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A Review on the Impact of 4-quinolones on the Normal Oropharyngeal and Intestinal Human Microflora

Summary: During the last few years the impact of the newer 4-quinolones, ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pefloxacin, on the human microflora has been studied by several investigators. This review article summarizes the published data concerning these studies. The results show that the oropharyngeal flora is affected only slightly or not at all by the 4-quinolones. All the newer 4-quinolones have a similar effect on the normal intestinal flora.The gram-negative aerobic flora is strongly suppressed during administration of 4-quinolones, while the gram-positive flora is only slightly affected. The anaerobic microflora is hardly affected at all. The emergence of resistant bacterial strains is uncommon, although one study shows increased MIC-values for anaerobes during ciprofloxacin administration. Replacement by yeasts or other inherently resistant microorganisms does not often seem to be a problem. High concentrations of the 4-quinolones are reached in faeces, values between 100–2,200 mg/kg being reported. Since the 4-quinolones do not cause marked ecological disturbances in the intestinal microflora, they may be suitable for selective decontamination in immunocompromised patients, for prophylaxis of urinary tract infections and for treatment of bacterial intestinal infections.

Zusammenfassung: *Einfluß der 4-Chinolone auf die normale oropharyngeale und intestinale Flora des Menschen. Übersicht.* In den vergangenen Jahren wurden mehrere Untersuchungen zur Beeinflussung der menschlichen Mikroflora durch die neuen 4-Chinolone Ciprofloxacin, Enoxacin, Norfloxacin, Ofloxacin und Pefloxacin durchgeführt. Die vorliegende Übersichtsarbeit faßt die aus diesen Studien publizierten Daten zusammen. Die Ergebnisse zeigen, daß 4-Chinolone die oropharyngeale Flora und auch die normale Darmflora kaum oder überhaupt nicht verändern. Unter der Therapie mit 4-Chinolonen ist die aerobe gramnegative Flora stark supprimiert, die grampositive Flora dagegen kaum beeinträchtigt. Die anaerobe Mikroflora wird kaum verändert. Nur selten treten resistente Bakterienstämme auf. In einer Studie wurden allerdings unter Behandlung mit Ciprofloxacin erhöhte MHK-Werte für Anaerobier festgestellt. Zu einer Verdrängung der normalen Flora zugunsten von Hefen oder anderen Mikroorganismen mit inhärenter Resistenz kommt es offensichtlich nur selten. 4-Chinolone werden in hoher Konzentration in den Faeces gefunden, die publizierten Konzentrationen liegen zwischen 100 und 2200 mg/kg. Da die 4-Chinolone die Ökologie der Mikroflora des Darmes nicht wesentlich beeinträchtigen, eignen sie sich möglicherweise für die selektive Dekontamination bei abwehrgeschwächten Patienten, die Prophylaxe von Harnwegsinfektionen und Behandlung intestinaler bakterieller Infektionen.

Introduction

The composition of the normal oropharyngeal and gastrointestinal microflora of man is remarkably stable, although there are interpersonal variations. This ecosystem, however, can be disturbed by certain factors such as antimicrobial therapy, diet, pathologic conditions and surgery of the gastrointestinal tract.

Although the role of the normal oropharyngeal and gastrointestinal microflora is not completely understood, it is obvious that it is important to maintain the normal status of the indigenous microflora (1). The normal microflora together with several other factors such as motility (chewing, swallowing, peristalsis), secretions (saliva, bile and mucus), secretory immunoglobulin A and mucosal cell turn-over contribute to maintain colonization resistance (2). The normal microflora mainly prevents colonization by non-commensal microorganisms by competing for nutrients and attachment sites, and by producing volatile fatty acids and bacteriocins (3).

