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Research Article

# Population pharmacokinetics of meropenem in Vietnamese adult patients

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## ABSTRACT

Meropenem is a broad-spectrum antimicrobial frequently used for serious infections. Understanding the pharmacokinetics of meropenem is crucial in optimizing the dosage regimen to treat critically ill patients but there has been no report on its population pharmacokinetic parameters for Vietnamese adult patients. The aim of our study was to develop a population model to describe the pharmacokinetics of meropenem in Vietnamese adult patients. A prospective study was conducted in 30 patients. Plasma meropenem concentrations were measured during the first dose infusion using 6 samples per patient. Concentration-time data were analyzed using a nonlinear mixed-effects modeling approach with MONOLIXSuit2016. Eight participants' covariates were analyzed to identify their potential influence on meropenem pharmacokinetics. The adequacy of the constructed model was assessed by good-of-fit plots and the precision of the parameters estimated. Data comprised 173 meropenem concentration measurements. A 2-compartment model with zero-order input and first-order elimination showed the best fit for the data. Creatinin clearance and vasopressor use were two influential covariates for clearance: CL (L/h) = 4.74 x exp(0.019 x ($CL_{CR}$ -51 mL/min)) if vasopressor was used and CL (L/h) = 9.97 x exp(0.019 x ($CL_{CR}$ -51 mL/min)) if vasopressor was not used. The intercompartmental clearance (Q), volume of the central compartment ($V_c$), volume of the peripheral compartment ($V_p$) were estimated as 36.5 L/h, 9.24 L, 11.7 L, respectively. The inter-individual variability of CL, Q, $V_c$, $V_p$ were 35.2%, 54.8%, 59.4% and 35.0%, respectively. The additive error was 0.0197 mg/L and the proportional error was 30.9%.

## 1. INTRODUCTION

Serious infections are currently a dramatic problem since mortality and morbidity rates remain high. Meropenem, which is a broad-spectrum beta-lactam antimicrobial with rapid and good distribution in most body tissues and fluids, is frequently indicated for treatment of a broad range of serious infections[1]. However, the antibiotic therapy may not always be effective, because pathophysiological changes associated with the course of disease and treatment interventions may often alter drug pharmacokinetics. According to the intrinsic physiochemical properties of antimicrobials, hydrophilic antimicrobials such as meropenem have to be considered at much higher risk of inter-individual pharmacokinetic variations[2]. Previous studies also suggested that. the pharmacokinetics of meropenem in critically ill patients differed

to healthy volunteers[3-5]. In fact, pathophysiological changes in patients had a profound effect on both volume of distribution (Vd) and clearance (Cl) of meropenem, thus confusing the percentage of patients who might reach the pharmacokinetics/pharmacodynamic target values associated with a therapeutic target[2].

From a pharmacokinetic/pharmacodynamic point of view, meropenem exhibited time-dependent *in vitro* activity, and the antibacterial effects closely correlated with the time during which the free drug plasma concentration is maintained above the minimum inhibitory concentration (MIC) for the bacterium between two consecutive doses (fT>MIC)[6]. The fT>MIC derived from Monte-Carlo simulation integrated with estimates of the pharmacokinetic parameters obtained by population pharmacokinetic analyses had been used to optimize dose regimen of meropenem[7-9]. Therefore, understanding the pharmacokinetics of meropenem is crucial in optimizing the dose regimen to treat serious infections but there has not been a report on its population pharmacokinetic parameters for Vietnamese adult patients.

The aim of our study was to develop a population model to describe the pharmacokinetics of meropenem in Vietnamese adult patients with serious infections.

## 2. MATERIALS AND METHODS

### 2.1. Study subjects

Patients admitted to ICU or General medicine department of Phu Tho general hospital between January 2017 and March 2017 with meropenem indication were enrolled in this study. The protocol was approved by the ethics committees of the Phu Tho general hospital. Each patient or representative of the patient was given written informed permission before entry into the study. Those who were allergic to meropenem, < 18 years old, pregnant or breastfeeding or on dialysis were excluded.

