

EFFECT OF FLUOROQUINOLONES ON INTESTINAL MICROFLORA

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Fluorokinolonların barsak mikroflorasına etkisi.

Ciprofloxacin

The effect of ciprofloxacin on the intestinal microflora was tested in 12 healthy male subjects taking 500 mg of ciprofloxacin orally bid for 7 days by Brumfitt et al.(3). In the aerobic colon microflora enterobacteria were eliminated on day 7, and the numbers of streptococci and staphylococci were significantly reduced. Anaerobic bacteria were little affected quantitatively but acquired resistance to ciprofloxacin. One week later the colonic microflora had returned to a state similar to that found before treatment.

In another investigation ciprofloxacin was given in a dose of 500 mg bid to 15 patients with acute leukemia during remission induction treatment for a mean duration of 42 days(17). Enterobacteria were eliminated within 3 to 5 days. *Bacteroides* and *Clostridium* spp. were not affected, but the numbers of anaerobic non-sporeforming Gram-positive rods and anaerobic cocci were decreased. Nine ciprofloxacin-resistant *Pseudomonas* and *Acinetobacter* spp. were recovered but without colonization or subsequent infection. Four of the five infections in the patients were caused by Gram-positive cocci.

The colonic microflora in 12 volunteers receiving 400 mg ciprofloxacin orally bid for 7 days was studied by Enzenberger et al.(9). *E.coli* was eliminated in all volunteers after 2 days of treatment. No selection of resistant enterobacteria could be observed. Anaerobic bacteria were not significantly affected and there was no selection of *C.difficile* strains.

The pharmacokinetics of ciprofloxacin and the effect of repeated dosages on the colon microflora in volunteers were investigated by Bergan et al.(1). Twelve volunteers received 500 mg ciprofloxacin tablets bid for 5 days. The numbers of enterobacteria and enterococci decreased markedly whereas the changes in the anaerobic microflora were minor. The colon microflora became normalized within 14 days after the drug was discontinued. No new colonization of ciprofloxacin-resistant bacteria was observed.

The impact of ciprofloxacin on the intestinal microflora with regard to colonization resistance was investigated by Van Saene et al.(18). Twelve volunteers received 50 mg ciprofloxacin qid for 6 days. In all volunteers enterobacteria were eliminated from faeces while the number of enterococci was slightly affected. A minor increase of *Candida* spp. was noticed. No new ciprofloxacin-resistant bacteria were recovered. One week after treatment the flora had returned to normal.

Holt et al.(11) studied the effect of ciprofloxacin on the faecal microflora of 6 volunteers. The volunteers received 500 mg ciprofloxacin daily for 5 days. There was a marked reduction of enterobacteria in all volunteers during the administration period. Two volunteers were colonized by resistant coagulase-negative staphylococci or corynebacteria. The total counts of anaerobic bacteria were almost unaffected during the administration period.

Esposito et al.(10) studied the alterations in the intestinal microflora of 14 patients with liver cirrhosis by ciprofloxacin therapy for intercurrent urinary tract infections or respiratory tract infections. The patients received 250 mg twice daily or 500 mg once daily. A marked decrease in enterobacteria was noticed with both doses. From day 3 to 6 of therapy enterobacteria disappeared completely and returned to normal levels 2 weeks after termination of treatment. No changes in the aerobic Gram-positive microflora or the anaerobic microflora were noticed. Two patients were colonized by *C.albicans* during therapy.

The effect of ciprofloxacin on the intestinal microflora in young and elderly volunteers were studied by Ljungberg et al.(13). Seven young and 7 elderly healthy volunteers received

500 mg ciprofloxacin bid for 5 days. The number of enterococci, streptococci, staphylococci, and enterobacteria decreased markedly in both age groups. The effects on the anaerobic bacteria were less pronounced. Despite larger absolute bioavailability of the first dose in the elderly (77 vs. 63%; $p < 0.05$), the effect of ciprofloxacin on the microflora was similar in the two groups of volunteers.

Brismar et al.(2) investigated the effect of ciprofloxacin on the colonic microflora in patients undergoing colorectal surgery. Ciprofloxacin was given orally in 2 doses of 750 mg each with a 12-h interval starting 24 h prior to surgery, 400 mg of ciprofloxacin was given intravenously at the induction of anaesthesia, and 400 mg of ciprofloxacin was given 12 h later to 21 patients undergoing elective colorectal surgery. During the ciprofloxacin administration period, the numbers of streptococci, enterococci, and enterobacteria decreased markedly. In the anaerobic microflora both Gram-positive and Gram-negative bacteria were suppressed during the first 3 days. No postoperative infections occurred.

The ecological effects of 3 days ciprofloxacin treatment (250 mg bid) of travellers' diarrhoea in 17 patients travelling to Mexico were studied by Wiström et al.(20). A significant suppression of enterobacteria was observed and a minor increase in the numbers of anaerobic cocci and bifidobacteria was found 2 to 4 days after treatment, compared with placebo-treated and asymptomatic travellers. The mean time to cure was 26 h for ciprofloxacin and 60 h for placebo-treated patients ($p = 0.03$).

