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ECOLOGICAL IMPACT OF ANTIMICROBIAL AGENTS ON HUMAN INTESTINAL MICROFLORA

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INTRODUCTION

Administration of antimicrobial agents has been shown to induce disturbances in the ecological balance of the intestinal microflora. The role of the normal microflora is still poorly understood, but there is evidence that alterations in the microflora may have important clinical consequences. One of the major functions of the endogenous gastrointestinal microflora is protection of new colonisation by potentially pathogenic microorganisms as well as protection of overgrowth of already present potentially pathogenic strains (*Edlund* and *Nord*, 1991). The anaerobic microflora outnumbers the aerobic and facultative anaerobic microflora with a factor of 1000:1. Experimental animal studies and studies on human volunteers and patients imply that the anaerobic part of the normal microflora plays a dominant role in protecting against potentially pathogenic microorganisms (*van der Waaij* et al., 1986). Most endogenous infections are caused by Gram-negative aerobic microorganisms, but Gram-positive and anaerobic infections originating from the gastrointestinal tract are also a severe problem in immunocompromised patients and in patients undergoing gastrointestinal surgery.

The intestinal microflora can be affected by incomplete absorption of orally administered agents and by secretion of the antimicrobial agent by the salivary glands, in the bile and from the intestinal mucosa. Antimicrobial agents are often inactivated to variable extent in the intestines by bacterial enzymes or by binding to bacteria and other faecal components. Nevertheless, the remaining activity in the gastrointestinal tract of many antimicrobial agents is sufficiently high to disturb the ecological balance. A decrease in the number of microorganisms due to antimicrobial therapy may lead to several unwanted effects (*Edlund* and *Nord*, 1991). One is overgrowth of already present microorganisms with natural resistance such as yeasts, which can cause systemic infections in immunocompromised patients and *Clostridium difficile*, which can lead to life-threatening diarrhoea and colitis. Secondly, establishment of new resistant pathogenic bacteria, mainly aerobic Gram-negative rods, which can colonise other areas of the host, may occur. A third effect is that bacterial overgrowth also promotes transfer of genetic elements carrying resistance factors among bacteria and bacterial groups.

It is of great clinical importance to gain knowledge about the ecological effects of different antimicrobial agents on the gastrointestinal microflora. During the last 15 years the impact of different antimicrobial agents on the human gastrointestinal microflora has been studied by several investigators. In a previous article we have reviewed the literature dealing with this subject (*Nord* and *Edlund*, 1990). Since then, several new antimicrobial agents and new

routes of administration of older agents have been investigated. We therefore find it necessary to update the previous data concerning ecological impact of antimicrobial agents.

IMPACT OF PENICILLINS ON THE INTESTINAL MICROFLORA

Phenoxymethylpenicillin

The impact of phenoxymethylpenicillin on the intestinal microflora was investigated by *Heimdahl* and *Nord* (1979a). Ten volunteers were given 800 mg phenoxymethylpenicillin capsules b.i.d. for 7 days. No antibiotic activity was found in the faecal samples during the observation period and no changes in the intestinal microflora were noticed (Table 1).

Ampicillin

Knothe and *Wiedemann* (1965) investigated the effect on the intestinal microflora of peroral daily administration of 1000 to 3000 mg ampicillin during five days to ten volunteers. The numbers of *Escherichia coli*, enterococci, bifidobacteria and anaerobic Gram-negative rods were significantly reduced, while an increased number of ampicillin-resistant *Citrobacter, Klebsiella,* and *Proteus* species was observed (Table 1).

Leigh (1979) studied the impact of peroral administration of ampicillin. Ten volunteers received 500 mg t.i.d. for five days. An increase in the numbers of enterobacteria was observed in six volunteers and two volunteers had overgrowth of *Candida* species. Five volunteers developed diarrhoea, which lasted for 1-2 days (Table 1).

Ampicillin/sulbactam

The influence of ampicillin plus sulbactam on the colonic microflora in patients undergoing colorectal surgery was studied by *Kager* et al. (1982). Ampicillin and sulbactam was given intravenously to 21 patients in 500 mg doses of each agent every eight hour for two days. Ampicillin was detected in faeces in the range of 0.1 to 21.6 mg/kg in 11 patients. No changes in the number of streptococci, enterococci, and enterobacteria were observed while anaerobic cocci, bifidobacteria, eubacteria, lactobacilli, and *Bacteroides* decreased in numbers. No new colonising aerobic or anaerobic bacteria were recovered during the investigation period. After two weeks the anaerobic microflora was normalised in all patients (Table 1).

In another study *Kager* et al. (1983a) investigated the effect of ampicillin and sulbactam in dosages of 1000 and 2000 mg, respectively, every eight hour for two days on the colon microflora in ten patients undergoing colorectal surgery. The numbers of streptococci, enterococci, enterobacteria, anaerobic cocci, anaerobic Gram-positive and Gram-negative rods decreased significantly during the prophylaxis period. The aerobic and anaerobic microflora was normalised in all patients after two weeks (Table 1).

Amoxicillin

The effect of 2000 mg amoxicillin per day for 15 or more days on the intestinal microflora in eight patients with respiratory tract infections was investigated by *Gipponi* et al. (1985). The total levels of microorganisms were reduced in four patients and three patients had increased numbers of *Candida* (Table 1).

The impact on the intestinal microflora in ten healthy volunteers receiving 250 mg amoxicillin t.i.d. perorally for five days was investigated by *Leigh* (1979). The number of enterobacteria was significantly increased in four vol-

unteers during the administration period. None of the volunteers developed diarrhoea (Table 1).

Forty-four patients received 250 mg amoxicillin t.i.d. orally for seven days as treatment for lower respiratory tract infections and the impact on the intestinal microflora was evaluated (*Christensson* et al., 1991). The intestinal microflora was partly influenced by amoxicillin treatment. There was a significant increase in the numbers of enterobacteria, anaerobic Gram-positive rods and *Bacteroides* (Table 1).

Brismar et al. (1993a) investigated the effect of amoxicillin on the normal intestinal microflora. Ten healthy volunteers were given 500 mg amoxicillin tablets every 8 hour for seven days. A minor decrease was observed in the numbers of streptococci, staphylococci and eubacteria. There was an overgrowth of *Klebsiella* in six volunteers and of *Enterobacter* in two volunteers. No overgrowth of *C. difficile* or yeast was observed (Table 1).

Amoxicillin/clavulanic acid

The effect of amoxicillin alone compared with amoxicillin plus clavulanic acid on the intestinal microflora was studied by *Mittermayer* (1983). Six volunteers received 500 mg amoxicillin and six volunteers 500 mg amoxicillin plus 125 mg clavulanic acid t.i.d. for seven days. The total number of aerobic and anaerobic bacteria was not affected by either treatment. The number of amoxicillin-resistant enterobacteria increased significantly in both groups of volunteers. Selection of amoxicillin-clavulanic acid-resistant enterobacteria occurred only in those volunteers receiving amoxicillin-clavulanic acid. No significant changes in the number of *Pseudomonas, Bacteroides*, or yeasts were observed during or after treatment (Table 1).

Lambert-Zechovsky et al. (1984a) studied the effect of amoxicillin-clavulanic acid on the intestinal flora in children. Seven patients received the antibiotic combination orally and four patients parenterally in a dosage of 27.5 mg/kg body weight q.i.d. during 10 to 11 days. Oral administration caused a greater impact on the microflora than did parenteral administration. An increase in amoxicillin-resistant *E. coli* strains was noticed after antibiotic treatment had stopped. No other significant changes in the intestinal microflora occurred (Table 1).

Wise and co-workers (1984) studied the effect of amoxicillin-clavulanic acid on the intestinal microflora in six subjects. The volunteers were given 500 mg amoxicillin and 250 mg clavulanic acid every eight hour for three days. No major changes in the intestinal flora were observed. One volunteer developed diarrhoea (Table 1).

