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Clinical Pharmacology of Imipenem/Cilastatin

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ABSTRACT

Imipenem is a β-lactam antibiotic and is market in combination with cilastatin a drug that inhibits the degradation of imipenem by renal tubular dipeptidase and extends the elimination half-life of imipenem. Imipenem binds to penicillin-binding proteins, disrupts bacterial cell wall synthesis, and causes depth of susceptible organisms. Imipenem is resistant to hydrolysis by most β-lactamases and is active against a wide variety of aerobic and anaerobic microorganisms. Streptococci (including penicillinase-resistant Streptococcus pneumoniae), Enterococcus faecalis, staphylococci (including penicillinase-producing strains but not methicillin-resistant Staphylococcus aureus), Listeria, Enterobacteriaceae (except for emerging carbapenemase-producing strains), most strains of Pseudomonas and Acinetobacter, and Bacillus fragilis are susceptible to imipenem/cilastatin. Imipenem/cilastatin effectively treats urinary-tract, lower respiratory, intraabdominal, gynaecologic, skin, soft-tissue, bone, and joint infections. The efficacy and safely of imipenem/cilastatin and the penetration of imipenem in muscle and in subcutaneous tissues have been reviewed. The pharmacokinetics of imipenem have been studied in heathy volunteers and in patients with severe renal failure and the elimination half-life of imipenem is longer in patients than in healthy volunteers. The treatment of bacterial infections and trials with imipenem/cilastatin have been reviewed. Imipenem penetrates into the cerebrospinal fluid in significant amounts and imipenem/cilastatin treats the meningitis caused by Haemophilus influenzae type b, Citrobacter diversus, or Acinetobacter anitratus. The aim of this study is to review imipenem/cilastatin efficacy and safely, treatment of bacterial infections, trials, and treatment of bacterial meningitis, imipenem diffusion in tissues, and pharmacokinetics of imipenem and cilastatin and penetration into the cerebrospinal fluid of imipenem and cilastatin.

Keywords: Cerebrospinal-Fluid; Cilastatin; Efficacy-Safely; Imipenem; Meningitis; Pharmacokinetics; Tissue-Concentration; Treatment; Trials

Introduction

Imipenem/Cilastatin

Imipenem is formulated in combination with cilastatin (imipenem/cilastatin), a drug that inhibits the degradation of imipenem by renal tubular dipeptidase and extends the elimination half-life of imipenem [1].

Antimicrobial Activity of Imipenem

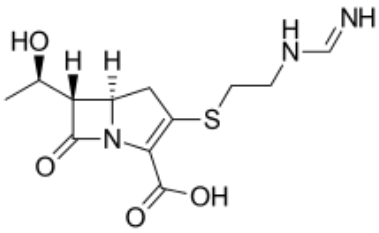
Imipenem, like other β-lactam antibiotics, binds to penicillin-binding proteins, disrupts bacterial cell wall synthesis and cause death of susceptible organisms. Imipenem is very resistant to hydrolysis by most β-lactamases. The in-vitro activity of imipenem is excellent across a wide variety of aerobic and anaerobic microorganisms. Streptococci (including penicillinase-resistant Streptococcus pneumoniae); Enterococcus faecalis, staphylococci (including penicillinase-producing strains but not methicillin-resistant Staphylococcus aureus); and Listeria (although ampicillin is more active) all are typically susceptible. Activity is excellent against Enterobacteriaceae with the exception of emerging carbapenemase-producing strains. Most strains of Pseudomonas and Acinetobacter are inhibited, but resistance to imipenem among these organisms is increasing and can emerge during therapy. Anaerobes, including Bacillus fragilis, are highly susceptible. Imipenem also displaces activity against Nocardia species and some species of rapidly growing mycobacteria. Addition of relebactam restores the activity of imipenem against carbapenemase-producing Enterobacterales but not metallo-β-lactamase producers; activity of the combination against imipenem-resistant Pseudomonas is variable [1].

Therapeutic Uses of Imipenem

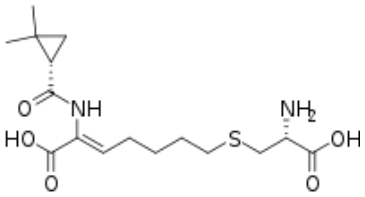
Imipenem, dosed at 500 to 1,000 mg intravenously every 6 to 8 hours in normal renal function is effective for a wide variety of infections, including urinary-tract and lower respiratory infections, intraabdominal, gynaecological, skin, soft-tissue, bone, and joint infections. Its primary role is for empirical treatment of serious infections in hospitalized patients who are at risk for resistant pathogens, such as those who have recently received other β-lactam antibiotics. When imipenem is used for treatment of severe Pseudomonas aeruginosa infection, resistant may develop during therapy [1].

Administration, Distribution, Metabolism, and Elimination of Imipenem

Imipenem is not absorbed orally. The drug is hydrolysed by a dipeptidase found in the brush border of the proximal tubule. Both imipenem and cilastatin have an elimination half-life of about 1 hour. When administered concurrently with cilastatin, about 70% of administered imipenem is recovered in the urine as the active drug. Dosage should be modified for patients with renal insufficiency. Nausea and vomiting are the most common adverse-effects (1% to 20%). Seizures have been noted in up to 1.5% of patients especially when high doses are given to patients with central nervous system lesions and those with renal insufficiency. Patients who are allergic to β-lactam antibiotics may have hypersensitivity reactions when given imipenem although the incidence of immediate-type hypersensitivity appears to be below 1% [1].



Imipenem molecular structure (molecular weight = 299.347 grams/mole)



Cilastatin molecular structure (molecular weight = 358.454 grams/mole)

Literature Search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "imipenem efficacy safely", "imipenem tissue concentration", "imipenem pharmacokinetics", "imipenem treatment", "imipenem trials", imipenem CSF", and "imipenem meningitis". In addition, the book: The pharmacological basis of therapeutics [1] has been consulted

