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CONTENT

Population Pharmacokinetics of Imipenem in Burn Patients

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Abstract

Introduction: Burn is complex injury with high risk of hospital resistant organism infection.The use of broad spectrum antibiotics such as imipenemis common. Nevertheless, substantial change in physiopathology including augmented renal clearance(ARC) observed in severe burn patients results in high pharmacokineticvariability.Toxicity or sub-therapeutics may occur. **Objectives:** This study aimed to estimate PKparameters of imipenem and those potential covariates. **Methods:** Burn patients with body surface area injured >20% andimipenem indicationwere recruited. Two set of plasma samples (30 min post-dose and 1-2 hours before next dose)were obtainedat imipeneminitiation and before the end of imipenem use. ARC was defined if 8h-urinary creatinine clearance (8hClcr) was above 130 mL.min-1173 m2. PK samplewas quantified by validated HPLC method. Population pharmacokinetic analysis were performedusingMonolix2016R1. **Results:** A total of47 sets with 94 plasma samples were collected from 24 patients. Of which 18 sets were obtainedat ARC time. One compartmental model with proportional error fitted the data best. The inclusion of inter-individual (IIV) and inter-occasion variation (IOV) improved the goodness of fit of the model. Population volume of distribution was 33.5 L with IIV and IOV of 18.2 % and 15.6%, respectively. Population clearance and the respective IIV and IOV were 18.8L.h-1, 27.0 % and 28.1 %. Age and ARC showed to besignificant covariates ($p<0.001$). Targeted PK/PD attainment appeared to be affectedas a consequent. **Conclusions:** Imipenem pharmacokinetics had significant IIV and IOV on burn patient and the ARC may influence the targeted PK/PD attainment.

Keywords:imipenem, burn, population pharmacokinetics, inter occasion variation, augmented renal clearance.

1. INTRODUCTION

Burn is a complicated injury with high mortality and cause serious consequence to patients. The pathophysiology of burn is represented by inflamatory response after injury related to increased microvascular permeability, eodema or infection and lead to severe conditions like sepsis or progresivemultiorgan dysfunction syndrome or death [1]. In burn patient, a severe complication is acute renal failure with poor pronosis. In constrast, patients may experience augmented renal clearance (ARC) at several occasions, especially in the early phase of burn[2]. The variation in renal function may have unfavorable effect to the treatment if drugs have large urinary elimination[3]. The pharmacokinetic characteristic of many drugs including antibiotics are changed in which two fundamental parameters including volume of distribution (Vd) and Clearance (Cl) are directly affected by renal function variation and the eodemacondition[4-6]. As a result, patient may experience risk of antibiotics over exposure or subtherapeutic and higher dose for empirical regimen were recommended[7-9].

Carbapenemswith time-dependent activity are backbone antibiotics for the treatment of hospital infectionswhichcommonly occur in burn patients. Unfortunately, microorganisms are gradually resistant to these reserved antibiotics. Under high resistant pressure environment like intensive care unit, the requirement of cautious use of these antibiotics deserved awareness. Antibiotics should be usedin a manner not only to cure serious infection but also to minimize the risk of resistant emergence. Therefore, the application of pharmacokinetic/pharmacodynamicappeared to be a rational approach[5-6]. In order to improve the probability targeted attainment for typical microorganisms in burn patients, increasing dose is the common recommendation [7]. Nevertheless, the high variation of pharmacokinetic during the treatment with high inter-occasion variability of PK parameters was observed for meropenem and therefore the fixed empirical dose should be questioned[9]. Indeed, a real-time therapeutic drug monitoring on the dose of carbapenems in critically ill burn patient was proposed[10].

The use of carbapenems including imipenem National Institute of Burns of Vietnam follow empirical approach where the pharmacokinetic characteristic on this special population had not been well understood. To evaluate the appropriateness of current practice, this study aimed to estimate the population pharmacokinetics parameters and the potential covariates influencing pharmacokinetics properties of imipenem on burn patients.

2. METHODS

2.1 Patients

From December 2016 to March 2017, burn patients recruited in Intensive Care Unit, National Burns Institute of Vietnam were received routine care for their injury. Eligible patients were adults (≥18 years old) patients hospitalized within 72 hours after injury with injured body surface area of more than 20% and imipenem indication. Patients with renal failure or any other serious conditions before the injury were excluded. The study procedure were reviewed

and approved by local ethical committee and informed consents were obtained from patients or their caregivers.

