

Imipenem Concentrations in Colorectal Surgery and Impact on the Colonic Microflora

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Twenty patients undergoing colorectal surgery were given, as prophylaxis, imipenem-cilastatin intravenously. Ten of them received a dose of 0.5/0.5 g of imipenem-cilastatin at induction of anesthesia, followed by subsequent doses of 0.5/0.5 g every 6 h for 48 h. The other 10 patients were given 1.0/1.0 g imipenem-cilastatin in the same way for 48 h. Samples from serum, intestinal mucosa, and feces were taken for analysis of imipenem concentrations during the day of surgery. The mean concentrations in serum at 1 h after the first imipenem dose were 15.9 ± 1.7 $\mu\text{g/ml}$ for the 0.5-g dose and 68.2 ± 8.2 $\mu\text{g/ml}$ for the 1.0-g dose. The mean half-lives were 1.5 and 1.4 h, respectively, and the mean areas under the serum concentration-time curve were 41.2 ± 6.0 and 128.3 ± 13.5 $\text{mg} \cdot \text{h/liter}$, respectively. The imipenem concentrations in the intestinal mucosa varied between <0.1 and 3.6 mg/kg for the 0.5-g dose and 3.2 and 13.4 mg/kg for the 1.0-g dose. The concentrations in the fecal samples varied between <0.1 and 5.0 mg/kg for the 0.5-g dose and 0.7 and 11.3 mg/kg for the 1.0-g dose. Fecal samples were also collected during the investigation period for cultivation of aerobic and anaerobic bacteria. The aerobic bacteria—staphylococci, streptococci, enterococci, and enterobacteria—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 microfloras were normalized after 2 weeks. There were no differences between the patients receiving 0.5-g doses of imipenem and those receiving 1.0-g doses of imipenem. No postoperative infections occurred.

The high risk of infection following colorectal surgery is significantly reduced by the administration of prophylactic antimicrobial agents. The agents should be directed against both aerobic and anaerobic bacteria. The antimicrobial agent should be given in the smallest dose and over a short period of time, consistent with a low rate of postoperative infections.

Imipenem has been shown to be active against most aerobic and anaerobic bacteria involved in intra-abdominal infections. Imipenem has low inoculum dependence and small differences between MICs and MBCs. Clinical trials have shown that imipenem is efficacious in the treatment of intra-abdominal infections (5).

The purpose of this study was to obtain data on concentrations of imipenem in serum, tissue, and feces and the effect of low versus high doses of imipenem prophylaxis on the colon microfloras in patients undergoing colorectal surgery.

MATERIALS AND METHODS

Patients. A total of 20 patients, 10 men and 10 women between 47 and 84 years old (median age, 66 years), undergoing colorectal surgery were included in the investigation. There were 6 patients with colonic cancers, 10 with rectal cancers, 3 with diverticulosis of the colon, and 1 with a colostomy stricture. The mean serum creatinine of the subjects was 86.2 ± 8.9 $\mu\text{mol/liter}$ (plus or minus the standard error [SE]). Preoperative preparation, including fluid diet and daily enemas, was carried out for 72 h. Thirteen patients underwent bowel resections with end-to-end anastomoses, six underwent abdominoperineal rectal

excisions, and one underwent a colostomy revision. Postoperative infections were registered by the method of Ljungqvist (6).

Imipenem administration. To 10 patients, an initial dose of 0.5/0.5 g of imipenem-cilastatin (Merck Sharp & Dohme, Rahway, N.J.) was given as an intravenous infusion over 30 min at the induction of anesthesia followed by subsequent doses of 0.5/0.5 g at 6-h intervals for 48 h. The other 10 patients received 1.0/1.0 g of imipenem-cilastatin in the same way for 48 h.

Collection of specimens for determination of imipenem concentration. On the day of surgery, blood samples were taken prior to the first dose of imipenem and at 1, 1.5, 2, 3, 4, and 6 h after administration. During the operation, samples of mucosal tissue and feces were collected from the intestine. Blood samples were immediately centrifuged, and serum was withdrawn. To reduce the possible degradation of imipenem, serum was mixed with equal volumes of a stabilizing solution made up of a 1:1 mixture of 1 M MES

TABLE 1. Mean concentrations of imipenem in serum after the first 0.5-g dose on the day of surgery in 10 patients^a

Time of sampling (h)	Concn of drug in serum ($\mu\text{g/ml} \pm \text{SE}$)
0	<0.1
1	15.9 ± 1.7
1.5	12.1 ± 1.1
2	8.9 ± 1.0
3	5.3 ± 0.8
4	3.5 ± 0.7
6	1.8 ± 0.5

^a The mean half-life was 1.5 h, and the mean AUC was 41.2 ± 6.0 $\text{mg} \cdot \text{h/liter}$.

