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# Prospective Randomized Controlled Study of Ciprofloxacin versus Imipenem-Cilastatin in Severe Clinical Infections

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**In a randomized prospective study, 66 patients with serious bacterial infections—mainly lower respiratory tract infections—were treated with either imipenem plus cilastatin (32 patients) or ciprofloxacin (34 patients); 30 patients in each group were evaluable for efficacy. Substantial underlying disease was present in most of the patients; pathogens isolated prior to treatment (77 isolates) consisted mainly of members of the family *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae*, and streptococci. Of the etiologic bacteria, 67% were eradicated by ciprofloxacin treatment and 79% by imipenem therapy; however, two patients (6.7%) failed in the ciprofloxacin group, and six patients (20%) did not respond to imipenem treatment ($P = 0.25$). All patients with therapeutic failures suffered from severe fatal underlying diseases, which had substantial impact on the outcome of treatment. Therapeutic drug monitoring in the ciprofloxacin patients revealed higher concentrations in serum at days 4 and 8 in comparison with day 1 of treatment, indicating that steady-state conditions were reached between days 1 and 4. The total number of side effects was relatively high—eight imipenem patients (25%) and six ciprofloxacin patients (18%) had reactions. Treatment had to be discontinued due to adverse reactions for three ciprofloxacin patients and two imipenem patients. Major side effects in both groups were gastrointestinal and central nervous system-related symptoms. In terms of clinical and bacteriological efficacy and safety, there was no statistical difference between the two groups, and both groups gave good to excellent results for bacterial infections that were difficult to treat.**

Infections in immunocompromised patients and in patients with severe underlying diseases remain major problems (30). The changing patterns of resistance in the etiological bacteria in such severe infections has led to a need for new antibacterial agents (20). In current antibacterial therapy, increasing use of single-antibiotic treatment, even in severe infections, can be seen.

Imipenem is a carbapenem antibiotic with a broad spectrum of antimicrobial activity and resistance to most known beta-lactamases (13, 16, 21). Clinically, imipenem is combined in a ratio of 1:1 with cilastatin, a renal dehydropeptidase I inhibitor, which blocks the extensive renal metabolism of imipenem (17).

Ciprofloxacin is a new carboxylic acid derivative with high antibacterial activity against gram-positive and gram-negative aerobic bacteria (6, 10, 26). The pharmacokinetic characteristics of ciprofloxacin, with a terminal half-life of 3.5 to 4 h, allows twice-daily administration by the parenteral or oral route (2, 29).

Since both substances cover a broad spectrum of clinically important bacterial pathogens, we designed a prospective randomized controlled study comparing ciprofloxacin with imipenem-cilastatin as single-antibiotic treatment against severe clinical bacterial infections.

## MATERIALS AND METHODS

**Study design.** This single-center study was prospective, randomized, and open. Adult patients whose infections were considered severe on the basis of medical history, physical examination, and radiographic and laboratory findings were included in the study. Inclusion and assignment of patients to treatment were based on a randomized unbiased selection process from a prepared random list. Patients between 17 and 82 years old who gave informed consent were eligible for the study. We excluded patients with infections caused by pathogens known to be resistant to the study drugs and patients who were pregnant or in shock or had previously had hypersensitivity reactions to either of the test drugs. The design of the study was approved by the local ethical review committee at Steglitz Medical Center of Freie Universität Berlin.

**Patients and treatment.** Between November 1983 and October 1984, 66 patients entered the study. Hospitalized adults were enrolled if they showed strong presumptive signs of bacterial infections in the respiratory tract (RTI), skin and skin structures, urinary tract (UTI), bones or joints, or abdomen, including intra-abdominal mixed infections, cardiac valve infections, and septicemia. To be enrolled in the study under any of these diagnostic categories the patient had to show signs and symptoms of infection at the site. These included, for RTI, coughing, purulent sputum production, and fever for diagnosis of purulent bronchitis and, in addition, persistent pulmonary infiltrates for the diagnosis of pneumonia; for skin and skin structure infections, purulent drainage, erythema, cellulitis, fever, and pain; for UTI, leukocyturia, fever, and positive urine cultures (100,000 bacteria per ml of urine); for infections of the bones and joints, pain, effusion, fever, and swelling; for endocarditis, at least two positive blood cultures, fever, and echocardiographic vegetations. The one patient with severe septicemic gastrointestinal infection had abdominal pain, nausea, vomiting, and diarrhea as well as three positive blood cultures. Of these patients, 34 received ciprofloxacin and 32 received imipenem. Table 1 lists the basic epidemiological data for the patients. There were no significant differences in age, sex distribution, underlying disorders, or proportion receiving immunosuppressive treatment between the two groups. Pa-