2.2 Sample collections

Eligible patients receiving two hours intermittent imipenem infusionwith the dose of 0.5 or 1.0 g and the interval of 6 or 8 hour relying on decision of physicians. A set of two plasma samples of 30 minutes post dose and one or two hours before next dose were obtained at least 12 hours after imipenem commencement to ensure that steady state condition were achieved.

Second set of two plasma samples were collectedbefore the end of imipenem course and an additional third set of plasma samples were considered if acute kidney injury occurred. An eight-hour- urinary creatinine clearance (8h-Clcr) was measuredin parallel with each occasions ofplasma sampling. Augmented renal clearance (ARC) was identified if 8h-Clcr> 130mLmin^{-1} 1.73 m^{-2}. For remaining days, patientswere daily monitored according to routine practice in which estimated glomerular filtration rate (eGFR) were calculated using Cockroft and Gault equation.

For each plasma sample, three milliliter of venous blood were collected into heparinized vacutainer. After centrifuging at 1800g, one milliliter of plasma was obtained and was mixed immediately with one milliliter of 3-(N-morpholino) propanesulfonic acid (MOPS) 0.5M. The sample were stored at -40^{0}C for no more than 7 days before analysis.

2.3 Sample analysis

Plasma samples stabilized with MOPS were analyzed using a validated high performance liquid chromatography (HPLC) method. In short, 400 µL of plasma was mixed with 100 µLmeropenem1mg/mL as internal standard and subsequently precipitated by 500 µL of acetonitrile. After centrifuging at 3900g in 10 minutes, the supernatant was evaporated under nitrogen stream and the residual were dissolved in 200 µL MOPS 0.5M. An injection volume of 50 µL was operated byAgilent 1200 chromatography system consist of columm XDB-C8 (4.6 x 150 mm, 5µm); mobile phase of phosphat buffer 0.1M pH 7.4: methanol (60:40); eluent rate of 0.5mL/minute for 19 minutes with UV detector monitoring at 298nm. The method showed acurate and precise (bias:-2.6%, 5% and -3.5%; precision:5.91%; 4.73% and 6.31% at concentrations of 0.5, 20 and 60 µg/mL, respectively) with lower limit of quantification of 0.5µg/mL. The linearity range were 0.5 to 80 µg/mL and the stability was proved at -40^{0}C for one week.

2.4 Population Pharmacokinetic

Population pharmacokinetic modeling was performedusing non-linear mixed effect model approached with the help of Monolix2016R1. Assumptions of one or two compartmentfor structural modelwith inter-individual and/or inter-occasion variability (IIV and IOV) of pharmacokinetic parameters weretested. The model selection were firstly performedwith basic pharmacokinetic model in which no covariates were added. The Bayesian information criterion (BIC) was used to test the significant improvement in description of data by the model as the number of observations in this study is limited. BIC reduction by more than 2 was considered to be significant improvement.The covariate models were subsequently tested using the best-fitted basic pharmacokinetic model in which covariates of consideration were age, gender, weight, burn area and 8h-Clcr. Likelihood ratio test was applied and the -2 log-likelihood reduction threshold of 3.84 ($p<0.05$) were considered to defined significant covariate. Individual pharmacokinetic parameters estimated from the last model were used to calculated targeted *f*T>MIC values.

3. RESULTS

A total number of 24 patients with burned surface areas of 50.8 ± 17.3 (%) hospitalized within median of 4.5 (IQR: 3-9.5) hours after injury. Patient had mean age of 38.9±17.5 yearsin which 15 (62.5%) were male. Most of patients have preserved renal function with eGFR of 85.9 ± 29.4 mL min^{-1} 1.73 m^{-2}. Patients were received intensive care during first days of admission to stabilized the injury condition and imipenem treatment were commenced after 5 (IQR: 3.3 – 7.0) days. Most of patient received 2 hours intermittent infusion dosing at 1g three to four times per day and the duration of imipenem treatment course lasted after 7 (IQR: 6-10) days. A total 47 pharmacokinetics sampling occasions were attained in which ARC was observed in 18 (38,3%) occasions of 13 (54.2%) patients. (Table 1).