The impact of amoxicillin-clavulanic acid on the intestinal microflora in eight volunteers was investigated by *Motohiro* et al. (1985). Four subjects were given 187.5 mg tablets and four subjects were given 375 mg tablets (ratio amoxicillin-clavulanic acid 2:1) t.i.d. for five days. The staphylococci were strongly suppressed while the number of enterobacteria increased significantly in both groups. The number of enterococci increased after the administration had stopped. There were no changes in the anaerobic intestinal microflora. Diarrhoea was observed in one subject in each group (Table 1).

Brumfitt et al. (1986) studied the effects on the intestinal microflora in six volunteers receiving 250 mg amoxicillin plus 125 mg clavulanic acid t.i.d. for seven days. Staphylococci were eliminated and the number of streptococci decreased significantly during the administration period. No other significant changes were observed (Table 1).

Table 1: Impact of penicillins on the intestinal microflora

Agent	Dose (mg/day)	Days of administration	Number of patients	Impact on: Entero-bacteria	Impact on: Aerobic Gr^+ cocci	Impact on: Anaerobic bacteria	Overgrowth of resistant strains: Entero-bacteria	Overgrowth of resistant strains: *C. difficile*	Overgrowth of resistant strains: *Candida*	Reference
Phenoxymethyl-penicillin	800x2	7	10	-	-	-	-	-	-	*Heimdahl* & *Nord*, 1979a
Ampicillin	1000-3000	5	10	↓↓	↓↓	↓↓	-	-	-	*Knothe* & *Wiedemann*, 1965
	500x3	5	10	↑	-	-	+	-	+	*Leigh*, 1979
Ampicillin/ sulbactam	500x3	2	21	-	-	↓	-	-	-	*Kager* et al., 1982
	1000x3	2		↓	↓	↓	-	-	-	*Kager* et al., 1983a
	2000x3	2		↓	↓	↓	-	-	-	*Kager* et al., 1983a
Amoxycillin	2000	≥15	8	↓	↓	↓	-	-	+	*Gipponi* et al., 1985
	250x3	5	10	↑	-	-	-	-	-	*Leigh*, 1979
	250x3	7	44	↑	-	↑	-	-	-	*Christensson* et al., 1991
	500x3	7	10	-	↓	-	+	-	-	*Brismar* et al., 1993a
	500x3	7	6	-	-	-	-	-	-	*Mittermayer*, 1983
Amoxycillin/ clavulanic acid	500/125x3	7	6	-	-	-	+	-	-	*Mittermayer*, 1983
	27.5mg/kgx4	10-11	11	-	-	-	+	-	-	*Lambert-Zechovsky*, 1984a
	500/250x3	3	6	-	-	-	-	-	-	*Wise* et al., 1984
	187.5x3 (2/1)*	5	4	↑	↓	-	+	-	-	*Motohiro* et al., 1985
	375x3 (2/1)*	5	4	↑	↓	-	+	-	-	*Motohiro* et al., 1985
	250/125x3	7	6	-	↓	-	+	-	-	*Brumfitt* et al., 1986
Bacampicillin	400x3	7	12	-	-	↓	-	-	-	*Heimdahl* et al., 1979
	1600	≥15	8	-	-	-	-	-	-	*Gipponi* et al., 1985
Pivampicillin	700x4	3	10	↑	-	-	+	-	+	*Knothe* & *Lembke*, 1973
Azlocillin	5000x3	7-8	6	↓	↓	↓	+	-	-	*Nord* et al., 1986
Piperacillin	4000x3	2	20	↓	↓	↓	-	-	-	*Kager* et al., 1983b
Piperacillin/ Tazobactam	4000/500x3	4-8	20	↓	↓	-	-	-	-	*Nord* et al., 1993

Table 1: Impact of penicillins on the intestinal microflora (continued)

Agent	Dose (mg/day)	Days of adminis-tration	Number of patients	Impact on:			Overgrowth of resistant strains			Reference
				Entero-bacteria	Aerobic Gr^+ cocci	Anaerobic bacteria	Entero-bacteria	*C. dif-ficile*	*Candida*	
Talampicillin	250x3	5	10	↑	-	-	+	-	-	*Leigh*, 1979
Pivmecillinam	600x4	7	10	↓↓	↑	↓	-	-	-	*Knothe*, 1976
	400x3	7	5	↓	↑	↓	-	-	-	*Knothe*, 1976
Ticarcillin/ clavulanic acid	5000/200x3	7	10	↓	↑	-	-	-	-	*Nord* et al., 1989

↓↓: strong suppression, >4 log10 CFU/g faeces.
↓: mild to moderate suppression, 2-4 log10 CFU/g faeces.
↑: increase in number of microorganisms during therapy.
-: no significant change.
*: ratio amoxycillin/clavulanic acid.

Bacampicillin

Heimdahl et al. (1979b) investigated the effect of bacampicillin on the colon microflora. Bacampicillin was given as tablets or syrup in doses of 400 mg t.i.d. for seven days to 12 subjects. No changes in the colon microflora were observed in the volunteers receiving tablets, while there was a decrease in the numbers of anaerobic bacteria in those volunteers taking syrup. No ampicillin was detected in the faecal samples during the investigation period and no increased resistance to ampicillin was observed in the colon microflora (Table 1).

The impact of bacampicillin on the intestinal microflora in eight patients receiving 1600 mg daily for at least 15 days was investigated by *Gipponi* (1985). Moderate microbial changes were observed in two of the patients. No *C. difficile* strains or toxins were isolated (Table 1).

Pivampicillin

The impact of pivampicillin on the intestinal microflora was investigated by *Knothe* and *Lembke* (1973). Ten volunteers received a dose of 700 mg q.i.d. for three days. Pivampicillin caused minor changes in the flora. The numbers of *E. coli* and *Candida* increased in seven respectively three volunteers (Table 1).

Talampicillin

Leigh (1979) studied the effect of talampicillin on the intestinal microflora. Ten volunteers were given talampicillin perorally in a dosage of 250 mg t.i.d. for five days. Six subjects had considerable increase in the numbers of enterobacteria and one volunteer developed diarrhoea (Table 1).

Azlocillin

The impact of parenteral azlocillin treatment on the intestinal microflora in six patients receiving 5000 mg azlocillin t.i.d. for seven to eight days was investigated by *Nord* et al. (1986). The numbers of *E. coli* and streptococci were suppressed markedly in two patients and in one patient the enterococci decreased. The numbers of anaerobic cocci, lactobacilli, clostridia and *Bacteroides* were also markedly decreased in two patients. No patients harboured *C. difficile* or had cytotoxin in their faecal samples during or after azlocillin treatment (Table 1).

Piperacillin

The influence of piperacillin on the colonic microflora in patients undergoing colorectal surgery was investigated by *Kager* et al. (1983). Piperacillin was given parenterally in doses of 4000 mg every eight hour for 48 hours to 20 patients undergoing colorectal surgery. Enterococci, streptococci, and enterobacteria decreased in five of the patients while anaerobic Gram-positive cocci and rods, fusobacteria and *Bacteroides* decreased in seven of the patients during the administration period. After the piperacillin treatment, the aerobic and anaerobic colon microflora returned to the pre-treatment levels in most patients (Table 1).

Piperacillin/Tazobactam

The effect of piperacillin/tazobactam on the intestinal microflora was studied in 20 patients with intra-abdominal infections (*Nord* et al., 1993). The patients received 4000 mg piperacillin combined with 500 mg tazobactam t.i.d. by intravenous injection during four to eight days. The numbers of enterobacteria and enterococci were slightly decreased during treatment. There was a minor decrease in the numbers of bifidobacteria, eubacteria, lactobacilli, clostridia and veillonella while the numbers of anaerobic Gram-positive cocci and *Bacteroides* were not influ-

enced by the treatment. None of the patients had *Clostridium difficile* or its cytotoxin in faeces or developed diarrhoea. After therapy, the aerobic and anaerobic microflora returned to normal levels in all patients (Table 1).

