fluoroquinolones & Non-fluoroquinolone Alternatives (2-12,20,23)

Drug	Indication	PO Dose (mg)	Interval	Duration (days)	Cost/Day of Therapy ($)

SMX-TMP DS	Uncomplicated UTI; Infectious Diarrhea	800/160	BID	3	<1
	AECB	800/160	BID	5-10	<1
	Acute Prostatitis	800/160	BID	14-28	<1
Amoxicillin	AECB	500	TID	10	<1
Doxycycline	CAP; Chlamydia	100	BID	7-10	1
Azithromycin	Uncomplicated N. Gonorrhea; Chlamydia	1000	1-dose	1-dose	6
	AECB; CAP	500 X1, then 250	QD	5	7
Ciprofloxacin	Uncomplicated UTI	100	BID	3	5
	Complicated UTI; Acute pyelonephritis	250-500	BID	7-14	7-8
	Uncomplicated N. gonorrhea	500	1-dose	1-dose	4
	AECB; CAP	500-750	BID	10-14	8
	Acute Prostatitis	500	BID	14-28	8
	Infectious diarrhea; Typhoid Fever	500	BID	3-5	8
Gatifloxacin	Uncomplicated UTI	400	QD	3	7
	Uncomplicated N. gonorrhea	400	1-dose	1-dose	7
	Complicated UTI; AECB; CAP; Acute pyelonepritis	400	QD	7-14	7
Levofloxacin	Uncomplicated UTI; Acute pyelonephritis	250	QD	10	7
	AECB; CAP;	500	QD	7-14	8
Norfloxacin	Uncomplicated & Complicated UTI; Acute pyelonephritis	400	BID	3-10	7
	Acute Prostatitis	400	BID	14-28	7
Lomefloxacin	Uncomplicated & Complicated UTI; AECB; Acute pyelonephritis	400	QD	3-14	7
Sparfloxacin	AECB, CAP	400 x1, then 200	QD	10	7

Cefuroxime	AECB; CAP	250	BID	10	8
Moxifloxacin	AECB; CAP	400	QD	5-10	8
Clarithromycin	AECB; CAP	500	BID	7-14	9
Amoxicillin / clavulanate	AECB	875/125	BID	7-10	9
Ofloxacin	Uncomplicated & Complicated UTI; Chlamydia	200	BID	3-10	8
	Uncomplicated N. gonorrhea	400	1-dose	1-dose	5
	AECB; CAP	400	BID	7-10	10
Ceftriaxone	Uncomplicated N. Gonorrhea	125 IM	1-dose	1-dose	13

Cost of therapy represents average cost calculated as AWP-13% or HCFA when available.
CAP = community acquired pneumonia; AECB = acute exacerbations of chronic bronchitis;
STD = sexually transmitted disease. N/A = not available

Discussion

Although many head to head trials have been conducted with the fluoroquinolones there is not enough evidence to determine if one drug is better than another within its given indication. Choices should therefore be made on culture and sensitivity, when available, then pharmacokinetic and safety profile.

There are basically two groups within the fluoroquinolones: the first are those with mainly gram-negative coverage used for UTIs. Norfloxacin, lomefloxacin, ofloxacin and ciprofloxacin are included in this group. Both Norfloxacin and lomefloxacin have limited indications. Ciprofloxacin and ofloxacin both have a wider list of indications. Ciprofloxacin is most notably used for its coverage against *Pseudomonas aeruginosa*. Its use is limited in the case of CAP due to ciprofloxacin resistant strains of *streptococcus* and *pneumococcal pneumoniae*. Phototoxicity is more likely to occur with norfloxacin, lomefloxacin and ciprofloxacin. CNS toxicity has been reported most frequently with norfloxacin. QT prolongation has been associated with the fluoroquinolones but the risk is much less in this group than with the later generations. Each of these four fluoroquinolones is dosed twice daily and must be taken on an empty stomach. One exception is in the case of ofloxacin where the affect of food on absorption has not yet been studied.

The later generations have an extended half-life, less CNS toxicity, a broader spectrum including gram-positive bacteria and some anaerobes. This group is comprised of levofloxacin, sparfloxacin, moxifloxacin and gatifloxacin. Moxifloxacin and gatifloxacin both have the potential to decrease bacterial resistance due to its increased binding affinity. Moxifloxacin has been highly associated with QT prolongation, but to a lesser extent with phototoxicity. No dosage adjustments are required for moxifloxacin for patients with renal impairment. Gatifloxacin is highly bioavailable and has been less associated with QT prolongation and phototoxicity. Levofloxacin is the active L isomer of Ofloxacin. It has a broad spectrum and a good side effect profile with no QT prolongation warning (although cases have been reported), and a decreased probability of causing phototoxic reactions. Sparfloxacin has unreliable coverage in some areas. It has also been associated with QT prolongation and phototoxicity.

Trovafloxacin's use is restricted to hospitalized patients with threat of loss of life or limb. This restriction was placed because of its association with liver failure. It does have great anaerobic

coverage similar to metronidazole except for Clostridium difficile.

Summary and Recommendations

Supportive rational is not seen for, lomefloxacin, sparfloxacin, moxifloxacin, and trovafloxacin, based on spectrum, safety and kinetic profile, in the clinical setting. Of the second-generation drugs, ciprofloxacin is necessary for its superior coverage of pseudomonas aeruginosa and it's broad list of indications. Ofloxacin's coverage of atypical pathogens and safety regarding QT prolongation makes the drug very favorable. Norfloxacin may be an alternative within its limited indications. Of the fluoroquinolones with extended spectrum for gram-positive pathogens both sparfloxacin and moxifloxacin have safety profiles concerning QT prolongation. Levofloxacin and gatifloxacin are both viable options.

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