Table1. *Characteristics of patients (n=24), imipenem usage and sampling.*

Parameters	**n (%)**
Gender (Male)	15 (62.5)
Age (yearrs)(#)	38.9 (17.5)
SOFA score($)	5 (4 - 6)
APACHE II score($)	14 (11 – 18)
eGFR (ml/phút/1,73m^2)(#)	85.9 (29.4)
Burned surface area (m^2) (#)	50.8 (17.3)
Time of hospitalization since injury (hrs)($)	4.5 (3 - 9.5)
Time of imipenem initiation (days)($)	5 (3.3– 7.0)
Imipenem dosage (n=47)	
1g q.i.d.	38 (80.9)
1g t.i.d.	7 (14.9)
0,5g q.i.d.	1 (2.1)
0,5g t.i.d.	1 (2.1)

Duration of Imipenem courses (days) [$]	7.5 (6 – 10)
Patients with ARC (N=24)	13 (54.2)
Occations with ARC(N = 47)	18 (38.3)
Sampling occation(s) per patient (*)	
1	6
2	30
3	3
4	8

[$] mean (interquartile range); [#] mean (standard deviation); (*) Patient may have two courses of imipenem, the second sampling occasion may not be available due to antibiotic switching, patient transfer or death.

In population pharmacokinetics modeling, log-normal distribution was assumed for pharmacokinetic parameters and the respective variation components. One compartmental model appeared to fit better as BIC were significantly lower. The subsequent incorporation of IIV and then IOV components to Vd and Clshowed significantly improvement in comparison with zero model (BIC of 512 and 505 vs. 615) and that defined the basic model. In basic model, IIV of Vd and Cl were 18.2% and 27% while theIOVwere 15.6% and 28.1%, respectively.

Among selected covariates, 8h-Clcr and age had significant impact(likelihood ratio test, $p<0.001$). In addition, these two covariates wereremained in multivariate model since withdrawing any of those resulted in significant increase of -2 log-likelihood value (466 and 463 vs. 446). For better interpretation, ARC occurrence was used instead of 8h-Clcr and it appeared to have similar effect on the model. Age showed significant inverse relationships with both PK parameters in which 10 year older was accounted for 13 percent reduction in Cl and Vd. ARC had no impact on Vd while Cl at ARC occasions were 1.5 folds higher than those without ARC (Table 2).

Table 2. *Population pharmacokinetics parameters of imipenem on burn patients*

	Estimations (95% CI)	
Basic pharmacokinetic model		
Volume of distribution (L)	33.5 (28.2-38.8)	
Inter-individual variability (CV%)	18.2	
Inter-occasion variability (CV%)	15.6	
Clearance (L/h)	18.8 (15.9-21.7)	
Inter-individual variability (CV%)	27.0	
Inter-occasion variability (CV%)	28.1	
Residual variability (CV%)	27.2	
Covariate model		**p**
Volume of distribution (L)		
Non-ARC, Age = 38.9	32.6 (26.7-38.5)	
ARC	33.6 (26.5-40.7)	0.83
Age (10 years) (*)	0.874 (0.802-0.952)	0.002
Clearance (L/h)		
Non-ARC, Age = 38.9	16.4 (14.24-18.56)	
ARC	24.9 (20.6-29.2)	<0.001
Age (10 years) (*)	0.872 (0.816-0.932)	<0.001

Age was centralized by mean value of 38.9; (*) present relative reduction of parameters;

As patients with ARC condition had higher imipenem clearance, the probability of targeted PK/PD attainment also was affected. The PTA for the target of 40% *f*T>MIC and 70% *f*T>MIC was presented in Figure.