Pivmecillinam

Knothe (1976) investigated the impact on the intestinal microflora of pivmecillinam. Ten volunteers were given 600 mg q.i.d. and five volunteers were given 400 mg t.i.d. for seven days, respectively. The changes were more pronounced after the higher dose of pivmecillinam. The numbers of *E. coli*, lactobacilli, and *Bacteroides* were significantly decreased while the numbers of enterococci increased (Table 1).

Ticarcillin/clavulanic acid

The influence of ticarcillin/clavulanic acid on the intestinal microflora was investigated by *Nord* et al. (1989). Ten volunteers were given 5000 mg ticarcillin plus 200 mg clavulanate intravenously t.i.d. for seven days. The numbers of enterococci and streptococci slightly increased, while there was a small decrease in the number of enterobacteria. Minor changes in the anaerobic microflora were observed. No measurable faecal concentrations of ticarcillin or clavulanate were found (Table 1).

Comments

Administration of ampicillin led to a strong suppression of both the aerobic and the anaerobic intestinal microflora. Phenoxymethylpenicillin and acid-resistant derivates of ampicillin like amoxicillin, bacampicillin, pivampicillin and talampicillin caused only minor suppression of the normal microflora, although overgrowth of resistant enterobacteria were observed. Administration of broad-spectrum penicillins, like azlocillin, piperacillin, pivmecillinam and ticarcillin resulted in marked changes in the intestinal microflora with strong suppression of the aerobic Gram-negative bacteria and often overgrowth of enterococci. These agents affected the anaerobic microflora only to a minor degree. None of the penicillins caused any major overgrowth of *C. difficile* or yeasts.

IMPACT OF PARENTERAL CEPHALOSPORINS ON THE INTESTINAL MICROFLORA

Cefazolin

Vogel and *Knothe* (1985) investigated the impact of cefazolin on the aerobic intestinal microflora in five patients receiving cefazolin (60-80 mg/kg per day). Treatment with cefazolin did not induce any changes in the aerobic flora except for colonisation with *Pseudomonas* species (Table 2).

Cefbuperazone

The influence of cefbuperazone on the intestinal microflora in patients undergoing colorectal surgery was studied by *Kager* et al. (1986). Ten patients were given cefbuperazone intravenously in a dose of 1000 mg at induction of anaesthesia, followed by a subsequent dose of 1000 mg 12 hours after the first dose. The cefbuperazone concentration in the faecal samples varied between 0 and 27.0 mg/kg. Streptococci, enterococci and enterobacteria were suppressed significantly during the prophylaxis period. Among the anaerobic bacteria, cocci, bifidobacteria, eubacteria, lactobacilli, clostridia, fusobacteria and *Bacteroides* decreased markedly

Table 2: Impact of parenterally administered cephalosporins on the intestinal microflora

Agent	Dose (mg/day)	Days of administration	Number of patients	Impact on: Entero-bacteria	Impact on: Aerobic Gr^+ cocci	Impact on: Anaerobic bacteria	Overgrowth of resistant strains: Entero-bacteria	Overgrowth of resistant strains: *C. difficile*	Overgrowth of resistant strains: *Candida*	Reference
Cefazolin	60-80mg/kg	4-11	5	–	-	a	+	-	-	*Vogel* & *Knothe*, 1985
Cefbuperazone	1000x2	1	10	↓	↓	↓	-	-	-	*Kager* et al., 1986
Cefepime	1000x2	8	8	↓	-	-	-	-	-	*Bächer* et al., 1992
Cefmenoxime	4000	3	15	↓	-	-	-	-	+	*Knothe* et al., 1985
Cefoperazone	2000x2	7-14	28	↓↓	↑↓	↓↓	-	+	-	*Alestig* et al., 1983
	100mg/kg	4-7	16	↓↓	↓↓	↓	-	-	+	*Lambert-Zechovskky*, 1984b
				↓↓	↑	a	+	-	+	*Guggenbichler&Kofler*,1984
Cefotaxime	100mg/kg	a	26	↓	↑	-	+	-	-	*Lambert-Zechovskky*, 1985
	60-80mg/kg	4-11	11	-	-	a	+	-	-	*Vogel* & *Knothe*, 1985
	a	a	6	↓	-	a	-	-	-	*Guggenbichler&Kofler*,1984
Cefotiam	6000	3	15	↓	-	-	+	-	+	*Knothe* et al., 1985
Cefoxitin	2000x4	2	20	↓	↑	↓	+	-	-	*Kager* et al., 1981a
	6000-12000	8-23	6	↓	↑	↑	+	+	-	*Mulligan* et al., 1984
Ceftazidime	4000	1	8	↓	-	-	-	-	-	*Knothe* et al., 1985
Ceftizoxime	4000	1	8	↓	-	-	+	-	-	*Knothe* et al., 1985
Ceftriaxone	1500x2	7-13	12	↓↓	↓↓	↓	-	+	+	*Nilsson-Ehle* et al., 1985
	?	?	9	↓↓	-	a	+	-	+	*Guggenbichler&Kofler*,1984
	2000	1	10	↓↓	-	-	-	-	-	*Cavallaro* et al., 1992
	1000	5	10	a	a	↓	-	+	-	*Welling* et al., 1991
Moxalactam	2000	1	10	↓	↑	↓	-	-	-	*Kager* et al., 1984
	2000x3	1	10	↓	↑	↓	-	-	-	*Kager* et al., 1984

↓↓: strong suppression, >4 log10 CFU/g faeces.
↓: mild to moderate suppression, 2-4 log10 CFU/g faeces.
↑: increase in number of microorganisms during therapy.
-: no significant change.
a: no data available

during the same period. The microflora was normalised in all patients after four weeks (Table 2).

Cefepime

The impact of cefepime on the intestinal microflora was studied by *Bächer* et al. (26). Eight volunteers received cefipime 1000 mg bid by constant infusion over 30 min for eight days. A decrease in the number of *E. coli* and bifidobacteria in faeces was observed, whereas *Bacteroides* spp. and *Clostridia* spp. showed a slight increase. The number of intestinal bacteria returned to normal 20 to 48 days after the study was completed (Table 2).

Cefmenoxime

The impact of cefmenoxime on the intestinal flora was evaluated by *Knothe* et al. (1992). Fifteen volunteers were given 4000 mg cefmenoxime daily intravenously for three days. The numbers of enterobacteria, bifidobacteria, and lactobacilli decreased significantly while the numbers of clostridia and *Candida* increased (Table 2).

Cefoperazone

The effect of cefoperazone on the intestinal microflora was investigated by *Alestig* et al. (1983). Twenty-eight patients were treated with 2000 mg cefoperazone b.i.d. intravenously for seven to 14 days. Enterobacteria, staphylococci and streptococci were significantly suppressed in numbers and the enterococci increased in most patients during and after cefoperazone treatment. There was a major decrease in the numbers of anaerobic cocci, *Bacteroides*, fusobacteria, bifidobacteria, eubacteria, and lactobacilli. Eight patients had *C. difficile* and its cytotoxin and five of these patients developed diarrhoea (Table 2).

The effect of cefoperazone on the intestinal microflora in 16 children was studied by *Lambert-Zechovsky* et al. (1984b). Streptococci, staphylococci, and enterobacteria were markedly reduced in numbers in 13 patients. Selection of cefoperazone-resistant yeast was observed in seven patients (Table 2).

Guggenbichler and *Kofler* (1984) analysed the impact of cefoperazone treatment on the aerobic intestinal microflora in five children with narcotising enterocolitis or septicaemia. Cefoperazone eliminated all susceptible enterobacteria within the first 24 hours and overgrowth with enterococci and *Candida* was seen. Resistant *Serratia, Klebsiella* and *Enterobacter* strains were isolated from two patients (Table 2).

Cefotaxime

Lambert-Zechovsky et al. (1985) studied the impact of cefotaxime on the intestinal microflora in 26 hospitalised children. Cefotaxime was given intravenously in doses of 100 mg/kg/day. The numbers of enterobacteria decreased while there was an increase in resistant enterococci during the cefotaxime treatment. Intestinal colonisation of *Pseudomonas* strains also occurred. No significant changes in the anaerobic microflora were observed (Table 2).

