

## Safety and Efficacy of High-Dose Treatment with Imipenem-Cilastatin in Seriously Ill Patients

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Imipenem-cilastatin was given in doses of 1 g intravenously every 6 h to 31 patients. Twenty-five patients, with 27 infections, were clinically evaluable and received 20 to 210 g of imipenem for a duration of 5 to 56 days (average 16.3 days). Infections included seven cases of osteomyelitis, seven of bacteremia, five of cellulitis, two of pneumonia, three of pelvic cellulitis, two of intraabdominal abscess, and one each of empyema, mediastinitis, and endometritis. Fifty-five percent of the infections were caused by gram-negative bacilli, 33% were due to gram-positive organisms, and 10% were caused by anaerobes. Twenty-two patients (81%) were cured, three improved, one relapsed, and one became superinfected with a resistant organism. In 5 of 11 cases with *Pseudomonas aeruginosa*, the imipenem MIC for organisms isolated by the end of treatment was higher than it was initially, raising concern that imipenem should not be used alone to treat *Pseudomonas aeruginosa* infections. Twenty-one patients had no adverse reaction; of the remaining 10 patients, 4 had nausea, 1 had urticaria, and 6 had mild abnormalities in hepatic function; three episodes of diarrhea included two with *Clostridium difficile* toxin in stool and one with pseudomembranous colitis, as determined by sigmoidoscopy. Levels of creatinine, hemoglobin, leukocytes, platelets, prothrombin, and urine components were unchanged. Imipenem-cilastatin is a clinically effective antibiotic with freedom from nephrotoxicity and hematological abnormalities in the large doses used in this study.

Imipenem is a stabilized amidine derivative of thienamycin, a carbapenem beta-lactam antibiotic produced by *Streptomyces cattleya* (9). In vitro, imipenem has a broad antibiotic spectrum and is very active against pathogens such as *Pseudomonas aeruginosa*, *Serratia* sp., *Bacteroides fragilis*, enterococci, and numerous other species (11, 14, 18, 21). Bactericidal in activity, the molecule is resistant to degradation by bacterial beta-lactamases (14, 17). Because imipenem is hydrolyzed by the kidney enzyme dehydropeptidase-I (10), it is administered in combination with cilastatin (MK791), a specific and highly active dipeptidase inhibitor, resulting in improved pharmacokinetics and urinary levels (15).

Most reported clinical studies have been carried out with dosages of 1 to 2 g per day (3, 12, 19). Normal volunteers who received 1 g intravenously every 6 h for a total of 40 doses showed no change in renal, hepatic, or eighth nerve function and reported only mild nausea or gastrointestinal complaints (6). The present study was conducted to test the clinical efficacy and safety of high-dose imipenem-cilastatin treatment (4 g per day) for serious infections in hospitalized patients.

### MATERIALS AND METHODS

**Patients.** All patients were hospitalized at the Hospital of the University of Pennsylvania from December 1982 through June 1983. Patients were eligible for the study if they had suspected or proven bacterial infections caused by pathogens presumed or known to be susceptible to imipenem and had not received antecedent appropriate therapy. Exclusion criteria included the following: (i) pregnancy, (ii) allergy to any beta-lactam antibiotic, (iii) central nervous system infection, (iv) infection requiring addition of another drug, (v) a creatinine level in serum of >3.0 mg/dl, and (vi) neutrope-

nia of <1,500 cells per mm. Patients were evaluable for efficacy if they received more than 5 days of treatment and pretreatment cultures yielded a susceptible organism(s). Informed consent was obtained from patients or next of kin before starting therapy. The study was approved by the University Human Subjects Committee.

**Definitions.** Clinical cure was defined as the lack of signs or symptoms of the initial infection remaining at the time that the patient was discharged. Improvement occurred when signs and symptoms improved on therapy which had to be discontinued prematurely. Relapses had resolution of signs and symptoms of infection, with recurrence after treatment was stopped. Superinfection was defined as improvement with treatment, followed by clinical superinfection with another organism.

The infecting pathogen was considered eradicated when it could not be isolated either during or after therapy. Persistence indicated that, despite clinical response, the organism still could be isolated during and after therapy. Superinfection indicated the emergence on therapy of a resistant organism which resulted in deterioration of the clinical condition of the patient.

**Drug administration.** Imipenem-cilastatin was provided by Merck Sharp & Dohme Research Laboratories, Rahway, N.J. Five hundred milligrams of each agent was dissolved in a total of 100 ml of 0.9% sodium chloride injectable or 5% glucose in water. One gram of each agent was administered intravenously every 6 h over 30 to 60 min.