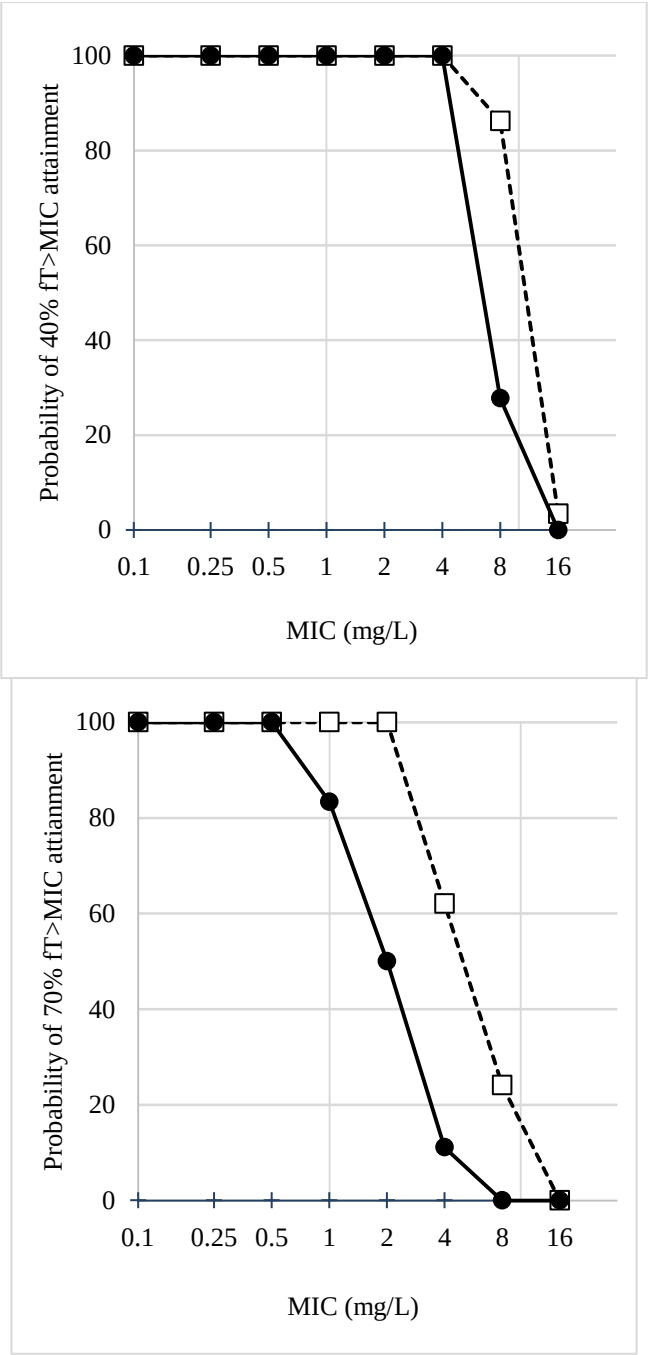

Figure 1. *The probability of target attainment (PTA) at 40% (left) and 70% fT>MIC (right) of imipenem on ARC (solid line, closed circle) and non-ARC (dash line, open square) burn patient*

4. DISCUSSION

This study showed that imipenem pharmacokinetics varied substantiallynot only between burn patients but also between occasions during the treatment. In addition, the age of patient and the development of ARC were significant covariates predicting pharmacokinetic alteration.

The population PK parameters including Vd and Cl estimated in this study are inline with previous finding [11]which was higher than those in healthy subjects. As limited sampling scheadule, the one compartment model appeared to better present PK data. The high IIV in Cl and Vd observed in this study suggested that empirical imipenem dose in approved label may not fit all patients and the risk of sub-therapeutic could be aware. Belzeberg et al. could not predict the pharmacokinetic of imipenemin critical ill patient with preserved renal function due to the high variability of PKparameters. Efforts were put on exploring covariates that could explain the high IIVof burn patients and only creatinine clearance appeared to have significant impact [11-12]. In our study, age showed significant prediction in which older patient may have lower Vd and Cl. Nevertheless,combiningeffect on half-life may be neutralized because this parameter depended on both Vd and Cl but in opposite direction. The drug exposure therefore was of minor alteration.

With the sampling schedule at different occasion, it enabled us to estimate the high IOV in both Vd and Cl. The IOV of about 20% in this study may partly explain the high PK variation of imipenemobserved in published result.It should be of note that this type of variation reflected the change of pathophysiological characteristic of patientsduring the treatment. Without monitoring drug level, afixedempirical dosemay result in sub-therapeutic or toxicity depending on patient's condition. Therefore, thereal-time therapeutic drug monitoring was proposed for this special situationand it was proved to have impact on altering empirical dosing of imipenem[10]. Nevertheless, real-time (TDM) was not simple practice for limited resources facilities. The alternative approach may come from our finding that the ARC emergence was the significant covariate and showed a high correlation with the estimated Cl. ARC were commonly observed in severe injured population [2] at the prevalence of about 50%. Closely monitoring this condition as a surrogate marker for the change in drug clearance could help to adjust the dose in time. With current empirical dose, the PTA for 40% *f*T>MIC may not be sufficient in ARC patient at MIC 8mg/L. The PTA curves of ARC and non-ARC patientswere futher split with the target of 70% *f*T>MIC and PTA of ARC patient were only 50% at MIC 2mg/L, the common threshold for defining susceptibility.

This study has several limitations. Small sample size and limited PK sampling schedule may lower the precision of estimated parameters and prevent the extrapolation in to larger population.

5. CONCLUSIONS

Pharmacokinetic of imipenem in burn patients characterized by a high inter-individual and inter-occasion variation which may undermine the empirical drug use. Close monitoring of renal function may help in dose adjustment during treatment to ensure the treatment efficacy.

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