### 2.2. Study protocol

The dose of meropenem was determined depending on the type and the severity of infection by treating clinician, ranging from 500 mg to 2000 mg given intravenous infusion every 8 hours in patients with normal renal function and appropriate dose adjustment according to renal function.

Blood sampling schedule in the first dose of meropenem was optimized using PFIM interface 4.0 software, using parameters from a prior population pharmacokinetics research of Li *et al*[10]. Parameters included: model compartment, estimated parameters and variance of parameters, interindividual variability and residual variability model. In details, six samples of blood (3 mL per sample) were collected into heparinized tubes at the following times: pre-dose, 15, 40, 90, 420 minutes after administration of the first dose of meropenem and just before the next dose. Demographic and physiopathological data were recorded for all subjects.

### 2.3. Sample handling, storage and assay

All blood samples were collected at Department of Hematology - Blood Transfusion, Phu Tho General Hospital and centrifuged (4000 ×g for 10 minutes) within 15 minutes after sampling to separate plasma. The plasma samples were then mixed with MOPS (3-(N-morpholino) propanesulfonic acid) buffer 2.64% (pH 6.8) (mixing ratio 1:1 v/v) and stored at -70$^{o}$C at Department of Hematology – Blood Transfusion, Phu Tho General Hospital. The samples were covered with dry ice and transported to Hanoi University of Pharmacy where they were unfrozen and analyzed within 1 week by a validated high performance liquid chromatography (HPLC) method[11]. The analysis procedure is briefly described as follow. On the analysis day, 100 µL of internal standard (imipenem at concentration of 20 ppm) was added to 400 µl sample. The protein in the mixture was precipitated with 500 µL acetonitrile. After centrifugation, 500 µL solution was evaporated under gentle nitrogen flow. The remained solid was dissolved in 200 µL MOPS and then 50 µL sample was injected to the HPLC system. The method used an Apollo C8 column (150x4.6 mm; 5 µm) as the stationary phase and the mixture of methanol and phosphate buffer 50 mM pH 7.4 as the mobile phase. Both meropenem and imipenem were detected at 298 nm. The method was validated in terms of selectivity, accuracy, precision, recovery, lower limit of quantitation, calibration curve, and stability according to the FDA guideline[12].

### 2.4. Population pharmacokinetic modeling

The population pharmacokinetic analysis was performed using the non-linear mixed effect modeling software MONOLIXSuit2016.

*2.4.1.Basic structural model*

The structural model for meropenem was developed by testing the following models: one-compartment or two-compartment with zero-order input and first-order elimination.
The additive model and the exponential model, as shown in following equation (1) and (2), respectively, were evaluated to describe the interindividual variability in the pharmacokinetic parameters.

$$P_{ij} = P_j' \times (1 + \eta_{ij}) \quad (1)$$

$$P_{ij} = P_j' \times \exp(\eta_{ij}) \quad (2)$$

Where $P_j'$ represents typical population value for the *j*th parameter; $P_{ij}$ represents the individual *j*th parameter for subject i and η is an independently distributed random variable with mean zero and variance $\omega^2$.

The additive error model, the proportional error model, the exponential error model, the combined additive and proportional model, the combined additive and exponential model, as shown in following equation (3) - (7), were evaluated to describe the residual variability.

$$C_{ij} = C_{ij}' + \varepsilon_{ij} \quad (3)$$

$$C_{ij} = C_{ij}' \times (1 + \varepsilon_{ij}) \quad (4)$$

$$C_{ij} = C_{ij}' \times \exp(\varepsilon_{ij}) \quad (5)$$

$$C_{ij} = C_{ij}' \times (1 + \varepsilon_{prop ij}) + \varepsilon_{add ij} \quad (6)$$

$$C_{ij} = C_{ij}' \times \exp(\varepsilon_{exp ij}) + \varepsilon_{add ij} \quad (7)$$

where $C_{ij}$ is the *j*th measured serum concentration for the ith subject, $C'_{ij}$ is the corresponding predicted serum concentration. ε is the residual variability representing independent distributed error with mean zero and variance $\sigma^2$ for serum concentration.