**Susceptibility testing.** Disk susceptibility testing was performed by the Kirby-Bauer method (2), using 10- $\mu$ g disks of imipenem (MK787; BBL Microbiology Systems, Cockeysville, Md.). Organisms with a zone of inhibition of less than 13 mm in diameter were considered resistant, whereas those with a zone equal to or greater than 16 mm in diameter were considered susceptible. The 13-mm zone corresponded to an MIC of >8  $\mu$ g/ml, a conservative breakpoint (H. Kropp and

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J. Birnbaum, personal communication). For some of the isolates, the MIC and MBC determinations as well as serotyping of *Pseudomonas aeruginosa* were performed by Daniel Shungu, Clinical Microbiologic Services, Merck Sharp & Dohme Research Laboratories. At this laboratory, the susceptibilities of the anaerobic isolates were also measured by the agar dilution method. Standardized agar dilution and microdilution methods were used as outlined by the National Committee for Clinical Laboratory Standards (13). Serotyping was accomplished through the use of the *Pseudomonas aeruginosa* antisera kit (Difco Laboratories, Detroit, Mich.).

**Patient monitoring.** Patients were examined daily for adverse reactions and for response to therapy. Each patient had the following studies performed before initiating therapy, biweekly for the first week of therapy, once weekly thereafter, and 1 to 2 days after the conclusion of therapy: complete blood cell count including platelet enumeration; measurement of prothrombin time; measurement of blood urea nitrogen, serum creatinine, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, total bilirubin, alkaline phosphatase, electrolytes, and uric acid; and urine analysis.

## RESULTS

**Patient characteristics.** Thirty-one patients were entered into the study; 25 were clinically evaluable, with a total of 27 infections. All patients entered were evaluable for safety, having received more than one dose. Men outnumbered women 19 to 12. Ages ranged from 21 to 82 years (mean, 51.5 years); 12 patients were over 60 years old. Total dosage of imipenem ranged from 20 to 210 g, with a mean of 69.4 g. Twenty-four percent of the patients received greater than 100 g, 28% received 50 to 100 g, and 48% received 20 to 49 g. Evaluable patients received therapy for a mean of 16.3 days, with a range of 5 to 56 days. Forty percent of the patients were treated for 5 to 10 days, 48% were treated for 11 to 30 days, and 12% were treated for >30 days. Notable underlying disease or other risk factors were present in 77%: nine patients had recently undergone major surgery, seven were receiving prednisone therapy, seven had cardiovascular disease, five had cancer, three had diabetes mellitus, two had paraplegia, and four had other diseases.

**Clinical response.** Twenty-two patients were considered cured (81%). Three patients improved on therapy, but the test drug had to be discontinued for clinical or laboratory abnormalities. The patient who relapsed had an abdominal abscess secondary to a gastric perforation. Although asymptomatic while receiving imipenem, he became febrile 5 days after discontinuing treatment and was found still to have an unresolved gastroperitoneal fistula. Superinfection developed in one patient with vasculitis, respiratory failure, and empyema with *Pseudomonas aeruginosa* and *Enterobacter cloacae*. After 11 days of therapy, his clinical course worsened, and the pleural fluid culture yielded *Pseudomonas aeruginosa* resistant to imipenem by Kirby-Bauer testing.

Table 1 shows the clinical response according to type of infection. Seven patients with osteomyelitis were entered into the study but one was not evaluable because the bone culture was sterile. Five of the remaining six patients were cured (no relapse after >12 months of follow-up), and one showed improvement with treatment but had to discontinue treatment with imipenem because of persistent vomiting. Seven patients were treated for bacteremia, and all rapidly improved. However, in one, with *Staphylococcus epidermidis* and *Streptococcus faecalis* bacteremia secondary to a

TABLE 1. Clinical responses of patients treated with imipenem-cilastatin

Diagnosis (no. of patients)	Response to treatment with imipenem-cilastatin (no. of patients)				
	Cured	Improved	Relapsed	Super-infected	Not evaluable
Osteomyelitis (7)	5	1			1
Bacteremia (7)	6	1			
Cellulitis (5)	5				
Pelvic cellulitis (3)	2				1
Pneumonia (2)	2				
Intraabdominal abscess (2)	1		1		
Mediastinitis (1)		1			
Empyema (1)				1	
Endometritis (1)	1				
No etiological agent recovered (2)					2
Miscellaneous (2)					2

Hickman catheter, initial disk susceptibility tests indicating resistance caused therapy to be stopped although MICs determined subsequently showed both organisms to be susceptible. All five patients with cellulitis showed good response to imipenem, including two patients with diabetes mellitus, two with decubitus ulcers, and one with septic thrombophlebitis. The unevaluable patient with pelvic cellulitis had therapy discontinued when she developed urticaria during infusion of the fifth dose. Two patients with intraabdominal abscesses were cured, but, as discussed above, one with a gastric perforation relapsed 5 days after stopping therapy. The two unevaluable patients in the miscellaneous category had pathogenic organisms which were resistant (*Candida parapsilosis*) or not able to be tested (*Actinomyces* sp.).