The impact of cefotaxime on the aerobic microflora in 11 patients was investigated by *Vogel* and *Knothe* (1985). Cefotaxime was given in a dosage of 60-80 mg/kg/day. Colonisation with *Pseudomonas* was frequently found. No other major ecological alterations were observed during treatment (Table 2).

The influence of cefotaxime treatment on the faecal aerobic microflora in six children with septicaemia, pulmonary or urinary tract infections was investigated by *Guggenbichler* and *Kofler* (1984). The numbers of aerobic bacteria decreased moderately during treatment but no emergence of resistant strains was observed. No cefotaxime was found in the faecal samples (Table 2).

Cefotiam

The impact of cefotiam in a dose of 6000 mg/day for three days on the intestinal microflora was determined by *Knothe* et al. (1985). The numbers of enterobacteria and lactobacilli were significantly suppressed while the numbers of *Pseudomonas* and *Candida* increased. No other changes in the microflora were observed (Table 2).

Cefoxitin

The impact of cefoxitin prophylaxis on the colon microflora in patients undergoing colorectal surgery was investigated by *Kager* et al. (1981). Cefoxitin was administered intravenously in doses of 2000 mg every six hour for two days to 20 patients. The cefoxitin concentrations in the faecal samples were between 1.5 and 35.5 mg/kg. In the aerobic microflora, cefoxitin-sensitive *E. coli* and other enterobacteria decreased significantly while cefoxitin-resistant enterococci, enterobacteria, and *Pseudomonas* proliferated. Among the anaerobic bacteria, *Bacteroides fragilis* and fusobacteria decreased significantly. After the antibiotic prophylaxis had stopped all cefoxitin-resistant bacterial strains decreased while the suppressed *E. coli* and *B. fragilis* strains increased (Table 2).

The effect of cefoxitin treatment on the intestinal microflora in six patients was studied by *Mulligan* et al. (1984). The patients received cefoxitin in daily doses of 6000 to 12000 mg for eight to 23 days. There were a proliferation of enterococci, coagulase-negative staphylococci, cefoxitin-resistant enterobacteria, *Pseudomonas* spp. and *Bacteroides fragilis*. *C. difficile* strains were isolated from five patients (Table 2).

Ceftazidime

Knothe et al. (1985) studied the effect of ceftazidime on the gut flora in eight volunteers. The volunteers received ceftazidime intravenously in a dose of 4000 mg for one day. The enterobacteria and the lactobacilli decreased considerably, while no effect on other microorganisms in the flora could be observed (Table 2).

Ceftizoxime

The influence of ceftizoxime on the intestinal flora in eight volunteers receiving 4000 mg ceftizoxime during one day was investigated by *Knothe* et al. (1985). Ceftizoxime administration significantly reduced the numbers of susceptible enterobacteria while *Citrobacter* and *Proteus* increased in numbers. No effect on enterococci, lactobacilli, and *Bacteroides* was observed (Table 2).

Ceftriaxone

Nilsson-Ehle, et al. (1985) studied the influence of ceftriaxone on the intestinal microflora in 12 patients with acute bacterial infections. The patients received 1500 mg ceftriaxone b.i.d. for seven to 13 days. The numbers of aerobic bacteria decreased significantly in all patients except two. These two patients had the lowest biliary clearance of ceftriaxone. In six patients overgrowth with *Candida* and *Torulopsis* was noticed during the treatment period. The aerobic microflora was normalised in all patients except one after one month. In the anaerobic microflora the cocci, bifidobacteria, eubacteria, *Bacteroides*, and fusobacteria decreased significantly. The two patients with low biliary excretion had only minor changes in the anaerobic flora. One patient had *C. difficile* and cytotoxin in faeces during and after treatment and had concomitant diarrhoea (Table 2).

The effect of ceftriaxone on the aerobic intestinal microflora in nine children with septicaemia was investigated by *Guggenbichler* and *Kofler* (1984). The aerobic susceptible Gram-negative bacteria was eradicated from the microflora

within 48 hours while *Klebsiella, Enterobacter, Citrobacter, Serratia,* and *E. coli* strains acquired resistance during therapy. Enterococci and *Candida albicans* dominated the aerobic microflora during treatment. Reappearance of aerobic Gram-negative bacteria was observed in all patients except two after the treatment had stopped (Table 2).

The influence of ceftriaxone on intestinal flora was investigated by *Cavallaro* et al. (1992) in ten patients undergoing colorectal surgery. Ceftriaxone were given intravenously in one 2000 mg dose before anaesthesia. The aerobic faecal microflora was considerably affected, enterobacteria were eliminated or strongly suppressed in all patients, while there was only minor changes in the number of aerobic Gram-positive bacteria. The anaerobic microflora showed only minor alterations. No new colonising microorganisms were isolated during the investigation period and no colonisation with ceftriaxone-resistant bacteria was observed (Table 2).

Welling et al (1991) studied the effect of ceftriaxone on the anaerobic intestinal microflora. Ten healthy volunteers received 1000 mg of ceftriaxone intramuscularly for five days. Ceftriaxone treatment resulted in a significant decrease in the total number of anaerobic microorganisms. Two patients were colonised by toxin negative *C. difficile* strains during the administration period (Table 2).

Moxalactam

Kager et al. (1984) studied the effect of single-dose as compared to three-dose prophylaxis with moxalactam on the colon microflora in patients undergoing colorectal surgery. Twenty patients were given an initial dose of 2000 mg moxalactam at the induction of anaesthesia. Ten of the patients received two subsequent doses at eight-hour intervals. The moxalactam concentrations in faeces varied between 0.2 and 23.0 mg/kg. There were no differences between the patients receiving one dose of moxalactam and those receiving three doses. Enterobacteria were markedly suppressed during the prophylaxis period, while streptococci and enterococci proliferated from day three to day five. Among the anaerobic bacteria, cocci, lactobacilli, bifidobacteria, clostridia, *Bacteroides*, and fusobacteria decreased significantly during the same period. After two weeks the microflora was normalised in all patients (Table 2).

Comments

Parenterally administered cephalosporins seemed in general to cause moderate effects on the intestinal microflora mostly in form of suppression of enterobacteria. However, administration of cefoperazone and ceftriaxone also led to a considerably decrease in the numbers of aerobic Gram-positive and anaerobic microorganisms. Most parenterally administered cephalosporins led to overgrowth of resistant enterobacteria and also sometimes to colonisation of *C. difficile* and yeasts.

IMPACT OF ORAL CEPHALOSPORINS ON THE INTESTINAL MICROFLORA

Cefaclor

Finegold et al. (1987) investigated the impact of cefaclor on the intestinal microflora in six volunteers receiving cefaclor orally 250 mg t.i.d. for 14 days. The aerobic flora was not significantly altered by cefaclor administration. In the anaerobic microflora bifido-

bacteria were eliminated in two subjects. Three volunteers were colonised by *C. difficile*, but none developed colitis (Table 3).

Cefaclor was given orally to 10 volunteers in doses of 250 mg t.i.d. for seven days by *Nord* et al. (1987). The aerobic intestinal microflora was not affected by cefaclor administration, while minor changes in the anaerobic intestinal microflora was observed. There was no new colonisation with cefaclor-resistant bacteria (Table 3).

Forty patients with lower respiratory tract infections were treated with 250 mg cefaclor orally t.i.d. for seven days, and the ecological alterations in the intestinal microflora were evaluated (*Christensson* et al., 1991). The numbers of streptococci, staphylococci and anaerobic cocci decreased significantly, while enterococci, enterobacteria, *Bacteroides* and *Candida albicans* increased significantly in numbers during cefaclor treatment (Table 3).

Cefixime

Finegold et al. (1987) evaluated the influence of 400 mg orally administered cefixime daily for 14 days on the intestinal microflora in six healthy subjects. A significant decrease in the numbers of *E. coli* occurred. In four subjects the enterococci increased markedly. In the anaerobic microflora, bifidobacteria disappeared from two subjects, clostridia from three subjects, and *B. fragilis* from one subject. *C. difficile* was isolated from four subjects without severe gastrointestinal symptoms. No development of resistance among the aerobic or anaerobic bacteria was seen (Table 3).