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TABLE 1. Clinical details of patients[a]

| Characteristic | Imipenem | Ciprofloxacin | Total |
|---|---|---|---|
| Evaluable for efficacy (no. accrued) | 30 (32) | 30 (34) | 60 (66) |
| Male/female | 16/14 | 17/13 | 33/27 |
| Mean age in yrs (range) | 54.6 (17–79) | 51.6 (18–82) | 53.1 (17–82) |
| Underlying disorders | | | |
| Cardiovascular diseases | 9 | 8 | 17 |
| Chronic respiratory diseases | 12 | 9 | 21 |
| Malignant diseases | 5 | 5 | 10 |
| Diabetes mellitus | 1 | 3 | 4 |
| Renal insufficiency | 1 | 2 | 3 |
| Hematologic diseases | 1 | 3 | 4 |
| Neurologic diseases | 3 | 1 | 4 |
| Surgery within 14 days preceding study | 4 | 5 | 9 |
| Immunosuppressive therapy | 8 | 7 | 15 |
| Mean duration of treatment in days (range) | 12.1 (6–28) | 16.2 (7–51) | 14.1 (6–51) |

[a] All values are number of evaluable patients, except where noted.

tients who were randomly assigned to the ciprofloxacin group received 100 mg of ciprofloxacin (Bayer AG, Research Laboratories, Wuppertal, Federal Republic of Germany) in 50 ml of saline as a short (20-min) intravenous infusion every 8 to 12 h; in a few patients at the beginning and in most patients after day 5 or 6 of treatment, ciprofloxacin was given orally in a dose of 250 to 500 mg every 8 or 12 h; the most common dose was 1,000 mg orally per day (500 mg twice a day). Ciprofloxacin concentrations in serum 1, 4, and 8 h after drug intake on days 1, 4, and 8 of treatment were measured by high-pressure liquid chromatography for each patient. Patients in the imipenem group received 500 to 1,000 mg of imipenem and 500 to 1,000 mg of cilastatin (Merck, Sharp & Dohme Co., Munich, Federal Republic of Germany) in 100 ml of saline as a short intravenous infusion every 6 or 8 h. The most commonly used dose was 2.0 g/day (500 mg four times a day).

The duration of treatment was based on the clinical course and outcome of the individual infection. A minimum treatment time of 5 days was required for efficacy evaluation; four patients with a shorter duration of therapy (three on ciprofloxacin, one on imipenem) were only included for safety evaluation (a minimum of 48 h of treatment was necessary). In the ciprofloxacin group, the duration of therapy varied between 7 and 51 days (median, 16 days), and in the imipenem group it varied between 6 and 28 days (median, 12 days).

**Bacteriological procedures.** Bacteriological samples (blood, sputum, secretions, urine, etc.) were sent to the microbiological laboratory of our hospital. Nearly half of the specimens from patients with RTI were collected by fiberoptic bronchoscopy. Results of bacteriological sputum analysis were used for clinical evaluation only if more than 20 granulocytes per high-power field were seen on microscopic investigation and a dominant culture of one bacterial species could be identified (3). Bacteriological workup of all materials and identification of the pathogens were done by standard protocols. The susceptibility testing was performed by the Kirby-Bauer method (5) with 10-μg disks of imipenem and 5-μg disks of ciprofloxacin. Organisms with an inhibition zone less than 13 mm (imipenem) or 12 mm (ciprofloxacin) in diameter were considered resistant, whereas those with a zone ≥16 mm (imipenem) or ≥18 mm (ciprofloxacin) in diameter were considered susceptible. The 13-mm zone corresponded to an MIC of 8 μg/ml (imipenem) and the 12-mm zone to an MIC of 2 μg/ml (ciprofloxacin).

**Laboratory tests.** The following laboratory measurements were made before and every 4 to 6 days during and after treatment: ESR, hemoglobin, hematocrit, total and differential leukocyte count in peripheral blood, platelet count, prothrombin time, Coombs's test, serum alanine and aspartate aminotransferases, serum bilirubin, serum alkaline phosphatase, serum HS-hydroxybutyrate dehydrogenase, serum creatinine, blood glucose, serum uric acid, serum cholesterol, calcium, chloride, phosphorus, potassium, sodium, total protein and albumin, and urinalysis.

