Imipenem Versus Moxalactam in the Treatment of Serious Infections

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Imipenem (formerly imipemide, *N*-formimidoyl thienamycin, or MK0787) was compared to moxalactam in a randomized therapeutic trial involving 39 evaluable patients with serious bacterial infections. Of those treated with imipenem, 89% were cured or improved versus 60% for moxalactam ($P = 0.06$). Although mucocutaneous fungal infections occurred in both groups (25 and 10%, respectively), *Streptococcus faecalis* superinfection was seen in two patients in the moxalactam group only. Adverse drug reactions occurred with both drugs, although bleeding occurred in three patients treated with moxalactam.

Imipenem (formerly imipemide, *N*-formimidoyl thienamycin, or MK0787) is a novel beta-lactam antibiotic having desthiocarbapenem as its nucleus. In vitro studies (5) suggest that the drug is extremely potent against a wide variety of bacteria. Whereas other new beta-lactam antibiotics such as moxalactam have decreased activity against *Staphylococcus aureus, Staphylococcus epidermidis*, and *Streptococcus* species and show relatively large inoculum effects on the minimum inhibitory concentrations (MICs) toward *Pseudomonas aeruginosa* and *Enterobacter* species, imipenem is relatively free of these problems (1). Moreover, imipenem retains good activity against *Streptococcus faecalis* and *Bacteroides fragilis*, unlike most other new cephalosporins. To determine the clinical relevance of these promising in vitro data, we undertook a clinical trial comparing imipenem to moxalactam in seriously ill patients with a variety of infections.

MATERIALS AND METHODS

Patients with septicemia, soft tissue, respiratory tract, and urinary tract infections were admitted to a randomized study at The Fairfax Hospital (Falls Church, Va.) comparing moxalactam (2 g intravenously every 8 h) to imipenem (0.5 g intravenously every 6 h) combined with MK0791, a structural analog of imipenem designed to block catabolism of the drug by the brush border of the kidney (6). The method of culturing, laboratory tests for safety, and informed consent have all been described previously (2), with the exception that Mueller-Hinton broth was used for the determination of MICs rather than Trypticase soy broth (BBL Microbiology Systems). Susceptibility to imipenem and moxalactam was initially determined for all isolates by using 10-µg disks for imipenem and 30-µg disks for moxalactam. Zones equal to or greater than 16 and 18 mm, respectively, were used to indicate sensitivity. Although we hoped that all isolates would be sensitive to both antibiotics, in several instances in the imipenem group, bacteria were resistant to moxalactam. One patient who had been started on moxalactam was dropped from the study when her *P. aeruginosa* isolate was shown to be moxalactam resistant. A second patient who developed a rash after a small dose of imipenem was also dropped from the study. Gram-stained specimens were examined for the presence of polymorphonuclear leukocytes and homogeneous populations of organisms (except in polymicrobial infections) in an attempt to distinguish pathogens from colonizers identified on cultures.

Wound infections showed signs of local inflammation with purulent drainage. Intraabdominal infections consisted of abscesses or cholangitis or both. Respiratory tract infections were diagnosed by the presence of purulent sputum or sinus drainage and radiological evidence of infection of the lung or sinus. Urinary tract infections had colony counts greater than 10^5 per ml of urine with pyuria noted on urinalysis. Septicemia was defined as the occurrence of two or more positive blood cultures.

Cure was defined as the complete resolution of signs of infection accompanied by sterilization of the infected site at the conclusion of therapy. When culture specimens were no longer available, assessment of response was made on clinical grounds alone. Improvement was defined as the subsiding of signs of infection and no need for further surgical or antibiotic therapy. For urinary tract infections, additional cultures were obtained 1 and 4 weeks after therapy. Statistical analysis was performed with the Fisher exact test (two-tailed).

RESULTS

Moxalactam and imipenem were administered to 20 and 21 patients, respectively, utilizing a randomization scheme generated by computer at Merck Sharp & Dohme Research Laboratories.

