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Quinolone Activity Against Anaerobes

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Abstract

The first generation of fluoroquinolones such as ciprofloxacin and ofloxacin are inactive against most anaerobic bacteria. However, some broad-spectrum quinolones, which have recently become clinically available or are under active development, have significant antianaerobic activity. This review summarises the *in vitro* activity of currently available, as well as experimental, quinolones against clinically significant anaerobic bacteria. Quinolones with low activity against anaerobes include ciprofloxacin, ofloxacin, levofloxacin, fleroxacin, pefloxacin, enoxacin and lomefloxacin. Compounds with intermediate antianaerobic activity include sparfloxacin and grepafloxacin. Trovafloxacin, gatifloxacin and moxifloxacin yield low MICs against most groups of anaerobes. Quinolones with the greatest *in vitro* activity against anaerobes include clinafloxacin and sitafloxacin (DU-6859a).

1. Background

Anaerobes are established causes of serious human infections, especially in debilitated hosts. Classification of anaerobes has changed markedly in recent years, and readers are referred to standard texts for full details.[1] A summary of anaerobes commonly encountered in human disease is presented in table I. Although infections caused by members of the *Bacteroides fragilis* group occur most commonly, infections caused by other Gram-negative anaerobic rods, as well as by Gram-positive cocci and rods, are increasingly encountered.[2] The susceptibility spectrum of clinically isolated anaerobes is changing: although β-lactamase production, and concomitant resistance to β-lactams, is the rule in the *B. fragilis* group, both phenomena are increasingly encountered in non-*B. fragilis* group *Bacteroides*, *Prevotella*, *Porphyromonas* and *Fusobacterium* species.[3-5] β-Lactamase production has also been described in *Clostridium butyricum*, *C. ramosum* and *C. clostridiiforme*.[3] Metronidazole resistance is common amongst Gram-positive non-spore-forming rods, but has also been reported in peptostreptococci, non-*C. perfringens* clostridia and members of the *B. fragilis* group. Additionally, clindamycin resistance is not unusual amongst anaerobic Gram-negative rods.[6]

Commercially available quinolones such as ciprofloxacin, ofloxacin, fleroxacin, pefloxacin, enoxacin and lomefloxacin are inactive or marginally active against anaerobes, with MICs either higher

Table I. Shortened classification of clinically significant anaerobes

Gram-positive spore-forming rods (clostridia)
Clostridium perfringens
C. novyi
C. septicum
C. difficile
Gram-positive non-spore-forming rods (microaerophils)
Propionibacteria
Actinomyces spp.
Lactobacilli
Eubacteria
Bifidobacteria
Gram-positive cocci
Peptostreptococci
Gram-negative rods
Bacteroides fragilis group
B. fragilis
B. thetaiotaomicron
B. distasonis
B. ovatus
Prevotella/*Porphyromonas*
P. melaninogenica
P. intermedia
P. bivia
P. disiens
Fusobacteria
Fusobacterium nucleatum
F. necrophorum
F. mortiferum
F. varium
Miscellaneous
Campylobacter gracilis (microaerophilic)
Bilophila wadsworthia
Sutterella wadsworthensis
Anaerobic Gram-negative cocci
Veillonella

Table II. *In vitro* activities of ciprofloxacin, ofloxacin and levofloxacin against anaerobes[7-10,16,18]

Group	MIC_{90} (mg/L)		
	ciprofloxacin	ofloxacin	levofloxacin
Bacteroides fragilis group	4.0-64.0	3.13-50.0	2.0-12.5
Prevotella/Bacteroides/Porphyromonas spp.	1.0-32.0	2.0-32.0	6.25-8.0
Fusobacterium spp.	2.0-32.0	1.56-64.0	0.39
Peptostreptococcus spp.	0.5-4.0	0.78-16.0	0.39-12.5
Non-spore-forming Gram-positive rods	2.0-16.0[a]	4.0-8.0[a]	No data
Clostridium spp.	4.0-32.0[b]	4.0-16.0[b]	2.0

a *Propionibacterium acnes*: ciprofloxacin 0.5 to 1.0 and ofloxacin 0.5 to 2.0 mg/L.
b *Clostridium perfringens*: ciprofloxacin 0.25 to 1.56 and ofloxacin 0.5 to 3.13 mg/L.
MIC_{90} = concentration required to inhibit 90% of strains.

than, or clustering around breakpoints for aerobic bacteria.[7-9] However, trovafloxacin (recently released in the US) as well as some other quinolones currently under development have significant activity against anaerobes. There is a clear need for availability of non-toxic oral or injectable quinolones or naphthyridone compounds, which are active against clinically significant anaerobic bacteria. In view of the activity of all broad-spectrum quinolones against *Enterobacteriaceae*, such compounds could then potentially be used as single-drug therapy for mixed infections caused by aerobes and anaerobes, both in outpatients and inpatients.

