ORIGINAL RESEARCH

Comparable Effect of Two-Step Versus Extended Infusions on the Pharmacokinetics of Imipenem in Patients with Sepsis and Septic Shock

Yingzi Huang · Kang Xu · Ying Zhan · Xian Zha · Songqiao Liu ·

Jianfeng Xie · Lin Liu · Qing Li · Hua Shao · Yi Yang

ABSTRACT

Introduction: The present study aimed to compare the pharmacokinetic/pharmacodynamic (PK/PD) parameters of imipenem administered by two-step (50% delivered in a 30-min bolus, 50% for the following 90 min) or extended (administered continuously for 2 h) infusion.

Methods: Patients with sepsis and septic shock were prospectively enrolled and randomized into four groups. Subjects in the two-step or extended groups were given two doses of imipenem (0.5 g *q6h* and 1.0 g *q8h*). The plasma imipenem concentrations were measured at given time points after the fifth dose. The PK/PD target was defined as the achievement of a fractional time above the minimal inhibitory concentration (MIC) of $> 40\%$.

Results: Thirty-five patients were eventually enrolled. No significant difference was observed in the percentage of patients achieving 40% $T > MIC$ between the different infusion modes with the same dosage, although the two-step groups exhibited a significantly shorter T_{max} compared with the extended groups (0.5 g *q6h*: 1.5 ± 0.8 vs. 2.0 ± 0.0 h; 1.0 g *q8h*: 1.0 ± 0.6 vs. 2.0 ± 0.0 h; both, $p < 0.05$). All four groups achieved 40% $T > MIC$ when MIC was 0.5–4.0 μg/ml, but only regimens with a higher dose (1.0 g *q8h*) achieved target when MIC was 8 μg/ml.

Conclusion: The two-step and extended regimens of imipenem are comparable to the PK/PD target in the treatment of sepsis and septic shock. A higher dose (1.0 g *q8h*) should be considered for target achievement at an MIC of > 8 μg/ml.

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Y. Huang · S. Liu · J. Xie · L. Liu · Q. Li ·
Y. Yang (✉)
Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China
e-mail: yiyiyang2004@163.com

K. Xu
Pharmacy Department, Hospital for Skin Diseases, Chinese Academy of Medical Sciences, Nanjing, China

Y. Zhan · X. Zha · H. Shao
Pharmacy Department, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China

Keywords: Imipenem; Infectious disease; Infusion mode; Minimal inhibitory concentration; Pharmacokinetic/pharmacodynamic; Sepsis

Key Summary Points

The present study is an exploratory prospective study that attempted to address a practical question: whether the efficacy of imipenem could be improved by the two-step infusion mode instead of the traditional extended infusion mode.

The differences in PK/PD parameters of imipenem between the two infusion modes were investigated in patients with sepsis and septic shock.

To our knowledge, these results are the first to confirm that both infusion modes are comparable in terms of the PK/PD target in the treatment of sepsis and septic shock.

INTRODUCTION

Sepsis and septic shock are life-threatening conditions with high morbidity and mortality [1, 2]. A prompt initiation of sufficient, appropriate and empiric antibiotics is critical for the treatment of sepsis and septic shock [3, 4]. Imipenem, a carbapenem antibiotic, is one of the most important antibiotics used to cover of a wide spectrum of pathogens, including gram-positive, gram-negative, aerobic, anaerobic and multidrug-resistant strains [5]. Imipenem exhibits time-dependent bactericidal activity, and the pharmacokinetic/pharmacodynamic (PK/PD) parameter that best predicts in vivo antimicrobial activity is $\%T >$ minimal inhibitory concentration (MIC), defined as the percentage of time during which the plasma concentration remains above the minimum inhibitory concentration of pathogens [6, 7]. However, in the clinical setting of sepsis and septic shock, not only substantial pathophysical changes, but also different infusion regimens significantly alter the antimicrobial PK/PD index [8, 9]. Thus, this may affect clinical outcome. Hence, the 2016 Surviving Sepsis Campaign (SSC) guidelines reinforced that antibiotic regimens should be optimized based on the PK/PD principle in patients with sepsis and septic shock [2].