Basic structural model discrimination was assessed using Akaike information criterion (AIC) value and BIC (Bayesian information criterion). The better model is the one with a smaller value of AIC and BIC (more than 2).

*2.4.2. Covariate model*

Gender (SEX), age (AGE), actual body weight (ABW), serum albumin (ALB), creatinine clearance (CLCR), UNIT (ICU/general medicine department), vasopressor (VASO) use (yes/no), mechanical ventilation (yes/no) were evaluated as covariates. Creatinine clearance was estimated according to the Cockcroft-Gault equation based on the patient's actual body weight.

CLcr(mL/min) = (140 – AGE) x ABW (kg)/72 x serum creatinine (mg/dL) (x0.85 for women)

The influence of the patient characteristics on the individual pharmacokinetic parameters obtained from the basic structural model was first explored graphically. Then, the effect of each covariate was assessed by likelihood ratio test. The stepwise forward inclusion and backward elimination method was applied for covariate model development.

The significance of the influence of the covariates was evaluated by the changes of OFV between hierarchial models. An OFV decrease of more than 3.84 from the base structural model ($P<0.05$; $\chi^2$ test) was considered statistically significant during the forward inclusion process. The most significant covariate in each step was added to the model and the process was repeated to arrive finally at the most complex model with as many as significant covariates called the full model.

The final model was developed by a backward elimination method. The covariates in the full model were excluded from the model one at a time, and an OFV increase of more than 6.63 from the full model ($P<0.01$; $\chi^2$ test) was considered statistically significant.

*2.4.3. Model validation*

Internal evaluation of the model was assessed based on good-of-fit (GOF) plots, the precision of the parameter estimates at each step during the model development. GOF was investigated by the plots of: observed versus population-predicted concentration, observed versus individual-predicted concentration, population weighted residual (PWRES) versus time after dose of meropenem, individual weighted residual (IWRES) versus time after dose of meropenem, PWRES versus population-predicted concentration and IWRES versus population-predicted concentration.

A visual predictive check (VPC) was used to assess model predictive performance, based on the simulation of 500 data sets.

## 3. RESULTS

### 3.1. Patients and samples

Thirty patients were enrolled in the study, including 21 patients in ICU and 9 remaining

patients in General medicine department. Indications for treatment with meropenem were pneumonia (n= 28), exacerbations of chronic obstructive pulmonary disease (n=2).

The demographics of the patients and sample information are given in Table 1. All patients were with median age of 74 years (range 22 – 91 years) and a body weight of 54.5 kg (range 45.0 – 75 kg). The median creatinine clearance was 51.0 mL/min (range 10.8 – 119.6 mL/min) calculated by the Cockcroft-Gault formula.

A total of 173 plasma drug concentration data were used for the population pharmacokinetic modeling. Figure 1 presents scatter plots of meropenem concentration versus time after meropenem administration for all patients.

## 3.2. Population pharmacokinetic modeling

### *3.2.1. Basic structural model*

Because AIC values indicated that the two-compartment model (AIC, 1123.23) described the data better than the one-compartment model (AIC, 1255.27), the two-compartment model was chosen as the basic structural model. Therefore, the pharmacokinetic parameters were: clearance (CL, L/h), volume of distribution of the central compartment ($V_c$, L), intercompartmental clearance (Q, L/h), and volume of distribution of the peripheral compartment ($V_p$, L).

