

Effect of Quinolones on Intestinal Ecology

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Abstract

Quinolones have a selective effect on the normal human intestinal microflora. Published data on 13 different quinolone agents [ciprofloxacin, enoxacin, norfloxacin, ofloxacin, pefloxacin, lomefloxacin, levofloxacin, sparfloxacin, rifloxacin, sitafloxacin (DU-6859a), gatifloxacin, trovafloxacin and moxifloxacin] show that Gram-negative aerobic bacteria, especially Enterobacteriaceae, are strongly suppressed or eliminated during therapy. Gram-positive aerobic cocci are affected strongly by administration of sitafloxacin and moxifloxacin and to minor degrees by the other quinolones. Three new quinolones – gatifloxacin, trovafloxacin and moxifloxacin – are very active against anaerobic bacteria *in vitro* but have minor effects on the anaerobic intestinal human microflora. Similar findings have been reported for the other 10 quinolones. Thus, the quinolone antibacterials have an ecological impact on the human intestinal microflora, mainly on the enterobacteria, that should be taken into account when these agents are used for prophylaxis or treatment of gastrointestinal bacterial infections.

Administration of antimicrobial agents is known to often result in disturbances in the ecological balance of the normal intestinal microflora. Antimicrobial administration may have a number of potential adverse effects in relation to the normal intestinal microflora. One is development of resistance to antimicrobials among bacteria in the normal microflora. A second consequence is the overgrowth of already present micro-organisms such as yeasts, which may cause systemic infections in immunocompromised patients, and *Clostridium difficile*, which may lead to diarrhoea and/or pseudomembranous colitis. A third effect is reduction of colonisation resistance, i.e. the resistance displayed by the host to implantation of new potential pathogenic micro-organisms in the normal microflora.

Several factors influence the extent to which a given antimicrobial agent will affect the normal microflora. Predominant among these factors is the incomplete absorption of orally administered drugs. Poorly absorbed drugs can reach the intestine in active form where they destroy susceptible micro-organisms and change the ecological balance.

In this article, published reports on the impact of quinolones on the human intestinal microflora are reviewed.

1. Effect of Individual Quinolones on the Intestinal Microflora

1.1 Ciprofloxacin

Brumfitt et al.^[1] investigated the effect of ciprofloxacin on the intestinal microflora in 12 volunteers taking ciprofloxacin 500mg twice daily for 7 days. Enterobacteria were eliminated and streptococci markedly decreased. No major impact on the anaerobic microflora was observed. The microflora had returned to normal 1 week after the administration of ciprofloxacin had stopped (table I).

Rozenberg-Arska et al.^[2] studied 15 patients with acute leukaemia receiving ciprofloxacin 500mg twice daily for a mean of 42 days. The numbers of enterobacteria decreased significantly as did the numbers of Gram-positive anaerobic cocci and rods. 9 ciprofloxacin-resistant strains of *Pseudomonas* and *Acinetobacter* were isolated, and 4 infections were caused by aerobic Gram-positive cocci (table I).

The intestinal microflora in 12 individuals taking ciprofloxacin 400mg twice daily for 7 days was analysed by Enzenberger et al.^[3] *Escherichia coli* strains were eliminated, whereas anaerobic bacteria were not influenced by the administration of ciprofloxacin. No *C. difficile* strains were recovered (table I).