One case in each group was dropped from the study because they were considered non-evaluable, but they were followed for safety. Of the 39 patients, 25 were males and 14 were females, ranging from 19 to 85 (mean, 46) years of age. The sex and age distribution were similar in each antibiotic group. Duration of therapy was 3 to 28 days, with a mean of 11.2 days in the moxalactam group and 11.9 days in the imipenem group. Of the 39 patients, 21 had serious underlying diseases or conditions (12 in the moxalactam group and 9 in the imipenem group) which would be expected to interfere with the patient's ability to combat infection. These included diabetes mellitus with unstable blood sugars and peripheral vascular disease (six cases), nondiabetic peripheral vascular disease in patients with infections of the lower extremities (three cases), steroid therapy (three cases), cancer (three cases), cystic fibrosis (one case), a Foley catheter in one patient with a urinary tract infection, and four cases of collagen vascular disease (systemic lupus erythematosis, rheumatoid arthritis, giant cell arteritis, and mixed connective tissue disease with nephrotic syndrome). Twenty-nine patients (15 treated with moxalactam and 14 treated with imipenem) had soft tissue infections. These consisted of four intraabdominal infections in each group, three surgical wound infections in each group, five traumatic wound infections (one received moxalactam), and four infected plantar ulcers in diabetic patients (one received moxalactam). Four patients had respiratory tract infections (one in the moxalactam group), four had urinary tract infections (three in the moxalactam group), and two had septicemia (one in each group).

Bacteria cultured initially were comparable in both groups (Table 1). The moxalactam group consisted of 26 isolates from 20 infections of which 4 were polymicrobial. The imipenem group consisted of 30 isolates from 19 infections of which 8 were polymicrobial. *P. aeruginosa* was isolated in five and nine instances, respectively, in the moxalactam and imipenem groups. *S. faecalis* was isolated initially from three patients in the imipenem group only. The remainder were fairly equally divided between the two groups. MICs of moxalactam and imipenem were determined for most isolates (Table 1). The bacteria were eradicated in 23 of 26 instances in the moxalactam group (88%) and in 26 of 30 instances in the imipenem group (87%). There were no instances of the development of drug resistance during therapy with either drug as reported previously (3, 4, 7). However, as described elsewhere (11), there were two cases of superinfection with *S. faecalis* in patients treated with moxalactam but not in patients treated with imipenem. Mucocutaneous candidiasis and candida superinfection were noted in two and five cases of patients treated with moxalactam and imipenem, respectively. The one case of candida superinfection was a case of sepsis from infected bile (see Table 4). Colonization of wounds by *Enterobacter* species was noted at the conclusion of imipenem therapy in two instances.

There was a satisfactory clinical response in 12 of the 20 patients (60%) treated with moxalactam, including 5 who were cured, 7 who were improved, and 8 who failed (Table 2). In comparison, 17 of the 19 patients (89%) treated with imipenem responded satisfactorily to the drug ($P = 0.06$) (Table 3). Of these, nine were cured, eight improved, and two failed. Four patients receiving moxalactam and four receiving imipenem had their therapy interrupted by adverse drug reactions. Of these, all four moxalactam patients were clinically improving at the time of discontinuation of drug therapy. Of the four imipenem patients, one was improving at the

TABLE 1. Initial bacterial isolates

Organism	No. eradicated/total		Mean (range) MIC (µg/ml)	
	Moxalactam	Imipenem	Moxalactam	Imipenem
P. aeruginosa	5/5	7/9	11 (1.25–20)	1 (0.3–3.5)
Proteus sp.	2/4	4/4	12.7 (0.3–50)	2.9 (0.4–10)
Escherichia coli	2/3	1/3	0.4 (0.3–0.6)	0.3 (0.2–0.6)
Serratia marcescens	3/3	1/1	0.4 (0.3–0.6)	0.3
Enterobacter sp.	2/2	1/1	0.6	0.5 (0.4–0.6)
Klebsiella sp.	1/1	2/2	0.3	0.3
Citrobacter diversus		1/1	2.5	0.3
Acinetobacter calcoaceticus		1/1	>50	1.25
S. aureus	2/2	1/1	4.5 (5–10)	0.2 (0.007–0.6)
S. faecalis		3/3	>50	1.5 (0.6–2.5)
Streptococcus sp. (non-*faecalis*)	2/2			
Peptostreptococcus sp.	1/1			
B. fragilis	2/2	3/3		
Fusobacterium sp.	1/1	1/1		

TABLE 2. Response of infections to moxalactam

Infection	Clinical response (no. of cases)			Bacteriological response (no. of cases)		
	Cured	Improved	Failed	Eradicated	Persisted	Superinfected
Wound						
Traumatic			1			1
Cellulitis		2	4	2	2	2
Surgical	1	1	1	3		
Plantar ulcer		1		1		
Intraabdominal	1	1	2	1	1	2
Respiratory tract	1			1		
Urinary tract	2	1		2		1
Septicemia		1		1		

time of interruption of drug therapy, one was deemed unevaluable, having received only one dose of the drug, and the two remaining were failing clinically at the time of drug discontinuation (and were therefore deemed therapeutic failures).