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TABLE 2. Concentrations of imipenem in serum, intestinal mucosa, and feces after the first 0.5-g dose in 10 patients

Patient no.	Time (h) ^a	Concn of drug			
		Serum (µg/ml)	Mucosa (mg/kg)	Ratio (mucosa/serum)	Feces (mg/kg)
1	0.8	19.5	3.0	0.2	3.9
2	1.5	10.2	3.6	0.4	3.6
3	1.7	14.0	2.5	0.2	4.3
4	2.5	7.3	1.0	0.1	1.7
5	3.0	4.8	1.1	0.2	1.2
6	3.0	10.6	2.0	0.2	0.5
7	3.0	3.2	2.0	0.6	5.0
8	3.3	2.1	0.4	0.2	<0.1
9	3.5	5.4	1.9	0.4	1.6
10	5.8	0.7	<0.1	— ^b	<0.1

^a Interval between drug administration and sampling of serum and tissue.
^b —, No sample.

(morpholineethanesulfonate buffer [pH 6.0]) and ethylene glycol before being frozen at -80°C. The intestinal mucosa was prepared free from muscles, and superficial blood was wiped off. After being weighed, the mucosa and feces were also mixed with the stabilizing solution before homogenization and freezing at -80°C. The samples were assayed within 2 weeks.

Assay of imipenem. The concentrations of imipenem were determined by the microbiological agar diffusion method, with agar wells 4 mm in diameter as diffusion centers. The medium used was brain heart infusion agar (Oxoid Ltd.), and the test strain was *Bacillus subtilis* ATCC 12432. From a frozen sample of stabilized standard stock solution of imipenem, daily working solutions were prepared in pooled human serum for serum assays and in phosphate buffer for assays of mucosa and feces. The method had a quantitation limit of 0.1 µg/ml. The reproducibility and variability of the assays were not greater than 3% at a 95% confidence limit.

The standard curves were calculated by linear regression of inhibition zones on log test concentrations. Serum half-lives were calculated by linear regression of log concentra-

TABLE 3. Mean concentrations of imipenem in serum after the first 1.0-g dose on the day of surgery in 10 patients^a

Time of sampling (h)	Concn of drug in serum (µg/ml ± SE)
0	<0.1
1	68.6 ± 8.2
1.5	33.2 ± 3.1
2	25.4 ± 2.4
3	15.4 ± 2.1
4	9.1 ± 1.2
6	4.4 ± 0.8

^a The mean half-life was 1.4 h, and the mean AUC was 128.3 ± 13.5 mg · h/liter.

tions of time. The area under the serum concentration-time curve (AUC) was calculated by use of the trapezoidal rule. The area beyond the last sampling point was estimated as the last concentration measured divided by the elimination rate constant, assuming first-order kinetics.

Collection and processing of specimens for microbiological studies. Stool specimens were taken for microbiological studies on the day before the operation, daily for 5 days, and then 2 weeks later. The specimens were collected in the morning in sterile plastic containers. The containers were placed in ice chests and transported to the laboratory as soon as possible. The specimens were processed as described by Kager et al. (2).

RESULTS

Imipenem concentrations in serum, intestinal mucosa, and feces. Imipenem concentrations in the group of 10 patients receiving 0.5-g doses are shown in Tables 1 and 2. The mean concentration of the drug in serum at 1 h after administration was 15.9 ± 1.7 µg/ml (plus or minus SE). The mean half-life was 1.5 h, and the mean AUC was 41.2 ± 6.0 mg · h/liter (plus or minus SE) (Table 1).