The optimal infusion regimen of imipenem in patients with sepsis and septic shock remains undetermined. Early studies in healthy volunteers have demonstrated that carbapenems administered by continuous infusion improved the blood concentrations above MIC compared with intermittent infusion regimens [10]. In critical patients with ventilator-associated pneumonia (VAP), continuous infusion was correlated with better clinical efficacy compared with intermittent infusion [11]. However, the practical application of carbapenems in continuous infusion mode remains challenging because of its inherent stability issue [12]. A 3-h infusion, instead of continuous infusion, was thereby developed because of its feasibility and superiority [13]. Evidence has revealed that the 3-h infusion results in greater $T > $ MICs than those after a bolus injection in patients with VAP [13]. A 3-h infusion of imipenem may improve the cumulative probability of target attainment (PTA) for various microorganisms compared with a 30-min infusion [14]. Recently, with the use of an in vitro pharmacodynamic model and the Monte Carlo simulation, the optimized two-step infusion therapy (rapid first-step infusion and slow second-step infusion) of meropenem has been proven to have better initial bactericidal effects than a prolonged infusion therapy due to the sufficient $\%T > $ MIC and $C_{\max}$, with a shorter $T_{\max}$ [15]. However, whether the two-step infusion regimen of imipenem elicits a greater $T > $ MIC than the conventional extended infusion method, especially in critical patients, is still unknown.

The present exploratory study evaluated the PK/PD changes of the two-step vs. extended infusion of imipenem for treating sepsis and septic shock due to various pathogens. The $\%T > $ MIC and other pharmacokinetic indices were compared in both regimens, with a dose of 0.5 g $q6h$ and 1.0 g $q8h$.

METHODS

Patients and Materials

This single-institution, prospective, randomized comparative study was performed in the Intensive Care Unit (ICU), Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China. The protocol was approved by the Ethics Committee of Zhongda Hospital. Written informed consent was obtained from all patients or their legal guardians. The present study was in compliance with the American Clinical Trials Register (ClinicalTrials.gov) agreement (registration no. NCT02616354).

Inclusion criteria were: (1) patients with severe sepsis or septic shock diagnosed within 48 h of admission; (2) patients prescribed imipenem, as recommended by the hospital microbiologists who had a role as consultants to assess the antibiotic consumption; (3) patients with an expected ICU stay duration ≥ 72 h. Sepsis/septic shock was defined according to the International Sepsis Definitions Conference and the updated sepsis 3.0 [1, 3].

Exclusion criteria were: patients who were < 18 or > 75 years old, patients who were allergic or had adverse effects to imipenem, cephalosprins, penicillins or other β-lactams, patients with acute or chronic renal failure defined as a serum creatinine concentration of > 280 μmol/l (or a creatinine clearance of < 20 ml/min), or requiring intermittent hemodialysis and continuous renal replacement therapy, patients with drug or alcohol abuse, patients with a susceptibility test revealing resistance or ineffectiveness to imipenem (such as viruses, fungi, etc.), patients who were pregnant and lactating, and patients who participated in other clinical trials.

Patient characteristics, including gender, age, weight, APACHE II score, liver and kidney function, and underlying diseases were collected on admission. The comorbidities, concomitant medications and risk factors (long-term use of corticosteroids, recent surgery, invasive mechanical ventilation, being immune compromised or using antimicrobial agents) were all recorded. Imipenem/cilastatin (Merck Sharp & Dohme B.V., Haarlem, Netherlands) was used for the present study.

Study Design

All eligible patients received either 0.5 g *q6h* or 1.0 g *q8h* of imipenem, as assessed by the type and severity of infection through a microbiology consultant. Then, these patients were randomized using the random permuted blocks method to receive either the two-step infusion or extended infusion regimen. In the two-step groups, 50% imipenem dose was given with a bolus in 30 min. Then, the remaining 50% dose was administered for 90 min. In the extended group, imipenem was administered within 120 min. Each dose of imipenem was infused using a central venous catheter through a separate lumen. A microbiologist blinded to the patient allocation assessed the microbiologic outcomes after a 72-h period to determine whether it was necessary to de-escalate or adjust the antibiotics. The study flow is presented in Fig. 1.

