Imipenem as monotherapy in the treatment of intensive care patients with severe infections

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In an open study, 24 intensive care patients were treated with imipenem/cilastatin as monotherapy for serious bacterial infections. Twenty-one patients were treated for bronchopulmonary infection, two patients for septicaemia, and one patient for an empyema. Initially all strains were susceptible to imipenem. Gram-negative bacilli accounted for 80% of these isolates. The most frequently isolated species were *Proteus mirabilis*, *Escherichia coli* and *Pseudomonas aeruginosa*. All 24 patients were considered clinically cured. Sixteen of these patients (67%) were both clinically and microbiologically cured.

In eight of the 24 patients (33%), the strains isolated initially persisted. In eight of the 24 patients (33%), colonization of the respiratory tract developed. Two of the five *Ps. aeruginosa* isolates developed resistance during therapy but in none of these patients was therapy considered to have failed. In 12 patients (50%), transient elevations in hepatic function tests were observed and these were probably drug-related. The present study supports the view that imipenem/cilastatin may be useful as monotherapy in the treatment of severe infections in intensive care patients.

Introduction

Imipenem is a stabilized amidine derivative of thienamycin, a carbapenem β-lactam antibiotic produced by *Streptomyces cattleya*. Because thienamycin tends to break down spontaneously at high concentrations, a more stable amidine derivative, *N*-formimidoyl thienamycin (MK0787, Merck, Sharp & Dohme, Rahway, New Jersey), was developed. It is administered in combination with an equal amount of cilastatin, a substance that was developed to inhibit metabolism of imipenem in the kidney. *In vitro*, imipenem has a broad antibiotic spectrum and is highly active against most clinically important species of bacteria, including isolates resistant to other antibiotics (Kropp *et al.*, 1980; Jones, 1985). This new drug may be useful particularly in the treatment of mixed bacterial infections for which a combination of antibiotics, often including an aminoglycoside, would otherwise be necessary.

In the present study imipenem/cilastatin was administered as monotherapy to 24 patients with serious bacterial infections admitted to an intensive care unit (ICU).

Patients and methods

Patient population

All patients were treated in the ICU. Diagnosis of bronchopulmonary infection was made by the primary physicians using the usual criteria of fever, purulent sputum, leucocytosis and the appearance of a new infiltrate seen on chest radiographs in the appropriate clinical setting. Diagnosis of septicaemia was made by the criteria of two positive blood cultures before therapy in combination with clinical signs of infection.

Reasons for exclusion from the study included: patients less than 12 years of age, pregnant or nursing women, previous hypersensitivity reactions to any of the β-lactam antibiotics, high probability of death within 48 h, patients whose initial pathogen was known to be resistant to imipenem prior to entry into the study, and patients who had received antimicrobial therapy known, or presumed to be, effective against the infecting pathogen(s) within 72 hr preceding the initiation of treatment. Informed consent was obtained from each patient or nearest family relative according to the declaration of Helsinki and the amendments of Tokyo (1978) and Venice (1983).

Drug administration

Imipenem was given with cilastatin parenterally in a total daily dose of 1·0–3·0 g, in two to four divided doses. The drugs were administered over a 20–30 min infusion time. Patients with creatinine clearances greater than 30 ml/min/1·73 m^2 received the standard dose. Patients with creatinine clearances of 30 ml/min/1·73 m^2 or less received half the recommended daily dose. Patients with a glomerular filtration rate of less than 10 ml/min/1·73 m^2 received not more than 500 mg of imipenem/cilastatin every 12 h. A supplementary dose was given after haemodialysis.

Laboratory studies

In septicaemic patients, blood specimens were collected prior to therapy, and cultured routinely in trypticase soy broth with sodium polyanethol-sulphonate and brain heart infusion broth with saponin (BHI). In bronchopulmonary infections, specimens of expectorated sputum were collected before therapy and cultured on 7% sheep blood agar, Levine EMB agar and *Haemophilus* selective blood agar (bacitracin and 5% rabbit blood). Potential pathogens were identified and their susceptibility to standard antibiotics, as well as to imipenem, was determined by disc testing. Sensitivity to imipenem was defined as an inhibition zone with a diameter > 16 mm (imipenem 10 μg disc, BBL Microbiology Systems, Cockeysville). MICs were also measured for most of the isolates by an agar dilution method (Washington, 1974). Sputum samples were also collected within three days of the termination of therapy.