**Table 1**. Demographic characteristics of patients

| Characteristics | Symbol | Median, Interquatile (Min-Max) |
|---|---|---|
| Gender* | | |
| *Male* | SEX | 13 (43.3%) |
| *Female* | | 17 (56.7%) |
| Age (years old) | AGE | 74.0, 57.0 – 81.3, 22 – 91 |
| Actual body weight (kg) | ABW | 54.5, 45.0 – 60.0, 45.0 – 75.0 |
| Creatinin clearance (mL/min) | CLCR | 51.0, 42.2 – 74.9, 10.8 – 119.6 |
| Serum albumin (g/dL) | ALB | 33.1, 30.4 – 36.9, 26.1 – 44.2 |
| Serum total protein (g/dL) | PRO | 66.1, 56.0 – 72.6, 44.8 – 80.4 |
| Dose | | |
| *500 mg* | DOSE | 4 (13.3%) |
| *1000 mg* | | 24 (80.0%) |
| *2000 mg* | | 2 (6.7%) |
| Mechanical ventilation* | | |
| *Yes* | VENT | 18 (60.0%) |
| *No* | | 12 (40.0%) |
| Unit* | | |
| *ICU* | UNIT | 21 (70.0%) |
| *General medicine* | | 9 (30.0%) |

** The value are expressed as frequency (percentage)*

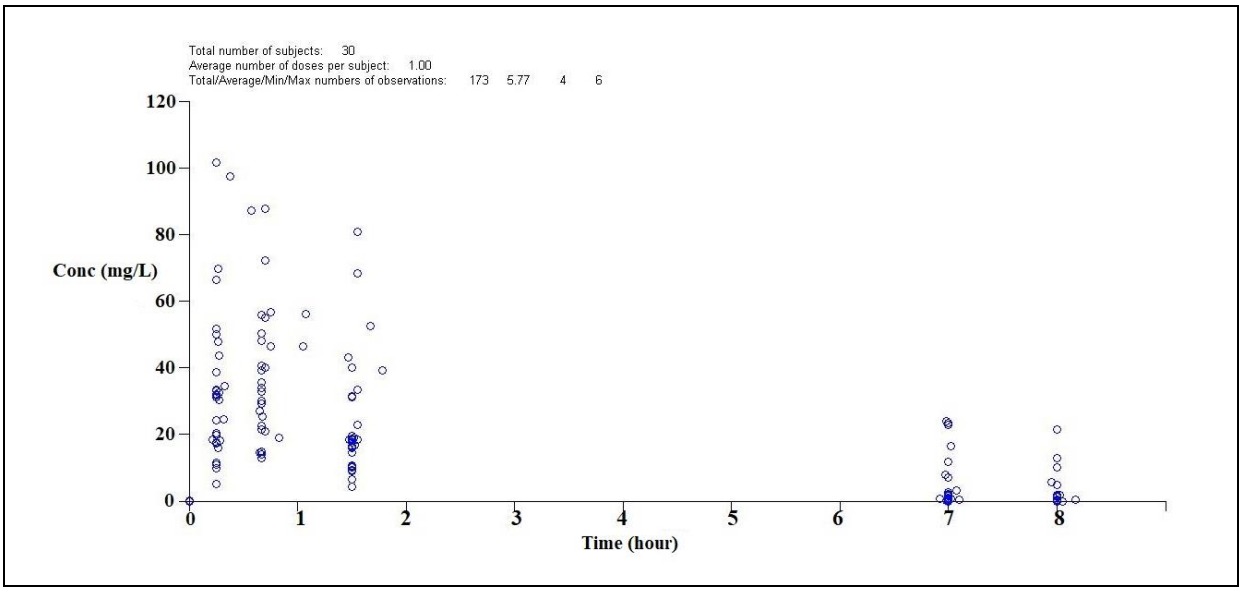


**Figure 1**. Scatter plot of meropenem plasma concentration vs time

**Table 2.** Parameter estimates of final population pharmacokinetics model

| Parameter | Estimate | SE | RSE% |
|---|---|---|---|
| ***Structural model*** | | | |
| CL (L/h) | CL (L/h) = CL*pop* x exp (betaClcr*(CLcr – 51)) x exp (betaVaso) if vasopressor was used<br>CL (L/h) = CL*pop* x exp (betaClcr*(CLcr – 51)) if vasopressor was not used | | |
| $CL_{pop}$ | 9.97 | 0.85 | 8 |
| *BetaClcr* | 0.019 | 0.0028 | 15 |
| *BetaVaso* | -0.744 | 0.18 | 24 |
| $V_c$ (L) | 9.24 | 1.8 | 20 |
| Q (L/h) | 36.5 | 12 | 32 |
| $V_p$ (L) | 11.7 | 1.7 | 14 |
| ***Interindividual variability*** | | | |
| $\omega CL$ | 0.352 | 0.056 | 16 |
| $\omega V_c$ | 0.594 | 0.13 | 23 |
| $\omega Q$ | 0.548 | 0.35 | 65 |
| $\omega V_p$ | 0.35 | 0.12 | 33 |
| **Residual variability** | | | |
| Additive error (mg/L) | 0.0197 | 0.0025 | 13 |
| Proportional error (%) | 0.309 | 0.03 | 10 |

Following a visual check of GOF plots, RSE and OFV, the exponential and the combined additive and proportional error model were used for the inter-individual and residual variability of the basic model, respectively.

*3.2.2. Covariate model*