The characteristics of all patients were collected, including the following: clinical and biochemical indicators, including age, gender, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, blood urea nitrogen (BUN), creatinine (Cr), creatinine clearance (CLcr), albumin, alanine aminotranferease (ALT), aspartate aminotransferase (AST), total bilirubin (TB), white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT) and infection site (Table 1).

Sampling and Imipenem Assay

Blood samples (2 ml) were collected after the fifth imipenem dose at 0, 0.5, 1.0, 2.0, 4.0 and 6.0 h for the 0.5 g *q6h* groups and at 0, 0.5, 1.0, 2.0, 4.0, 6.0 and 8.0 h for the 1.0 g *q8h* groups. Furthermore, urine samples were concurrently collected. The imipenem concentrations in plasma and urine were determined by high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. Briefly, 250 μl of the plasma sample was added to 250 μl of
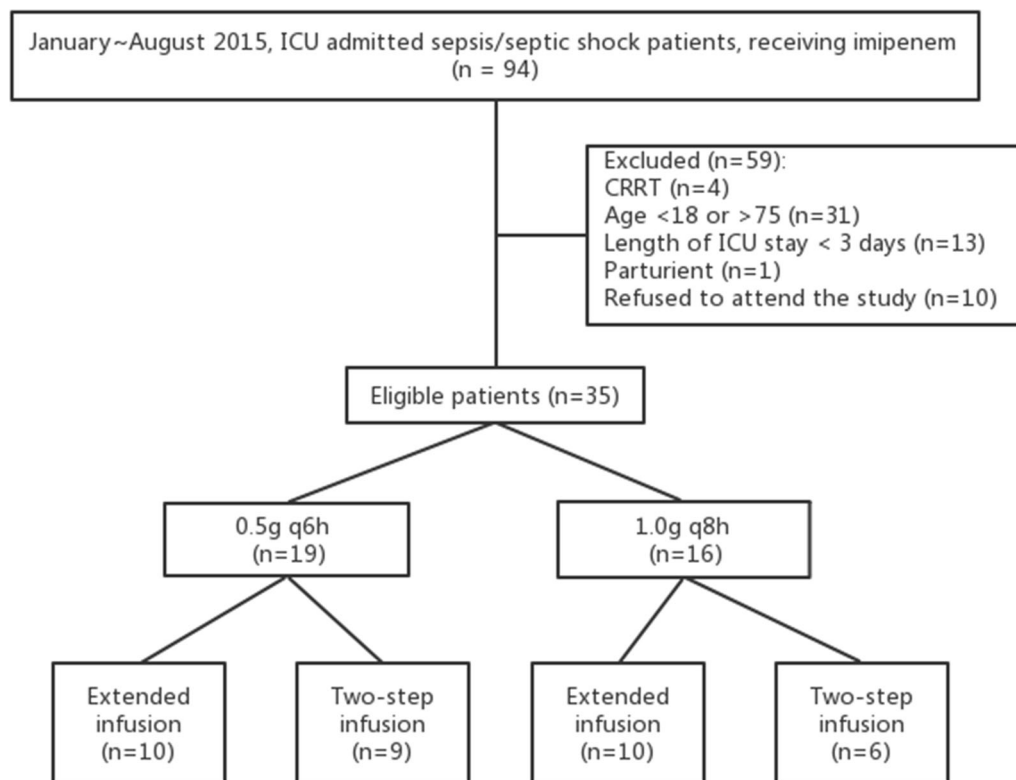
Fig. 1 Study flowchart

stabilizing solution and subjected to ultrafiltration for 10 min at 6000 g. Then, the sample was injected with an automated system onto an Alltima HP Hilic Column (4.6 × 250 mm, 5 μm), with acetonitrile (10 mmol/l)-ammonium acetate (2%) (60:40) as the mobile phase. The flow rate was 1 ml/min, and the column temperature was 35 °C. The detector was operated at 298 nm [16, 17]. The lowest detectable concentration in plasma and urine was 0.02 mg/l.