The concentrations of imipenem in intestinal mucosa were rather low during the whole observation time, with a mean of

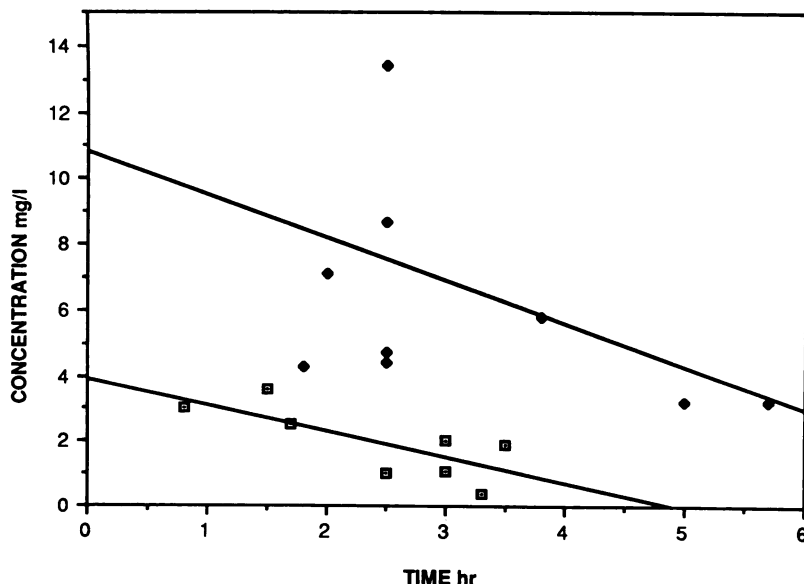


FIG. 1. Imipenem concentration in intestinal mucosa after the first 0.5-g (□) and 1.0-g (◆) doses of imipenem.

TABLE 4. Concentrations of imipenem in serum, intestinal mucosa, and feces after the first 1.0-g dose in 10 patients

Patient no.	Time (h) ^a	Concn of drug			
		Serum (μg/ml)	Mucosa (mg/kg)	Ratio (mucosa/serum)	Feces (mg/kg)
1	1.8	17.5	4.3	0.3	1.3
2	2.0	26.1	7.1	0.3	0.7
3	2.5	11.5	4.7	0.4	5.3
4	2.5	32.7	13.4	0.4	3.1
5	2.5	17.7	4.4	0.3	— ^b
6	2.5	26.7	13.4	0.5	3.0
7	2.5	22.0	8.7	0.4	0.8
8	3.8	9.8	5.8	0.6	11.3
9	5.0	8.1	3.2	0.4	0.6
10	5.7	9.4	3.2	0.3	2.6

^a Interval between drug administration and sampling of serum and tissue.
^b —, No sample.

1.8 ± 0.4 mg/kg (plus or minus SE). Higher levels were observed when the tissues were removed 2 h or earlier after administration (Table 2 and Fig. 1). The mean mucosa/serum concentration ratio was 0.3 (range, 0.2 to 0.6). The imipenem concentrations in feces ranged from <0.1 to 5.0 mg/kg with a mean of 2.2 ± 0.6 mg/kg (plus or minus SE) (Table 2).

Imipenem concentrations in the group of 10 patients receiving 1-g doses are shown in Tables 3 and 4. The mean concentration of the drug in serum at 1 h after administration was 68.6 ± 8.2 μg/ml (plus or minus SE). The mean half-life was 1.4 h, and the mean AUC was 128.3 ± 13.5 mg · h/liter (plus or minus SE) (Table 3).

The concentrations of imipenem in intestinal mucosa were high when the tissues were removed 2.5 h or earlier after administration of the drug, with a mean of 8.0 ± 1.5 mg/kg (plus or minus SE). The concentrations declined when the

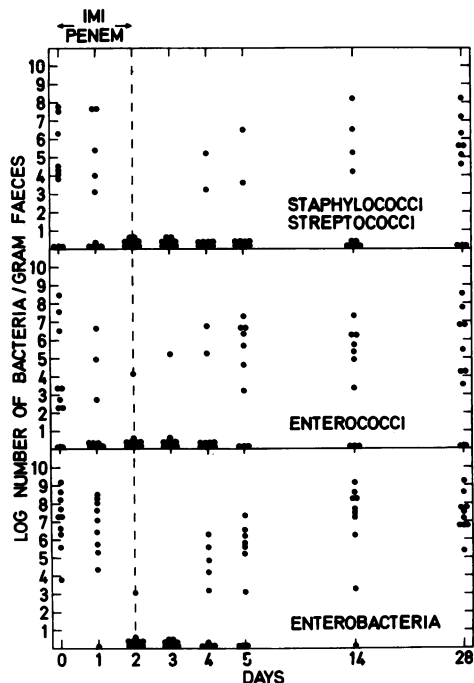


FIG. 2. Effect of imipenem on the aerobic colon microfloras in 10 patients receiving 0.5 g of imipenem every 6 h for 2 days. The viable counts are given in log mean values of CFU per gram of feces.