The ecological effects on the normal intestinal microflora in ten healthy persons after 200 mg cefixime tablets bid for seven days was studied by *Nord* et al. (1988). The numbers of streptococci and *E. coli* decreased while the numbers of enterococci increased during the administration of cefixime. In the anaerobic microflora, the numbers of cocci, clostridia and *Bacteroides* were suppressed significantly. *C. difficile* was isolated from 5 volunteers but cytotoxin was only detected in one volunteer. The intestinal microflora was normalised within two weeks after treatment had stopped (Table 3).

Cefpodoxime-proxetil

Brismar et al. (1993a) investigated the effect of cefpodoxime-proxetil on the normal intestinal microflora. Ten healthy volunteers were given 200 mg cefpodoxime-proxetil tablets every 12 hour for seven days. The numbers of streptococci, enterobacteria and clostridia were strongly reduced in the faecal flora, while there was an overgrowth of enterococci. Beta-lactamase activity was detected in six subjects. Three volunteers had high concentrations of cefpodoxime in faeces and no detectable beta-lactamase activities. These subjects were colonised by *C. difficile* and yeast (Table 3).

Cefprozil

Lode et al. (1992) studied the multiple-dose pharmacokinetics of orally administered cefprozil and its impact on intestinal microflora of healthy volunteers in a randomised double-blind placebo controlled trail. Eight volunteers received cefprozil 500 mg b.i.d. for eight days. Analysis of the faecal microflora showed a limited ecological impact of cefprozil on the intestinal microflora, such as a moderate decrease in enterobacteria and a slight increase in enterococci, staphylococci and *Bacteroides* during the study. *C. difficile* strains were detected in three volunteers but no toxins could be found. Four days after the administration period the number of all bacteria was normalised (Table 3).

Table 3: Impact of perorally administered cephalosporins on the intestinal microflora

Agent	Dose (mg/day)	Days of adminis-tration	Number of patients	Impact on:			Overgrowth of resistant strains			Reference
				Entero-bacteria	Aerobic Gr^+ cocci	Anaerobic bacteria	Entero-bacteria	*C. dif-ficile*	*Candida*	
Cefaclor	250x3	14	6	–	-	-	-	+	-	*Finegold* et al., 1987
	250x3	7	10	-	-	-	-	-	-	*Nord* et al., 1987
	250x3	7	40	-	↓	-	+	-	+	*Christensson* et al., 1991
Cefixime	400	14	6	↓	↑	↓	-	+	-	*Finegold* et al., 1987
	200x2	7	10	↓	↑	↓↓	-	+	-	*Nord* et al., 1988
Cefpodoxime-proxetil	200x2	7	10	↓↓	↓↑	↓	-	+	+	*Brismar* et al., 1993a
Cefprozil	500x2	8	8	↓	↑	-	-	-	-	*Lode* et al., 1992
Ceftibuten	400x1	10	14	↓	↑	-	-	+	+	*Brismar* et al., 1993b
Cefuroxime-Axetil	600x3	3	6	↓	↓	↓	-	-	+	*Wise* et al., 1984
	250x2	10	10	-	↑	-	-	+	+	*Edlund* et al., 1993
Cephradine	1000x2	7	6	-	-	-	-	-	-	*Brumfitt* et al., 1986
Loracarbef	200x2	7	20	-	-	-	-			*Nord* et al., 1991

↓↓: strong suppression, >4 log10 CFU/g faeces.
↓: mild to moderate suppression, 2-4 log10 CFU/g faeces.
↑: increase in number of microorganisms during therapy.
-: no significant change.

Ceftibuten

The effect of ceftibuten on the normal intestinal microflora was studied in fourteen healthy subjects given 400 mg ceftibuten tablets once daily for ten days (*Brismar* et al., 1993b). The numbers of *E. coli* and anaerobic cocci were partly reduced, while there was an overgrowth of enterococci during the administration period. Six volunteers were colonised by *C. difficile* during days 4 to 17. Beta-lactamase activity was detected in faecal samples from eight volunteers (Table 3).

Cefuroxime-axetil

The effect of cefuroxime-axetil on the intestinal microflora in six healthy subjects was studied by *Wise* et al. (1984). The volunteers were given 600 mg cefuroxime-axetil orally every eight hours for three days. The number of enterobacteria decreased in three volunteers who developed diarrhoea. The enterococci were also significantly suppressed and the numbers of *Candida* increased in two of these three volunteers. *Bacteroides*, peptococci, and peptostreptococci decreased significantly in three volunteers (Table 3).

Edlund et al (1993) studied the impact of cefuroxime-axetil on the normal intestinal microflora. Ten healthy volunteers were given 250 mg cefuroxime-axetil tablets b.i.d. for ten days. There was an overgrowth of enterococci and staphylococci while the levels of bifidobacteria and clostridia decreased during the administration period. The numbers of enterobacteria, eubacteria and *Bacteroides* were unaffected. Low cefuroxime concentrations in faeces corresponded to high beta-lactamase activities and minor alterations in the normal microflora, while high cefuroxime concentrations in faeces corresponded to low beta-lactamase activities and considerable ecological disturbances in the intestinal microflora (Table 3).

Cephradine

Brumfitt et al. (1986) studied the effects on the intestinal microflora in six volunteers receiving 1000 mg cephradine b.i.d. for seven days. Staphylococci were eliminated during administration while no other significant changes were observed (Table 3).

Locarbef

Nord et al. (1991) studied the effect of Loracarbef on the normal intestinal microflora. Twenty healthy volunteers received loracarbef capsules 200 mg bid for seven days. In the intestinal aerobic microflora the numbers of enterococci and streptococci increased slightly, while staphylococci, micrococci, corynebacteria, bacillus and enterobacteria were not affected. The numbers of bifidobacteria and eubacteria in the anaerobic microflora decreased, while no other bacterial groups were affected. One week after withdrawal of loracarbef, the intestinal microflora had returned to normal. No new colonising loracarbef resistant microorganisms were observed during the investigation period (Table 3).

Comments

Orally administered cephalosporins often resulted in minor decreases in the number of enterobacteria. However cefixime and high doses of cefuroxime-axetil led to alterations in the anaerobic microflora. Most orally administered cephalosporins were associated with an increase in the numbers of enterococci and colonisation with *C. difficile*.

IMPACT OF MONOBACTAMS AND CARBAPENEMS ON THE INTESTINAL MICROFLORA

Aztreonam

The impact of aztreonam on the colonic microflora in 20 patients undergoing colorectal surgery was studied by *Kager* et al. (1985). Aztreonam was given intravenously in a dose of 1000 mg at induction of anaesthesia, followed by subsequent doses of 1000 mg at 8 hours intervals over 48 hours. Enterobacteria were significantly suppressed during the antimicrobial prophylaxis period while enterococci proliferated. There was a significant increase of staphylococci in 10 patients. Three of these patients developed postoperative infections with staphylococci. In the anaerobic microflora only minor changes were observed. The microflora was normalised in all patients after two weeks (Table 4).

De Vries-Hospers et al. (1984) studied the effect on the intestinal microflora of orally administered aztreonam in 10 volunteers with three regimens: 60, 300, and 1500 mg daily for five days. The enterobacteria decreased significantly in all patients. Patients given the highest dose had increased numbers of aztreonam resistant enterococci and yeast. The anaerobic intestinal microflora was not significantly affected. The faecal concentrations increased with the dose of aztreonam and varied between 0.1 and 100 mg/kg faeces (Table 4).

Jones et al. (1984) studied the impact of aztreonam on the intestinal microflora of 18 patients with haematological malignancies. Nine patients received 1000 mg aztreonam t.i.d. and nine patients received 2000 mg aztreonam t.i.d. for seven to nine days. There was a significant decrease in the aerobic Gram-negative rods during the administration of aztreonam. The impact on anaerobic bacteria was variable. Most isolates of *Bacteroides* species persisted but all strains of *B. fragilis* were eliminated. Eight of 12 *Clostridium* strains disappeared in the patients receiving 2000 mg t.i.d. No *C. difficile* strains were isolated during the investigation period (Table 4).