Bergan et al.^[4] studied the impact of ciprofloxacin

Table I. Effect of quinolones on the intestinal microflora

Agent	Daily dosage (mg)	Duration of administration (days)	No. of patients	Impact on			Overgrowth of resistant strains			Reference
				enterobacteria	aerobic G+ cocci	anaerobic bacteria	enterobacteria	<i>C. difficile</i>	<i>Candida</i>	
Ciprofloxacin	500 × 2	7	12	↓↓	↓	NC	NC	NC	NC	1
	500 × 2	Mean 42	15	↓↓	NC	↓	+	NC	NC	2
	400 × 2	7	12	↓↓	NC	NC	NC	NC	NC	3
	500 × 2	5	12	↓↓	↓	↓	NC	NC	NC	4
	50 × 4	6	12	↓↓	↓	NC	NC	NC	+	5
	500 × 1	5	6	↓↓	NC	NC	NC	NC	NC	6
	250 × 2	5-10	7	↓↓	NC	NC	NC	NC	NC	7
	500 × 1	5-10	7	↓↓	NC	NC	NC	NC	NC	7
	500 × 2	5	14	↓↓	↓	NC	NC	NC	NC	8
	750 × 2 + 400 × 2	2	21	↓↓	↓	↓	NC	NC	NC	9
Enoxacin	250 × 2	3	17	↓↓	NC	NC	NC	NC	NC	10
	400 × 2	7	10	↓↓	NC	NC	NC	NC	+	11
Norfloxacin	200 × 1	7	10	↓↓	NC	NC	NC	NC	NC	12
	400 × 2	7	10	↓↓	NC	NC	NC	NC	NC	12
	100 × 2	5	10	↓↓	NC	NC	NC	NC	NC	13
	200 × 2	5	10	↓↓	NC	NC	NC	NC	NC	13
	400 × 2	5	10	↓↓	↓	NC	NC	NC	NC	13
	400 × 2	8	10	↓↓	NC	NC	NC	NC	NC	14
	200 × 2	5	6	↓↓	NC	NC	NC	NC	NC	15
	400 × 2	5	6	↓↓	↓	NC	NC	NC	NC	15
	200 × 2	7	10	↓↓	NC	NC	NC	NC	NC	16
	200 × 2	5	5	↓↓	↓	NC	NC	NC	+	17
Ofloxacin	400 × 1	1	24	↓↓	↓	↓	NC	NC	NC	18
	400 × 1	7	10	↓↓	↓	NC	NC	NC	NC	19
	400 × 2	7	15	↓↓	↓	NC	NC	NC	NC	5
Pefloxacin	400 × 2	10	6	↓↓	↓	NC	NC	NC	+	20
	400 × 1	7	10	↓↓	NC	NC	NC	NC	NC	21
Lomefloxacin	500 × 1	7	10	↓↓	↓	NC	NC	NC	NC	19
Sparfloxacin	200 × 1	7	8	↓↓	↓	NC	NC	NC	NC	22
Rufloxacin	200 × 1	11-35	32	↓↓	NC	↓	NC	NC	NC	23
Sitafloxacin (DU-6859a)	100 × 3	7	6	↓↓	↓↓	↓	NC	+	+	24
Gatifloxacin	400 × 1	10	18	↓↓	↓	NC	NC	NC	NC	25
Trovafloxacin	100 × 2	10	12	↓↓	↓	NC	NC	NC	NC	26
Moxifloxacin	400 × 1	7	12	↓↓	↓↓	NC	NC	NC	NC	27

G+ = Gram-positive; ↓↓ indicates strong suppression [$>4 \log_{10}$ colony-forming units (cfu)/g faeces]; ↓ indicates mild to moderate suppression (2 to 4 \log_{10} cfu/g faeces); + indicates increase in number of micro-organisms during therapy; **NC** indicates no significant change.

on the intestinal microflora in 12 volunteers receiving ciprofloxacin 500mg twice daily for 5 days. Enterobacteria and enterococci were suppressed, and the anaerobic bacteria showed minor changes. The microflora returned to normal after 14 days and no new colonisation of ciprofloxacin-resistant bacteria was observed (table I).

The effect of ciprofloxacin on the intestinal microflora was also analysed by Van Saene et al.^[5] in 12 individuals taking ciprofloxacin 50mg 4 times daily for 6 days. The enterobacteria were eliminated and the enterococci were slightly affected. Overgrowth of *Candida albicans* in low numbers was observed, but no ciprofloxacin-resistant bacteria were isolated. The microflora returned to normal within 1 week (table I).

In another study, 6 participants took ciprofloxacin 500mg once daily for 7 days.^[6] In the intestinal microflora the enterobacteria were suppressed and 2 participants were colonised by ciprofloxacin-resistant coagulase-negative staphylococci and corynebacteria. There were no changes in the anaerobic microflora (table I).