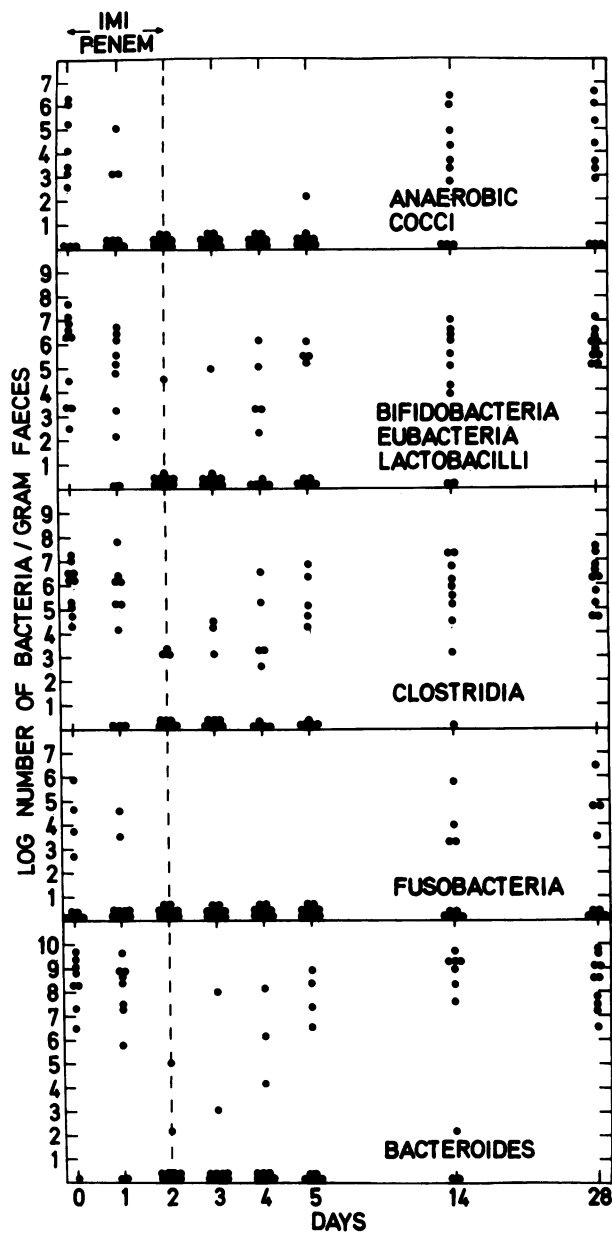


FIG. 3. Effect of imipenem on the anaerobic colon microfloras in 10 patients receiving 0.5 g of imipenem every 6 h for 2 days.

tissues were removed later, with a mean of 4.1 ± 0.9 mg/kg (plus or minus SE) (Table 4 and Fig. 1). The mean mucosa/serum concentration ratio was 0.4 (range, 0.3 to 0.6). The imipenem concentrations in feces ranged from 0.7 to 11.3 mg/kg with a mean of 3.2 ± 1.1 mg/kg (plus or minus SE) (Table 4).

Effect of imipenem on the colon microflora. Figure 2 shows the effect of 0.5 g of imipenem prophylaxis given every 6 h for 2 days on the aerobic colon microfloras in 10 patients. During the imipenem administration period, the numbers of gram-positive cocci—staphylococci, streptococci, and enterococci—decreased significantly. The numbers of enterobacteria were also suppressed during the first 3 days and then slowly increased to the same level as before the imipenem administration.