Van der Waaij (1985) investigated the effect of oral administration of different dosages of aztreonam on the intestinal microflora in 10 volunteers. The aerobic Gram-negative flora was suppressed in most persons receiving 60 to 1500 mg aztreonam daily. The anaerobic microflora remained unchanged during and after treatment with doses of 60 to 300 mg/day while the highest daily dose of 1500 mg aztreonam caused a slight suppression of anaerobes in four volunteers (Table 4).

Imipenem

The impact of imipenem/cilastatin treatment on colon microflora was studied by *Nord* et al. (1984). Ten patients received 500 mg imipenem combined with 500 mg cilastatin q.i.d. by intravenous infusion for 6 to 11 days. The numbers of enterobacteria and enterococci decreased slightly during the treatment period. There was also a minor decrease in the numbers of anaerobic cocci and *Bacteroides* during the treatment period. *C. difficile* or its cytotoxin was not present in faecal samples during or after imipenem therapy and no patient developed diarrhoea. No colonisation with imipenem-resistant bacteria was observed during the investigation period (Table 4).

In a study by *Kager* et al. (1989) imipenem/cilastatin were given intravenously, as prophylaxis, to twenty patients undergoing colorectal surgery. Ten patients received a dose of 500/500 mg and 10 patients were given

Table 4: Impact of monobactams and carbapenems on the intestinal microflora

Agent	Dose (mg/day)	Days of administration	Number of patients	Impact on:			Overgrowth of resistant strains			Reference
				Entero-bacteria	Aerobic Gr^+ cocci	Anaerobic bacteria	Entero-bacteria	*C. difficile*	*Candida*	
Aztreonam	1000x3	2	20	↓	↑	-	-	+	-	*Kager* et al., 1985
	60	5	10	↓	-	-	-	-	-	*de Vries-Hospers* et al., 1984
	300	5	10	↓↓	-	-	-	-	-	*de Vries-Hospers* et al., 1984
	1500	5	10	↓↓	↑	-	-	-	+	*de Vries-Hospers* et al., 1984
	1000x3	7-9	9	↓↓	-	-	-	-	-	*Jones* et al., 1984
	2000x3	7-9	9	↓↓	-	↓	-	-	-	*Jones* et al., 1984
	20x3	5	10	↓	-	-	-	-	-	*van der Waaij* et al., 1985
	100x3	5	10	↓↓	-	-	-	-	-	*van der Waaij* et al., 1985
	500x3	5	10	↓↓	-	-	-	-	-	*van der Waaij* et al., 1985
Imipenem/ cilastatin	500/500x4	6-11	10	↓	↓	↓	-	-	-	*Nord* et al., 1984
	1000/1000x4	2	10	↓	-	↓↓	-	-	-	*Kager* et al., 1989
Meropenem	500x3	7	10	↓	↑	↓	-	-	-	*Bergan* et al., 1991

↓↓: strong suppression, >4 log10 CFU/g faeces.
↓: mild to moderate suppression, 2-4 log10 CFU/g faeces.
↑: increase in number of microorganisms during therapy.
-: no significant change.

1000/1000 mg of imipenem/cilastatin every six hour for 48 hours. The aerobic intestinal bacteria were suppressed significantly during the imipenem prophylaxis period. Among the anaerobic bacteria, cocci, bifidobacteria, eubacteria, lactobacilli, clostridia, fusobacteria, and *Bacteroides* decreased markedly during the same period. The microflora was normalised after two weeks. There were no differences between the patients receiving different dose regimens of imipenem. No postoperative infections occurred (Table 4).

Meropenem

Bergan et al. (1991) studied the effect of meropenem on the intestinal microflora of health volunteers. Ten subjects were given 500 mg meropenem by intravenous infusion over 30 min t.i.d. for seven days. The number of enterobacteria and streptococci decreased during the administration period, while the numbers of enterococci increased. There was a decrease in the number of clostridia, *Bacteroides* and Gram-negative cocci, while the numbers of Gram-positive cocci and rods were unchanged. The intestinal microflora returned to normal in all volunteers within two weeks after the termination of meropenem administration (Table 4).

Comments

Administration of aztreonam resulted in elimination or strong suppression of intestinal enterobacteria. Imipenem and meropenem caused moderate reductions in the numbers of both aerobic and anaerobic bacteria. None of these agents were associated with colonisation of *C. difficile*.

IMPACT OF MACROLIDES ON INTESTINAL MICROFLORA

Erythromycin

Heimdahl and *Nord* (1982) studied the effect of erythromycin on the intestinal microflora in healthy volunteers. Ten subjects received 500 mg erythromycin b.i.d. for seven days. The number of enterobacteria was significantly suppressed in all subjects and enterococci and streptococci were eliminated in three subjects. In the anaerobic colon microflora *Bacteroides* strains were eliminated in four subjects, fusobacteria in three subjects, and *Veillonella* in two subjects. New colonisation with erythromycin resistant enterobacteria, staphylococci, or yeast occurred in all patients. New resistant clostridial strains colonised the colonic microflora in three subjects (Table 5).

Clarithromycin

Brismar et al. (1991) compared the effects of clarithromycin and erythromycin on the normal intestinal microflora. Ten healthy volunteers received 250 mg of clarithromycin orally b.i.d. for seven days, and ten other volunteers received 1000 mg of erythromycin ethylsuccinate orally b.i.d. for seven days. In the clarithromycin group, the numbers of streptococci and enterobacteria decreased while in the erythromycin group streptococci, enterococci and enterobacteria decreased and staphylococci increased during antibiotic administration. The anaerobic intestinal microflora was also affected. The alterations were more pronounced in the volunteers receiving erythromycin than in those having clarithromycin (Table 5).

Dirithromycin

The impact of dirithromycin on the normal intestinal microflora was evalu-

Table 5: Impact of macrolides, tetracyclines, nitroimidazoles and clindamycin on the intestinal microflora

Agent	Dose (mg/day)	Days of administration	Number of patients	Impact on:			Overgrowth of resistant strains			Reference
				Entero-bacteria	Aerobic Gr^+ cocci	Anaerobic bacteria	Entero-bacteria	*C. difficile*	*Candida*	
Erythromycin	500x2	7	10	↓↓	↓	↓↓	+	-	+	*Heimdahl* & *Nord*, 1982
	1000x2	7	10	↓	↓↑	↓	+	-	+	*Brismar* et al., 1991
Clarithromycin	250x2	7	10	↓	↓	-	+	-	-	*Brismar* et al., 1991
Dirithromycin	500x1	7	20	↓↓	↑	↓	+	-	-	*Eckernäs* et al., 1991
Roxithromycin	150x2	5	6	↓	-	-	-	-	-	*Pecquet* et al., 1991
Tetracycline	250x4	8-10	15	-	-	-	+	-	+	*Bartlett* et al., 1975
Doxycycline	200+100x1*	8-10	15	-	↑	-	-	-	+	*Bartlett* et al., 1975
	100x1	7	10	↓	↓	-	+	-	-	*Heimdahl* & *Nord*, 1983
Metronidazole	400x3	5-7	10	-	-	-	-	-	-	*Nord*, 1990
Tinidazole	150x2	7	10	-	-	-	-	-	-	*Heimdahl* et al., 1980
	800+400x2**	2	20	-	↑	↓	-	-	-	*Kager* et al., 1981b
Clindamycin	150x4	7	10	-	↑	↓↓	-	+	-	*Heimdahl* & *Nord*, 1982
	600x3	3	15	-	↓↑	↓↓	-	+	-	*Kager* et al., 1981c

↓↓: strong suppression, >4 log10 CFU/g faeces.
↓: mild to moderate suppression, 2-4 log10 CFU/g faeces.
↑: increase in number of microorganisms during therapy.
-: no significant change.
*: 200 mg was given as a loading dose.
**: 800 mg was given as a loading dose.

ated by *Eckernäs* et al. (1991). Twenty healthy volunteers received 500 mg of dirithromycin orally once daily for seven days. The numbers of enterobacteria decreased significantly in the aerobic intestinal microflora, while streptococci and staphylococci increased. New colonising dirithromycin resistant enterobacteria were isolated during and after treatment. In the anaerobic microflora, the numbers of Gram-positive cocci, bifidobacteria, eubacteria and *Bacteroides* decreased, while the number of clostridia and lactobacilli increased (Table 5).