**Evaluation of efficacy and safety.** Response to therapy was evaluated on the basis of clinical, radiological, and bacteriological aspects. To be evaluable for efficacy, the patient had to have clinical signs of systemic or parenchymal infection and had to meet the following criteria: confirmed bacterial etiology of the infection, adequate bacteriological follow-up samples during and after treatment, and a minimum treatment time with test drugs of 5 days. Patients who met all the criteria were classified as cured if there were no remaining symptoms or signs of infection at the end of treatment with trial drugs and as improved if there was no further need for antibiotic treatment and there was a pronounced reduction of the signs and symptoms of infection. Treatment was considered to have failed if there was no reduction in the signs and symptoms of infection or the patient died of infection.

The bacteriological outcome was classified as eradication (elimination of pretherapy organisms), relapse (temporary elimination during treatment, followed by isolation of the same causative organism after the end of treatment), reinfection (isolation of a different organism after the end of therapy), persistence (continuous isolation of the causative organism during therapy), superinfection (isolation of a different organism during therapy), or failure (causative organisms present at end of therapy). When adverse clinical reactions (each patient was seen and interviewed daily during the study) or laboratory reactions were registered, the statements were qualified as probably, possibly, or doubtfully drug related. The reactions were graded as mild (requiring no special treatment and generally not interfering with usual activities), moderate (ameliorated by simple therapeutic measures; may impair usual activities), and severe (requiring therapeutic intervention; interrupt usual activities).

Differences in percentages among the groups were tested for statistical significance by chi-squared analysis (with Yates's correction). In none of the analyses in which chi-squared was tested were more than 20% of the expected values less than 5.

## RESULTS

A total of 66 patients were included in the study (Table 1); 60 were clinically evaluable for efficacy. Four patients (three on ciprofloxacin, one on imipenem) were treated for 2 to 4 days and were only included for tolerance evaluation. One of these patients (female, 64 years old) received imipenem for only 2 days (*Escherichia coli* UTI with septicemia); treatment was discontinued due to nausea, vertigo, and headache. Three patients in the ciprofloxacin group received treatment for only 2 to 4 days. Therapy had to be discontin-

TABLE 2. Clinical outcome in evaluable patients

| Infection type | No. of patients (no. with septicemia) | | | | | |
|---|---|---|---|---|---|---|
| | Imipenem | | | Ciprofloxacin | | |
| | Cure | Improvement | Failure | Cure | Improvement | Failure |
| Pneumonia | 7 | 5 | 4 | 5 | 3 | 1 (1) |
| Lower RTI | 3 | 4 | 1 | 1 | 8 | |
| Septicemia without identified focus | 2 | | | 2 | | |
| Complicated UTI | 3 (2) | | | 3 (1) | 2 (1) | |
| Abdominal | | | | | | 1 |
| Skin and soft tissue | | | | 1 (1) | | |
| Endocarditis | | | | 1 (1) | | |
| Meningitis | | | 1 (1) | | | |
| Bone | | | | | 1 | |
| Enteric | | | | | 1 (1) | |

ued for one patient because of nausea and vomiting (female, 61 years), a second patient because of rash (male, 18 years), and a third patient because of the necessity for combination therapy with other antibiotics (male, 63 years; penicillin G plus metronidazole due to necrotizing pneumonia).

Two other patients (one on ciprofloxacin, one on imipenem) were not evaluable for final analysis of efficacy because of combination treatment; one patient (female, 78 years) received imipenem plus erythromycin and netilmicin (pneumonia due to *Legionella pneumophila* and superinfection with *Pseudomonas aeruginosa*). The second patient (female, 26 years) received ciprofloxacin together with clindamycin and netilmicin for a mixed infection with *Pseudomonas maltophilia* and *Clostridium spp.* (moderately susceptible to ciprofloxacin). Twenty-five patients with pneumonia, 17 with lower RTI, 4 with septicemias without identified focus, 8 with complicated UTI (4 bacteremic), and 6 with other severe infections were treated (Table 2). Table 2 gives the results of antibiotic treatment for the 60 patients. Treatment failed in two patients (6.7%) of the ciprofloxacin group, whereas failures of treatment and deaths from infection occurred in 6 patients (20%) in the imipenem group (not significant by chi-squared test; $P = 0.25$).