Results

Efficacy and Safely of Imipenem/Cilastatin

Imipenem/cilastatin administered intravenously at a daily dose of 1.5 grams for 10 days effectively and safely treats patients with complicated intraabdominal infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia [2]. Twenty-seven immunocompromised patients suffering from severe bacterial infections received imipenem/cilastatin intravenously at a daily dose of 2 grams for 8 days and this treatment effectively and safely cures the infections [3]. Imipenem/cilastatin was administered intravenously at a daily dose 1.5 to 2 grams for an average of 8.6 days (range, 3 to 44) to 34 patients with bacterial septicaemia. This treatment is well-tolerated and effectively and safely treats septicaemia but 3 patents (8.8%) developed mild phlebitis [4]. Imipenem/cilastatin was administered intravenously at a dose of 0.5 grams 4 times-daily for 8 days to 58 patients with severe bacterial septicaemia. Imipenem/cilastatin is well-tolerated and effectively and safely treats severe septicaemia [5]. Imipenem/cilastatin was administered intravenously at a daily dose of 1 gram for 5 to 56 days (mean, 16.3) and effectively and safely treats patents with osteomyelitis, bacteraemias, cellulitis, bacterial pneumonia, pelvic cellulitis, intraabdominal abscess, empyema, mediastinitis, and with endometritis. Infections were caused by gram-negative organisms in 55% of patients and by gram-positive organisms in 45% of patients [6]. Imipenem/cilastatin was administered intravenously at a dose of 1 gram 4 times-daily to 1,723 patients with infection caused by gram-positive or by gram-negative aerobic and anaerobic bacteria and the clinical efficacy of imipenem/cilastatin is demonstrated in 92.0% of patients [7]. Imipenem/cilastatin was administered intravenously to 569 patients with intraabdominal and respiratory-tract infections. The daily dose of imipenem/cilastatin was 1 gram in 47.1% of patients and 2.0 grams to 52.9% of patients and the clinical efficacy of imipenem/cilastatin is observed in 82.1% of patients [8]. Imipenem/cilastatin was administered intravenously at a dose of 0.5 grams thrice-daily to 47 patients with urinary-tract infection which was caused by Pseudomonas aeruginosa in 58% of patients. This treatment is well-tolerated, sterilized the urine, and all patients experienced clinical improvement. Thus imipenem/cilastatin effectively and safely treats urinary-tract infection [9].

Diffusion Of Imipenem into Body-Tissues

Imipenem was administered intravenously at a daily dose of 1 gram to patients with renal failure and with impaired liver, heart, or lung function and also to healthy volunteers. The concentration of imipenem in muscle and in subcutaneous tissues of patients is 2.3±1.5, 12.8±1.6, and 10.7±1.0 μg/ml for muscle and subcutaneous tissue, respectively, in healthy volunteers. The distribution-rate con-

stant of imipenem for muscle and subcutaneous tissues is 1.96±0.6 and 1.1±0.2 h-1, respectively, in patients, and 5.2±1.0 and 6.6±1.7 h-1, respectively, in healthy subjects. The area under the plasma concentration-time curve is 37.4±5.9 μg*h/ml in patients and 46.0±4.4 μg*h/ml in healthy subjects. The total body clearance is 6.3±0.8 and 13.2±1.4 L/h in patients and healthy subjects, respectively. These data indicate that the pharmacokinetic parameters of imipenem are altered in patients [10].

Pharmacokinetics of Imipenem in Healthy Volunteers

Jaruratanasirikul, et al. [11] studied the pharmacokinetics of imipenem in 15 healthy volunteers who received imipenem in three regimens: (1) 0.5 grams 4 times-daily infused 0.5 hour for 3 doses; (2) 0.5 grams 4 times-daily infused for 2 hours for 3 doses; and (3) 1 gram 4 times-daily infused for 2 hours for 3 doses. The pharmacokinetic parameters of imipenem have been obtained on the third dose. Subjects were non-smoking, non-alcoholic, and non-obese healthy volunteers. All subjects were male, their age was 28.25±4.98 years (range, 24 to 39), their body-weight was 58.75±8.61 kg (range, 51 to 75), and their body-mass index was 20.61±2.70 kg/m^2 (range, 17.2 to 25.3).

Table 1 [11] shows that the pharmacokinetic parameters of imipenem vary with imipenem dose and with the length of infusion. Imipenem in rapidly eliminated as the mean elimination half-life of imipenem ranges from 1.02 to 2.42 hours and the distribution volume of imipenem is smaller than the water volume.

Table 1: Pharmacokinetic parameters of imipenem which have been obtained in 15 healthy volunteers. Values are the mean+SD, by Jaruratanasirikul, et al. [11].

	Duration of infusion		
	0.5 hours	**2 hours**	
	Dose of imipenem		
Parameter	0.5 grams	0.5 grams	1 gram
Peak concentration (μg/ml)	48.43±5.89	21.64±2.22[a]	43.91±5.73[b]
Minimum concentration (μg/ml)	0.62±0.31	1.05±0.45	2.27±0.72[a,b]
$AUC_{0-\infty}$ (μg*h/ml)	63.71±1.04	59.00±6.76	127±17.32[a,b]
Total body clearance (L/h)	7.95±1.04	8.58±1.05	8.00±1.12[b]
Elimination half-life (h)	1.32±0.27	1.02±1.49[a]	2.42±0.27[a,b]
Elimination-rate constant (h^{-1})	0.57±0.18	0.70±0.17[a]	0.29±0.03[a,b]
Distribution volume (L)	9.41±1.44	9.44±1.76	11.60±1.99[a,b]

Note: AUC = area under the concertation-time curve. [a]P-value < 0.05, 0.5 grams of imipenem infused 0.5 hours versus 0.5 grams of imipenem infused 2 hours. [b]P-value < 0.05, 1 gram of imipenem infused for 2 hours versus 0.5 grams of imipenem infused for 2 hours.

Pharmacokinetics of Imipenem and Cilastatin Sodium in Patients with Severe Renal Failure

Verbist, et al. [12] investigated the pharmacokinetics of imipenem and cilastatin sodium in 6 patients with severe renal failure who received imipenem/cilastatin sodium intravenously at a dose of 500 mg twice-daily for 5 days. The patients were aged 52.3 years (range, 32 to 66), weighed 64.0 kg (range, 48 to 84), had a body-surface area of 1.69 m^2 (range, 1.39 to 2.00), and had a creatinine clearance corrected for body-surface area of 1.04 ml/min 1.73 m^2 (range 5.34 to 14.8).

Table 2 shows that the pharmacokinetic parameter of both imipenem and cilastatin sodium are similar on the 1st and 5th day of administration. The elimination half-life of imipenem is about one half than that of cilastatin sodium. The total body clearance of both imipenem and cilastatin sodium is greater than the urinary clearance and the distribution volume of both imipenem and cilastatin sodium is smaller than the water volume. Imipenem is eliminated mainly by renal route thus the elimination half-life of imipenem is longer in patients with severe renal failure than in healthy volunteers. For comparison with healthy volunteers see Table 1. The comparison of the other pharmacokinetic parameters of imipenem between patients with severe renal failure and healthy volunteers cannot be carried out because the pharmacokinetic parameters are expressed in different units in patients and healthy volunteers.

Table 2: Pharmacokinetic parameters of imipenem and cilastatin sodium which have been obtained in 6 patients with severe renal failure on the 1st and 5th day of imipenem/cilastatin sodium administration. Imipenem/cilastatin sodium was administered intravenously at a dose of 500 mg twice-daily for 5 days. Values are the mean±SD, by Verbist, et al. [12].