The most common and significant cause of disturbances in the normal oropharyngeal and gastrointestinal flora is the administration of antimicrobial agents (4). When the number of bacteria is reduced during therapy, the resistance to colonization is decreased, which may lead to several unwanted effects. One is overgrowth of already present microorganisms with natural resistance, such as yeasts, which may cause systemic infections in immunocompromised patients (5) and *Clostridium difficile,* which may lead to diarrhoea and/or colitis. A second consequence is the establishment of new resistant pathogenic bacteria, which may also colonize other areas of the host. A third effect is the fact that bacterial overgrowth also encourages the transfer of resistance factors among bacteria.

Several factors influence the extent to which a given antimicrobial agent will reduce the normal microflora. Pre-

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dominant among these factors is the incomplete absorption of agents administered orally. Poorly absorbed drugs can reach the colon in active form where they suppress susceptible microorganisms and disturb the ecological balance. Antimicrobial drugs that are secreted by the salivary glands, in the bile or from the intestinal mucosa also tend to affect the normal microflora.

Ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pefloxacin belong to a new group of antimicrobial agents called 4-quinolones. Their antibacterial spectrum is directed primarily against aerobic gram-negative bacteria (6–8); MIC_{90} values against most Enterobacteriaceae species are 0.015–2.0 mg/l, *Pseudomonas aeruginosa* 0.5–4 mg/l, and *Neisseria gonorrhoeae* 0.004–0.25 mg/l. The 4-quinolones have a moderate effect on gram-positive aerobic bacteria with MIC_{90} values of 2–32 mg/l against streptococci and 0.5–8.0 mg/l against staphylococci. Poor *in-vitro* activity has been reported against anaerobic bacteria. MIC_{90} values against *Bacteroides fragilis* are 4–128 mg/l, *Bacteroides non-fragilis* spp. 8–128 mg/l, *Clostridium* spp. 1.0–128 mg/l and *C. difficile* 16–64 mg/l. Ciprofloxacin and ofloxacin seem to have somewhat higher *in-vitro* activity compared to the other 4-quinolones.

The therapeutic effect of the 4-quinolones is particularly good in urinary tract infections, but they may also be suitable for treatment of bacterial intestinal infections, for prophylaxis in complicated urinary tract infections and for selective decontamination in immunocompromised patients. review article summarizes the published data concerning the impact of ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pefloxacin on the oropharyngeal and intestinal human microflora (Table 1).

Impact of Ciprofloxacin on the Oropharyngeal and Intestinal Microflora

Brumfitt et al (9) investigated twelve male healthy subjects taking 500 mg of ciprofloxacin (tablets) every 12 h for seven days. Marked changes in the aerobic colon microflora were observed. Enterobacteria were absent on day seven, and the numbers of streptococci and staphylococci were significantly reduced. One week later the colonic microflora had returned to a state similar to that found before treatment. Anaerobic bacteria were little affected quantitatively but acquired resistance to ciprofloxacin. On day seven the faecal concentrations of ciprofloxacin were high, 185–2,200 mg/kg.

In another study ciprofloxacin was given prophylactically in a dose of 500 mg every 12 h to 15 patients with acute leukemia during remission induction treatment for a mean duration of 42 days (10). The effect on the colon microflora was studied. A rapid elimination of enterobacteria within three to five days was observed. *Bacteroides*

Table 1: Effect of ciprofloxacin (CIP), enoxacin (ENO), norfloxacin (NOR), ofloxacin (OFL) and pefloxacin (PEF) on the intestinal microflora.