Treatment failures mainly occurred in patients with fatal or ultimately fatal basic disorders. The two failures in the ciprofloxacin group both occurred in patients in the intensive care unit. One patient (male, 42 years) who suffered from acute necrotizing pancreatitis and severe enteritis after partial pancreatic resection, splenectomy, and cholecystectomy, combined with acute renal failure and long-term mechanical ventilation, had *Salmonella typhimurium* isolated from his feces for 11 days. He was treated with ciprofloxacin with eradication of the strain, but died 7 days after treatment. The other patient (male, 44 years) suffered from pneumonia caused by *P. aeruginosa* during mechanical ventilation: the underlying disease was an esophagal carcinoma operated on in 1982, with cerebellar metastases, and ventriculo-atrial shunt after cerebral surgery. He received ciprofloxacin for 9 days and had breakthrough *P. aeruginosa* bacteremia and meningitis on the last day of treatment.

Six treatment failures were seen with imipenem. All patients suffered from ultimately fatal underlying diseases (three carcinomas, two cerebral insults) and had severe chest infections caused by *Staphylococcus aureus* or *P. aeruginosa*. Two patients died during treatment, both because of severe infection together with progressive neoplastic lung disease. Another two patients died during the first week after treatment, one of still active pneumonic infection due to *S. aureus*, the other of persistent infection together with cerebral damage following a previous stroke.

Since infection could not be excluded as an important factor contributing to the death of the study patients, all patients who died during or shortly after treatment were considered treatment failures.

A total of 77 bacterial pathogens were isolated from the different infections: 15 *P. aeruginosa*, 11 *E. coli*, 9 *S. aureus*, 8 *Haemophilus influenzae* or *Haemophilus parainfluenzae*, 8 *Streptococcus faecalis*, 7 *Streptococcus* spp. (non-*S. faecalis*), 4 *Klebsiella* spp., 3 *Enterobacter* spp., 3 *Proteus* spp., 3 *Serratia liquefaciens*, 2 *Salmonella* spp., 2 *Citrobacter freundii*, and 2 *Bacteroides fragilis*. From the 36 patients in the ciprofloxacin group, 43 bacteriological pathogens were isolated before treatment; 29 (67%) of the strains isolated were eradicated by ciprofloxacin treatment, the persistence rate for *P. aeruginosa* (7 of 12) being high. The MICs for all strains before treatment were between 0.25 and 2 mg/liter; for the majority of persistent *Pseudomonas* strains there was an increase in the MIC from 0.25 to 0.5 mg/liter before treatment to 2 to 8 mg/liter after treatment.

From the 32 patients in the imipenem group, 34 isolates were recovered before treatment; 27 of these pathogens (79%) were eradicated by antibiotic therapy. MICs for all strains against imipenem could be determined to be between 0.25 and 2.0 mg/liter before treatment. For two *P. aeruginosa* strains, the MIC before treatment was 1.0 mg/liter and increased to 16 mg/liter during treatment.

Determination of ciprofloxacin concentrations in serum yielded mean levels between 0.7 and 0.8 mg/liter 1 h after parenteral administration of the first dose of 100 mg and mean trough concentrations (8 h) between 0.06 and 0.32 mg/liter. Steady-state conditions with slightly higher concentrations in serum were apparently reached by day 4 of a three-times-daily 100-mg dose of intravenous ciprofloxacin (Fig. 1).

Steady-state concentrations were also attained between days 1 and 4 in patients receiving an oral ciprofloxacin dose

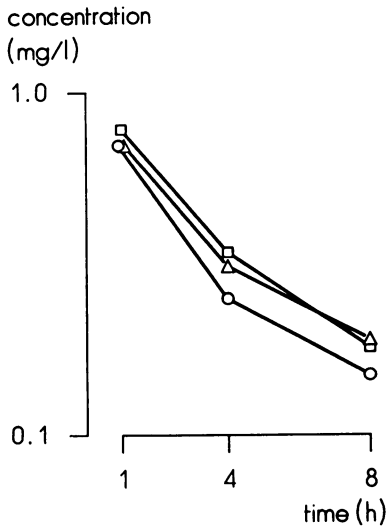


FIG. 1. Mean concentrations in plasma following intravenous administration of 100 mg of ciprofloxacin. Symbols: ○, day 1 ($n$ = 20); □, day 4 ($n$ = 15); △, day 8 ($n$ = 8).