The changes in the intestinal microflora of 14 patients with liver cirrhosis induced by ciprofloxacin treatment were investigated by Esposito et al.^[7] The patients were treated with ciprofloxacin 200mg twice daily or 500mg once daily. The numbers of enterobacteria were significantly suppressed during treatment but returned to normal levels 14 days after the treatment had stopped. No alterations in the aerobic Gram-positive bacterial flora or the anaerobic bacterial flora were observed during the investigation period (table I).

Ljungberg et al.^[8] studied the impact of ciprofloxacin on the intestinal microflora in young adults and elderly individuals. Ciprofloxacin 500mg was given twice daily for 5 days to 7 young and 7 elderly persons. In both age groups enterococci, streptococci, staphylococci and enterobacteria were suppressed, but the impact on the anaerobic microflora was minor. The effect of ciprofloxacin was similar in both age groups despite the higher bioavailability of ciprofloxacin in the elderly group (table I).

The effect of ciprofloxacin on the lower intestinal microflora was studied by Brismar et al.^[9] in 21 patients undergoing colorectal surgery. Ciprofloxacin was given orally as 2 doses of 750mg separated by a 12-hour interval starting 24 hours prior to surgery, 400mg of ciprofloxacin was administered intravenously at the induction of anaesthesia and 400mg of ciprofloxacin was administered 12 hours later. Streptococci, enterococci and enterobacteria were decreased significantly, whereas anaerobic Gram-positive and

Gram-negative bacteria were suppressed to a minor extent. No postoperative infections were observed (table I).

Wiström et al.^[10] studied the impact of ciprofloxacin on the intestinal microflora in 17 tourists travelling to Mexico. Patients with travellers' diarrhoea received ciprofloxacin 250mg twice daily for 3 days. The numbers of enterobacteria decreased significantly while the numbers of anaerobic cocci and bifidobacteria increased compared with the placebo-treated and asymptomatic participants. The ciprofloxacin-treated patients were cured within 26 hours and placebo patients within 60 hours (table I).

1.2 Enoxacin

The impact of enoxacin on the intestinal microflora was investigated by Edlund et al.^[11] in a study where 10 healthy volunteers were given enoxacin 400mg orally twice daily for 7 days. During administration of enoxacin, enterobacteria decreased significantly while enterococci, streptococci, micrococci and bacilli were not significantly affected. *C. albicans* was isolated in low numbers during enoxacin administration. Minor changes were observed in the anaerobic microflora. No development of resistance in the intestinal microflora was observed during the trial period. On day 7 the mean concentration of enoxacin in faeces was 348 mg/kg. The microflora had returned to normal 2 weeks after withdrawal of enoxacin (table I).

1.3 Norfloxacin

The effect of norfloxacin on the intestinal microflora of 10 healthy individuals was studied by Meckenstock et al.^[12] Norfloxacin was given as 200mg once daily or 400mg twice daily for 7 days with an interval between the 2 administration periods.

Enterobacteria were suppressed by both dosages, whereas enterococci and anaerobic bacteria were not significantly influenced (table I).

Norfloxacin was used for selective decontamination of the intestinal microflora by De Vries-Hospers et al.^[13] 10 volunteers received norfloxacin 100, 200 or 400mg twice daily for 7 days with treatment intervals. Elimination of aerobic Gram-negative rods was observed with all 3 dosages, and the number of enterococci was partly decreased. The anaerobic microflora was not affected (table I).

Leigh et al.^[14] investigated the impact of norfloxacin on the faecal microflora in 10 patients receiving 400mg twice daily for 8 days. Aerobic bacteria, mainly enterobacteria, were suppressed but there was no effect on the anaerobic bacteria. The microflora returned to normal within 14 days after administration and no norfloxacin-resistant strains were isolated (table I).

In the study by Pecquet et al.,^[15] 12 patients received norfloxacin 400 or 800mg daily for 5 days for selective decontamination of the intestinal tract. Enterobacteria were significantly suppressed while streptococci were partly decreased. The administration of norfloxacin did not affect the anaerobic microflora (table I).

The effect of norfloxacin on the colonic microflora was investigated by Edlund et al.^[16] 10 participants received norfloxacin 200mg twice daily for 7 days. There was a strong suppression of enterobacteria, but aerobic Gram-positive cocci were not significantly affected. No changes in the anaerobic microflora were noticed (table I).

