Research Article

Pharmacokinetic/pharmacodynamic profiling of imipenem in patients admitted to an intensive care unit in India: A nonrandomized, cross-sectional, analytical, open-labeled study

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Abstract

Background and Aim: Widespread use of imipenem in intensive care units (ICUs) in India has led to the development of numerous carbapenemase-producing strains of pathogens. The altered pathophysiological state in critically ill patients could lead to subtherapeutic antibiotic levels. Hence, the aim of this study was to investigate the variability in the pharmacokinetic and pharmacodynamic profile of imipenem in critically ill patients admitted to an ICU in India. **Materials and Methods:** Plasma concentration of imipenem was determined in critically ill patients using high performance liquid chromatography, at different time points, by grouping them according to their locus of infection. The elimination half-life ($t_{½}$) and volume of distribution (V_d) values were also computed. The patients with imipenem trough concentration values below the minimum inhibitory concentration (MIC) and 5 times the MIC for the isolated pathogen were determined. **Results:** The difference in the plasma imipenem concentration between the gastrointestinal and the nongastrointestinal groups was significant at 2 h (P = 0.015) following drug dosing; while the difference was significant between the skin/cellulitis and nonskin/cellulitus groups at 2 h (P = 0.008), after drug dosing. The imipenem levels were above the MIC and 5 times the MIC for the isolated organism in 96.67% and 50% of the patients, respectively. **Conclusions:** The pharmacokinetic profile of imipenem does not vary according to the locus of an infection in critically ill patients. Imipenem, 3 g/day intermittent dosing, maintains a plasma concentration which is adequate to treat most infections encountered in patients admitted to an ICU. However, a change in the dosing regimen is suggested for patients infected with organisms having MIC values above 4 mg/L.

Keywords: Antibiotic-resistance, critically ill patients, imipenem, intensive care unit, pharmacokinetics/pharmacodynamics

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.167036

Quick Response Code:

Introduction

Imipenem administered intermittently in a dose of 3 g/day is a broad spectrum antibiotic used commonly in most intensive care units (ICUs) in India.[1] Critically ill patients demonstrate variability in the pharmacokinetics and pharmacodynamics of imipenem due to several

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How to cite this article: Abhilash B, Tripathi CD, Gogia AR, Meshram GG, Kumar M, Suraj B. Pharmacokinetic/pharmacodynamic profiling of imipenem in patients admitted to an intensive care unit in India: A nonrandomized, cross-sectional, analytical, open-labeled study. Indian J Crit Care Med 2015;19:587-92.

covariates such as low renal clearance, low plasma proteins, abnormal volumes of distribution, and the presence of renal/hepatic dysfunction.[2] This can lead to imipenem levels falling below the minimum inhibitory concentration (MIC) for the cultured pathogens thus causing antibiotic failure/resistance. India has been known to develop numerous strains of resistant bacteria such as the New Delhi metallo-beta-lactamase-1 producing strains of *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter* spp., *Pseudomonas* spp., *Shigella boydii*, and *Vibrio cholerae*.[3] One of the explanations for the rise of these carbapenem-resistant strains in India could be due to the subtherapeutic levels of carbapenems achieved. The emergence of these strains is of global concerns due to the high mortality rates, limited treatment options available, and high dissemination rates.[4] Despite the Indian population having a different genetic pool than the Western population and exposed to a higher risk of antibiotic resistance, no pharmacokinetic/pharmacodynamic studies on imipenem in the Indian population have been conducted so far. Moreover, the pharmacokinetic studies of imipenem in critically ill patients have been conducted in specific subsets of patients, that is, patients with pulmonary infections, burn patients, etc., without comparing the variability in the drug levels according to the site of infection.[5,6] Therefore, the aim of this study was to evaluate the variability in the plasma concentration of imipenem in critically ill patients of the Indian population, by dividing them according to their site of infection, taking into account the MIC for the cultured pathogens at various time intervals. The variability in the pharmacokinetics/pharmacodynamics of imipenem observed in our study by therapeutic drug monitoring will enable physicians to modify the present dosing regimen of imipenem in critically ill patients more accurately so as to prevent subtherapeutic drug levels and thus reducing the risk of antibiotic failure/resistance.

Materials and Methods

Setting and patient population

This nonrandomized, cross-sectional, analytical, and open-labeled study was conducted in the Department of Pharmacology and Medical ICU, Department of Anaesthesia of Vardhman Mahavir Medical College and Safdarjung Hospital (VMMC and SJH) from January 2012 to March 2013. The study conforms to the guidelines approved by the 'Institutional Human Ethics Committee' of VMMC and SJH and to the Helsinki Declaration of 1975, as revised in 2000.