**Microbiological results.** The following numbers of isolates were detected in pretherapy cultures: 11 *Pseudomonas aeruginosa*, 5 *Enterobacter cloacae*, 4 *Klebsiella* spp., 4 *Proteus mirabilis*, 3 *Serratia marcescens*, 3 *Escherichia coli*, 1 *Salmonella enteritidis*, 1 *Citrobacter freundii*, 7 streptococci (group A, B, nontypable), 5 enterococci, 4 *Staphylococcus aureus*, 3 *Staphylococcus epidermidis*, 6 anaerobes, and 1 *Candida parapsilosis*. Gram-negative aerobic bacilli made up 55% of the organisms isolated, and a third of these (11) were *Pseudomonas aeruginosa*. Gram-positive aerobic organisms constituted 32.7% of the organisms isolated; one-fourth of them were enterococci. Ten percent of the organisms isolated were anaerobes, including one *Peptococcus* sp., two *Bacteroides fragilis*, one *Bacteroides* sp., one *Actinomyces* sp., and one streptococcus lost on subculturing. The overall bacteriological cure rate was 84%. In 11 of 12 patients with infection caused by a single organism, the organism was eradicated. In one patient with osteomyelitis, *Staphylococcus aureus* persisted but remained sensitive to imipenem. Fifteen patients had infections with two or more organisms. All organisms were eradicated in eight cases, one of the organisms persisted in six cases, and superinfection occurred in one case. One persisting organism was a *Staphylococcus aureus* and one was a *Proteus mirabilis*. Both remained sensitive to imipenem. *Pseudomonas aeruginosa* persisted in five cases, and all final isolates were resistant to imipenem by Kirby-Bauer testing. Before treatment, zones of inhibition ranged from 21 to 24 mm, with MICs of 2 µg/ml. In contrast, after therapy, zones ranged from 9 to 11 mm, with MICs from 8 to 16 µg/ml. The clinically significant

superinfection with a resistant *Pseudomonas aeruginosa* occurred in the patient with empyema. Serotyping was performed on three pairs of pre- and posttherapy *Pseudomonas* sp. isolates: for two patients, both organisms were serotype 2; and in one, the initial isolate was nontypable, whereas the posttreatment isolate was serotype 6.

**Adverse reactions.** Twenty-three patients had no clinical side effects. Three had intermittent nausea which did not prevent completion of therapy, but one had persistent vomiting which necessitated discontinuation of treatment with imipenem. Three patients had diarrhea (Table 2). One of these patients had diarrhea at the time of admission and received imipenem for only 3 days before the failure to isolate an organism required the discontinuation of the test drug. However, diarrhea worsened, and sigmoidoscopy showed pseudomembranous colitis. Neither *Clostridium difficile* nor its toxin were detected. In the other two patients, the diarrhea was mild and began after treatment with imipenem was stopped. *Clostridium difficile* toxin was found in the stool in both cases. Urticaria occurred in one patient who had no known previous beta-lactam allergy.

Twenty-four patients had no adverse laboratory test effects. Six others had abnormalities in hepatic function, manifested as elevations in serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, or bilirubin, which were less than 50% above the upper limit of normal and returned to normal by the end of therapy. Azotemia was noted in one patient whose creatinine level had risen to 3.5 mg/dl before starting therapy and whose course of progressive azotemia did not appear to be affected by the use of imipenem.

**DISCUSSION**

Imipenem, at 1 and 2 g per day, has proven clinical efficacy for a broad range of infections in hospitalized patients. It compares well with first generation cephalosporins, cefotaxime, and selected combination therapies (3, 12, 19). The present study expands the experience with imipenem to long-term, high-dose therapy for serious infections.