This review summarises current information on the *in vitro* susceptibility of anaerobes to available and experimental quinolones, as well as current clinical information on activity of certain quinolones against anaerobic infections in humans.

2. *In Vitro* Antianaerobic Activity of Quinolones

Results of published papers on *in vitro* activity of a broad range of quinolone/naphthyridone compounds against the major anaerobe groups[7-24] are summarised in tables II-VI. Previous broad-spectrum quinolones with excellent *in vitro* activity against anaerobes (e.g. Win 57273, Bay y3118)[14,15] proved to be too toxic to permit further development. It should be noted that, apart from trovafloxacin (susceptible ≤2.0 mg/L, intermediate 4.0 mg/L, resistant ≥8.0 mg/L)[25] there are currently no recommended breakpoints for quinolones against anaerobes, so results are presented throughout as MIC_{90}s (mg/L) against the major anaerobe groups.

Ciprofloxacin and ofloxacin (table II) are only active against *Propionibacterium acnes* and some *C. perfringens* strains and usually yield MIC_{90}s ≥4.0 mg/L for all other organisms. Levofloxacin generally has MICs 1 or 2 doubling dilutions lower than those for ofloxacin (table II). By comparison, fleroxacin, lomefloxacin, pefloxacin and enoxacin are inactive against anaerobes (table III).

Among other quinolones, grepafloxacin yields MICs that are one or 2 dilutions lower than those for ciprofloxacin (table IV), but values are still too high to suggest clinical efficacy. Sparfloxacin yields MICs slightly lower than those of grepafloxacin (table IV). Trovafloxacin has been found to be very active against anaerobes, with most workers reporting an overall MIC_{90} of 1.0 mg/L and all groups of strains susceptible at an MIC_{90} of ≤1.0 mg/L. Some authors have reported trovafloxacin MICs of 4.0 mg/L, but this would still be in the therapeutic range with the intravenous formulation (table V). Gatifloxacin and moxifloxacin have been shown to yield MICs that are a little higher than those of trovafloxacin, but no

Table III. *In vitro* activities of fleroxacin, lomefloxacin, pefloxacin and enoxacin against anaerobes[11-13]

Group	MIC_{90} (mg/L)
Bacteroides fragilis group	8.0->64.0
Prevotella/Bacteroides/Porphyromonas sp.	8.0-32.0
Fusobacterium spp.	32.0->64.0
Peptostreptococcus spp.	8.0-16.0
Non-spore-forming Gram-positive rods	8.0-32.0
Clostridium spp.	16.0->64.0[a]

a *Clostridium perfringens*: fleroxacin and lomefloxacin 1.0 to 4.0 mg/L.
MIC_{90} = concentration required to inhibit 90% of strains.

Table IV. *In vitro* activities of grepafloxacin and sparfloxacin against anaerobes[13-15,17,19]

Group	MIC_{90} (mg/L)	
	grepafloxacin	sparfloxacin
Bacteroides fragilis group	3.13-25.0	1.0-4.0
Prevotella/Bacteroides/Porphyromonas spp.	4.0-25.0	4.0-16.0
Fusobacterium spp.	8.0	4.0-16.0
Peptostreptococcus spp.	1.0-3.13	0.5-4.0
Non-spore-forming Gram-positive rods	25.0	0.25-8.0
Clostridium spp.	12.5	0.5-8.0

MIC_{90} = concentration required to inhibit 90% of strains.

Table V. *In vitro* activities of trovafloxacin, gatifloxacin and moxifloxacin against anaerobes[19-23]

Group	MIC_{90} (mg/L)		
	trovafloxacin	gatifloxacin	moxifloxacin
Bacteroides fragilis group	0.5-1.0	2.0	4.0
Prevotella/*Bacteroides*/*Porphyromonas* spp.	1.0	4.0	0.5-2.0
Fusobacterium spp.	1.0-2.0	4.0	0.5-8.0
Peptostreptococcus spp.	0.25-1.0	1.0	0.25
Non-spore-forming Gram-positive rods	1.0-4.0	1.0	0.25 (few strains)
Clostridium spp.	0.25-1.0	2.0	0.5-1.0

MIC_{90} = concentration required to inhibit 90% of strains.

breakpoints have yet been established for these compounds (table V).