Patients were eligible for the study if they were at least 18 years of age, admitted to the ICU for any infectious cause and treated with imipenem. A valid written informed consent was obtained from the patient/patient party. Excluded from the study were patients with a grave prognosis, as diagnosed by the treating physician, owing to lesser turnaround time and patients with creatinine clearance <5 ml/min. A total of 30 patients were included in the study, and the sample size was considered adequate to observe the pharmacokinetic/pharmacodynamic outcome of the antibiotic therapy.

Drug administration and blood sampling

The choice of the antibiotic was made by treating physician on the basis of the available clinical and microbiological data. No recommendations were made by the study investigator for the purpose of the study. The planned duration of imipenem therapy was 7 days. 1 g imipenem was infused intravenously over a period of 40 min, in 3 dosages per day, at intervals of 8 h each.[7] Imipenem was discontinued if the isolated microorganism was shown to be resistant.

Two milliliters of blood was withdrawn from the patients through the intravenous route on day 3 of imipenem therapy at time points of 1, 2, 4, and 8 h postdrug infusion, and analyzed within 15 min from the time of blood withdrawal.

Drug assay

Imipenem concentration in plasma was estimated using reverse-phase high performance liquid chromatography with ultraviolet detection system as described by Carlucci *et al*.[8] Plasma was deproteinized by ultrafiltration, thus leading to the free fraction of the drug. The separation was done on the analytical column 250 × 4.6 ODS (Waters Corporation, Milford, USA). The mobile phase consisted of 0.2 M boric acid buffer and 100 mM methanol (Fisher Scientific, Loughborough, England) mixed in the ratio of 90:10, by adjusting the pH with 1 M sodium hydroxide (Sisco Research Laboratories, New Delhi, India). The flow rate of the mobile phase was 1.0 ml/min. The stabilizing solution was 0.5 M 3-morpholinopropane sulfonic acid mixed with water and ethylene glycol (Sisco Research Laboratories, New Delhi, India) in a ratio of 2:1:1. Detection of imipenem was done at the wavelength of 313 nm using waters UV2489 detector. Imipenem (Savior Lifetech Corporation, Chunan Chen, Taiwan) served as the internal standard. The calibration curve obtained by quadratic regression for the assay was linear over the range of 1 to 100 μg/ml with an "r^2" value of more than 0.99. The mean retention time observed was approximately 4.05 min. The standard equation obtained was y = 29.413x + 22.345. The accuracy was calculated as the percent deviation from the target value

and ranged from 3.5% to 5.9% for three quality control concentrations (1 µ/ml, 5 µg/ml, 10 µg/ml). The intraday and interday coefficients of variation ranged from 2.0% to 9.9% and 9.0% to 10.2%, respectively, for concentrations ranging from 1 to 100 µg/ml.

Microbiological analysis

Microbiological culture sensitivity tests were performed for patients while they were admitted in the ICU. A 5–10 ml blood sample was withdrawn from each patient and inoculated into 1 BD BACTEC Plus Aerobic/F® vial and into 1 BD BACTEC Lytic Anaerobic/F® vial. Blood cultures were then incubated in a BACTEC 9240 (Becton Dickinson Diagnostic Instrument Systems, Towson, USA) for 5 days. Other samples for the microbiological culture were taken depending on the site of the infection. The MIC for the isolated organisms to imipenem was determined using the *E*-test method (AB Biodisk, Solna, Sweden).

Pharmacokinetic/pharmacodynamic analysis

The patients enrolled in the study were divided according to their locus of infection into renal, pulmonary, gastrointestinal, and skin/cellulitis groups. The plasma concentration of imipenem was calculated for each of the patients at time points of 1, 2, 4, and 8 h after drug dosing. The plasma concentration of imipenem in the renal, pulmonary, gastrointestinal, and skin/cellulitis groups was compared with that of the total number of patients included in the study other than that of the group being compared with.

The elimination half-life ($t_{½}$) and volume of distribution (V_d) values of imipenem were determined by standard noncompartmental analysis and computed using published methodologies.[6] $t_{½}$ was calculated using the formula $t_{½} = t/\log_2 (N_o/N_t)$ where t = time, N_0 = initial drug quantity infused, and N_t = drug quantity at 8 h after infusion. V_d was calculated using the formula $V_d = D/C_0$ where D = dose, and C_0 = initial postinfusion concentration of imipenem.