Agent	Reference	Dose (mg/day)	Days of treatment	Number of patients	Peak serum concentration (mg/l ± SD)	Peak faecal concentration (mg/kg ± SD)	Impact on Enterobacteria	Impact on Enterococci	Impact on Anaerobic bacteria
CIP	*Brumfitt* et al. (9)	500 × 2	7	12	2.8[a]	185–2220[b]	+++	++	–
	Rozenberg-Arska et al. (10)	500 × 2	mean 42	15	nd	nd	+++	+	+[c]
	Enzenberger et al. (11)	400 × 2	7	12	nd	nd	+++	+	–
	Bergan et al. (12)	500 × 2	5	12	2.8±1.3	nd	+++	++	+[d]
	van Saene et al. (13)	50 × 4	6	12	nd	nd	+++	+	–
	Holt et al. (14)	500 × 1	5	6	2.7	nd	+++	+	+[e]
	Esposito et al. (15)	250 × 2	5–10	14[f]	nd	nd	+++	–	+[g]
		500 × 1	5–10		nd	nd	+++	–	+[g]
ENO	*Edlund* et al. (16)	400 × 2	7	10	nd	100–500	+++	–	–
NOR	*Meckenstock* et al. (17)	200 × 1	7	10[e]	nd	72–960	+++	–	–
		400 × 2	7		nd	120–1400	+++	–	–
	De Vries-Hospers et al. (19)	100 × 2	5		nd	nd	+++	+	–
		200 × 2	5	10[e]	nd	nd	+++	+	–
		400 × 2	5		nd	nd	+++	+	–
	Leigh et al. (20)	400 × 2	8	10	1.58±0.37	nd	+++	–	–
	Pecquet et al. (21)	200 × 2	5	6	1.0±0.3	2271±859[h]	+++	–	–
		400 × 2	5	6	1.9±0.9		+++	+	–
	Edlund et al. (22)	200 × 2	7	10	0.75±0.15	303–1906	+++	–	–
	Cofsky et al. (23)	400 × 1	1	12	nd	207–2716	nd	nd	nd
OFL	*Chida* et al. (25)	200 × 3	6	5	nd	nd	+++	nd	–
	Pecquet et al. (24)	200 × 2	5	5	4.23±1.63[i]	327±274	+++	++	–
PEF	*van Saene* et al. (26)	400 × 2	7	15	nd	nd	+++	+	–

+++ very strong suppression >4 $\log_{10}$ CFU/g faeces; ++ strong suppression ~ 3 $\log_{10}$ CFU/g faeces; + mild suppression ~ 2 $\log_{10}$ CFU/g faeces; – no significant change.

nd not done; [a] serum concentration on day seven; [b] range; [c] reduction in numbers of anaerobic non-sporeforming gram-positive bacilli and anaerobic cocci; [d] minor reduction in numbers of anaerobic cocci, bacteroides and fusobacteria; [e] one of six volunteers had significant reduction in total counts of anaerobic bacteria; [f] the same patients participated in treatment with different dose-schedules; [g] reduction in numbers of bacteroides; [h] no significant differences between the two dose-schedule treatment; [i] serum concentration on day five.

and *Clostridium* species were not affected, but the numbers of anaerobic non-sporeforming gram-positive rods and anaerobic cocci were decreased. Nine ciprofloxacin-resistant *Pseudomonas* and *Acinetobacter* species (MIC 1–12 mg/l) were recovered but without colonization or subsequent infection. Four of the five infections in the patients were caused by gram-positive cocci.

Enzensberger et al. (11) studied the colonic microflora in 12 volunteers receiving 400 mg ciprofloxacin orally every 12 h for seven days. Faecal samples were taken prior to and several times after beginning treatment, and qualitative and quantitative analysis of microflora were performed. *Escherichia coli* was eliminated in all volunteers after two days of treatment. No selection of resistant enterobacteria could be observed. The number of *Bacteroides* and *Bifidobacterium* species remained unchanged during the trial and there was no selection of *C. difficile* strains.