Statistical and Pharmacokinetic Analysis

Data were processed using Microsoft Excel (Microsoft Excel 2007, Microsoft Corp.). The pharmacokinetic parameters were calculated using the non-compartmental method, and the bioequivalence evaluation was performed using the BAPP 3.1 statistical software (China Pharmaceutical University, China). The imipenem plasma peak concentration (C_{max}), peak time (T_{max}), elimination of half-life ($T_{1/2}$), imipenem clearance (Cl), renal clearance (Ccr), apparent distribution volume (Vd), area under the concentration-time curve (AUC_{0-t}) and area under the concentration from zero to the end of the dosing period (AUC_{0-tau}) were calculated. C_{max}: the highest detection limit for each patient. T_{max}: time to reach C_{max}. $T_{1/2}$: the time required for the concentration of the drug to reach half of its original value. AUC: The integral of the concentration-time curve. The PK/PD target was defined as $\%T > MIC$ for 40% [18].

Data were expressed as mean ± standard deviation (SD) or median (interquartilerange), as appropriate. Continuous variables were compared using one-way ANOVA test and t test, and categorical data were analyzed using X^2 or Fisher's exact test. Data were analyzed using the SPSS 20.0 statistical software (SPSS Inc. Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Table 1 Baseline characteristics

Characteristics	Two-step		Extended	
	0.5 g *q6h* (*n* = 9)	1.0 g *q8h* (*n* = 6)	0.5 g *q6h* (*n* = 10)	1.0 g *q8h* (*n* = 10)
Age (years)	59.4 ± 16.7	65.7 ± 9.4	68.1 ± 11.4	64.2 ± 9.3
Gender (male/female)	8/1	5/1	9/1	7/3
Weight (kg)	66.7 ± 9.7	70.8 ± 7.4	70.0 ± 8.5	68.5 ± 7.1
APACHE II score	19.3 ± 4.3	21.2 ± 4.1	22.2 ± 4.5	21.7 ± 6.2
SOFA score	11.8 ± 3.0	11.3 ± 3.3	11.1 ± 3.0	11.7 ± 4.0
BUN (mmol/l)	33.0 ± 58.8	9.2 ± 4.4	32.4 ± 56.0	10.9 ± 4.9
Cr (μmol/l)	141.7 ± 46.5	102.2 ± 48.2	204.8 ± 226.8	142.8 ± 124.9
CL_{Cr} (ml/min)	52.6 ± 26.3	72.2 ± 33.9	62.1 ± 69.8	61.2 ± 33.5
ALB (g/l)	27.1 ± 3.4	29.3 ± 5.0	28.5 ± 4.2	28.7 ± 4.7
ALT (IU/l)	538.4 ± 851.1	20.3 ± 17.5	536.6 ± 809.0	36.6 ± 32.2
AST (IU/l)	937.8 ± 1332.0	23.3 ± 9.5	891.3 ± 1264.2	52.7 ± 61.4
TB (μmol/l)	20.4 ± 12.3	11.1 ± 2.1	21.8 ± 11.5	16.4 ± 7.9
WBC (10^9/l)	14.9 ± 3.1	13.5 ± 5.9	12.5 ± 5.2	12.8 ± 5.2
CRP (mg/l)	109.2 ± 77.7	141.1 ± 91.6	70.9 ± 59.4	142.7 ± 86.2
PCT (ng/ml)	8.3 ± 10.0	1.7 ± 2.2	4.4 ± 5.0	6.0 ± 9.5
Infection site, *n* (%)*				
Pulmonary	5 (55.5)	6 (100.0)	8 (80.0)	9 (90.0)
Abdominal	4 (44.4)	0 (0)	2 (20.0)	1 (10.0)
Blood stream	0 (0)	0 (0)	1 (10.0)	0 (0)
Others	1 (11.1)	0 (0)	1 (10.0)	1 (10.0)

Data were expressed as mean ± SD, or number (percentage)

APACHE acute physiology and chronic health evaluation, *BUN* blood urea nitrogen, *Cr* creatinine, *CLcr* creatinine clearance, *ALB* albumin, *ALT* alanine aminotranferease, *AST* aspartate aminotransferase, *TB* total bilirubin, *WBC* white blood cell count, *CRP* C-reactive protein, *PCT* procalcitonin

*Several patients had combined infection sites

RESULTS

A total of 94 patients were screened. Finally, 35 patients were enrolled in the present study, with a mean (SD) age of 64.3 ± 12.1 years (range 31–82 years old) and a mean (SD) body weight of 68.9 ± 8.1 kg (range 55–80 kg) (Fig. 1). The majority of these patients were male (82.9%).