The trough concentration of imipenem was measured at 8 h after drug dosing, on day 3 of imipenem therapy and patients with drug levels below the MIC and below 5 times the MIC for the cultured microorganism were determined.

Statistical analysis

Statistical comparison between various subgroups within the main group was carried out by Student's independent *t*-test followed by Levene's test of equality of variances. The results were expressed as a mean ± standard deviation unless otherwise specified. Statistical significance was accepted for $P < 0.05$. All the parameters were analyzed by using SPSS 16.0 version (IBM Corporation, New York, USA).

Results

Patient characteristics

The characteristics of the patients included in the study are depicted in Table 1. Out of the 30 patients recruited, two mortalities were reported. The causative organisms for these two mortalities were *Pseudomonas aeruginosa* and *Acinetobacter* spp., respectively. There was no correlation found between the weight of the patients and the plasma concentration of imipenem achieved, at all time points.

Microbiological analysis

The microorganisms isolated after the microbiological analysis were *Klebsiella* spp. (*n* = 10), *Proteus* spp. (*n* = 6), *Citrobacter fruendii* (*n* = 4), *P. aeruginosa* (*n* = 3), *Acinetobacter* spp. (*n* = 4), *Staphylococcus aureus* (*n* = 2), and *Bacteroides fragilis* (*n* = 1) [Table 2].

Pharmakokinetic/pharmacodynamic analysis

There was no significant difference found in the plasma concentration of imipenem between the renal and nonrenal groups and also between the pulmonary and the nonpulmonary groups, at all times. Whereas, the gastrointestinal and the nongastrointestinal groups; the skin/cellulitis and the nonskin/cellulitis groups showed a significant difference ($P = 0.015$ and $P = 0.008$, respectively) in the plasma imipenem level at 2 h, after drug administration. The $t_{½}$ and V_d values did not show any significant intergroup variation [Table 3].

The trough concentration of imipenem, measured at 8 h, on day 3, after imipenem infusion exceeded the MIC for all the isolated organisms, except for *Acinetobacter*

Table 1: Characteristics of enrolled patients

Characteristics	Values
Total number of patients	30
Age (years) (mean, range)	43 (23-81)
Gender (%)	Males: 23 (76.67) Females: 7 (23.33)
Mean weight (kg) ± SD (range)	64.10 ± 10.74 (38-83)
Creatinine clearance (range)	30-181 ml/min
Diabetes mellitus (%)	8 (26.67)
Hypertension (%)	13 (43.33)
Site of infection	
Renal	11
Pulmonary	6
Gastrointestinal	6
Skin	7

SD: Standard deviation

spp. (n = 1). The trough concentration of imipenem was below 5 times the MIC, for *Acinetobacter* spp. (n = 4), *P. aeruginosa* (n = 3), *B. fragilis* (n = 1), *Staphyloccus aureus* (n = 2), *Proteus* spp. (n = 4), and *Klebsiella* spp. (n = 1) [Table 4].

Discussion

In this study, the patient demographics showed a skewed distribution of the sex ratio as only 23.33% of the patients enrolled were females. The probable reason for this skewed distribution is that in the Indian scenario, female populations are reluctant to utilize health care facilities, even if they are critically ill, especially women from the lower socioeconomic strata.[9]

The most important covariate which determines the pharmacokinetics of most beta-lactam antibiotics is the creatinine clearance.[10] In this study, the lowest

Table 2: Collection of microbiological samples according to the diagnosis

Diagnosis	Samples collected	Samples positive	Organisms isolated‡
Renal cases (11)	Midstream urine (8)†,*	4	*Klebsiella* spp. (3)
Complicated urinary tract infections (11)	Catheter tip (6)†	4	*Proteus* (4)
	Blood (11)	4	*Citrobacter* (2)
			Acinetobacter spp. (1)
			Pseudomonas aeruginosa (1)
Pulmonary cases (6)	Sputum (6)†,*	3	*Klebsiella* spp. (3)
Ventilator associated pneumonia (4)	Bronchoalveolar lavage (3)†	2	*Acinetobacter* spp. (1)
Community acquired pneumonia (2)	Blood (6)	3	*Pseudomonas aeruginosa* (1)
			Staphylococcus aureus (1)
Gastrointestinal cases (6)	Blood (6)	6	*Klebsiella* spp. (2)
Hepatic abscess (5)			*Proteus* (2)
Biliary abscess with stones (1)			*Citrobacter* (2)
Skin cases (7)	Surface swab (7)	6	*Klebsiella* spp. (2)
Burns with sepsis (3)	Blood (7)	2	*Acinetobacter* spp.(2)
Diabetic foot with cellulitis (3)			*Pseudomonas aeruginosa* (1)
Infected surgical wound (1)			*Bacteroides fragilis* (1)
			Staphylococcus aureus (1)