Bergan et al. (12) investigated the pharmacokinetics of ciprofloxacin and the effect of repeated dosages on the oropharyngeal and colon microflora in 12 volunteers. The volunteers received 500 mg ciprofloxacin tablets every 12 h for five days. The changes in the oropharyngeal microflora were minor and affected only the aerobic gram-negative cocci i.e. neisseriae. In the aerobic microflora of the colon, the numbers of enterobacteria and enterococci decreased markedly, whereas the changes in the anaerobic microflora were minor. Fourteen days after the drug was discontinued, the oropharyngeal and colon microflora had become normal. No new colonization of ciprofloxacin-resistant bacteria for which MICs were above 1.0 mg/l was observed. *C. difficile* or its cytotoxin was not detected.

van Saene et al. (13) investigated the impact of ciprofloxacin on the intestinal microflora with regard to colonization resistance. Twelve volunteers received 50 mg ciprofloxacin every six hour for six days. Enterobacteriaceae strains were eliminated from faeces in all volunteers after two-three days of ciprofloxacin administration. Enterococci were slightly affected and only a minor increase of *Candida* spp. was noticed. New ciprofloxacin resistant bacteria were not acquired by the volunteers. One week after treatment the flora had returned to normal.

The effect of ciprofloxacin on the faecal flora of six volunteers was studied by *Holt* et al. (14). Faecal specimens were cultured quantitatively for aerobic and anaerobic microorganisms before, during and after a five-day course of ciprofloxacin. There was a marked reduction of Enterobacteriaceae strains from approximately 10^6–10^7 to less than 10^4 CFU/g faeces in all volunteers during the administration period. Two volunteers were colonized by resistant coagulase-negative staphylococci or corynebacteria, but these strains were not detected after the eighth day. Total counts of anaerobic bacteria were almost unaffected in five of the volunteers, although in the sixth volunteer the total count fell from 10^{12} to 10^9 CFU/g faeces.

The modification of the colonic microflora in 14 patients with liver cirrhosis by ciprofloxacin therapy for intercurrent urinary tract infections or respiratory tract infections was examined by *Esposito* et al. (15). The doses were 250 mg twice daily or 500 mg once daily. A marked decrease in enterobacteria was noticed during the first days with both doses. From day three to six of therapy enterobacteria disappeared completely and returned to normal levels two weeks after termination of treatment. No changes in the aerobic gram-positive microflora were noticed. The anaerobic microflora was not affected by ciprofloxacin except for *Bacteroides* spp., which were detected in lower concentrations during therapy than before therapy. Two patients (one receiving 250 mg and the other 500 mg) harboured *Candida albicans* in faeces during therapy, which was still detectable 14 days after the end of treatment.

Impact of Enoxacin on the Intestinal Microflora

Edlund et al. (16) studied the effect of enoxacin on the colonic microflora of ten healthy volunteers. The subjects received 400 mg of enoxacin orally b.i.d. for seven days. The number of enterobacteria was strongly suppressed during the enoxacin administration, while enterococci, streptococci, staphylococci, micrococci and *Bacillus* species were not significantly affected. Low numbers of yeasts, mostly *C. albicans,* were detected during the administration period. Two weeks after withdrawal of enoxacin the colonic microflora had returned to normal. The anaerobic flora was only slightly affected by the administration of enoxacin. No emergence of resistance was noticed during the investigation period. The mean concentration of enoxacin on days seven and nine were 348 and 247 mg/kg faeces (range 100–500 and 49–453 mg/kg), respectively.

Impact of Norfloxacin on the Oropharyngeal and Intestinal Microflora

The effect of norfloxacin on the faecal flora of 10 healthy volunteers was studied by *Meckenstock* et al. (17). The dose schedules for each volunteer were 400 mg twice daily for seven days and 200 mg once daily for seven days with an appropriate interval between the two treatment periods. The gram-negative aerobic microflora was eliminated by the higher dose and strongly suppressed by the lower dose, while enterococci and anaerobic bacteria were not significantly reduced. The concentration of norfloxacin in faeces on days five and six ranged from 72–960 mg/kg and 120–1,400 mg/kg for the low and high doses, respectively.