TABLE 2. Adverse reactions in patients treated with imipenem-cilastatin

Reaction	No. of patients
<b>Clinical</b>	
Nausea .....	4
<b>Diarrhea</b>	
Pseudomembranous colitis .....	1
<i>C. difficile</i> toxin positive .....	2
Urticaria .....	1
<b>Laboratory</b>	
<b>Hepatic function</b>	
SGOT and SGPT <sup>a</sup> .....	1
SGOT, SGPT, and alkaline phosphatase .....	2
Alkaline phosphatase and bilirubin .....	1
Alkaline phosphatase .....	2
<b>Renal function (blood urea nitrogen and serum creatinine).....</b>	
	1

<sup>a</sup> SGOT, Serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Twenty-five patients with 27 infections were treated with 20 to 210 g of imipenem-cilastatin for a total of 5 to 56 days. Twenty-five infections (92.6%) were cured (22) or improved (3), one relapsed, and one patient became clinically superinfected. These results are very similar to those recently reported by Winston et al. (23) and further support the clinical efficacy of imipenem-cilastatin in the treatment of serious infections.

Imipenem offers significant advantages as monotherapy for polymicrobial infections. Of the 27 infections treated in this study, 19 (70%) would have required treatment with two or more antibiotics, either because of infection with multiple organisms (15), or because of gram-negative bacteremia (4). Drug combinations often would have included antibiotics with potential for serious renal or gastrointestinal toxicity and would have involved varying dosing schedules as well as multiple intravenous delivery systems. Thus, imipenem-cilastatin was not only clinically effective but also provided greater safety, convenience, and ease of delivery.

Antibiotic resistance developed during treatment only for *Pseudomonas aeruginosa*. Imipenem was effective as single drug therapy for this organism, leading to clinical cures in 11 cases. However, in the 5 cases in which the organism was not eradicated during therapy, isolates were found by the end of treatment for which imipenem MICs were two to four times higher than pretreatment MICs; one of these was clinically significant. Of interest, Winston et al. reported the emergence of resistance on treatment in 6 of 17 cases of *Pseudomonas aeruginosa* infection (23). The mean peak level of imipenem in serum in our patients was 35 µg/ml, well above the MICs for the "resistant" strains and probably accounting for the clinical cures in all but one case. Even though the resistant organisms were still inhibited by the peak levels in serum achieved, the potential for stepwise increases in resistance to imipenem in nosocomial strains of *Pseudomonas aeruginosa* suggests that these infections should not receive monotherapy with imipenem. The emergence of resistance during monotherapy for *Pseudomonas aeruginosa* is a property shared by beta-lactam antibiotics (8, 22).

Adverse reactions were generally mild and comparable to those reported previously by others for imipenem (4, 23) and for other beta-lactam drugs (5, 20). Nausea and vomiting were the most frequent clinical side effects, but only one case required discontinuation of therapy. No cases of candida superinfection or infusion-site phlebitis developed. The 9.6% incidence of diarrhea was surprising because others have found much lower rates (4, 12, 19, 23); moreover, Norrby et al. reported that less than 1% of intravenously administered radiolabeled imipenem was recovered in the feces of normal volunteers (16). Therefore, one would not expect much change in normal bowel flora to allow for overgrowth of other organisms. Perhaps the high doses of imipenem used in this study caused more drug to enter the gastrointestinal tract either through the bile or by simple mass action. The relation between imipenem treatment and detection of *Clostridium difficile* toxin is unclear in our two cases, as the patients had received other antibiotics before imipenem therapy and had not been tested for *Clostridium difficile* before starting imipenem. Antimicrobial agents implicated in *Clostridium difficile* toxin-associated diarrhea were reviewed recently by Bartlett (1).

Transient elevations in hepatic function tests were the most common changes noted in laboratory tests (6 of 31). Calandra et al., comparing the effects of imipenem, cephalothin, and cefazolin, noted that patients in the imipe-

nem-treated group developed slightly more transient liver function abnormalities than did patients in the cephalosporin-treated group (4). In contrast, Eron et al. found no difference in the frequency of liver test changes between imipenem- or moxalactam-treated patients in a randomized trial (7). Neutropenia was not noted in our series despite the high doses of imipenem used. Also, no nephrotoxicity occurred in this high-dose trial or in other studies (3, 4, 12, 16, 19, 23). Twelve of our patients were over 60 years old and were treated with 4 g per day for 2 to 4 weeks without change in renal function.

In summary, imipenem-cilastatin, in the high doses used in our study, was effective and safe as a single-drug therapy for a wide range of serious infections in seriously ill patients. It is ideally suited for the treatment of polymicrobial infections, offering an extremely broad spectrum against aerobic and anaerobic organisms, combined with the low level of toxicity common for beta-lactam antibiotics.

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