For analyses, only pathogen with highest was used in case of polymicrobial flora. Values in parenthesis represent '*n*'. †In some patients sputum/bronchoalveolar lavage/midstream urine/catheter tip samples could not be obtained. *In some patients sputum/midstream urine samples were collected more than once. ‡In some patients if both the site specific and blood culture reports were positive, then the organism isolated in the blood culture was considered for analyses. MIC: Minimal inhibitory concentration

Table 3: Pharmacokinetic parameters of imipenem according to the site of infection

Groups	Parameters				$t_{½}$ (h)	V_d (L/kg)
	Imipenem concentration (mg/L)					
	1 h	2 h	4 h	8 h		
Renal (n=11)	30.89±2.73	11.20±1.11	6.57±0.66	3.50±0.40	0.98±0.02	0.51±0.21
Nonrenal (n=19)	29.07±2.33	10.46±1.26	6.40±0.76	3.27±0.67	0.97±0.03	0.54±0.17
Gastrointestinal (n=6)	29.65±2.18	10.33±1.13*,a	6.26±0.67	3.27±0.49	0.96±0.01	0.53±0.08
Nongastrointestinal (n=24)	30.36±3.16	11.40±1.11*,a	6.74±0.68	3.52±0.61	0.98±0.01	0.51±0.19
Pulmonary (n=6)	29.62±2.90	10.58±1.18	6.73±1.06	3.45±0.85	0.97±0.02	0.53±0.22
Nonpulmonary (n=24)	30.05±2.66	10.88±1.26	6.44±0.63	3.37±0.50	0.97±0.03	0.52±0.11
Skin/cellulitis (n=7)	30.35±3.39	11.85±0.91*,b	6.71±0.46	3.43±0.48	0.98±0.04	0.51±0.33
Nonskin/cellulitis (n=23)	29.87±2.47	10.52±1.16*,b	6.42±0.76	3.37±0.59	0.97±0.01	0.52±0.25

Unpaired Student's *t*-test followed by Levene's test of equality of variances. Values are the mean±SD. *,aP<0.05, when gastrointestinal group is compared to nongastrointestinal group. *,bP<0.05, when skin/cellulitis group is compared to nonskin/cellulitis group. $t_{½}$: The elimination half-life of imipenem; V_d: Volume of distribution of imipenem in the body; SD: Standard deviation

Table 4: Trough concentration of imipenem according to the organisms isolated

Organism	n	MIC for the organism in mg/L (range/mean)	Trough imipenem concentration in mg/L (mean±SD)	Patients with imipenem concentration < MIC	Patients with imipenem concentration <5 times MIC
Klebsiella spp.	10	0.25-1.00 (0.60)	3.30±0.56	0	1
Citrobacter	4	0.38-0.75 (0.64)	3.12±0.39	0	0
Proteus	6	0.25-2.00 (1.23)	3.65±0.35	0	4
Staphylococcus aureus	2	1.00-2.00 (1.50)	3.65±0.49	0	2
Bacteroides fragilis	1	1.50	2.90±0.00	0	1
Acinetobacter spp.	4	2.00-4.00 (3.60)	3.70±0.54	1	4
Pseudomonas aeruginosa	3	2.00-3.00 (3.40)	3.47±0.39	0	3

SD: Standard deviation; MIC: Minimal inhibitory concentration

creatinine clearance value reported in the renal group was 30 ml/min, and we did not estimate the between-occasion variability of the creatinine clearance as our sampling schedule was sparse. Hence, no significant difference was found in the pharmacokinetics of imipenem between the renal and nonrenal groups. Imipenem dosing is to be decreased in patients with creatinine clearance of 5–20 ml/min and imipenem is contraindicated in patients with creatinine clearance of <5 ml/min.[11]

The significant variation in the plasma concentration of imipenem between the gastrointestinal and nongastrointestinal group, at 2 h, following drug infusion, may be misleading due to low confidence intervals (<20%). Previous pharmacokinetic studies have shown that no appreciable absorption of imipenem occurs in the gastrointestinal tract.[12] Moreover, experimental studies in rats have revealed that there is no significant difference between the concentration-versus-time curves of imipenem between the intraperitoneal fluid and blood.[13]