	Imipenem		Cilastatin sodium	
Parameter	**Day 1**	**Day 5**	**Day 1**	**Day 5**
Peak conc. (μg/ml)	42.1±12.0	43.7±9.8	44.6±13.2	58.6±10.5
$AUC_{0\text{-}12h}$ (μg*h/ml)	158±37	152±31	270±60	351±37
$AUC_{0\text{-}\infty}$ (μg*h/ml)	166±38	158±32	346±62	455±69
Distribution volume (L/kg)	0.21±0.03	0.20±0.03	0.17±0.03	0.16±0.02
Elimination half-life (h)	2.75±0.97	2.49±1.23	5.45±1.02	5.24±1.56
TBC (ml/min/1.73 m^2)	57.4±10.2	59.0±12.5	23.4±3.6	21.7±3.4
UC (ml/min/1.73 m^2)	7.5±3.7	6.4±3.0	9.8±3.9	10.3±4.5

Treatment of Bacterial Infections with Imipenem/Cilastatin

It was compared the therapeutic efficacy of imipenem/clavulanate to that of meropenem/clavulanate in treatment of 84 patients with multi-drug-resistant tuberculosis or with extensive-drug-resistant tuberculosis. Patients received either imipenem/clavulanate or meropenem/clavulanate for a median of 187 days (range, 60 to 428) and 85 days (range, 49 to 156), respectively. The sputum smear-rate (P-value = 0.02), the culture conversion-rate (P-value < 0.0001), and the success-rate (P-value = 0.03) are higher following meropenem/clavulanate. The adverse-effects following imipenem/clavulanate and meropenem/clavulanate are reported in only 5.4% and 6.5% of patients, respectively. Meropenem/clavulanate is more effective than imipenem/clavulanate in treating patients with multi-drug-resistant tuberculosis and with extensive-drug-resistant tuberculosis and both treatments are well-tolerated [13]. Patients with serious bacterial infection received either meropenem (N = 87) or imipenem/cilastatin (N = 91) and both drugs were administered intravenously at a dose of 1 gram thrice-daily. The overall satisfactory clinical response-rate is similar in both treatments thus meropenem is efficacious (clinically and bacteriologically) as imipenem/cilastatin in treating serious bacterial infection [14]. Imipenem/cilastatin was administered intravenously at a dose of 500 mg thrice-daily to 21 patients with bacterial infection and with AIDS or with AIDS-related complex and the treatment results in rapid control of the infection in 80.1% of patients [15]. It was evaluated the pharmacokinetic/pharmacodynamic profile of imipenem in 51 burn patients with bacterial infection who had a median age of 38.7 years, a median body-weight of 68.0 kg, and 36.3% of the body-surface area was burn. The median elimination half-life of imipenem is 2.2 hours, the median plasma clearance of imipenem is 16.2 h^{-1}, and the median distribution volume of imipenem is 0.86 L/kg.

It was suggested that the imipenem daily dose for the control of infection in burn patients with normal renal function is 31.1±9.7 mg/kg and must be reduced to 17.2±9.7 mg/kg in burn patients with renal failure to avoid neurotoxicity [16]. It was compared the efficacy of cefoperazone/sulbactam to that of imipenem/cilastatin in treatment of patients with Acinetobacter bacteraemia. Thirty-five patients received cefoperazone/sulbactam and 12 patients received imipenem/cilastatin. The favourable clinical response after 72 hours of treatment is similar in both treatments. Thus cefoperazone/sulbactam is effective as imipenem/cilastatin in treatment of Acinetobacter bacteraemia [17]. It was compared the efficacy of ampicillin/sulbactam to that of imipenem/cilastatin in treatment of patients with Acinetobacter ventilator-associated bacterial pneumonia. Ampicillin/sulbactam treats 93.3% of patient and imipenem/cilastatin treats 83.1% of patients, the mortality-ate, the duration of mechanical ventilation, and the length of stay in hospital are similar in both treatments thus ampicillin/sulbactam treats Acinetobacter ventilator-associated bacterial pneumonia as imipenem/cilastatin [18].

The clinical efficacy of imipenem/cilastatin was assessed in 45 patients with severe septicaemia, intra-abdominal abscesses, respiratory-tract, urinary-tract, skin, soft-tissue, and bone infection caused by gram-negative or by gram-positive bacteria. Patients received imipenem/cilastatin intravenously at a daily dose of 1.5 to 2 grams, the clinical cure is achieved in 82.3% of patients and 13.3% of patients show marked clinical improvement, and the adverse-effects are noted in 4.4% of patients. Imipenem/cilastatin is well-tolerated and effectively treats life-threatening infections [19]. The clinical utility of imipenem/cilastatin sodium was studied in patients with chronic bronchitis (N = 5), with diffuse pan-bronchiolitis (N = 2), and with bronchopneumonia (N = 2) caused by Pseudomonas aeruginosa. Imipenem/cilastatin sodium was administered intravenously at a daily dose of 1.5 grams and the clinical efficacy is good in 66.7% of patients, fairly good in 11.1% of patient, and poor in 22.2% of patients. Imipenem/cilastatin sodium effectively treats respiratory-tract infections caused by Pseudomonas aeruginosa [20]. Imipenem/cilastatin sodium was administered intravenously at a daily dose of 2 grams to 54 patients with lung cancer and with lung infection caused by Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus species, Enterococcus faecalis, Pseudomonas aeruginosa, or by Acinetobacter species. The eradication of these organisms occurs in 81.8% of patients thus imipenem/cilastatin effectively treats lung bacterial in-

fections in patients with lung cancer [21]. Imipenem/cilastatin was administered intravenously at a dose of 500 to 750 mg twice-daily to 31 patients with abscesses, 20 patients with cellulitis, and 23 patients with wound infections. Sixty patients (81.1%) were cured, 12 patients (16.2%) improved, 2 patients (2.7%) failed to improve, and the adverse-effects occurred in only 8 patients (10.8%) thus this treatment is well-tolerated and cure the patients [22]. Ten patients had bacterial septicaemia, 6 patients had intraabdominal-sepsis, 6 patients had bacterial pneumonia, 6 patients had Legionnaires' dosage, 4 patients had skin and soft-tissue infection, and 13 patients had other diseases and the patients received imipenem/cilastatin intravenously at a dose of 500 to 1,000 mg 4 times-daily. Imipenem/cilastatin is well-tolerated and treats a variety of infections [23].

For-hundred-sixty-five infected patients were enrolled and the severity of the infection was moderate in 58.9% of patients, mild in 37.2% of patients, and severe in 3.9% of patients. The most common site of infection was the skin (46.2%), soft-tissue (36.2%), and intra-abdominal (17.6%). Imipenem/cilastatin was administered intravenously at a dose of 500 mg twice-daily to 45.1% of patients, at a dose of 750 mg twice-daily to 36.2% of patients, and a dose of 500 mg thrice-daily in 18.7% of patients. The treatment is well-tolerated in 87.1% of patients and moderately well-tolerated in 12.9% of patients, and the overall clinical outcome is favourable in 95.1% or more patients with various infections [24].