Laboratory tests performed prior to therapy, at five days into therapy, and after the termination of therapy included a complete blood cell count, differential count, a platelet count, and estimations of blood urea nitrogen, creatinine, serum glutamic oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, total bilirubin, potassium, sodium, chloride and urinalysis. Chest radiography was performed before and after therapy and at other times when indicated. Examination of the injection site was performed daily.

Evaluation of patients

Patients were excluded from evaluation if no pathogens were isolated from sputum samples, if the total course of imipenem was less than five days, or the patient received concomitant antibiotic therapy that was potentially active against the aetiological organism.

Clinical cure was defined as resolution of signs and symptoms of infection and sustained improvement as shown by chest radiography in respiratory tract infection. Microbiological response was classified as cure, cure with superinfection, cure with colonization, and failure. Microbiological cure was defined as eradication of the initial causative organism without relapse. Superinfection was defined as the appearance of a new pathogenic organism that was either susceptible, or resistant to the study drug, and subsequently required further antibiotic treatment. Colonization was defined as the appearance of a new organism that was susceptible, or resistant to the study drug, without clinical symptoms of infection. Microbiological and clinical cure was defined as eradication of the presumed pathogen and elimination of the clinical parameters of infection.

Results

Of the 30 patients initially included in the study, 24 were considered evaluable: six women with a mean age of 47 years (range 17–74) and eighteen men with a mean age of 45 years (range 18–72). Of those excluded, five had no pathogens isolated from their sputum samples, and one received a therapeutic course that was too short.

Twenty-one patients were treated for a bronchopulmonary infection, two patients for septicaemia (of urinary origin), and one patient for an empyema. The patients were all mechanically ventilated. Significant underlying diseases were present in all patients (Table I). Twenty-three patients had central venous lines. Twenty patients had indwelling urinary catheters. Thirteen patients had received previous antibiotic treatment one week prior to imipenem. The average length of imipenem therapy for the entire group was 9·1 days (6–13 days).

Table I. Underlying conditions in intensive care patients
treated with imipenem

Underlying condition	Number of patients	
Post-traumatic	6	
Post-surgical	12	
abdominal		3
cardiac		6
thoracotomy		1
neurosurgical		1
amputation		1
Rejected renal graft	1	
Intra-abdominal abscesses		
(pancreatitis)	2	
Aspiration	2	
Guillain Barré syndrome	1	
Total	24	

Microbiology

Forty bacterial isolates were cultured before therapy in the 24 evaluable patients. Sputum isolates were considered pathogenic if they were the only or predominant organism, and had been recognized as a cause of pneumonia. Twelve of the 20 patients had more than one pathogen isolated from sputum samples. One patient had a positive blood culture (*Streptococcus faecalis*).

Two patients were treated for septicaemia. The source of the septicaemia was the urinary tract in both cases (*Escherichia coli, Pseudomonas aeruginosa* + *Enterobacter cloacae*). One patient was treated for an empyema (*Str. agalactiae*).

All strains were susceptible to imipenem initially. Gram-negative bacilli accounted for 80% of these isolates (Table II), of these *Proteus mirabilis* (5), *Esch. coli* (5), *H. influenzae* (5) and *Ps. aeruginosa* (4) were the most frequent.

Outcome

All 24 patients were considered clinically cured. Sixteen of these patients (67%) were both clinically and microbiologically cured. In eight of the 24 patients (33%), the strains isolated initially persisted but the patients were considered clinically cured. In two patients, persistence was associated with the emergence of *Ps. aeruginosa* resistant to imipenem (Table III). In six patients, the persistent isolates were still sensitive to imipenem. In eight of the 24 patients (33%) colonization of the respiratory tract developed with five different isolates (Table IV).

Bacteria recovered included: *Ps. maltophilia* (one), *Pr. mirabilis* (one), *Ent. cloacae* (two), *Morganella morganii* (one) and *Staphylococcus epidermidis* (four). Four of the nine isolates were resistant to imipenem: *Ps. maltophilia* (one), *M. morganii* (one) and *Staph. epidermidis* (two). None of these resistant isolates was associated with clinical deterioration (Table V).

