

# IMIPENEM/CILASTATIN THERAPY IN THE MANAGEMENT OF INFECTIONS IN THE OUTPATIENT SETTING

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From 1986 to early 1992, we treated 214 patients with imipenem every 8 hours in our outpatient intravenous therapy clinic. Patients ranged in age from 13 to 68 years and were treated for a variety of moderate-to-severe gynecologic, skin and soft tissue, bone and joint, pulmonary, upper respiratory tract, intraabdominal, blood, and central nervous system infections. We observed an overall cure rate of 91% among those considered to be efficacy evaluable. Eleven percent reported drug-related events that required premature discontinuation. Our experience with imipenem in outpatients mirrors clinical cure rates in controlled studies in hospitalized patients. Treatment failures were more often due to side effects than to lack of efficacy or relapse.

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IMIPENEM/CILASTATIN IS A POTENT broad-spectrum antibiotic consisting of *N*-formimidoyl-thienamycin (imipenem) and cilastatin, a dehydropeptidase inhibitor, which blocks metabolism of imipenem in the kidney and prevents renal toxicity [1]. This carbapenem antibiotic is well known for its comprehensive in vitro coverage against many clinically important aerobic gram-positive and gram-negative pathogens, including *Pseudomonas aeruginosa*, *Serratia* species, and *Enterobacter*, as well as most anaerobes [2,3]. Notable exceptions to the broad-spectrum activity of imipenem are *Enterococcus faecium*, *Stenotrophomonas (Xanthomonas) maltophilia*, *Pseudomonas cepacia*, and methicillin-resistant *Staphylococcus aureus* [4]. During the last decade of imipenem's use, the antibiotic has maintained continued broad-spectrum potency, and the number of reports of emerging resistance has been low compared with that concerning other  $\beta$ -lactam antibiotics [5].

Imipenem has been extensively studied in hospitalized patients and shown to be highly effective for a variety of clinical infections in that setting [6,7]. Most U.S. studies have administered imipenem to patients in intravenous doses ranging from 500 mg to 1 g every 6 hours. Because dosing imipenem every 6 hours is inconvenient, a limited number of studies has examined the effectiveness of imipenem following an every-8-hour dosage regimen [8-14]; no studies have investigated its safety and efficacy in the outpatient setting.

This report summarizes our experience of the effectiveness and safety of intravenous imipenem/cilastatin when administered at a dose of 500 mg every 8 hours to outpatients with a variety of infectious diseases.

## Patients and Methods

From 1986 to early 1992, we administered 500 mg of imipenem/cilastatin (Primaxin, Merck Sharp & Dohme, West Point, Pennsylvania) every 8 hours to patients with infections that required broad-spectrum coverage but not initial or continued hospitalization. Selection criteria for outpatient imipenem therapy included the physical and mental ability of the patient or a designated caregiver to be trained in home antibiotic administration; the availability of reliable telephone communication with the patient or caregiver; a safe, clean home environment; and the ability of the patient to attend regular clinic follow-up visits. Patients were ex-

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cluded for allergy to imipenem, seizure disorders, active drug or alcohol use within 1 year of study entry, and documented or suspected inability to comply with therapy and follow-up visits.

Because imipenem has limited stability following admixture at room temperature (i.e., 10% loss of activity after 4 hours), the use of a portable cassette pump was not practical. As such, patients prescribed imipenem for use in the outpatient setting were trained to mix and administer imipenem using the Advantage system (Abbott Laboratories, North Chicago, Illinois) through a peripherally inserted central intravenous catheter. The Advantage system allowed the patient to reconstitute imipenem with the appropriate diluent immediately before use and then administer the medication by gravity flow. This method of administration also was pharmacoeconomic in that pharmacist costs were unnecessary.

Patients were retrospectively evaluated by chart review. Demographic and medical characteristics (age, sex, site of infection) were recorded for each patient. In addition, clinical response to imipenem therapy and severe adverse effects (i.e., requiring treatment discontinuation) during the antibiotic's administration were assessed. Clinical success was defined as "complete resolution" of all signs and symptoms or "improved" if therapy was completed with oral antibiotics. Patients whose infections relapsed after a full course of therapy or who were unable to complete a full course of therapy ( $\geq 3$  days of antibiotic) for any reason were considered "treatment failures." Patients who did not complete a full course of treatment were evaluated to determine why therapy was discontinued.