One-hundred-sixty-four patients had intraabdominal infection caused by Staphylococcus epidermidis, Morganella morganii, or by Fusobacterium varium and received imipenem/cilastatin intravenously at a daily dose of 1.5 grams. The frequency of clinical cure or improvement is obtained in 91.2% of patients thus imipenem/cilastatin is a useful antibiotic to treat intraabdominal infections [25]. One-hundred-fifty-two patients with bacterial pneumonia received either ciprofloxacin administered intravenously at a daily dose of 800 to 1,200 mg or imipenem/cilastatin administered intravenously at a daily dose of 2 to 4 grams. The success-rate is generally good and both ciprofloxacin and imipenem/cilastatin effectively treat the pneumonia [26]. Forty children with infection caused by Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae, or by Pseudomonas aeruginosa were enrolled. Children aged < 3 years received imipenem/cilastatin intravenously at a daily dose of 100 mg/kg and children aged > 3 years received imipenem/cilastatin intravenously at a daily dose of 60 mg/kg. All children respond favourably to treatment, no serious adverse-effects are observed, and the infective bacteria are eradicated in all children. Thus Imipenem/cilastatin is well-tolerated and effectively treats the infections [27].

One-hundred-four infants and children, aged 22 days to 15 years, with bacterial infection were enrolled. Children aged up to 3 years received imipenem/cilastatin intravenously at a daily dose of 100 mg/kg and older children received imipenem/cilastatin intravenously at a daily dose of 60 mg/kg. Twenty percent children had bronchopneumonia with or without empyema, 16.1% had peritonitis complicating appendicitis, 14.0% children had skin infection and soft-tissue abscesses, 11.1% children had bacterial septicaemia, and 38.8% children had miscellaneous infections. The infective agents were Proteus mirabilis, Salmonella typhi, Staphylococcus aureus, or Escherichia coli. Imipenem/cilastatin is well-tolerated by 91.3% of children and has excellent clinical efficacy in treating a variety of infections [28]. Two-hundred-eighteen children, aged 2.5 to 16.8 years, were hospitalized for appendectomy, the appendix was perforated in 54 children (24.8%), and all children received imipenem/cilastatin intravenously at a daily dose of 80 mg/kg. Children respond favourably to the treatment and it is well-tolerated [29]. Febrile neutropenic patients with lung cancer and bacterial pneumonia received imipenem/cilastatin intravenously at a daily dose of 2 grams. The overall response-rate ranges from 70.2% to 77.1% and this treatment is adequate in these patients [30]. Two-hundred-ten neutropenic cancer patients had bacteriological infection and 30 patients (14.3%) also had bacterial septicaemia and all patients received imipenem/cilastatin intravenously at a daily dose of 2 grams. The clinical and laboratory adverse-effects are mild and imipenem/cilastatin effectively treats infection and septicaemia[31]. Forty-five patients had bacterial infection and underlying malignancy with an absolute neutrophil count 500/mm^3 and received imipenem/cilastatin intravenously at a daily dose of 2 grams and this treatment effectively treats the infection [32]. Fifty patients with peritonitis in continuous ambulatory peritoneal dialysis received imipenem/cilastatin sodium intravenously at a daily dose of 1 gram. The primary response-rate occurs in 95.1% of patients and the complete cure-rate without relapse occurs in 85.0% of patients. Imipenem/cilastatin sodium is an effective treatment of peritonitis in patients during continuous ambulatory peritoneal dialysis [33].

Trials with Imipenem/Cilastatin

A multicentre, international, double-blind, randomized, prospective trial was conducted in hospitalized patients with complicated skin and skin-structure infection to evaluate the efficacy of meropenem administered intravenously at a dose of 500 mg thrice-daily versus that of imipenem/cilastatin administered intravenously at a dose of 500 mg thrice-daily. One-thousand-seventy-six patients were enrolled, 692 patients (64.3%) received meropenem and 384 patients (35.7%) received imipenem/cilastatin. The cure-rate is 86.2% in patients treated with meropenem and is 82.9% in patients treated with imipenem/cilastatin thus meropenem has comparable efficacy as imipenem-cilastatin in treatment of complicated skin and skin-structure infection [34]. A trial was conducted to test the efficacy of meropenem administered intravenously at a dose of 1 gram thrice-daily versus imipenem/cilastatin administered intravenously at a dose of 500 mg 4 times-daily to treat serious bacterial infections. Imipenem/cilastatin is more effective and more economical than meropenem in treatment of serious bacterial infections [35].

A trial was conducted to test the efficacy of imipenem/cilastatin versus that of piperacillin/tazobactam in 3,071 patients with nosocomial pneumonia caused by Pseudomonas aeruginosa or with acute peritonitis. Patients were assigned to receive either imipenem/cilastatin administered intravenously at a dose of 500 mg 4 times-daily or piperacillin/tazobactam administered intravenously at a dose of 4.5 grams thrice-daily. Piperacillin/tazobactam is effective as imipenem/cilastatin in treatment of nosocomial bacterial pneumonia or acute peritonitis [36]. An open, randomized, multinational, multicentre-trial was conducted to compare the efficacy, safely, and tolerability of levofloxacin administered intravenously at a dose of 500 mg twice-daily to 178 hospitalized patients with bacteraemia and sepsis versus imipenem/cilastatin administered intravenously at a dose of 1 gram thrice-daily to 147 hospitalized patients with bacteraemia and sepsis. The clinical and bacteriological response occurs in 87.3% of patients treated with levofloxacin and in 83.6% of patients treated with imipenem/cilastatin and both treatments are well-tolerated. Thus levofloxacin is effective and well-tolerated as imipenem/cilastatin in treatment of hospitalized patients with bacteraemia and sepsis [37]. It was conducted a randomized clinical trial to compare the efficacy of imipenem/cilastatin versus that of a combination of latamoxef and tobramycin in the management of fever and neutropenia in patients with lung cancer.

Fifty-nine patients received imipenem/cilastatin intravenously at a dose of 1 gram twice-daily and 51 patients received latamoxef intravenously at a daily dose of 2 grams plus tobramycin administered intravenously at a dose of 90 mg twice-daily. The clinical response-rate is 82.1% in patients treated with imipenem/cilastatin and 80.0% in the combination therapy. Imipenem/cilastatin has therapeutic efficacy as latamoxef plus tobramycin in treatment of febrile neutropenic patients with lung cancer [38]. A randomized clinical trial was conducted in 441 patients with bacterial infection to test the efficacy, safely, and tolerability of imipenem/cilastatin and those of moxalactam. Significantly more organisms are susceptible to imipenem than to moxalactam, the clinical outcome is significantly better in patients treated with imipenem/cilastatin but moxalactam was less irritating at the site of injection than imipenem/cilastatin [39].

A randomised clinical trial was conducted in 50 neutropenic cancer patients with fever and sepsis to test the efficacy of imipenem/cilastatin versus that of ceftriaxone/gentamicin. Twenty-six patients received imipenem/cilastatin and 24 patients received ceftriaxone/gentamicin. The initial clinical response-rate is 62.5% in patients treated with ceftriaxone/gentamicin and is 84.6% in patients treated with imipenem/cilastatin (P-value = 0.075). Imipenem/cilastatin is equivalent to ceftriaxone/gentamicin for the treatment of neutropenic cancer patients with fever and sepsis [40]. A randomised clinical trial was conducted to test the efficacy of imipenem/cilastatin versus that of other β-lactam antibiotics in treatment of patients with infections caused by gram-positive or by gram-negative bacteria. The clinical efficacy and the clinical and laboratory adverse-effects are similar in patients treated with imipenem/cilastatin and in those treated with other β-lactam antibiotics. The frequency of colonization and superinfection is similar in patients treated with imipenem/cilastatin and in those treated with other β-lactam antibiotics. Imipenem/cilastatin and other β-lactam antibiotics have comparable clinical efficacy and clinical and laboratory adverse-effects [41].