The microorganisms identified in the culture mainly included *Acinetobacter baumannnii*, *Klebsiella pneumonia subsp. pneumoniae*, and *Pseudomonas aeruginosa* (Table 2). The results of microorganisms were all from respiratory isolates although we collected isolates respectively from the respiratory tract, blood, drainage and cerebrospinal fluid.
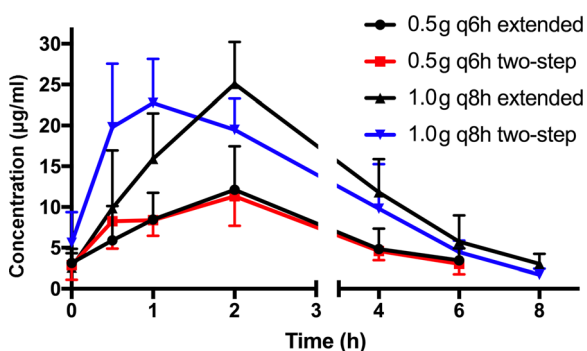
Table 2 Organisms identified on culture

Pathogens*	Two step		Extended	
	0.5 g *q6h* (*n* = 9)	1.0 g *q8h* (*n* = 6)	0.5 g *q6h* (*n* = 10)	1.0 g *q8h* (*n* = 10)
Total number of microorganisms	6	4	5	12
Acinetobacter baumannii	3 (50.0)	1 (25.0)	4 (80.0)	4 (33.3)
Klebsiella pneumoniae subsp.pneumoniae	1 (16.7)	2 (50.0)	1 (20.0)	3 (25.0)
Pseudomonas aeruginosa	1 (16.7)	1 (25.0)	/	3 (25.0)
Proteus mirabilis	1 (16.7)	/	/	
Enterobacter cloacae	/	/	/	1 (8.3)
Enterobacter aerogenes	/	/	/	1 (8.3)

*Several patients had combined pathogens

When imipenem was applied in the two-step method, the T_{max} was significantly shortened compared with the corresponding extended groups (0.5 g *q6h*: 1.5 ± 0.8 vs. 2.0 ± 0.0 h, $p < 0.05$; 1.0 g *q8h*: 1.0 ± 0.6 vs. 2.0 ± 0.0 h, $p < 0.05$). Furthermore, the C_{max} was significantly greater in groups with a dose of 1.0 g *q8h* compared with that of 0.5 g *q6h*, irrespective of the infusion method (two-step groups: 24.9 ± 4.9 vs. 11.9 ± 3.9 μg/ml, $p < 0.05$; extended groups: 24.9 ± 4.0 vs. 12.5 ± 5.1 μg/ml, $p < 0.05$). Similarly, the AUC_{0-t} and AUC_{0-tau} were significantly higher in groups with a dose of 1.0 g *q8h*. However, there was no significant difference among the four groups in terms of $T_{1/2}$, Cl and Vd (Fig. 2, Table 3). In

Fig. 2 Concentration-time profile of each regimen in patients with sepsis and septic shock. All values are presented as mean ± SD

addition, comparisons of PK data between patients with positive and negative microbiology showed that there was roughly no significant difference in PK data between the two groups except that CL in the two-step group (0.5 g *q6h*) differed possibly because of the limited sample size (Supplemental Table 1).

For pathogens with an MIC of 0.5, 1.0, 2.0 or 4.0 μg/ml, all four groups achieved 40% $T >$ MIC. However, when MIC was 8 μg/ml, a higher dose of 1.0 g *q8h* regimen achieved 40% $T >$ MIC, regardless of the infusion, in both the two-step and extended mode. For pathogens with an MIC of 16 μg/ml, none of the four groups reached 40% $T >$ MIC (Table 4).