Schaeffer and Sisney (18) investigated the impact of norfloxacin on enterobacteria in the anal and vaginal flora. Twenty women with uncomplicated urinary tract infections received 400 mg of norfloxacin b.i.d. for ten days. Bacterial samples were taken by swabbing the mucosal surface with two cotton applicator sticks. All patients had Enterobacteriaceae in the anal flora, and 90% of the patients were colonized with Enterobacteriaceae in the vaginal vestibule at the time of the bacteruria. In seven patients, no Enterobacteriaceae strains could be detected from the anal swabs during norfloxacin therapy. The en-

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terobacteria was reestablished in the anal flora in five of these patients after termination of norfloxacin therapy. The remaining 13 patients had continued colonization with sensitive strains in the anal flora during and after norfloxacin therapy. With regard to vaginal colonization, 15 of 20 patients showed absence of Enterobacteriaceae strains during norfloxacin therapy. Three of these patients became recolonized with sensitive enterobacteria after therapy. Five patients continued to be colonized with sensitive enterobacteria in their vaginal flora during and after norfloxacin therapy.

In another study, selective decontamination of oral and faecal microflora by administration of norfloxacin was evaluated (19). Three different dosages of norfloxacin, 100 mg, 200 mg and 400 mg b.i.d., were administered to ten healthy volunteers for five days. Oral washings and faecal samples were collected for bacteriological investigations. The oral flora was not influenced by norfloxacin treatment. The three dosages tested were almost equally effective in eliminating aerobic gram-negative rods from the faecal samples. Enterococci tended to decrease during the administration period. At 100 mg b.i.d. no changes in the anaerobic microflora were seen, as measured by overgrowth of resistant potentially pathogenic microorganisms and by the appearance of beta-aspartylglycine in faeces.

Leigh et al. (20) studied the pharmacokinetics of norfloxacin and the effect on the faecal flora. Ten healthy volunteers were given 400 mg twice daily for a total of 15 doses. Norfloxacin caused a rapid loss of gram-negative aerobic bacteria but there was no effect on the anaerobic bacteria. Replacement with gram-positive organisms was seen frequently but re-establishment of the normal faecal flora was found 14 days after treatment had stopped. No resistant strains of gram-negative aerobic bacteria were detected. Saliva concentrations of norfloxacin were high and in many cases similar to the serum concentrations. Norfloxacin could be detected in the faeces up to seven days after the last dose.

Selective decontamination of the digestive tract by norfloxacin was studied by *Pecquet* et al. (21). Twelve human volunteers were treated with 400 or 800 mg of oral norfloxacin daily for five days. Enterobacteriaceae strains were eliminated in faeces, and streptococci were affected to various degrees. During treatment, the numbers of anaerobes remained above 9.8 $\log_{10}$ CFU/g faeces. The mean faecal concentrations were not significantly different for the two regimens. The faecal concentrations peaked at day 5 (2,271 ± 859 mg/kg faeces). Norfloxacin activity in faeces was still detectable five days after the administration had stopped (462 ± 570 mg/kg) but was undetectable two days later.

Edlund et al. (22) studied the effect of norfloxacin on human oropharyngeal and colonic microflora and its multiple-dose pharmacokinetics. Ten healthy volunteers received 200 mg norfloxacin orally b.i.d. for seven days. The changes in the oropharyngeal flora were minor and only *Branhamella* and *Haemophilus* were affected. In the colonic flora, the number of enterobacteria was strongly depressed while only minor changes in the aerobic gram-positive flora were noticed. The anaerobic colonic flora was not affected except for *Veillonella* and *Clostridium perfringens,* which were reduced in number. Two weeks after the administration period, both the oropharyngeal and colonic microflora had returned to normal. The saliva concentrations were approximately 30% of the serum levels, measured 1–1.5 h after administration. No accumulation in faeces was found during the administration period and mean concentrations were 940 mg/kg (range 303–1,906 mg/kg).