## Results

**Demographic and medical characteristics.** From 1986 through February 1992, 214 patients were treated with imipenem every 8 hours in our outpatient intravenous therapy clinic. Patients ranged in age from 13 to 68 years (mean age, 34) and included 170 females and 44 males. The predominance of females reflected a large number of referrals for treatment of subacute relapsing pelvic inflammatory disease (PID) and postpartum endometritis. The types of infections treated with outpatient imipenem therapy included gynecologic ( $n = 134$ ), skin and soft tissue ( $n = 23$ ), osteomyelitis ( $n = 15$ ), pulmonary ( $n = 14$ ), intraabdominal ( $n = 10$ ), upper respiratory tract (sinus;  $n = 6$ ), catheter-associated bacteremia ( $n = 6$ ), joint (bursa;  $n = 5$ ), and central nervous system (CNS) (brain abscess;  $n = 1$ ). Therapy was prematurely discontinued in 31 patients

**TABLE 1. Clinical response rate by infection type for intent-to-treat population**

Site	Response		
	Success n/N (%)	Failure n	Unevaluable
Gynecologic	105/134 (77)	9	20
Skin, soft tissue	19/23 (83)	1	3
Pulmonary	13/14 (93)	1	0
Osteomyelitis	12/15 (80)	2	1
Intraabdominal	6/10 (60)	0	4
ENT	5/6 (83)	1	0
Bacteremia	6/6 (100)	0	0
Joint, bursa	4/5 (80)	1	0
CNS	0/1 (0)	0	1
TOTAL	170/214 (79)	15	29

Note. Abbreviations used: ENT, ear, nose, and throat; CNS, central nervous system.

(15%). Reasons for early discontinuation of imipenem included possible drug-related side effects ( $n = 24$ ), antimicrobial resistance ( $n = 3$ ), early drug failure (no response;  $n = 3$ ), and suspected pregnancy ( $n = 1$ ). In addition, one patient was lost to follow-up.

**Clinical outcome.** Clinical success (cure or improvement) occurred in 170 (79%) of 214 patients who were administered imipenem therapy (Table 1). Excluding those patients who were prematurely discontinued because of side effects, antimicrobial resistance, or unsuspected pregnancy, and the one patient lost to follow-up (total  $n = 29$ ), an overall cure rate of 91% (170/187) was observed among those considered to be efficacy evaluable.

Clinical failure was reported in 15 patients in this study; of these, nine treatment failures (60%) occurred among females with gynecologic infection, all with PID. Six of these patients failed imipenem therapy, including one relatively late failure after 15 days of treatment. The remaining three patients experienced a relapse following completion of imipenem outpatient therapy. Three women required surgical interventions, one was subsequently diagnosed with endometriosis, and one woman was cured with piperacillin/gentamicin combination therapy. Two additional failures occurred in patients with osteomyelitis, including one late relapse. Another patient with a diagnosis of bursitis due to *Staphylococcus aureus* failed therapy. Sinusitis due to *Acinetobacter* species and *Serratia* species failed to respond to imipenem therapy; subsequent treatment with clindamycin and ceftriaxone yielded a positive outcome. One patient with an intraabdominal/pelvic abscess initially responded to imipenem therapy but relapsed and required surgical intervention. Finally,

**TABLE 2. Drug-related side effects requiring premature discontinuation of outpatient imipenem/cilastatin therapy in the intent-to-treat population**

Reason	No. (%)
Nausea and vomiting	11 (5)
Drug rash	5 (2)
Headache	2 (1)
Chest tightness	1 (0.5)
Leukopenia	1 (0.5)
Neuropathy	1 (0.5)
Fatigue	1 (0.5)
Abdominal pain	1 (0.5)
Insomnia	1 (0.5)
TOTAL	24 (11)

another patient with a wound infection required additional antibiotic therapy.