In the first selection step, CLCR, AGE, ALB were found to be significant covariates for CL of meropenem ($P < 0.005$, 0.001 and 0.0001, respectively), SEX, UNIT, CLCR were significant covariates for Q, $V_c$, $V_p$, respectively. CLCR on CL, which gave the most significant reduction in OFV (-17.68), was introduced in first selection step. In the second, third, fourth selection step, VASO on CL, AGE on $V_p$, ABW on $V_p$ were introduced, respectively

During the backward step, ABW and AGE were excluded from the model due to OFV increase were 3.3 and 3.99, respectively.

Therefore, in the final model, there were two significant covariates describing the CL of meropenem: CLCR and VASO. There was no significant covariate that explained the Q, $V_c$ and $V_p$. The final model is displayed in Table 2 and summarized as follows:

CL (L/h) = 4.74 x exp(0.019 x ($CL_{CR}$ -51 mL/min)) if vasopressor was used

CL (L/h) = 9.97 x exp(0.019 x ($CL_{CR}$ -51 mL/min)) if vasopressor was not used.

Q (L/h) = 36.5

$V_c$ (L) = 9.24

$V_p$ (L) = 11.7

As compared to the basic structural model, the inter-individual variability of CL, Q, $V_p$ decreased from 65.3% to 35.2%, 73.6% to 54.8%, 46.0% to 35%, respectively, while the inter-individual variability of $V_c$ increased from 50.5% to 59.4%.

The additive error was 0.0197 mg/L and the proportional error was 30.9%.

*3.2.3. Model validation*

Scatter plots of population predicted and individual predicted meropenem concentrations were shown together with residual plots in Figure 2. The plots of observed vs predicted concentration (Fig. A,B) showed good correlation, indicating a good fit between the model and the data. In the WRES plots (Fig. C,D,E,F), no outliers or systematic deviations were observed. Therefore, goodness-of-fit plots revealed that the final model was consistent with the observed data and there was no apparent visual bias for the predictions.

The $2.5^{th}$, $50^{th}$ and $97.5^{th}$ percentiles of simulated concentrations based upon the final model and observed concentrations are shown in Figure 3 as VPC plot. The results showed that practically all observations dropped into the 95% CI and confirmed the predictive performance of the model. These findings implied that the final model had adequate predictive ability to describe the measured meropenem concentration.