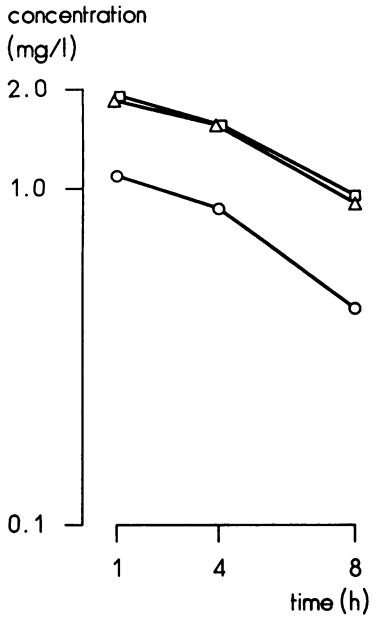


FIG. 2. Mean concentrations in plasma following oral administration of 500 mg of ciprofloxacin. Symbols: ○, day 1 ($n$ = 2); □, day 4 ($n$ = 3); △, day 8 ($n$ = 6).

of 500 mg twice daily; concentrations in serum on days 4 and 8 were remarkably higher than on day 1 but reached no significant level of difference due to the small number of patients (Fig. 2).

All 66 patients were included in the safety and tolerance analysis (Table 3). Eight imipenem patients (25%) with 11 symptoms and six ciprofloxacin patients (17%) with 9 symptoms had reactions considered definitely, probably, or possibly related to the test drugs (no significant difference in chi-squared test). Serious side effects in the imipenem group included diarrhea in two patients, isolation of *Clostridium difficile* without toxin production in one, and generalized seizure on day 23 of therapy in one, a 73-year-old female with recurrent *Klebsiella pneumoniae* infection and moderate renal insufficiency (creatinine clearance, 35 ml/min). The imipenem concentration in serum 5 h after administration on day 23 was 8.9 mg/liter and in cerebral fluid it was 0.76 mg/liter. In two patients, treatment with imipenem had to be discontinued due to adverse reactions, one on day 2 (nausea and headache), and one on day 23 (seizure). Gastrointestinal symptoms in three patients were the most common side effects in the ciprofloxacin group. Concentrations of ciprofloxacin in serum showed only a slight tendency to higher peak concentrations in the range between 4.5 and 5.5 mg/liter in patients with side effects.

TABLE 3. Adverse clinical reactions

| Side effect | No. of patients[a] | | |
|---|---|---|---|
| | Imipenem (definitely or probably related) | Ciprofloxacin | |
| | | Definitely or probably related | Possibly related |
| Diarrhea[b] | 2 | 1 | |
| Nausea and vomiting | 1 (1) | 3 (2) | |
| Rash | | 1 (1) | |
| Candidiasis | 2 | | |
| Arthralgia | | 1 | 1 (1) |
| Generalized seizure | 1 (1) | | |
| Thrombophlebitis | 2 | | |

[a] Numbers in parentheses are numbers of patients whose treatment was discontinued because of adverse effects.
[b] *C. difficile* was found in one case of diarrhea.

TABLE 4. Laboratory abnormalities considered to be drug related

| Parameter | No. of reactions caused by test drug | | |
|---|---|---|---|
| | Definitely or probably ciprofloxacin | Possibly | |
| | | Imipenem | Ciprofloxacin |
| Rise in S-ASAT or S-ALAT[a] | 3 | 1 | 2 |
| Rise in alkaline phosphatases | 2 | 1 | 2 |
| Rise in serum creatinine | | 2 | |
| Prolonged prothrombin time | | | 1 |

[a] S-ASAT, Serum aspartate; S-ALAT, serum alanine aminotransferase.

For four patients, ciprofloxacin treatment was discontinued due to adverse reactions, one on day 2 of treatment because of nausea, another on day 3 due to an acute rash. For the two other patients, ciprofloxacin therapy was discontinued on day 10 (due to nausea and vomiting) and on day 11 (due to arthralgia).

Adverse laboratory reactions considered to be definitely, probably, or possibly drug related are shown in Table 4. Four events were seen in three patients (10%) in the imipenem group and 10 events were seen in six patients (18%) in the ciprofloxacin group (no significant difference). A transient rise in liver enzymes was the leading reaction in the ciprofloxacin group, and an increase in serum creatinine concentration in two patients was the major biochemical alteration in the imipenem group. None of these reactions resulted in discontinuation of treatment.

## DISCUSSION

An increasing number of investigations demonstrate the efficacy of imipenem (4, 9, 22, 24) and ciprofloxacin (1, 11, 12, 23, 27) in severe UTI, RTI, septicemias, soft tissue, nosocomial, and *P. aeruginosa* infections. However, most of these studies are open and noncomparative; only a few studies in the literature compare one of the new substances with older, standard regimens (7, 22, 24).