Penetration of Imipenem and Cilastatin in to the Cerebrospinal Fluid (CSF)

Jacobs, et al. [42] studied the penetration of imipenem and cilastatin into the CSF of 20 children, aged 52±17 months (range, 4 months to 11 years), with meningitis caused by Haemophilus influenzae type B (N = 9), Streptococcus pneumoniae (N = 3), Neisseria meningitidis (N =4), Escherichia coli (N = 1), Staphylococcus aureus (N = 1), or Staphylococcus epidermidis (N = 2). Imipenem/cilastatin was administered by intravenous infusion at a dose of 25 mg/kg thrice-daily (multiple doses) to 10 children or 25 mg/kg once-daily (single dose) to 10 children and both treatments lasted 10 days. The minimum inhibitory concentration was: 0.08 μg/ml for Haemophilus influenzae, 0.12 μg/ml for Streptococcus pneumoniae, 0.06 μg/ml for Neisseria meningitidis, 0.25 μg/ml for Escherichia coli, 0.10 μg/ml for Staphylococcus aureus, and 1.5 μg/ml for Staphylococcus epidermidis.

Table 3 [42] shows that the time from the end of imipenem infusion to serum sampling time is 136 min "early" and 135 min "late" (single dose) and is 125 min "early" and 150 min "late" (multiple doses). The time from end of imipenem infusion to CSF sampling time is 148 min "early" and 133 min "late" (single dose) and 102 min "early" and 147 min "late" (multiple doses). The ratio of the concentration of imipenem in CSF to that in serum is < 1 for both single dose and multiple doses. The concentration of imipenem in CSF is higher than minimum inhibitory concentration of the organisms causing the meningitis. In addition, there is a remarkable interindividual variability in the parameters and this variability is accounted by the wide variation in child age and disease.

Table 3: Concentration of imipenem in serum and in CSF of 20 children, aged 52±17 months, with bacterial meningitis. Values are the mean, standard error of the mean, range, and number of children, by Jacobs, et al. [42].

	Ts (min)		Serum conc. (μg/ml)		T_{CSF} (min)		CSF conc. (μg/ml)		CSF to serum concentration ratio	
Single dose										
	Early	**Late**	**Early**	**Late**	**Early**	**Late**	**Early**	**Late**	**Early**	**Late**
Mean	136	135	8.59	9.96	148	133	1.36	2.08	0.15	0.27
±SEM	3.5	10.3	0.95	2.3	9.6	8.0	0.32	1.4	0.03	0.15
Range	121-160	86-175	3.4-14.4	4.1-23.1	118-212	105-155	0.5-3.7	0.3-9.4	0.06-0.37	0.05-1.12
N	9	7	9	7	9	7	9	7	9	9
Multiple doses										
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Mean	125	150*	11.97	9.57	102	147	1.87	1.22	0.22	0.17
±SEM	6.5	8.8	2.03	1.76	9.2	11.2	0.29	0.11	0.05	0.04
Range	103-165	110-183	3.8-25.0	2.9-19.2	92-185	105-214	0.27-3.5	0.7-1.8	0.01-0.31	0.07-0.42
N	9	9	9	9	9	9	9	9	9	9

Note: Ts = time from end of imipenem/cilastatin infusion to serum sampling time. T_{CSF} = time from end of imipenem/cilastatin infusion to CSF sampling time. *P-value < 0.05, "Ts Late" single dose versus multiple doses. N = number of children. Early = treatment conducted during the first 3 days of therapy. Late = treatment conducted during the last 3 days of therapy.

Table 4 shows that time from the end of imipenem/cilastatin infusion to serum sampling time is 136 min "early" and 135 min "late" (single dose) and 124 min "early" and 150 min "late" (multiple doses). The time from end of imipenem/cilastatin infusion to CSF sampling time is 145 min "early" and 133 min "late" (single dose) and 120 min "early" and 147 min "late" (multiple doses). The ratio of the concentration of cilastatin in CSF to that in serum is < 1. In addition, there is a remarkable interindividual variability in the parameter and this variability is due to the wide variation of child age and child disease. The penetration of imipenem and cilastatin into the CSF was assessed in 10 adult patients with bacterial meningitis who received 4 doses of 1 gram daily of imipenem/cilastatin intravenously. The concentrations of imipenem in CSF ranges from 0.5 to 11 μg/ml and that of cilastatin ranges from 1.1 to 10.5 μg/ml, thus imipenem penetrates into the CSF in significant amounts and the concentration of cilastatin in CSF is higher than that of imipenem [43].

Table 4: Concentration of cilastatin in serum and in CSF which has been obtained in 20 children, aged 52±17 months, with bacterial meningitis. Values are the mean, standard error of the mean, range, and number of children, by Jacobs, et al. [42].

	Ts (min)		Serum conc. (μg/ml)		T_{CSF} (min)		CSF conc. (μg/ml)		CSF to serum concentration ratio	
	Early	**Late**	**Early**	**Late**	**Early**	**Late**	**Early**	**Late**	**Early**	**Late**
Single dose										
Mean	136	135	7.41	5.73	145	133	1.10	1.70	0.16	0.66*
±SEM	3.5	10.3	1.56	1.45	9.6	8.0	0.24	1.01	0.04	0.22
Range	121-160	86-175	4.0-16.8	1.2-13.3	118-212	105-160	0.5-2.6	0.5-6.2	0.06-0.35	0.30-1.14
N	9	7	7	7	9	7	8	5	6	4
Multiple doses										
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Mean	124	150	9.50	7.61	120	147	1.59	1.04**	0.29	0.21***
±SEM	6.6	8.8	2.33	1.87	9.2	11.2	0.21	0.12	0.08	0.07
Range	103-165	110-183	1.6-24.0	1.5-15.7	92-185	105-214	0.9-2.6	0.6-1.7	0.06-0.81	0.04-0.67
N	9	9	8	9	9	9	8	9	8	8

Note: Ts = time from the end of imipenem/cilastatin infusion to serum sampling time. T_{CSF} = time from the end of imipenem/cilastatin infusion to CSF sampling time. Early = treatment conducted during the first 3 days of therapy. Late = treatment conducted during the last 3 days of therapy. *P-value < 0.05, CSF to serum concentration ratio "Early" versus "Late". **P-value < 0.05, CSF concentration single dose versus multiple doses. ***P-value < 0.05, CSF to serum ratio single dose versus multiple doses. N = number of children.