Cofsky et al. (23) studied the recovery of norfloxacin in faeces after administration of a single oral dose to human volunteers. Twelve healthy volunteers received a 400 mg oral dose of norfloxacin. During the following 48 h, 8.3–53.3% (mean 28%) of the dose was recovered from faeces. Peak drug concentration in faecal specimens ranged from 207 to 2,716 mg/kg.

Impact of Ofloxacin on the Intestinal Microflora

The effect of ofloxacin on faecal bacteria in human volunteers was investigated by *Pecquet* et al. (24). Five volunteers received 400 mg ofloxacin daily for five days. The number of Enterobacteriaceae strains dropped sharply after ofloxacin administration. No Enterobacteriaceae strains were detectable in the faeces four days after the treatment had started. Six days after the end of ofloxacin administration, the Enterobacteriaceae strains had not yet returned to pretreatment levels. The number of enterococci decreased significantly during ofloxacin treatment, but increased again to pretreatment numbers within four days after the end of treatment. All five volunteers were colonized by low numbers of *Candida* spp. after four days of treatment. The number of anaerobic bacteria always remained over 10.5 $\log_{10}$ CFU/g faeces. No emergence of resistance in the intestinal flora to ofloxacin was seen. Faecal concentrations of ofloxacin were 327 ± 274 mg/kg after four days treatment.

Chida et al. (25) studied the effect of ofloxacin on human faecal flora and its correlation to the faecal drug concentrations. Five volunteers received 200 mg ofloxacin t.i.d. for six days. The Enterobacteriaceae strains were eliminated within two days of drug administration, and more than one week was required for recovery to normal levels. Among anaerobic bacteria, lecithinase-negative clostridia increased, while lecithinase-positive clostridia decreased during drug administration. The other anaerobes remained unchanged. The microflora returned to normal after four to five weeks. Degrees of alteration in the faecal flora correlated well with faecal concentrations. Ofloxacin caused reduction and elimination of the sensitive bacteria together with increased faecal concentrations.

Impact of Pefloxacin on the Intestinal Microflora

The impact of pefloxacin on the colonic flora in human volunteers with regard to colonization resistance was

studied by *van Saene* et al. (26). Fifteen healthy volunteers received 400 mg pefloxacin tablets every 12 hours for one week. One to three days after the first dose, all volunteers were free of Enterobacteriaceae strains. Recolonization with enterobacteria was seen one week after the end of administration. The number of *Streptococcus faecalis* decreased slightly and *Candida* spp. did not change during the observation period. Using β-aspartylglycine as a marker for flora alterations, no effect of pefloxacin on the indigenous anaerobic microflora was detected.

Conclusion

The newer 4-quinolones – ciprofloxacin, enoxacin, norfloxacin, ofloxacin and pefloxacin – seem to have a similar effect on the intestinal microflora. Typical changes in the microflora include complete elimination or strong suppression of the enterobacteria and often a minor effect on the enterococci. The impact on other aerobic bacteria does not follow any typical pattern and is seldom significant. Anaerobic bacteria are scarcely affected by administration of 4-quinolones, even though minor changes have been reported. Based on 15 of 17 studies cited, ciprofloxacin and ofloxacin affect the aerobic gram-positive flora to a somewhat higher extent than the other 4-quinolones. Faecal concentrations seem to be very high, much higher than the changes in the microflora imply. Concentrations of 100–2,200 mg/kg have been reported.

The impact on the oropharyngeal flora is minor, only gram-negative aerobic cocci are affected by the administration of 4-quinolones. Saliva concentrations have been reported at 30–100% of the serum concentrations.

The emergence of resistant bacterial strains is uncommon, although one study has shown increased MIC-values for anaerobes during ciprofloxacin administration. Replacement by yeasts or other inherently resistant microorganisms does not often seem to be a problem.

The results so far suggest that the newer 4-quinolones do not induce marked ecological disturbances in the oropharyngeal and intestinal microflora. They may be suitable for selective decontamination in immunocompromised patients, for prophylaxis of urinary tract infections and for treatment of bacterial intestinal infections.

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