A Scandinavian study group (22) reported on a multicenter study of imipenem versus gentamicin-clindamycin in serious bacterial infections. A total of 118 patients (56 in the imipenem group, 62 in the other group) were evaluable and treatment failure was significantly higher in the gentamicin-clindamycin patients than in those receiving imipenem (nine versus two). The elimination of causative pathogens was also higher in the imipenem group, so the authors concluded that "in terms of clinical and bacteriological efficacy and safety, the imipenem/cilastatin combination was superior to gentamicin/clindamycin" (22).

A similar study design was used by Solomkin et al. (24) in 74 evaluable patients, 50 of whom had intra-abdominal sepsis. No significant difference was noted in the outcome between the two groups, but a major difference was seen in

toxicity, with a 20% incidence of nephrotoxicity in the gentamicin-clindamycin group.

Studies comparing ciprofloxacin with nalidixic acid (1), co-trimoxazole (1), norfloxacin (19), or mezlocillin (27) were only done for UTI; the therapeutic results with ciprofloxacin were equal (norfloxacin) or superior (nalidixic acid, co-trimoxazole, mezlocillin) to those with the other regimens.

Until now, no prospective randomized study comparing new quinolone derivatives with new beta-lactam antibiotics has been published.

Another interesting aspect of current antibacterial therapy is single-antibiotic treatment, which may even be possible for neutropenic patients. Johnson et al. (14) found monotherapy with imipenem to be as effective as any of the currently available synergistic antibiotic combinations in the *P. aeruginosa*-infected rat model. For ciprofloxacin, Strunck et al. demonstrated equal efficacy compared with a combination of azlocillin plus tobramycin in the *P. aeruginosa* endocarditis model (23). Kemmerich et al. (13) obtained better results with ciprofloxacin and ofloxacin than with azlocillin or ceftazidime plus aminoglycosides in the mouse pneumonia model.

Our data obtained from 60 evaluable patients with severe bacterial infections, mainly RTI, are in agreement with the excellent in vitro results of the two new substances. Twenty-eight of 30 patients (93.3%) treated with ciprofloxacin and 24 of 30 patients (80%) in the imipenem group could be evaluated as clinically cured or improved, resulting in slightly better results with ciprofloxacin than with imipenem. However, all treatment failures occurred in patients with severe underlying diseases, which had a strong influence on the outcome of therapy. Comparing our current therapy with ciprofloxacin or imipenem with the results of other studies with modern beta-lactam antibiotics in a similar patient population, we reached similar percentages, ranging between 72 and 86%, with mezlocillin, cefotaxime, and ceftazidime (18, 28). However, we also encountered problems with persistence of *P. aeruginosa* in both treatment groups, a phenomenon which was recently described by Scully et al. (23) and which underlines the limitations of antibacterial therapy in these specific infections. However, modern quinolones are the first chemotherapeutic agents which can be used effectively for oral treatment of *Pseudomonas* infections.

An interesting point in the therapeutic drug monitoring of ciprofloxacin patients was the higher concentrations in serum on days 4 and 8 than on day 1, indicating that a steady-state concentration plateau was reached between days 1 and 4. This increase in concentration may be of therapeutic use but may also contribute to intolerance reactions, especially in patients with renal or hepatic insufficiency. In this context also, the higher ciprofloxacin concentrations in serum in elderly patients, which had been reported by Ball et al. (2), should be considered.

Major side effects were relatively specific for the different substances. Gastrointestinal reactions were leading events in the ciprofloxacin group, and diarrhea and candidiasis dominated in the imipenem-treated patients. However, the most important side effect of the imipenem group was a seizure in a 73-year-old female with a 3-week treatment for relapsing *Klebsiella* pneumonia. No other reason for this severe central nervous system reaction could be detected, and the seizures stopped 1 day after discontinuation of treatment. Central nervous system reactions are also possible in connection with other antibiotics (8). A careful analysis of the risk for seizures in patients under antibiotic therapy (31) revealed an incidence of 26 seizures among 1,723 patients (1.5%) treated with imipenem and 21 seizures among 1,280 (1.6%) patients treated with other beta-lactam antibiotics.

In summary, both new antibacterial substances showed good to excellent clinical results in patients with severe bacterial, mainly respiratory, infections. Both agents cover most of the etiologic pathogens in complicated RTI and septicemias of patients with severe basic diseases. Treatment of these infections with these new single agents seems to be possible. Careful monitoring of resistance patterns and of specific tolerance problems in patients is necessary.

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