Treatment of Bacterial Meningitis with Imipenem/Cilastatin

Imipenem/cilastatin was administered intravenously at a daily dose of 100 mg/kg to 21 infants and children, aged 3 to 48 months, with bacterial meningitis. Eradication of bacteria from the cerebrospinal fluid was demonstrated within 24 hours of antibiotic therapy in 19 infants and children. Two patients, who had the meningitis caused by Haemophilus influenzae type b, achieved bacteriologic cure after 2 to 3 days of therapy. The penetration of imipenem and cilastatin was determined at various times after drug administration and the cerebrospinal fluid to serum ratio of imipenem is 0.14 and that of cilastatin is 0.10. The study was terminated when 7 patients (33.3%) developed seizure activity after initiation of antibiotic therapy. The usefulness of imipenem/cilastatin for the treatment of bacterial meningitis in infants and children may be limited by a possible incidence of drug-related seizure activity [44]. Twenty infants and children had the meningitis caused by Citrobacter diversus and were treated with imipenem/cilastatin intravenously at a daily dose of 80 mg/kg and the meningitis was cured in all infants and children [45]. Ten adult patients had the meningitis caused by Acinetobacter anitratus and were treated with imipenem/cilastatin intravenously at a dose of 1 gram 4 times-daily. The minimal inhibitory concentration of imipenem against Acinetobacter anitratus is ≤ 0.04 μg/ml, the patients tolerate the drug well, and the meningitis is cured after 12 days of therapy [46].

Discussion

Imipenem is a β-lactam antibiotic and is market in combination with cilastatin a drug that inhibits the degradation of imipenem by renal tubular dipeptidase and extends the elimination half-life of imipenem. Imipenem binds to penicillin-binding proteins, disrupts bacterial cell wall synthesis, and causes death of susceptible organisms. Imipenem is very resistant to hydrolysis by most β-lactamases. The in-vitro activity of imipenem is excellent across a variety of aerobic and anaerobic microorganisms. Streptococci (including penicillinase-resistant Streptococcus pneumoniae), Enterococcus faecalis, staphylococci (including penicillinase-producing strains but not methicillin-resistant Staphylococcus aureus), Listeria (although ampicillin is more active) all are typically susceptible. Activity is excellent against Enterobacteriaceae with the exception of emerging carbapenemase-producing strains. Most strains of Pseudomonas and Acinetobacter are inhibited, but resistance to imipenem among these organisms is increasing and can emerge during therapy. Aerobes, including Bacillus fragilis, are highly susceptible. Imipenem also displaces activity against Nocardia species and some species of rapidly growing mycobacteria.

Addition of relebactam restores the activity of imipenem against carbapenemase-producing Enterobacterales but not metallo-β-lactamase producers; activity of the combination against imipenem-resistant Pseudomonas is variable. Imipenem is not absorbed orally and is administered intravenously or intramuscularly. Imipenem dosed at 500 to 1,000 mg intravenously every 6 to 8 hours to patients with normal renal function effectively treats a wide variety of infections including urinary-tract, lower respiratory, intraabdominal, gynaecological, skin, soft-tissue, bone, and joint infections and the dosage of imipenem must be reduced in patients with renal failure. Imipenem/cilastatin is used to treat serious infections in hospitalized patients who are at risk of pathogens which became resistant following the administration of β-lactam antibiotics. The efficacy and safely of imipenem/cilastatin have been reviewed.

Imipenem/cilastatin administered intravenously at a daily dose of 1.5 grams for 10 days effectively and safely treats complicated intraabdominal infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia [2], imipenem/cilastatin administered intravenously at a daily dose of 2 grams for 8 days effectively and safely treats severe bacterial infections [3], imipenem/cilastatin administered intravenously at a daily dose of 1.5 to 2 grams for an average of 8.6 days is well-tolerated and effectively and safely treats bacterial septicaemia but some patients developed mild phlebitis [4], imipenem/cilastatin administered intravenously at a dose of 0.5 grams 4 times-daily for 8 days is well-tolerated and effectively and safely treats septicaemia [5], imipenem/cilastatin administered intravenously at a daily dose of 1 gram for a mean of 16.3 days effectively and safely treats patients with different infections caused by gram-negative or by gram-positive bacteria [6], imipenem/cilastatin administered intravenously at a dose of 1 gram 4 times-daily effectively treats patients with infection caused by gram-positive or by gram-negative aerobic and anaerobic bacteria [7], imipenem/cilastatin was administered intravenously at a daily dose of 1 gram to 47.1% of patients and at a daily dose of 2 grams to 52.9% of patients.

Patients had intraabdominal and respiratory-tract infections and the clinical efficacy of treatment is observed in 82.1% of patients [8], imipenem/cilastatin was administered intravenously at a dose of 0.5 grams thrice-daily to patients with urinary-tract infection which was caused by Pseudomonas aeruginosa in 58% of patients and this treatment effectively and safely treats the patients [9]. These results indicate that imipenem/cilastatin effectively and safely treats different infections. The diffusion of imipenem into the muscle and subcutaneous tissues has been reviewed. Imipenem was administered intravenously at a daily dose of 1 gram to patients with renal failure and with impaired liver, heart, or lung function and also to healthy volunteers. The concentration, the distribution-rate constant, the area under the concentration-time curve, and the total body clearance of imipenem in muscle and subcutaneous tissues are altered in patients [10]. The pharmacokinetics of imipenem have been studied in 15 healthy volunteers who received imipenem intravenously at a dose of 0.5 grams 4 times-daily infused for 0.5 hours for 3 days (A) or at a dose of 0.5 grams 4 times-daily infused for 2 hours for 3 doses (B) or at a dose of 1 gram 4 times-daily infused for 2 hours for 3 doses (C) [11]. The mean elimination half-life of imipenem is 1.32 hours (A), 1.02 hours (B), and 2.42 hours (C) thus imipenem is rapidly eliminat-

ed. The pharmacokinetic parameters of imipenem vary with the dose of imipenem and with the length of imipenem infusion. The pharmacokinetics of imipenem and cilastatin sodium have been studied in 6 patients with severe renal failure who received imipenem/cilastatin sodium intravenously at a dose of 500 mg twice-daily for 5 days and the pharmacokinetic parameters of imipenem and cilastatin sodium have been obtained on day 1 and on day 5 of therapy [12].

The elimination half-life of imipenem is 2.75 and 2.49 hours on day 1 and 5, respectively, of therapy. Imipenem is eliminated mainly by renal route and the elimination half-life of imipenem is longer in patients with renal failure than in healthy volunteers. The elimination half-life of cilastatin sodium is 5.45 and 5.24 hours on day 1 and on day 5, respectively, of therapy. In addition, the peak concentration of imipenem and cilastatin sodium in serum is similar on day 1 and day 5 of therapy indicating that imipenem and cilastatin sodium do not accumulate in serum. The treatment of bacterial infections with imipenem/cilastatin has been reviewed. Patients with multi-drug-resistant tuberculosis or with extensive-drug-resistant tuberculosis received either imipenem/clavulanate or meropenem/clavulanate. Meropenem/clavulanate is more effective than imipenem/clavulanate in treating multi-drug-resistant tuberculosis and extensive-drug-resistant tuberculosis and both treatments are well-tolerated [13]. Patients with serious bacterial infection received either meropenem or imipenem/cilastatin and both drugs were administered intravenously at a dose of 1 gram thrice-daily.