DISCUSSION

To our knowledge, the present study is the first to investigate the PK/PD differences between the two-step and extended regimens of imipenem in patients with sepsis and septic shock. The present findings revealed that both regimens similarly achieved targets of 40% $T >$ MIC. This further implies that an easier extended infusion mode, instead of two-step infusion, may be the optimal administration method of imipenem for the treatment of sepsis and septic shock.

Table 3 Comparisons of PK parameters of different regimens

Parameters	Two step (0.5 g q6h)	Extended (0.5 g q6h)	Two step (1.0 g q8h)	Extended (1.0 g q8h)	p value
C_{max} (µg/ml)	11.9 ± 3.9^a	12.5 ± 5.1^b	24.9 ± 4.9	24.9 ± 4.0	0.000
T_{max} (h)	1.5 ± 0.8^c	2.0 ± 0.0	1.0 ± 0.6^d	2.0 ± 0.0	0.000
$T_{1/2}$ (h)	1.9 ± 0.5	2.1 ± 0.8	1.8 ± 0.6	1.7 ± 0.6	0.565
CL (l/h)	10.9 ± 2.6	10.9 ± 2.8	11.2 ± 1.4	10.5 ± 1.8	0.975
Vd (l)	28.7 ± 8.9	33.0 ± 16.5	28.0 ± 7.9	25.1 ± 7.6	0.480
AUC_{0-t} (µg h/ml)	50.1 ± 20.9^e	38.0 ± 15.4^e	83.4 ± 7.5	85.9 ± 14.3	0.000
AUC_{0-tau} (µg h/ml)	44.7 ± 10.5^e	41.0 ± 11.1^e	91.0 ± 11.2	97.7 ± 16.4	0.000

C_{max} peak concentration, T_{max} peak time, $T_{1/2}$ elimination of half-life, CL imipenem clearance, Vd apparent distribution volume, AUC_{0-t} area under the concentration–time curve, AUC_{0-tau} area under the concentration from zero to the end of the dosing period

[a] $p < 0.05$ compared with two-step infusion (1.0 g q8h)
[b] $p < 0.05$ compared with extended infusion (1.0 g q8h)
[c] $p < 0.05$ compared with extended infusion (0.5 g q6h)
[d] $p < 0.05$ compared with two-step infusion (0.5 g q6h)
[e] $p < 0.05$ compared with extended or two-step infusion (1.0 g q8h)

Table 4 Probability of meeting 40% $T > $ MIC in patients with sepsis and septic shock receiving imipenem

MIC (µg/ml)	0.5 g q6h		1.0 g q8h	
	Two-step (n = 9)	Extended (n = 10)	Two-step (n = 6)	Extended (n = 10)
0.5	100	100	100	100
1	100	100	100	100
2	100	100	100	100
4	89	80	100	100
8	11	30	100	80
16	0	10	0	0

MIC minimum inhibitory concentration

The percentage of patients achieving 40% $T > $ MIC was comparable to the extended mode in the treatment of sepsis and septic shock. Within the MIC range of 0.5–16.0 µg/ml, it was found that these two administration regimens did not significantly differ with regard to the target achievement of 40% $T > $ MIC, although T_{max} was shorter when imipenem was given in a two-step manner. This result was partly in line with that observed in studies on meropenem. A previous in vitro study revealed that the PTA of the two-step infusion of meropenem completed within 2 h was not apparently superior to those with a prolonged 2-h infusion. However, the difference on PTA increased when infusion time was prolonged to 4–6 h [15]. Notably, this study

was based on the in vitro pharmacodynamics model, which only targeted *Pseudomonas aeruginosa*, while the present study was a real-world exploratory study conducted in critical patients with various pathogens. In addition, an infusion that lasted no longer than 2 h was designed in the present study because of the consideration of stability and clinical feasibility. Therefore, comments on the efficacy of the two-step infusion regimen fulfilled in a longer duration could not be made.