Imipenem also caused marked changes in the anaerobic

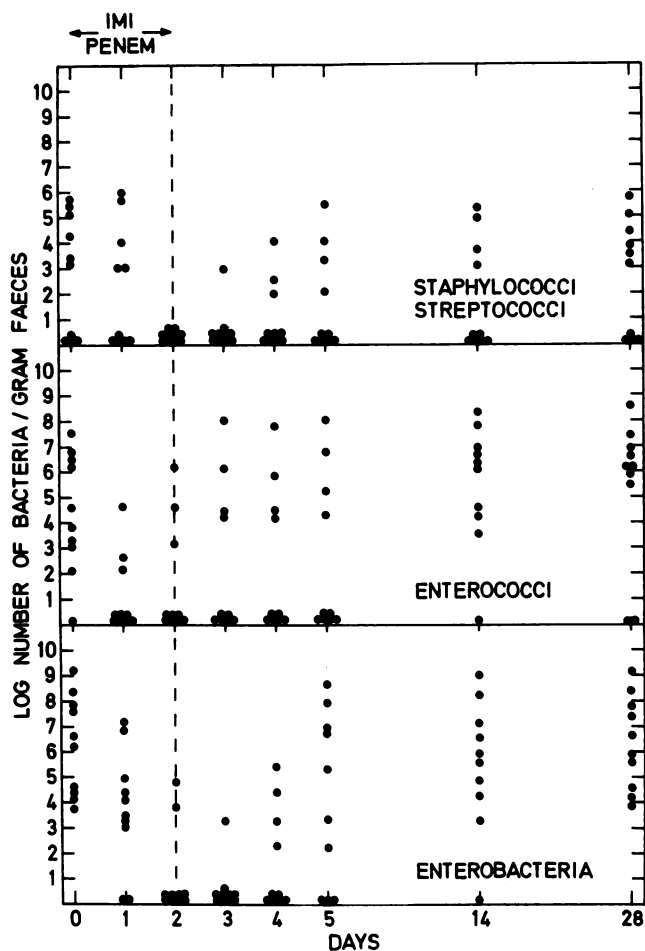


FIG. 4. Effect of imipenem on the aerobic colon microfloras in 10 patients receiving 1.0 g of imipenem every 6 h for 2 days.

colon microfloras of the patients (Fig. 3). Thus, both gram-positive and gram-negative anaerobic bacteria—cocci, bifidobacteria, eubacteria, lactobacilli, clostridia, fusobacteria, and bacteroides—significantly decreased from day 0 to day 3. The anaerobic floras returned to normal after 2 weeks.

The effect of imipenem on the aerobic colon microfloras in the patients receiving 1.0 g of imipenem every 6 h for 2 days is shown in Fig. 4. The numbers of staphylococci, streptococci, enterococci, and enterobacteria were suppressed significantly during the imipenem prophylaxis period. The aerobic colon microfloras were normalized after 2 weeks.

The anaerobic colon microfloras were also affected by imipenem administration (Fig. 5). Anaerobic cocci and gram-positive rods decreased markedly during days 1 and 4. Fusobacteria and bacteroides were also suppressed during the same period. The anaerobic colon microfloras became normal after 14 days.

There were no significant differences between the changes in the microfloras of patients receiving 0.5-g doses of imipenem and those in the microfloras of patients receiving 1.0-g doses.

Clinical findings. No postoperative infections occurred, and no adverse effects were registered.

DISCUSSION

The concentrations of imipenem in serum showed a large increment between the two dose regimens, and the AUCs