1.4 Ofloxacin

Pecquet et al.^[17] studied the effect of ofloxacin on the intestinal microflora in 5 individuals receiving ofloxacin 400mg daily for 5 days. Enterobacteria were eliminated and enterococci were suppressed during the administration of ofloxacin. The anaerobic microflora was not significantly affected and all participants were colonised by low numbers of *C. albicans* during treatment. The microflora returned to normal after the investigation period (table I).

The impact of ofloxacin on the intestinal microflora was studied in 24 patients undergoing gastric surgery.^[18] A single dose of ofloxacin 400mg was given 2 to 4 hours before surgery. The number of enterobacteria was strongly suppressed, and enterococci, lactobacilli, bifidobacteria, eubacteria, *Veillonella* and *Bacteroides* spp. were partly reduced. The aerobic and anaerobic microflora had returned to normal 4 weeks after the administration of ofloxacin (table I).

1.5 Pefloxacin

Van Saene et al.^[5] investigated the effect of pefloxacin on the intestinal microflora in 15 volunteers receiving 400mg twice daily for 7 days. Enterobacteria were eliminated during pefloxacin administration, and enterococci decreased slightly. No effect on the anaerobic microflora was observed. The aerobic microflora had returned to normal 1 week after the administration was stopped (table I).

Vollaard et al.^[20] also studied the influence of pefloxacin on intestinal colonisation resistance in 6 volunteers receiving pefloxacin 400mg twice daily for 10 days. The numbers of enterobacteria were significantly reduced and there was a minor decrease of enterococci. There was a significant increase of yeasts in 3 volunteers during pefloxacin administration (table I).

1.6 Lomefloxacin

Edlund et al.^[21] studied the impact of lomefloxacin on the intestinal microflora in 10 volunteers receiving lomefloxacin 400mg once daily for 7 days. Enterobacteria were eliminated or strongly reduced, but aerobic cocci were not changed in number during the administration of lomefloxacin. Minor alterations in the anaerobic microflora were observed at the same time. The microflora had returned to normal 2 weeks after withdrawal of lomefloxacin (table I).

1.7 Levofloxacin

Edlund et al.^[19] compared the effects of levofloxacin and ofloxacin on the normal oral and intestinal microflora. 10 persons received levofloxacin 500mg and 10 persons received ofloxacin 400mg orally every 24 hours for 7 days. The mean concentrations of levofloxacin in faeces were 20.9 mg/kg on day 2, 87.4 mg/kg on day 4, 93.7 mg/kg on day 7, 64.9 mg/kg on day 9 and 15.2 mg/kg on day 11. The mean concentrations of ofloxacin were 36.0 mg/kg on day 2, 50.6 mg/kg on day 4, 78.1 mg/kg on day 7, 37.0 mg/kg on day 9 and 9.2 mg/kg on day 11. The impact of levofloxacin and ofloxacin on the intestinal microflora was similar. Enterococci and enterobacteria were reduced significantly in both treatment groups. Among the anaerobic bacteria, the numbers of clostridia were suppressed in both groups (table I). After 2 weeks the microflora had returned to pretreatment levels. No new colonising levofloxacin- or ofloxacin-resistant micro-organisms were isolated from the gut microflora.

1.8 Sparfloxacin

Ritz et al.^[22] investigated the influence of sparfloxacin on the intestinal microflora. 8 volunteers received sparfloxacin 400mg orally on day 1 followed by 200mg every 24 hours for 7 days. The mean sparfloxacin concentrations in faeces were 760 mg/kg on day 2, 672 mg/kg on day 4 and 476 mg/kg on day 8. The numbers of *E. coli* were suppressed significantly, and there was a moderate reduction of enterococci. In the anaerobic microflora, bifidobacteria were slightly decreased (table I). The intestinal microflora had returned to pretreatment levels after 4 weeks.