The most active quinolones currently under development against anaerobes are clinafloxacin and sitafloxacin (DU-6859a), with MICs ≤0.5 mg/L for most groups (table VI). MICs of clinafloxacin and sitafloxacin are significantly lower than those of any other quinolones currently under development. No breakpoints are available for either compound, and their clinical potential will depend on their pharmacokinetic/pharmacodynamic properties (see below) as well as their toxicology.

Factors other than MIC play a role in the potential therapeutic usefulness of quinolones against anaerobes. Activity of quinolones has been proved to be dose related. Craig[26] has reported that, in order to be active, 24-hour AUC (area under the plasma concentration-time curve)/MIC ratios for quinolones must be at least 25 after therapeutic doses, and at least 125 for seriously ill patients. Current data suggest that trovafloxacin, gatifloxacin, moxifloxacin, clinafloxacin and sitafloxacin all yield AUC/MIC values of at least 25 against most anaerobes, with clinafloxacin and sitafloxacin, followed by trovafloxacin, having values of ≥125, indicating potential use in seriously ill, hospitalised patients.

Time-kill studies performed in our laboratory have demonstrated that bacteriostatic/bactericidal concentrations of trovafloxacin after 48 hours for 6 Gram-positive and -negative anaerobes were 0.03 to 1.0/0.03/1.0 mg/L. Table VII shows bacteriostatic/bactericidal concentrations of trovafloxacin compared with other quinolone and nonquinolone antibacterial agents. Against 11 different anaerobes, sitafloxacin was bactericidal at the MIC (0.06 to 0.5 mg/L) against all strains after 48 hours (table VIII). Time-kill studies have not been reported for other quinolones with improved antianaerobic activity.[27,28] However, the clinical significance of *in vitro* bactericidal activity of drugs against anaerobes is unknown at the present time.

Table VI. *In vitro* activities of clinafloxacin and sitafloxacin (DU-6859a) against anaerobes

Group	MIC_{90} (mg/L)	
	clinafloxacin	sitafloxacin
Bacteroides fragilis group	0.125-2.0	0.06-0.5
Prevotella/*Bacteroides*/*Porphyromonas* spp.	0.125-0.5	0.25-0.39
Fusobacterium spp.	0.06-1.0	0.06-0.5
Peptostreptococcus spp.	0.125-0.5	0.06-0.1
Non-spore-forming Gram-positive rods	0.06	0.25
Clostridium spp.	0.5-2.0	0.06-0.5

MIC_{90} = concentration required to inhibit 90% of strains.

Other factors may play a role in the *in vivo* susceptibility of anaerobes to the quinolone group. Appelbaum and co-workers[29] have found ciprofloxacin to reduce counts of anaerobic organisms in saliva of human volunteers, 91.3 to 100% of strains inhibited for all anaerobe groups. Goldstein and Citron[30] have found that ofloxacin + metronidazole usually showed additive or indifferent, but no antagonistic activity, when tested against anaerobes isolated from intra-abdominal infections. Metronidazole + fleroxacin have been shown to be at least as active as clindamycin + gentamicin against all anaerobe species in an experimental intra-abdominal abscess model, and significantly more effective against clostridia.[31] In *in vitro* and animal studies, fleroxacin and sparfloxacin have been found to be bactericidal against *Escherichia coli* under anaerobic conditions, and also bactericidal against *B. fragilis*.[32,33]

3. Clinical Studies

Clinical results for quinolone treatment of mixed aerobic-anaerobic infections are only available for clinafloxacin and trovafloxacin. Wilson[34] compared clinafloxacin versus imipenem/cilastatin in the treatment of intra-abdominal infection in a multicentre trial. At the major testing facility (University of California at Irvine), clinafloxacin inhibited 126 anaerobic isolates from 44 patients (100%) at a concentration of <1 mg/L and imipenem inhibited 124 strains (98.4%) at <4.0 mg/L. Of clinically evaluable patients, clinafloxacin at a dosage of 200mg every 12 hours resulted in cure in 76.5% and failure in 22.5%, with 1.0% not assessed. Corresponding results for imipenem/cilastatin (500mg every 6 hours) were 71.5, 27.6 and 0.9%.[34]

Table VII. Bacteriostatic/bactericidal concentrations (mg/L) of trovafloxacin compared to other agents after 48 hours