Table II. MICs of imipenem against 40 initial isolates from intensive care patients

Isolate	Number of isolates with MICs (mg/l) of:									
	≤ 0·03	0·06	0·125	0·25	0·50	1·0	2·0	4·0	8·0	16
Str. pneumoniae	1									
Str. faecalis						1				
Str. agalactiae	1									
Acinetobacter anitratus			1	1	2					
Pr. mirabilis							1	3	1	
H. influenzae	2(S)*			1		2				
Staph. aureus	5									
Klebsiella pneumoniae						2				
K. oxytoca					1					
Pasteurella multocida				1						
Aeromonas hydrophila				1						
Esch. coli			2	2	1					
Ent. cloacae				1			1			
Citrobacter freundii							1			
Serratia marcescens							1			
Ps. aeruginosa							2	2		

*Sensitive strains in agar diffusion (Kirby-Bauer), which were lost before MIC determination.

Table III. Susceptibility to imipenem of organisms persisting after treatment

Patient number	Persisting organism	Imipenem MIC (mg/l)
4	Ser. marcescens	2
8	Esch. coli	0·5
10	Ps. aeruginosa	32
12	Ps. aeruginosa	4
14	Ps. aeruginosa	32
14	Pr. mirabilis	4
21	Pr. mirabilis	8
23	Pr. mirabilis	4

Infections due to Ps. aeruginosa

Four patients with a broncho-pulmonary infection and with *Ps. aeruginosa* isolated from sputum samples, and one patient with a septicaemia (*Ent. cloacae*) and *Ps. aeruginosa* isolated from urine samples, were treated with imipenem. Initially the isolated strains were sensitive to imipenem (MIC, 2–4 mg/l). Two of the five *Ps. aeruginosa* isolates developed resistance during therapy (MIC, 32 mg/l). Resistant organisms were encountered after an average treatment period of $6·8 \pm 2·2$ days. In none of the patients in whom imipenem-resistant *Ps. aeruginosa* developed was therapy considered to have failed clinically.

Tolerance and adverse effects

In 12 patients (50%) transient elevation in hepatic function tests was observed and was probably drug-related. Incompatibility with other drugs was not observed.

Discussion

Infection remains a problem in intensive care units (Thorp, Richards & Telfer, 1979). Bacterial pneumonia is one of the most common infections and the one most often associated with significant morbidity and mortality. The patient who is intubated or has a tracheostomy is particularly susceptible to respiratory tract infections (Gaya,

Table IV. Susceptibility of colonizing organisms after imipenem treatment

Patient number	Colonizing organism after treatment	Imipenem MIC (mg/l)
6	Ps. maltophilia	>128
8	Ent. cloacae	0·5
14	M. morganii	>128
16	Staph. epidermidis	32
25	Staph. epidermidis	32
25	Ent. cloacae	2
28	Pr. mirabilis	8

Table V. Bacteriological response to therapy

Infecting isolate	eradicated	Number of isolates persisting	colonizing
Str. agalactiae	1		
Str. pneumoniae	1		
Str. faecalis	1		
Acin. anitratus	4		
Pr. mirabilis	2	3	1
M. morganii			1
H. influenzae	5		
Staph. aureus	5		
K. pneumoniae	2		
K. oxytoca	1		
Past. multocida	1		
Aerom. hydrophila	1		
Esch. coli	4	1	
Ent. cloacae	2		2
C. freundii	1		
Ser. marcescens		1	
Ps. aeruginosa	1	3	
Ps. maltophilia			1
Staph. epidermidis			4

1976). Optimal choice of antibiotics for bacterial pneumonia is problematical because of the multitude of potential bacterial pathogens and the difficulty in making a specific aetiological diagnosis. In this prospective open trial we have demonstrated the high efficacy and relative safety of imipenem/cilastatin as treatment for bronchopulmonary infections in intensive care patients.