Reasons for clinical failure are illustrated in Table 4. Of the eight moxalactam failures, superinfection seemed to be the major explanation, including two cases with *S. faecalis*, two with *Streptococci* (other than group D), and one with yeast. Two infections involving anaerobic bacteria (*Peptostreptococcus* and *Fusobacterium*) did not readily respond to moxalactam and required clindamycin for cure. A final case of moxalactam failure actually was initially thought to be a polymicrobial hip disarticulation wound infection (*P. aeruginosa, Streptococcus viridans*, and *B. fragilis*). However, it was ultimately shown to involve a Dacron vascular graft deep within the abdomen, which required graft removal (from which *Pseudomonas* species was ultimately cultured). The two clinical failures involving imipenem were both cases that failed to improve before discontinuation of the drug due to adverse drug reactions as discussed above.

Of the five cases of superinfection of moxalactam-treated cases, four were due to *Streptococcus* species as indicated above. One patient, a 26-year-old female with a traumatic foot wound infection due to *Serratia* species, received moxalactam for 8 days. During this time, no

clinical improvement was noted, and *S. faecalis* was cultured and observed on Gram-stained specimens of purulent drainage from the wound. She was switched to piperacillin and was cured on this drug. A second moxalactam patient superinfected with *S. faecalis* was an 85-year-old male with cholangitis due to *Klebsiella* species and *P. aeruginosa*. His disease was complicated by an obstructed biliary duct due to cancer, liver failure, and percutaneous biliary drainage catheters. After 5 days of moxalactam, he became septic with *S. faecalis* isolated from blood and bile. He improved when changed to ampicillin and gentamicin. A third patient, a 54-year-old male, was treated with moxalactam for a cellulitis of the foot due to *Proteus mirabilis* that developed after excision and debridement of an onychomycotic nail. After 3 days of therapy during which the patient did not improve, a lymphangitic streak up the leg was noted and a nongroupable *Streptococcus* species was cultured. He was cured on ampicillin. The fourth case also involved cellulitis of the foot due to *P. mirabilis*, this time in a diabetic 46-year-old male. He received moxalactam for 7 days during which time he failed to improve. On day 7, *Streptococcus* group A was cultured from his wound, and he was switched to penicillin on which he was cured.

Adverse drug reactions were deemed serious enough to terminate therapy in four cases in the moxalactam group and in four cases in the

TABLE 3. Response of infection to imipenem

Infection	Clinical response (no. of cases)			Bacteriological response (no. of cases)		
	Cured	Improved	Failed	Eradicated	Persisted	Superinfected
Wound						
Traumatic	2	2		3	1	
Surgical	1	2		3		
Plantar ulcer	2	1		3		
Intraabdominal	1	3		3	1	
Respiratory tract	1		2	2	1	
Urinary tract	1			1		
Septicemia	1			1		

TABLE 4. Clinical failures of moxalactam and imipenem therapy

Age/sex	Drug	Infection	Underlying illness	Organism	MIC (µg/ml)	Duration	Outcome
25/M	Moxalactam	Cellulitis of penis		Peptostreptococcus		5 days	Continued sterile drainage, required clindamycin for cure
26/M	Moxalactam	Traumatic foot wound		S. marcescens	0.3	8 days	S. faecalis superinfection, required change of antibiotic
54/M	Moxalactam	Cellulitis of foot		P. mirabilis	0.3	3 days	Streptococcal superinfection with lymphangitis, required change of antibiotic
67/M	Moxalactam	Surgical wound, hip disarticulation (vascular graft)	Diabetes mellitus	P. aeruginosa, S. viridans, B. fragilis	1.25, 0.6, not done	6 days	Patient required removal of Dacron graft for cure
46/M	Moxalactam	Cellulitis of foot	Diabetes mellitus	P. mirabilis	0.6	7 days	Streptococcal superinfection, required change of antibiotic
85/M	Moxalactam	Cholangitis	Cancer, liver failure with percutaneous biliary drainage catheters	P. aeruginosa, Klebsiella sp.	10, 0.3	5 days	S. faecalis superinfection of bile and blood, required change of antibiotic
47/M	Moxalactam	Cellulitis of axilla and perineum	Hidradenitis suppurativa	P. mirabilis, Fusobacterium sp.	1.25, not done	4 days	Continued drainage of P. mirabilis, required clindamycin for cure
58/M	Moxalactam	Intraabdominal abscess	Giant cell arteritis, on steroids	E. coli	0.6	5 days	Yeast superinfection, required change in antibiotic
22/F	Imipenem	Pneumonia	Cystic fibrosis	P. aeruginosa	0.3	4 days	Drug discontinued due to adverse reaction
64/M	Imipenem	Pneumonia	COPD and tuberculosis	P. aeruginosa	3.5	5 days	Drug discontinued due to adverse reaction