Drug	*Bacteroides fragilis*	*Bacteroides thetaiotaomicron*	*Prevotella melaninogenica*	*Fusobacterium mortiferum*	*Peptostreptococcus magnus*	*Clostridium perfringens*
Trovafloxacin	0.25/0.5	0.25/0.5	1.0/1.0	0.5/1.0	0.015/0.06	0.03/0.03
Ciprofloxacin	16.0/32.0	8.0/16.0	4.0/4.0	2.0/2.0	1.0/2.0	0.25/0.25
Sparfloxacin	2.0/8.0	0.5/1.0	2.0/4.0	0.5/1.0	1.0/1.0	0.06/0.06
Metronidazole	1.0/1.0	2.0/2.0	1.0/1.0	1.0/2.0	64.0/64.0	1.0/1.0
Cefoxitin	16.0/32.0	1.0/1.0	0.5/1.0	2.0/2.0	4.0/8.0	0.125/0.125
Piperacillin	64.0/64.0	16.0/32.0	8.0/8.0	1.0/1.0	0.25/0.5	0.125/0.125
Piperacillin/tazobactam	2.0/8.0	2.0/4.0	0.125/0.25	1.0/1.0	0.25/0.5	0.06/0.125

Donahue and co-workers,[35] in a double-blind multicenter study, compared 2 sequential antibacterial regimens following surgical intervention of a documented intra-abdominal infection with a mixed aerobic/anaerobic flora. These were intravenous alatrofloxacin 300mg daily followed by oral trovafloxacin 200mg daily or imipenem/cilastatin 1g 3 times daily intravenously followed by oral amoxicillin/clavulanic acid 500mg 3 times daily for up to 14 days. At study end, cure or improvement occurred in 83% (129/156) and 84% (127/152) of clinically evaluable patients in the trovafloxacin and comparative groups, respectively.[35] Pathogen eradication rates and adverse event profiles were comparable between groups.

4. Conclusions

In summary, quinolones with low *in vitro* activity against anaerobes include ciprofloxacin, ofloxacin, levofloxacin, fleroxacin, pefloxacin, enoxacin and

Table VIII. Comparative sitafloxacin time-kill results after 24 and 48 hours. Number of anaerobic strains showing reduction of 1, 2 and 3 $\log_{10}$ cfu/ml in bacterial numbers after exposure to sitafloxacin and other antibacterial agents

Drug	24 hours			48 hours		
	–1[a]	–2[a]	–3[a]	–1	–2	–3
Sitafloxacin						
4 x MIC	11	10	9	11	11	11
2 x MIC	11	10	7	11	11	11
MIC	11	9	5	11	11	11
Ciprofloxacin						
4 x MIC	11	10	7	11	11	11
2 x MIC	11	9	4	11	11	11
MIC	11	8	0	11	11	11
Levofloxacin						
4 x MIC	11	11	8	11	11	11
2 x MIC	11	10	6	11	11	11
MIC	11	10	4	11	11	11
Sparfloxacin						
4 x MIC	11	10	7	11	11	11
2 x MIC	10	10	5	11	11	11
MIC	10	8	3	11	11	11
Piperacillin						
4 x MIC	11	8	6	11	11	11
2 x MIC	10	8	6	11	11	11
MIC	10	7	5	11	11	11
Piperacillin/tazobactam						
4 x MIC	11	7	6	11	11	11
2 x MIC	10	7	6	11	11	11
MIC	10	7	5	11	11	11
Imipenem						
4 x MIC	11	9	7	11	11	11
2 x MIC	11	8	7	11	11	11
MIC	11	8	6	11	11	11
Clindamycin						
4 x MIC	11	11	8	11	11	11
2 x MIC	11	9	5	11	11	11
MIC	11	3	4	11	11	11
Metronidazole						
4 x MIC	11	9	4	11	11	11
2 x MIC	10	7	4	11	11	11
MIC	8	6	3	11	11	11

a $\Delta \log_{10}$ cfu/ml.

lomefloxacin. Compounds with intermediate anaerobe activity include sparfloxacin and grepafloxacin. Quinolones very active against anaerobes include clinafloxacin and sitafloxacin, followed by trovafloxacin, gatifloxacin and moxifloxacin. More pharmacokinetic, toxicological and clinical studies are necessary before firmer conclusions can be drawn as to the therapeutic value of quinolones against anaerobic infections in humans. For clinafloxacin and trovafloxacin, clinical studies have been performed which document the usefulness of these compounds as single-drug therapy for intra-abdominal infections caused by a mixed aerobic/anaerobic flora.

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