**Safety analysis.** Among 214 patients treated with imipenem/cilastatin, 24 patients (11%) reported drug-related events requiring premature discontinuation (Table 2). The most common adverse events included nausea and vomiting ( $n = 11$ ) and drug rash ( $n = 5$ ). CNS-related events were rare—only two patients with headache had to be taken off of imipenem.

## Discussion

This large, single-center study provided the first opportunity to evaluate the effectiveness and tolerability of a regimen of 500 mg of imipenem/cilastatin administered intravenously three times a day in an outpatient setting. Clinical cure rates were high (91%) among those who completed at least 3 days of therapy and in whom premature discontinuation of imipenem was not required because of an adverse event. The majority of participating patients were women with gynecologic infections, primarily PID. Accordingly, the largest number of treatment failures occurred in patients with PID (9 of 15), including three cases of relapse. Specifically, true treatment failure (i.e., those patients requiring surgical intervention) occurred in 56% of women with PID. When considering the intent-to-treat population, the overall clinical success rate was lower (79%). However, to reflect real-life clinical practice, our definition of success included only those patients who responded and who were able to complete a full course of therapy; treatment was considered to have failed if there was lack of improvement or therapy discontinuation for any reason. Most cases of failure in the overall population were attributed to adverse events that led to early discontinuation of imipenem therapy.

When imipenem/cilastatin was initially approved by the U.S. Food and Drug Administration, it was often

reserved for the treatment of hospitalized patients with severe and multiresistant infections. Extensive experience over the last decade has proven imipenem to be a safe and effective agent for a variety of infections because of its broad-spectrum activity and to be reasonably efficacious as a monotherapy in seriously ill, hospitalized patients with pneumonia [14]. Increased imipenem use has not led to marked increase in resistance. Imipenem is prescribed more frequently for the empiric management of infections potentially due to mixed pathogens and is not limited to use in the intensive care setting. Over the last decade, we have established a large outpatient referral intravenous antibiotic program for the treatment of moderate to severe infections in carefully selected patients. Imipenem monotherapy has been one preferred regimen for treating a variety of infections. Our experience with imipenem in outpatients mirrors clinical cure rates observed in controlled studies in hospitalized patients. Of additional note, only three of 214 (1.4%) patients had isolates resistant to imipenem at study entry, and none were observed to develop resistance during therapy. True clinical failures with imipenem often occurred in patients who required adjunctive surgery or had completed therapy (relapse).

In the hospital setting, imipenem is often administered every 6 hours because it mimics dosages proven effective in Phase III clinical trials. Because of imipenem's relative instability following reconstitution and the commonly used 6-hour dosage interval, the carbapenem has rarely been considered for outpatient use. However, based on pharmacodynamics, postantibiotic effect, and limited experience with an every-8-hour dosage regime [8–13], we considered imipenem a reasonable candidate for outpatient therapy. Our high success rates appear to support the fact that free drug concentrations often exceed the MIC<sub>90</sub>s of several important pathogens (*Escherichia coli*, *Neisseria gonorrhoeae*, *Klebsiella* species, and *S. aureus*) for well over a 6-hour period [15].

As with prior experience [7], imipenem was associated with few adverse events in this outpatient trial. The most common drug-related events necessitating premature discontinuation included nausea and/or vomiting (5%), drug rash (2%), and headache (1%). It is possible that the nausea was related to the speed of infusion, although patients were carefully instructed on administration techniques. Furthermore, infusion site reactions were not reported by this cohort of patients.

In summary, most patients with appropriate infections were successfully treated with 500 mg of imipenem/cilastatin administered every 8 hours in an out-

patient intravenous antibiotic program. Administration of intravenous imipenem three times a day was well accepted by our patient population with a low rate of adverse events. Treatment failures were more often due to side effects than lack of clinical response to therapy or relapse of infection. The use of this outpatient imipenem regimen in patients with stable but moderate-to-severe infections may result in fewer admissions or decreased hospital stay, reduced morbidity, and significant cost-savings (i.e., reduced number of hospital stays, avoidance of pharmacy admixture fees). Although the selection of an outpatient intravenous antibiotic must consider patient-specific and pharmacoeconomic factors, imipenem may be a reasonable choice for serious infections that would often require combination therapy.

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