The majority of patients had significant underlying diseases. These included cardiopulmonary, neurological and renal diseases as well as diabetes, endotracheal intubation, recent surgery and prior antibiotic administration. The majority of isolates were aerobic Gram-negative rods reflecting the high proportion of hospital-acquired infections and the serious underlying conditions of patients. Excluding *H. influenzae*, Gram-negative bacilli accounted for 70% of pre-therapy isolates.

The results presented in this study are similar to those reported by other investigators (Scandinavian Study Group, 1984; Salata *et al.*, 1985; Zajac *et al.*, 1985), and further support the clinical efficacy of imipenem/cilastatin as monotherapy in the treatment of serious polymicrobial infections. The spectrum indicated by other in-vitro studies (Kropp *et al.*, 1980; Jones 1985) was confirmed by the susceptibility data in this study. Strains with MICs for imipenem above 8 mg/l were found only in *Pseudomonas* spp., *Staph. epidermidis* and *M. morganii*. In agreement with these microbiological findings a high proportion of the less sensitive bacterial strains isolated persisted at the end of treatment or colonization of the respiratory tract occurred during treatment.

The emergence of two isolates of *Ps. aeruginosa* resistant to imipenem occurred in this study; neither was associated with a clinical deterioration. The potential for a stepwise increase in the resistance to imipenem in nosocomial strains of *Ps. aeruginosa* suggests that these infections should not receive monotherapy with this drug. The

emergence of resistance during monotherapy for *Ps. aeruginosa* is also seen with other β-lactam antibiotics (Wardle *et al.,* 1981; Berger & Arango, 1985).

Transient elevations in hepatic function tests were the most common changes noted in laboratory tests. No cases of infusion site phlebitis developed. No incompatibility with other drugs was observed.

In conclusion it may be said that monotherapy with imipenem/cilastatin was well-tolerated and effective, but caution should be exercised when this agent is used alone for the treatment of serious pseudomonas infections. In view of its extremely broad spectrum of activity, physicians may be tempted to use imipenem/cilastatin for a variety of purposes. One should be aware, however, that intensive use of the drug might lead to the selection of resistant strains in the hospital environment.

References

Berger, R. & Arango, L. (1985). Etiologic diagnosis of bacterial nosocomial pneumonia in seriously ill patients. *Critical Care Medicine* **13,** 833–6.

Gaya, H. (1976). Infection control in intensive care. *British Journal of Anaesthesia* **48,** 9–12.

Jones, N. R. (1985). Review of the in-vitro spectrum of activity of imipenem. *American Journal of Medicine* **78,** Suppl. 6A, 22–32.

Kropp, H., Sundelof, J. G., Kahan, J. S., Kahan, F. M. & Birnbaum J. (1980). MK0787 (*N*-formimidoyl thienamycin): evaluation of in-vitro and in-vivo activities. *Antimicrobial Agents and Chemotherapy* **17,** 993–1000.

Salata, R. A., Gebhart, R. L., Palmer, D. L., Wade, B. H., Scheld, W. M., Groschel, D. H., Wenzel, R. P., Mandell, G. L. & Duma, R. J. (1985). Pneumonia treated with imipenem/cilastatin. *American Journal of Medicine* **78,** Suppl. 6A, 104–9.

Scandinavian Study Group (1984). Imipenem/cilastatin versus gentamicin/clindamycin for treatment of serious bacterial infections. *Lancet i,* 868–71.

Thorp, J. M., Richards, W. C. & Telfer, A. B. M. (1979). A survey of infection in an intensive care unit. *Anaesthesia* **34,** 643–50.

Wardle, J. K., Selkon, J. B., Ingham, H. R. & Freeman, R. (1981). Ceftazidime in Gram-negative infections: three case reports. *Journal of Antimicrobial Chemotherapy* **8,** Suppl. B, 313–6.

Washington, J. A. & Barry, A. L. (1974). Dilution test procedures. In *Manual of Clinical Microbiology*, Vol. 1, 2nd edn. (Lenette, E. H., Spaulding, E. H. & Truant, J. P., Eds), pp. 410–7. American Society for Microbiology, Washington, D.C.

Zajac, B. A., Fisher, M. A., Gibson, G. A. & McGregor, R. R. (1985). Safety and efficacy of high-dose treatment with imipenem/cilastatin in seriously ill patients. *Antimicrobial Agents and Chemotherapy* **27,** 745–8.