Meropenem is efficacious as imipenem/cilastatin in treating serious bacterial infections [14]. Imipenem/cilastatin was administered intravenously at a dose of 500 mg thrice-daily to patients with acute bacterial infection and with AIDS or with AIDS-related complex and this treatment manages the infection in most of patients [15]. The pharmacokinetic/pharmacodynamic profile of imipenem was assessed in burn patients and it has been suggested that the daily dose of imipenem is 31.1±9.7 mg/kg in burn patients with normal renal function and must be reduced to 17.2±9.7 mg/kg in burn patients with renal failure to avoid neurotoxicity [16]. Patients with Acinetobacter bacteraemia received either cefoperazone/sulbactam or imipenem/cilastatin and both drugs have similar efficacy in treating bacteraemia [17]. Patients received either ampicillin/sulbactam or imipenem/cilastatin to treat acinetobacter ventilator-associated bacterial pneumonia and both drugs have similar efficacy in treating this disease and are well-tolerated [18]. Patients had severe septicaemia, intraabdominal abscesses, urinary-tract, skin, soft-tissue, and bone infection caused by gram-negative or by gram-positive bacteria and patients received imipenem/cilastatin intravenously at a daily dose of 1.5 to 2 grams. The clinical cure is achieved in 82.3% of patients, 13.3% patients show marked clinical improvement, and the adverse-effects are noted in 4.4% of patients thus imipenem/cilastatin effectively treats life-threatening infections and is well-tolerated [19]. Imipenem/cilastatin sodium was administered intravenously at a daily dose of 1.5 grams to patients with chronic bronchitis, diffuse pan-bronchiolitis, and bronchopneumonia caused by Pseudomonas aeruginosa. The clinical efficacy is good in 66.7% of patients, fairly good in 11.1% of patients, and poor in 22.2% of patients thus imipenem/cilastatin sodium effectively treats respiratory-tract infections caused by Pseudomonas aeruginosa [20].

Patients with lung cancer and with lung infection caused by Staphylococcus aureus, Staphylococcus epidermis, Staphylococcus species, Enterococcus faecalis, Pseudomonas aeruginosa, or by Acinetobacter species received imipenem/cilastatin sodium intravenously at a daily dose of 2 grams and the eradication of these organism occurs in 81.8% of patients thus this treatment cures the infection [21]. Patients with abscessus, cellulitis, and wound infections received imipenem/cilastatin intravenously at a dose of 500 to 750 mg twice-daily and 81.1% of patients were cured, 16.2% of patients improved, 2.7% of patients failed to improve, and the adverse-effects occurred in only 10.8% of patients thus this treatment cures the patients and is well-tolerated [22], and patients with septicaemia, intraabdominal-sepsis, bacterial pneumonia, Legionnaires' disease, skin, and soft-tissue infection received imipenem/cilastatin intravenously at a dose of 500 to 1,000 mg 4 times-daily and this treatment is well-tolerated and cures a variety of infections [23]. The infection was moderate in 58.9% of patients, mild in 37.2% of patients, and severe 3.9% of patients and the site of infection was the skin, soft-tissue, or intraabdominal. Imipenem/cilastatin was administered intravenously at a dose of 500 mg twice-daily to 45.1% of patients, at a dose of 750 mg twice-daily to 36.2% of patients, and at a dose of 500 mg thrice-daily to 18.7% of patients.

This treatment is well-tolerated in 87.1% of patients, moderately well-tolerated in 12.9% of patients, and the overall clinical outcome is favourable in 95% or more patients [24], patients had intraabdominal infection caused by Staphylococcus epidermidis, Moraxella morganii, or by Fusobacterium varium and received imipenem/cilastatin intravenously at a daily dose of 1.5 grams and the frequency of clinical cure or improvement is obtained in 91.2% of patients [25], patients with bacterial pneumonia received either ciprofloxacin administered intravenously at a daily dose of 800 to 1,200 mg or imipenem/cilastatin administered intravenously at a daily dose of 2 to 4 grams and the success-rate is generally good with both treatments [26], children had infection caused by Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae, or by Pseudomonas aeruginosa. Children aged < 3 years received imipenem/cilastatin intravenously at a daily dose of 100 mg/kg and children aged > 3 years received imipenem/cilastatin intravenously at a daily dose of 60 mg/kg and the treatment is well-tolerated and children respond favourably to this treatment [27], infants and children had bronchopneumonia with or without empyema, peritonitis complicating appendicitis, skin infection, soft-tissue abscessus, bacterial septicaemia, and miscellaneous infections and the infective agents were Proteus mirabilis, Salmonella typhi, Streptococcus aureus, or Escherichia coli.

Children aged up to 3 years received imipenem/cilastatin intravenously at a daily dose of 100 mg/kg and older children received imipenem/cilastatin at a daily dose of 60 mg/kg and the treatment

is well-tolerated and has excellent clinical efficacy [28], children were hospitalized for appendectomy and the appendix was perforated in 24.8% of children. Children received imipenem/cilastatin intravenously at a daily dose of 80 mg/kg and respond favourably to treatment and it is well-tolerated [29], febrile neutropenic patients with cancer and bacterial pneumonia received imipenem/cilastatin intravenously at a daily dose of 2 grams and the overall response-rate ranges from 70.2% to 77.1% and this treatment is adequate in these patients [30], neutropenic cancer patients had bacteriological infection and 14.3% of patients also had bacterial septicaemia and patients received imipenem/cilastatin intravenously at a daily dose of 2 grams and this treatment effectively cures the infection and septicaemia and the adverse-effects are mild [31], patients had bacterial infection and underlying malignancy with an absolute neutrophil count < 500/mm^3 and received imipenem/cilastatin intravenously at a daily dose of 2 grams and this treatment cures the bacterial infection [32], and patients with peritonitis in continuous ambulatory peritoneal dialysis received imipenem/cilastatin sodium intravenously at a daily dose of 1 gram. The primary response-rate occurs in 95.1% of patient and the complete cure-rate without relapse occurs in 85.0% of patients thus this treatment effectively cures the peritonitis [33].

These results indicate that imipenem/cilastatin treats different infections. Trials were conducted to test the efficacy, safely, and tolerability of imipenem/cilastatin versus those of other drugs. A trial was conducted to test the efficacy of meropenem administered intravenously at a dose of 500 mg thrice-daily versus that of imipenem/cilastatin administered intravenously at a dose of 500 mg thrice-daily for treating complicated skin and skin-structure infection and meropenem has comparable efficacy as imipenem/cilastatin in treating skin and skin-structure infection [34], meropenem was administered intravenously at a dose of 1 gram thrice-daily and imipenem/cilastatin was administered intravenously at a dose of 500 mg 4 times-daily to patients with serious bacterial infections.