imipenem group (Table 5). The side effects included bleeding with a prolonged prothrombin time (three patients on moxalactam), vomiting or diarrhea (two patients on imipenem), and rash (one on moxalactam and two on imipenem). Vitamin K was not administered to any patient prophylactically. There were no cases of leukopenia or anemia, although clinically insignificant eosinophilia, thrombocytosis, and a positive direct Coombs test were seen mostly in patients on moxalactam. One Antabuse-like reaction occurred in a patient on moxalactam.

DISCUSSION

Despite their early promise of efficacy, third-generation cephalosporins have not entirely lived up to all expectations in the therapy of cephalothin-resistant infections (3, 4, 7). At least part of the explanation may lie in the inoculum effect on their MICs in the cases of *Pseudomonas, Serratia*, and *Enterobacter* species (1). In addition, they may have somewhat less activity in treating staphylococcal and streptococcal infections than older cephalosporins (8). Finally, their somewhat decreased activity against *B. fragilis* makes them somewhat less attractive in the therapy of intraabdominal abscesses (9).

When imipenem was compared in this randomized trial with the new oxy-beta-lactam, moxalactam, several possible differences were noted. Therapeutic efficacy (patients cured or improved) was demonstrated in 89% of patients treated with imipenem but in only 60% of those receiving moxalactam ($P = 0.06$). The moxalactam clinical efficacy rate falls within the 50 to 79% range reported previously (3, 4, 7). Part of this discrepancy could be explained by the maldistribution of cases of cellulitis (all six received moxalactam), by the slightly higher frequency of underlying diseases in the moxalactam group (60%) compared with the imipenem group (45%), or by the nonblinded nature of the study.

The patients with cellulitis did surprisingly poorly with moxalactam, and it is possible that this result has unfairly skewed this study against moxalactam. Alternatively, the clinical efficacy results with respect to the two drugs, although not quite statistically significant, may reflect their differential potency and spectrum of activity and with larger numbers this could become significant. Although the differences between the MICs of imipenem and moxalactam were quite large for many bacterial isolates, moxalactam was as effective as imipenem with respect to microbiological eradication of the initial isolates. Superinfection with *S. faecalis* was observed in two patients treated with moxalactam. This was not unexpected based on the in vitro data and previous reports of this problem with moxalactam (11).

With regard to adverse reactions, patients treated with moxalactam showed evidence in three cases of bleeding due to its effect on the prothrombin time as well as perhaps to its inhibition of platelet aggregation (10). Imipenem appears to be free of this side effect, which can be life threatening in critically ill patients.

Although the number of patients was small, rendering statistical analysis somewhat tenuous, imipenem showed a tendency toward superior efficacy, less *S. faecalis* superinfection, and fewer bleeding abnormalities compared to moxalactam. With its extreme potency against a broader spectrum of bacteria than the third-generation cephalosporins, the temptation may be to employ it widely in patients with serious bacterial infections. However, further studies should be undertaken to confirm the above findings and to determine what the effect of the widespread use of imipenem on the nosocomial flora will be, especially in view of a 25% rate of mucocutaneous candidiasis in this group.

TABLE 5. Adverse drug reactions

Reaction	No. of adverse reactions		No. requiring drug termination	
	Moxa-lactam	Imip-enem	Moxa-lactam	Imip-enem
Eosinophilia	4	2		
Thrombocytosis	1			
Prolonged prothrombin time with bleeding	4		3	
Positive direct Coombs test	1			
Rash	1	2	1	2
Antabuse-like reaction	1			
Vomiting or diarrhea		2		2

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