Our observations also indicate that the plasma concentration of imipenem does not vary significantly in patients with pulmonary infections and nonpulmonary infections and is in agreement with similar studies conducted in the Western population.[14,15]

The significant difference in the imipenem levels between the skin/cellulitis group and the nonskin/cellulitis group at 2 h, postinfusion also appears to be misleading due to the low confidence intervals (<20%). A previous study on bed ridden patients with skin infections and renal impairment indicated that the variation in the plasma imipenem levels in such patients was only related to the failing renal indices rather than the infection itself.[16]

An interpatient variability was observed in the t½ and V_d values as reported in previous studies.[5,6] However, no intergroup variability was observed in these two parameters, further strengthening the fact that the locus of infection does not play a role in the dose selection of imipenem.

Plasma level of an antibiotic above the MIC value, for the isolated organism, is one of the surrogate pharmacodynamic markers to predict microbiological and clinical success. If the drug level falls below the MIC values, breakthrough bacterial growth will occur.[17] In this study, 96.67% (29/30) of the patients had imipenem levels above the MIC for the isolated organism. Previous studies have recommended that the free imipenem plasma concentration should be above the MIC, for the infecting pathogen, for at least 40–50% of the time period between each dosing to ensure maximal bactericidal effect and clinical efficacy.[18] However, the patient infected with *Acinetobacter* spp., having imipenem levels below the MIC, succumbed to his infection despite meeting the above criteria. The reason for the inadequate imipenem levels achieved in this patient could be due to the intermittent dosing regimen. Numerous dosing regimens for imipenem infusion have been proposed without a common consensus.[6,15,18] The continuous infusion of beta-lactam antibiotics, after an initial loading dose, has been advocated so as to avoid subtherapeutic trough concentrations.[19] In Indian scenario, the intermittent dosing of 0.5–1 g imipenem at intervals of 6–8 h is preferred over the continuous dosing regimen in critically ill patients due to the absence of substantial studies.

The second death observed in the study was of a patient infected with *P. aeruginosa.* The cause of death was acute multiorgan dysfunction syndrome. The presence of cardiovascular failure, a risk factor, was critical in worsening the prognosis of the patient thus attributing to his death. The trough imipenem levels, in this patient, were above the MIC for *P. aeruginosa* raising a suspicion for carbapenemase producing strains of *Pseudomonas* species, linked epidemiologically with the Indian subcontinent.[20] However, the absence of a polymerase chain reaction based gene screening of the isolated organism, a drawback of this study, make such doubts only speculative. Moreover, it is a well-known fact that the plasma levels of imipenem are higher than in tissues, which could have affected the therapeutic outcome in this patient.[18]

Maximum bacterial killing rates of beta-lactam antibiotics are achieved at concentrations 4–5 times the MIC, for the isolated organism.[21] In this study, 50% (15/30) of the enrolled patients, infected with *Klebsiella* spp., *Proteus*, *S. aureus*, *B. fragilis*, *Acinetobacter* spp., and *P. aeruginosa*, had trough imipenem levels below 5 times their respective MIC values. It is obvious from the above observations that the dosing regimen of 1 g imipenem, infused intravenously for 40 min, 8 hourly is adequate to provide protection against most organisms isolated in ICUs, however, it is inadequate to produce optimal bactericidal activity. This may be crucial; keeping in mind the rising rates of carbapenem resistance, hence larger clinical trials are warranted to evaluate alternative dosing regimens. A dose escalation of imipenem could lead to an increased risk of a seizure attack hence the risk-benefit ratio must be carefully assessed before any

change in the dosing regimen. Second, factors which could predispose the patients to a seizure attack such as kidney dysfunction, prior history of seizure, metabolic derangements, anoxia, and phenytoin discontinuation should be ruled out.[22]

Conclusion

There was no variability observed in the pharmacokinetics of imipenem, in critically ill patients admitted to an ICU in India, when they were grouped according to their locus of infection. Imipenem, 3 g/day intermittent dosing, maintains a trough plasma concentration which is adequate to treat most infections encountered in patients admitted to an ICU. However, we suggest a change in the dosing regimen for patients infected with organisms having MIC values more than 4 mg/L so as to achieve optimal antibiotic efficacy and prevent the emergence of resistance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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