Roxithromycin

The ecological impact on the intestinal microflora of six volunteers when roxithromycin was given orally 150 mg twice every day for five days was studied by *Pecquet* et al. (1991). The faecal concentrations of active roxithromycin were in the range of 100 to 200 mg/kg faeces. The total number of enterobacteria decreased, while the rest of the aerobic and the anaerobic microflora was only affected to a minor degree. No overgrowth of roxithromycin resistant microorganisms was observed (Table 5).

Comments

Administration of macrolides resulted in suppression of both the aerobic and anaerobic intestinal microflora as well as in overgrowth of resistant microorganisms. Erythromycin and dirithromycin seemed to cause greater ecological alterations in the intestinal microflora compared to roxithromycin.

IMPACT OF TETRACYCLINES ON INTESTINAL MICROFLORA

Bartlett et al. (1975) compared the effect of tetracycline and doxycycline of the aerobic and anaerobic faecal flora in 30 healthy volunteers. Fifteen volunteers received 200 mg doxycycline the first day followed by 100 mg in a single daily dose for eight to 10 days. The other 15 subjects received tetracycline hydrochloride (250 mg q.i.d.) for eight to 10 days. Neither tetracycline hydrochloride nor doxycycline had a major impact on the total numbers of aerobic or anaerobic bacteria. Nine subjects acquired new aerobic strains during antibiotic administration. In the volunteers receiving tetracycline, enterococci, *Citrobacter freundii*, and *C. albicans* were recovered and, in those volunteers taking doxycycline, *S. aureus*, enterococci, and *C. albicans* were found. Patients receiving tetracycline hydrochloride had a mean increase of 10^4 resistant *E. coli* strains/g faeces compared to 10^1 resistant *E. coli* strains/g faeces in patients receiving doxycycline. This difference between the two tetracyclines was significant (Table 5).

The influence of doxycycline on the colon microflora was investigated by *Heimdahl* and *Nord* (1983). Ten volunteers received doxycycline orally in doses of 100 mg once daily for seven days. The number of enterococci and streptococci decreased 23 log cycles in eight volunteers and the number of enterobacteria also decreased 2-3 log cycles in five volunteers. Three subjects were colonised by new doxycycline resistant strains such as *K. pneumoniae, Proteus mirabilis,* and *E. cloacae.* Among the anaerobic bacteria, fusobacteria were eliminated during the administration period. A marked emergence of resistance to doxycycline among both aerobic and anaerobic bacteria in the colon microflora was observed (Table 5).

Comments

Administration of tetracycline and doxycycline caused no or only minor suppression of the normal intestinal microflora. However, both agents led to a major overgrowth of resistant aerobic and anaerobic microorganisms during the administration period.

IMPACT OF NITROIMIDAZOLES ON INTESTINAL MICROFLORA

Metronidazole

Metronidazole was given orally to 10 patients as tablets in a dose of 400 mg t.i.d. for 5-7 days (*Nord*, 1993). The aerobic microorganisms were only slightly affected during and after the treatment. Only minor changes in the anaerobic microflora occurred at the same period. The microflora was normalised in all patients after the treatment was terminated (Table 5).

Tinidazole

Heimdahl et al. (1980) investigated the effect of orally administered tinidazole on the intestinal microflora. Tinidazole was given in doses of 150 mg b.i.d. for seven days to 10 volunteers. No tinidazole was detected in the faecal samples and no changes in the colon microflora were noticed (Table 5).

Kager et al. (1981b) investigated the impact of tinidazole prophylaxis on the intestinal microflora in patients undergoing colorectal surgery. Tinidazole was given intravenously to 20 patients in an initial dose of 800 mg given at the induction of anaesthesia and then in doses of 400 mg every 12 h for two days. Staphylococci and enterococci proliferated during the tinidazole prophylaxis period while anaerobic bacteria decreased significantly. No bacterial strains resistant to tinidazole were recovered (Table 5).

Comments

Orally administered metronidazole and tinidazole did not cause any significant alterations in the intestinal microflora while parenterally administered tinidazole reduced the number of anaerobic bacteria and caused overgrowth of staphylococci and enterococci.

IMPACT OF CLINDAMYCIN ON INTESTINAL MICROFLORA

Heimdahl and *Nord* (1982) investigated the effect of orally administered clindamycin on the intestinal microflora. Clindamycin capsules (150 mg) were given to 10 subjects q.i.d. for seven days. Pronounced changes in the aerobic and anaerobic intestinal microflora occurred. Among the aerobes clindamycin-resistant enterococci proliferated and among the anaerobes the number of cocci and Gram-negative rods significantly decreased. In four volunteers, clindamycin-resistant clostridia were recovered and one of the volunteers developed *C. difficile*-associated diarrhoea (Table 5).

Kager et al. (1981c) studied the effect of clindamycin prophylaxis on the colon microflora in 15 patients undergoing colorectal surgery. An initial dose of 600 mg clindamycin was given as a short-term infusion during the induction of anaesthesia followed by six subsequent doses of 600 mg at eight hours intervals. Enterococci and streptococci decreased postoperatively during the first two days and then proliferated during the following three days. In the anaerobic colon flora anaerobic cocci, Gram-positive rods, and Gram-negative rods decreased significantly. The aerobic and anaerobic colon microflora was

normalised in most patients after two weeks (Table 5).

Comments

The numbers of anaerobic intestinal microorganisms were strongly suppressed during administration of clindamycin. Resistant clostridia and enterococci were frequently isolated.

IMPACT OF QUINOLONES ON INTESTINAL MICROFLORA

Ciprofloxacin

The effect of ciprofloxacin on the intestinal microflora were tested in 12 male healthy subjects taking 500 mg of ciprofloxacin orally bid for seven days by *Brumfitt* et al. (1984) In the aerobic colon microflora enterobacteria were eliminated on day seven, 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 (Table 6).

In another investigation ciprofloxacin was given in a dose of 500 mg b.i.d. to 15 patients with acute leukaemia during remission induction treatment for a mean duration of 42 days (*Rozenberg-Arska* et al., 1985). Enterobacteria were eliminated within three to five days. *Bacteroides* 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 were recovered but without colonisation or subsequent infection. Four of the five infections in the patients were caused by Gram-positive cocci (Table 6).

The colonic microflora in 12 volunteers receiving 400 mg ciprofloxacin orally b.i.d. for seven days were studied by *Enzensberger* et al. (1985). *E. coli* was eliminated in all volunteers after two 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 (Table 6).

The pharmacokinetics of ciprofloxacin and the effect of repeated dosages on the colon microflora in volunteers were investigated by *Bergan* et al. (1986). Twelve volunteers received 500 mg ciprofloxacin tablets b.i.d. for five days. The numbers of enterobacteria and enterococci decreased markedly, whereas the changes in the anaerobic microflora were minor. The colon microflora became normalised within fourteen days after the drug was discontinued. No new colonisation of ciprofloxacin-resistant bacteria was observed (Table 6).

The impact of ciprofloxacin on the intestinal microflora with regard to colonisation resistance was investigated by *van Saene* et al. (1986). Twelve volunteers received 50 mg ciprofloxacin q.i.d. for six days. In all volunteers enterobacteria were eliminated from faeces while the number of enterococci were 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 (Table 6).