1.9 Rufloxacin

D'Antonio et al.^[23] studied the impact of rufloxacin on the intestinal microflora. Rufloxacin 200 mg/day was given as a single dose as prophylaxis in patients undergoing cytotoxic treatment for cancer. The impact

on the microflora could be assessed in 32 patients who had a median duration of prophylaxis of 16 days (range 11 to 35 days). There was a significant decrease in the mean number of enterobacteria in all patients and a significant reduction in the numbers of *Bacteroides* spp. in 25% of the patients. No significant changes were noticed in enterococci, staphylococci, anaerobic cocci and clostridia. The mean log₂ minimum inhibitory concentration (MIC) of rifloxacin for enterococci increased significantly from 1.8 to 3.3 during the second week of treatment. No infections caused by Gram-negative rods occurred (table I).

1.10 Sitafloracin

The effect of sitafloracin (DU-6859a), a broad-spectrum fluoroquinolone with high activity against both aerobic and anaerobic micro-organisms, on the normal faecal microflora was studied by Inagaki and Yamamoto.^[24] Sitafloracin 100mg was given 3 times daily for 7 days to 6 healthy volunteers. The total viable count decreased transiently during the administration due to changes in the number of *Bacteroides* strains. The other anaerobic micro-organisms and most aerobic bacteria were suppressed markedly by sitafloracin. Enterobacteria and most anaerobic species except *Bacteroides* strains were reduced below the detection limit in all participants from the third day of administration to 1 day after discontinuation of the drug. *C. difficile* was detected in 1 participant at the end of administration. An increase of yeasts was noticed during the administration period. The proportion of resistant *Bacteroides* strains (MIC ≥ 6.25 mg/L sitafloracin) were increased in 5 of 6 participants. High concentrations of sitafloracin were detected in faeces during administration. Recovery from the effect of the drug administration was not complete in any volunteer at 14 days after termination of treatment (table I).

1.11 Gatifloxacin

The influence of gatifloxacin on the intestinal microflora in healthy volunteers was studied by Edlund and Nord.^[25] Gatifloxacin 400mg was given orally once daily for 10 days to 18 healthy males. Faecal samples were collected prior to administration (days -4 and -1), during the administration period (days 5 and 10) and after withdrawal of gatifloxacin (days 12, 16, 22, 30 and 50). In the aerobic intestinal microflora, *E. coli* strains were eliminated or strongly suppressed during the administration period and the numbers of enterococci decreased significantly; the numbers of staphylococci increased at the same time. In the anaerobic microflora, the numbers of clostridia

and fusobacteria decreased significantly during the administration period but no other major changes occurred. The microflora had returned to normal by 40 days after gatifloxacin was discontinued. No selection or overgrowth of resistant bacterial strains or yeasts occurred (table I).

1.12 Trovafloxacin

The effect of trovafloxacin on the intestinal microflora was studied in a double-blind placebo-controlled parallel-group study.^[26] 12 healthy male volunteers received trovafloxacin 200mg daily for 10 days and faecal samples were collected at several occasions before, during and after the administration period. No enterobacteria were found in samples from days 4 to 10, and the prevalence and number of Gram-positive bacteria were rapidly reduced. No significant alterations were noticed in the anaerobic microflora (table I). There was no increase in MIC values during the study period for the isolated *E. coli* strains.

1.13 Moxifloxacin

Moxifloxacin 400mg was given orally once daily for 7 days to 12 healthy volunteers in order to study the impact on the normal intestinal microflora.^[27] Faecal samples were collected 3 days and 1 day before the onset of administration (days -3 and -1) and on days 2, 4, 7, 14, 21 and 35. The number of enterococci and Enterobacteriaceae were significantly reduced during the administration period, a limited reduction in the number of clostridia was noticed, but the total anaerobic count was not significantly affected. No emergence of resistant strains was found during the administration period. The intestinal microflora had returned to normal 2 weeks after administration of moxifloxacin had stopped (table I).

2. Conclusions

Quinolone antimicrobial agents have a selective effect on the normal human intestinal microflora, mainly directed against the aerobic Gram-negative microflora. The numbers of enterococci are partly suppressed by some of the agents, whereas the dominant anaerobic microflora is more or less unaffected, even by the new broad-spectrum quinolones such as gatifloxacin, trovafloxacin and moxifloxacin. Overgrowth of yeasts and *C. difficile*, as well as development of resistant strains during administration, are rare; these factors make this class of antimicrobial agent favourable from an ecological point of view.

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