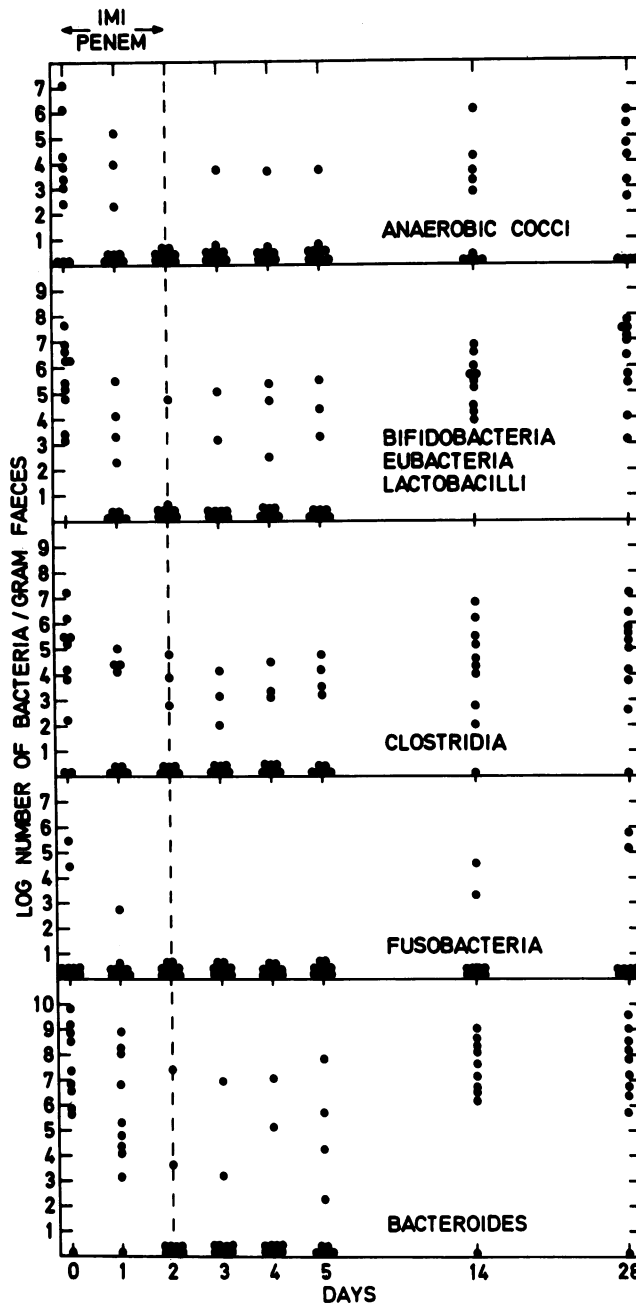


FIG. 5. Effect of imipenem on the anaerobic colon microfloras in 10 patients receiving 1.0 g of imipenem every 6 h for 2 days.

were more than double when the doses were doubled. This dose independence is not in agreement with other reported data (10, 12) and may be explained by the conditions of the patients due to the effects of surgical trauma, anesthesia, and advanced age. The half-lives were equal, in agreement with studies involving healthy subjects showing that there is no dose dependence of the half-life for imipenem (12). However, the individual half-lives in these surgical patients were longer than in healthy volunteers, although the kidney function was normal. Similar results have been reported for other beta-lactam antibiotics—piperacillin and ampicillin-sulbactam—given to elderly patients undergoing colorectal surgery (3, 4). The levels in intestinal mucosa were higher

when the higher dose was given. However, the mucosa/serum concentration ratios were similar for both dose regimens (0.3 to 0.4). The levels were higher for both doses when the tissues were removed within 2 and 2.5 h after dose administration and exceeded the MICs for all common enterobacteria and bacteroides. Gartell et al. (1) reported similar findings in patients undergoing elective colorectal surgery.

Radiometric studies in healthy volunteers have shown that less than 2% of imipenem is excreted with feces (11). There are also some studies in patients reporting low concentrations of imipenem in gastrointestinal secretions (7), in gallbladder bile and common duct bile (13), and in pancreatic fluid (Brattström et al., to be published). The concentrations in feces reported in the present investigation, although much lower than levels in serum, are above the MICs for 90% of the strains of most aerobic and anaerobic bacteria in the colon microflora (8). The changes in the flora may be explained by the achieved imipenem concentrations in the intestinal mucosa and feces during surgery. An *in vitro* effect of imipenem on the microorganisms in the stool specimens may also occur.

With the introduction of broad-spectrum beta-lactam antibiotics, it has become evident that their suppressive activities are directed not only against invading pathogenic bacteria but also against the patient's resident microflora (9). The profound changes in the gastrointestinal microflora can result in overgrowth of microorganisms, proliferation of beta-lactam-resistant strains, and increased susceptibility to colonization by new microorganisms. Imipenem has a broad antibacterial spectrum against both the aerobic and anaerobic intestinal microflora, but only minor changes in the microfloras of patients receiving this drug have been observed because of the low fecal elimination (9). However, in the present investigation both the aerobic and anaerobic bacteria were significantly suppressed, probably because of the relatively high concentrations obtained in the intestinal mucosa and feces. No new colonizing imipenem-resistant bacteria were observed during the investigation period, and the colonic microflora returned to normal within 2 weeks. No postoperative infections occurred. Imipenem may therefore be useful as a prophylactic agent in elective colorectal surgery.

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