Altered PK/PD patterns have been found with a carbapenem antibiotic used under different disease conditions, resulting in insufficient blood drug concentrations. Previous studies have demonstrated that the total CL and Vd of imipenem markedly fluctuated in critically ill patients compared with normal volunteer populations [19]. For patients with severe sepsis and septic shock, the values of both Vd and CL of imipenem in the present study appeared to be higher than those observed in healthy volunteers, but these were similar to those in patients with ventilator-associated pneumonia [19, 20]. The explanation for the pharmacokinetic alteration is that pathophysical changes during septic conditions compromise the absorption, distribution, metabolism and excretion of drugs. On one hand, decreased cardiac output and microcirculation shield the microcirculatory distribution of drugs. On the other hand, the increase in capillary permeability and interstitial edema may enhance drug distribution. Furthermore, the underlying impaired hepatic and renal function also affect the metabolism and clearance of drugs [21].

A high-dose regimen is required for the effective elimination of pathogens less susceptible to imipenem. In the present study, the percentage of cases achieving targets of 40% $T > \mathrm{MIC}$ was nearly 100% at an MIC of 1–4 μg/ml, regardless of whether imipenem was administered with 0.5 g *q6h* or 1.0 g *q8h*. However, when MIC was increased to 8 μg/ml, the percentage of patients reaching 40% $T > \mathrm{MIC}$ was only 11–30% at a dose of 0.5 g *q6h* and 80–100% at a dose of 1.0 g *q8h*. Previous studies on pneumonia have reported a high PTA (40% $T > \mathrm{MIC}$) at an MIC of 1–2 μg/ml when imipenem was used at a dose of 1.0 g *q8h* or 0.5 g *q6h*

[20, 22]. However, imipenem at 1.0 g *q8h* or 1.0 g *q6h* was required for pathogens with a higher MIC in critically ill patients [23]. It is thereby recommended that a maximum imipenem dose of 1.0 g *q6h* should be considered for treating less susceptible pathogens in patients with sepsis and septic shock. However, further large-scale studies are still needed to confirm this statement. In addition, susceptibility in different pathogenic species should be considered. In the present study, almost all regimens achieved 40% $T > \mathrm{MIC}$ against *Klebsiella* spp. and *Escherichia coli*, while only a small proportion of imipenem therapies achieved targets against *Pseudomonas aeruginosa* and *Acinetobacter* spp., because most of the isolates from the present study revealed that MIC was higher than the resistant breakpoints (data not shown).

There were a few limitations to the present study. First, the sample size was relatively small, and further large clinical studies are warranted to confirm these results. Second, the study was not double-dummy for blind randomization, which may have produced biased results. Third, sepsis and septic shock are actually a disease syndrome that refers to a variety of underlying diseases and pathogens. Furthermore, patient heterogeneity may have affected the results. Fourth, the clinical efficacy of both regimens was not compared because the ultimate outcome would be affected by multiple factors other than antibiotics. Fifth, although previous studies have demonstrated that 40% $T > \mathrm{MIC}$ is associated with the optimal activity for imipenem, recent studies have suggested that a target of 100% $T > \mathrm{MIC}$ might be more appropriate for critically ill patients with severe sepsis [24]. However, the issue of whether the two-step infusion mode is better than the extended infusion mode has been well validated, even when 40% $T > \mathrm{MIC}$ was applied as the target of the present study. Finally, we did not analyze the infection outcome because the aim of this study was to explore the pharmacokinetics of imipenem and we speculate that the infection outcome would be affected by multiple confounding factors during a longer observation period. The comparison of PK data between patients with positive and negative microbiology was performed, and the results are shown in

Supplemental Table 1, which revealed that there were no significant differences in PK data between the two groups except that CL in the two step (0.5 g *q6h*) differed slightly, possibly because of the limited sample size. It is also noticeable that analysis was infeasible in the other two groups because of the limited sample size. We plan to further study the PK data for patients with positive and negative microbiology in the future with a larger sample size.

CONCLUSIONS

In conclusion, it was found that both the two-step and extended regimens were comparable to the PK/PD target. For an MIC of eight MIC of 1–2 μg/ml g/ml, a higher dose (1.0 g *q8h*) of imipenem should be considered.

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