Imipenem/cilastatin is more effective and more economic than meropenem in treating serious bacterial infections [35], patients with nosocomial pneumonia caused by Pseudomonas aeruginosa or with acute peritonitis received either imipenem/cilastatin administered intravenously at a dose of 500 mg 4 times-daily or piperacillin/tazobactam administered intravenously at a dose of 4.5 grams thrice-daily and the clinical success-rate is comparable in both treatments [36], hospitalized patients with bacteraemia and sepsis received either levofloxacin intravenously at a dose of 500 mg twice-daily or imipenem/cilastatin intravenously at a dose of 1 gram thrice-daily and both treatments have similar efficacy and tolerability [37], patients with fever, neutropenia, and with lung cancer received either imipenem/cilastatin intravenously at a dose of 1 gram twice-daily or latamoxef administered intravenously at a daily dose of 2 grams plus tobramycin administered intravenously at a dose of 90 mg twice-daily and both treatments have similar efficacy [38], a trial was conducted to test the efficacy, safely, and tolerability of imipenem/cilastatin versus those of moxalactam in patients with bacterial infection. Imipenem/cilastatin is associated with a better clinical outcome and moxalactam is less irritating at the site of injection [39], neutropenic cancer patients with fever and sepsis received either imipenem/cilastatin or ceftriaxone/gentamicin and both drugs have similar efficacy [40], a trial was conducted to test the efficacy of imipenem/cilastatin versus that of other β-lactam antibiotics in treatment of infections caused by gram-positive or by gram-negative bacteria.

The clinical efficacy and the clinical and laboratory adverse-effects are similar in both treatments [41]. The penetration of imipenem and cilastatin into the cerebrospinal fluid has been reviewed. The penetration of imipenem and cilastatin into the cerebrospinal fluid has been studied in 20 children, aged 52±17 months, with the meningitis caused by Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitis, Escherichia coli, Staphylococcus aureus, or by Staphylococcus epidermidis and imipenem/cilastatin was administered intravenously at a dose of 25 mg/kg thrice-daily (multiple doses) for 10 days to 10 children or at a dose of 25 mg/kg once-daily (single dose) for 10 days to 10 children. Specimens of serum and cerebrospinal fluid were sampled during the first 3 days of therapy (early treatment) and during the last 3 days of treatment (late treatment) [42]. Following the single dose of imipenem/cilastatin the concentration of imipenem in the cerebrospinal fluid is 1.36 (early treatment) and 2.08 μg/ml (late treatment).

The minimum inhibitory concentration of the organisms causing the meningitis ranges from 0.08 to 1.5 μg/ml indicating that imipenem reaches significant concentration in the cerebrospinal fluid. The ratio of the concentration of imipenem in the cerebrospinal fluid to that is serum is 0.15 (early treatment) and 0.27 (late treatment) indicating that imipenem resides more in serum than in the cerebrospinal fluid. Following multiple doses of imipenem/cilastatin the concentration of imipenem in the cerebrospinal fluid is 1.87 (early treatment) and 1.22 μg/ml (late treatment) and the ratio of the concentration of imipenem in the cerebrospinal fluid to that is serum is 0.22 (early treatment) and 0.17 (late treatment). Following the single dose of imipenem/cilastatin the concentration of cilastatin in the cerebrospinal fluid is 1.10 (early treatment) and 1.70 μg/ml (late treatment) indicating that the concentration of cilastatin in the cerebrospinal fluid is higher than that of imipenem. The ratio of the concentration of cilastatin in the cerebrospinal fluid to that of serum is 0.16 (early treatment) and 0.66 (late treatment) indicating that cilastatin resides more in serum than in the cerebrospinal fluid.

Following multiple doses of imipenem/cilastatin the concentration of cilastatin in the cerebrospinal fluid is 1.59 (early treatment) and 1.04 μg/ml (late treatment) and the ratio of the concentration of cilastatin in the cerebrospinal fluid to that of serum is 0.29 (early treatment) and 0.21 (late treatment). The penetration of imipenem and cilastatin into the cerebrospinal fluid of 10 adult patients was assessed following the administration of 4 doses of 1 gram daily of imipenem/cilastatin [43].

The concentration of imipenem in the cerebrospinal fluid ranges from 0.5 to 11 μg/ml and that of cilastatin ranges from 1.1 to 10.5

μg/ml indicating that imipenem reaches significant concentration in the cerebrospinal fluid and the concentration of cilastatin in the cerebrospinal fluid is higher than that of imipenem. The treatment of bacterial meningitis with imipenem/cilastatin has been reviewed. Imipenem/cilastatin was administered intravenously at a daily dose of 100 mg/kg to 21 infants and children, aged 3 to 48 months, with bacterial meningitis [44]. The eradication of bacteria from the cerebrospinal fluid was demonstrated within 24 hours of therapy in 19 infants and children. Two patients, who had the meningitis caused by Haemophilus influenzae type b, achieved bacteriologic cure after 2 to 3 days of therapy. The cerebrospinal fluid to serum ratio of the concentration of imipenem and cilastatin is 0.14 and 0.10, respectively, indicating that imipenem and cilastatin reside more in serum than in the cerebrospinal fluid. Seven patients (33.3%) developed seizure after antibiotic therapy thus the usefulness of imipenem/cilastatin for treatment ofbacteria meningitis in infants and children is limited by the incidence of drug-related seizure. Twenty infants and children with meningitis caused by Citrobacter diversus were treated with imipenem/cilastatin intravenously at a daily dose of 80 mg/kg and the meningitis is cured in all patients [45]. Ten adult patients had the meningitis caused by Acinetobacter anitratus and were treated with imipenem/cilastatin intravenously at a dose of 1 gram 4 times-daily and the meningitis is cured after 12 days of therapy and the treatment is well-tolerated [46].

In conclusion, imipenem is a β-lactam antibiotic and is market in combination with cilastatin a drug that inhibits the degradation of imipenem by renal tubular dipeptidase and extends the elimination half-life of imipenem. Imipenem binds to penicillin-binding proteins, disrupt bacterial cell wall synthesis, and causes death of susceptible organisms, and is very resistant to most β-lactamases. Imipenem is active against a wide variety of aerobic and anaerobic microorganisms. Imipenem/cilastatin effectively treats urinary-tract, lower respiratory, intraabdominal, gynaecologic, skin, soft-tissue, bone, and joint infection. Imipenem is not absorbed orally and is administered intravenously or intramuscularly. The efficacy and safely of imipenem/cilastatin have been reviewed. The diffusion of imipenem has been studied in muscle and subcutaneous tissues of patients with renal failure and with impaired liver, heart, or lung function and also in healthy volunteers and the pharmacokinetic parameters of imipenem in these tissues are altered in patients. The pharmacokinetics of imipenem have been studied in healthy volunteers and in patients with severe renal failure and the elimination half-life of imipenem is longer in patients than in healthy volunteers. The treatment and trials with imipenem/cilastatin have been reviewed, imipenem penetrates into the cerebrospinal fluid in significant amounts, and imipenem/cilastatin treats bacterial meningitis. The aim of this study is to review the clinical pharmacology of imipenem/cilastatin.

Conflict of Interest

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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