Holt et al. (1986) studied the effect of ciprofloxacin on the faecal microflora of six volunteers. The volunteers received 500 mg ciprofloxacin daily for five days. There was a marked reduction of enterobacteria in all volunteers during the administration period. Two volunteers were colonised by resistant coagulase-negative staphylococci or corynebacteria. The total counts of an-

Table 6: Impact of quinolones on the intestinal microflora

Agent	Dose (mg/day)	Days of administration	Number of patients	Impact on: Entero-bacteria	Impact on: Aerobic Gr^+ cocci	Impact on: Anaerobic bacteria	Overgrowth of resistant strains: Entero-bacteria	Overgrowth of resistant strains: *C. difficile*	Overgrowth of resistant strains: *Candida*	Reference
Ciprofloxain	500x2	7	12	↓↓	↓	-	-	-	-	*Brumfitt* et al., 1984
	500x2	mean 42	15	↓↓	-	↓	+	-	-	*Rozenberg-Arska* et al., 1985
	400x2	7	12	↓↓	-	-	-	-	-	*Enzenberger* et al., 1985
	500x2	5	12	↓↓	↓	↓	-	-	-	*Bergan* et al., 1986
	50x4	6	12	↓↓	↓	-	-	-	+	*van Saene* et al., 1986
	500x1	5	6	↓↓	-	-	-	-	-	*Holt* ete al., 1986
	250x2	5-10	7	↓↓	-	↓	-	-	-	*Esposito* et al., 1987
	500x1	5-10	7	↓↓	-	↓	-	-	-	*Esposito* et al., 1987
	500x2	5	14	↓↓	↓	↓	-	-	-	*Ljungberg* et al., 1990
	750x2+400x2	2	21	↓↓	↓	↓	-	-	-	*Brismar* et al., 1990
	250x2	3	17	↓↓	-	-	-	-	-	*Wiström* et al., 1992
Enoxacin	400x2	7	10	↓↓	-	-	-	-	+	*Edlund* et al., 1987a
Norfoxacin	200x1	7	10	↓↓	-	-	-	-	-	*Meckenstock* et al., 1985
	400x2	7	10	↓↓	-	-	-	-	-	*Meckenstock* et al., 1985
	100x2	5	10	↓↓	-	-	-	-	-	*de Vries-Hospers* et al., 1985
	200x2	5	10	↓↓	-	-	-	-	-	*de Vries-Hospers* et al., 1985
	400x2	5	10	↓↓	↓	-	-	-	-	*de Vries-Hospers* et al., 1985
	400x2	8	10	↓↓	-	-	-	-	-	*Leigh* et al., 1985
	200x2	5	6	↓↓	-	-	-	-	-	*Pecquet* et al., 1986
	400x2	5	6	↓↓	↓	-	-	-	-	*Pecquet* et al., 1986
	200x2	7	10	↓↓	-	-	-	-	-	*Edlund* et al., 1988
Ofloxacin	200x2	5	5	↓↓	↓	-	-	-	+	*Pecquet* et al., 1987
	400x1	1	24	↓↓	↓	↓	-	-	-	*Edlund* et al., 1988
Pefloxacin	400x2	7	15	↓↓	-	-	-	-	-	*van Saene* et al., 1986
Lomefloxacin	400x1	7	10	↓↓	-	-	-	-	-	*Edlund* et al., 1990

↓↓: strong suppression, >4 log10 CFU/g faeces.
↓: mild to moderate suppression, 2-4 log10 CFU/g faeces.
↑: increase in number of microorganisms during therapy.
-: no significant change.

aerobic bacteria were almost unaffected during the administration period (Table 6).

Esposito et al. (1987) 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 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 or the anaerobic microflora were noticed. Two patients were colonised by *C. albicans* during therapy (Table 6).

The effect of ciprofloxacin on the intestinal microflora in young and elderly volunteers were studied by *Ljungberg* et al. (1990). Seven young and seven elderly, healthy volunteers received 500 mg ciprofloxacin b.i.d. for five 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 bio-availability 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 (Table 6).

Brismar et al. (1990) investigated the effect of ciprofloxacin on the colonic microflora in patients undergoing colorectal surgery. Ciprofloxacin was given orally in two 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 three days. No postoperative infections occurred (Table 6).

The ecological effects of three days ciprofloxacin treatment (250 mg b.i.d.) of travellers' diarrhoea in 17 patients travelling to Mexico were studied by *Wiström* et al. (1992). A significant suppression of enterobacteria was observed and a minor increase in the numbers of anaerobic cocci and bifidobacteria was found two to three 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 ($p=0.03$) (Table 6).

Enoxacin

Edlund et al. (1987a) studied the effect of enoxacin on the intestinal microflora of ten healthy volunteers. The subjects received 400 mg enoxacin orally b.i.d. for seven 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 two weeks after withdrawal of enoxacin. The mean concentration of enoxacin on day seven was 348 mg/kg faeces (Table 6).

Norfloxacin

Meckenstock et al. (1985) investigated the effect of norfloxacin on the faecal flora of ten healthy volunteers.

The volunteers were given 200 mg once daily or 400 mg b.i.d. 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 markedly affected (Table 6).

De Vries-Hospers et al. (1985) 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 b.i.d., for five days. Aerobic 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 (Table 6).

The pharmacokinetics of norfloxacin and the effect on the faecal flora was studied by *Leigh* et al. (1985). 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 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 (Table 6).

Pecquet et al. (1986) 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 five days. Enterobacteria were eliminated while streptococci were partly suppressed. The anaerobic intestinal microflora was not affected by administration of norfloxacin (Table 6).

Edlund et al. (1987b) studied the impact of norfloxacin on the intestinal microflora and its multiple-dose pharmacokinetics. Ten healthy volunteers were given 200 mg norfloxacin orally b.i.d. for seven 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 (Table 6).

Ofloxacin

The impact of ofloxacin on the intestinal microflora in human volunteers was investigated by *Pecquet* et al. (1987). Five volunteers were given 400 mg ofloxacin daily for five days. Enterobacteria were eliminated in faeces four days after the treatment had started. Six days after the end of ofloxacin administration, the enterobacteria had not yet returned to pre-treatment levels. Enterococci decreased significantly during ofloxacin treatment, but increased again to pre-treatment numbers within four days after the end of treatment. All five volunteers were colonised by low numbers of *Candida* spp. after four days of treatment. The number of anaerobic bacteria were not significantly affected (Table 6).

Edlund et al. (1988) 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 two to four hours before surgery. Enterobacteria were eliminated in 12 patients and strongly suppressed in eight patients. The numbers of enterococci, lactobacilli, bifidobacteria, eubacteria, *Veillonella* and *Bacteroides* were also suppressed. Anaerobic cocci and clostridia remained unaffected during the investigation period. The intestinal microflora returned to normal four weeks after the administration of ofloxacin (Table 6).

Pefloxacin

The effect of pefloxacin on the intes-

tinal flora in human volunteers with regard to colonisation resistance was studied by *van Saene* et al. (1986). Fifteen healthy volunteers received 400 mg pefloxacin tablets bid for seven days. Enterobacteria were eliminated in all subjects three days after the first dose. Recolonisation with enterobacteria was seen one week after the end of administration. *E. faecalis* decreased slightly in numbers while *Candida* spp. did not change during the observation period. The anaerobic microflora was not affected by pefloxacin administration (Table 6).

The influence of pefloxacin, 400 mg b.i.d. for ten days on microbial colonisation resistance in six health volunteers was investigated by *Vollaard* et al. (1992). There was an elimination or strong reduction in the numbers of enterobacteria during the administration period while enterococci decreased slightly in numbers. In three volunteers impairment of colonisation resistance was indicated by a significant increase in the faecal concentration of yeasts (Table 6).

Lomefloxacin

The influence of lomefloxacin on the intestinal microflora was studied by *Edlund* et al. (1990). 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 normalised two weeks after administration of lomefloxacin had stopped (Table 6).

Comments

Administration of quinolones resulted in elimination or strong suppression of intestinal enterobacteria. Ciprofloxacin and ofloxacin also affected enterococci and anaerobic microorganisms to a minor degree. The quinolones did not induce overgrowth of resistant bacteria or yeasts.

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