Enoxacin

Edlund et al.(8) studied the effect of enoxacin on the intestinal microflora of 10 healthy volunteers. The subjects received 400 mg enoxacin orally bid for 7 days. Enterobacteria was strongly suppressed in numbers during the enoxacin administration while enterococci, streptococci, staphylococci, micrococci, and *Bacillus* spp. were not significantly affected. Low numbers of yeast, mostly *C.albicans*, were detected during the administration period. The anaerobic flora was only slightly affected by the administration of enoxacin. No emergence of resistance was noticed during the investigation period. The intestinal microflora became normal within 2 weeks after withdrawal of enoxacin. The mean concentration of enoxacin on day 7 was 348 mg/kg faeces.

Norfloxacin

Meckenstock et al.(14) investigated the effect of norfloxacin on the faecal flora of 10 healthy volunteers. The volunteers were given 200 mg once daily or 400 mg bid for 7 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 markedly affected.

De Vries-Hospers et al.(4) evaluated selective decontamination of the intestinal microflora by administration of norfloxacin. Ten healthy volunteers received three different dosages of norfloxacin, 100 mg, 200 mg and 400 mg bid for 5 days. Anaerobic Gram-negative rods were eliminated from the faecal samples with all the three dosages tested. Enterococci tended to decrease during the administration period. No major changes in the anaerobic microflora were seen.

The pharmacokinetics of norfloxacin and the effect on the faecal flora were studied by Leigh et al.(12). Ten healthy volunteers were given 400 mg twice daily for a total of 15 doses. Gram-negative aerobic bacteria were eliminated but there was no effect on the anaerobic bacteria. Replacement with Gram-positive organisms was seen frequently but reestablishment of the normal faecal flora was found 14 days after treatment had stopped. No resistant strains of Gram-negative aerobic bacteria were detected.

Pecquet et al.(16) studied selective decontamination of the digestive tract by norfloxacin. Twelve human volunteers were treated with 400 mg or 800 mg of oral norfloxacin daily for 5 days. Enterobacteria were eliminated while streptococci were partly suppressed. The anaerobic intestinal microflora was not affected by administration of norfloxacin.

Edlund et al.(5) studied the impact of norfloxacin on the intestinal microflora and its multiple-dose pharmacokinetics. Ten healthy volunteers were given 200 mg norfloxacin orally bid for 7 days. The number of enterobacteria was strongly depressed while only minor changes in the

aerobic Gram-positive flora were observed. The anaerobic colonic flora was not significantly affected.

Ofloxacin

The impact of ofloxacin on the intestinal microflora in human volunteers was investigated by Pecquet et al.(15). Five volunteers were given 400 mg ofloxacin daily for 5 days. Enterobacteria were eliminated in faeces 4 days after the treatment had started. Six days after the end of ofloxacin administration, the enterobacteria had not yet returned to pretreatment levels. Enterococci decreased significantly during ofloxacin treatment, but increased again to pretreatment numbers within 4 days after the end of treatment. All 5 volunteers were colonized by low numbers of *Candida* spp. after 4 days of treatment. The number of anaerobic bacteria was not significantly affected.

Edlund et al.(7) evaluated the effect of ofloxacin on the intestinal microflora in 24 patients undergoing gastric surgery. A single oral dose of 400 mg ofloxacin was given to each patient 2-4 h before surgery. Enterobacteria were eliminated in 12 patients and strongly suppressed in 8 patients. The numbers of enterococci, lactobacilli, bifidobacteria, cubacteria, *Veillonella* and *Bacteroides* were also reduced. Anaerobic cocci and clostridia remained unaffected during the investigation period. The intestinal microflora returned to normal 4 weeks after the administration of ofloxacin.

Pefloxacin

The effect of pefloxacin on the intestinal flora in human volunteers with regard to colonization resistance was studied by Van Saene et al.(18). Fifteen healthy volunteers received 400 mg pefloxacin tablets bid for 7 days. Enterobacteria were eliminated in all subjects 3 days after the first dose. Recolonization with enterobacteria was seen one week after the end of administration. *Enterococcus faecalis* decreased slightly in numbers while *Candida* spp. did not change during the observation period. The anaerobic microflora was not affected by pefloxacin administration.

The influence of pefloxacin, 400 mg bid for 10 days, on microbial colonization resistance in 6 healthy volunteers was investigated by Vollaard et al.(19). There was an elimination or strong reduction in the numbers of enterobacteria during the administration period while enterococci decreased slightly in numbers. In 3 volunteers impairment of colonization resistance was indicated by a significant increase in the faecal concentration of yeasts.

Lomefloxacin

The influence of lomefloxacin on the intestinal microflora was studied by Edlund et al.(6). Ten volunteers were given 400 mg lomefloxacin orally once daily for 7 days. The numbers of enterobacteria were strongly reduced or eliminated on days 2-9, while the aerobic Gram-positive microflora did not alter in number during the investigation period. In the anaerobic intestinal microflora only minor changes were seen. The intestinal microflora was normalized 2 weeks after administration of lomefloxacin had stopped.

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