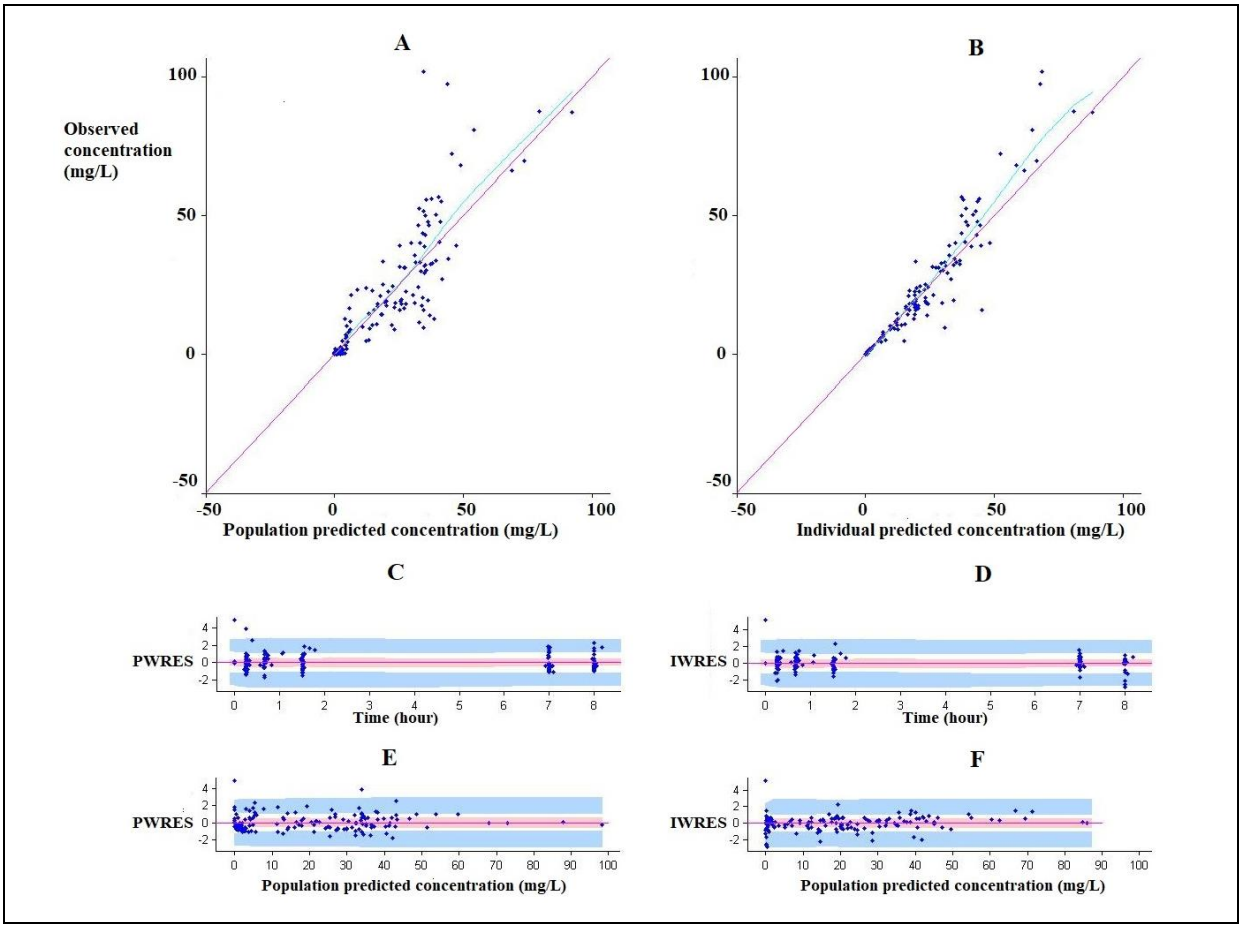


**Figure 2.** GOF plots of final models showing observed versus population predicted concentration (A), observed vs individual predicted concentration (B), PWRES vs time after dose of meropenem (C), IWRES versus time after dose of meropenem (D), PWRES vs population-predicted concentration (E) and IWRES vs population-predicted concentration (F)

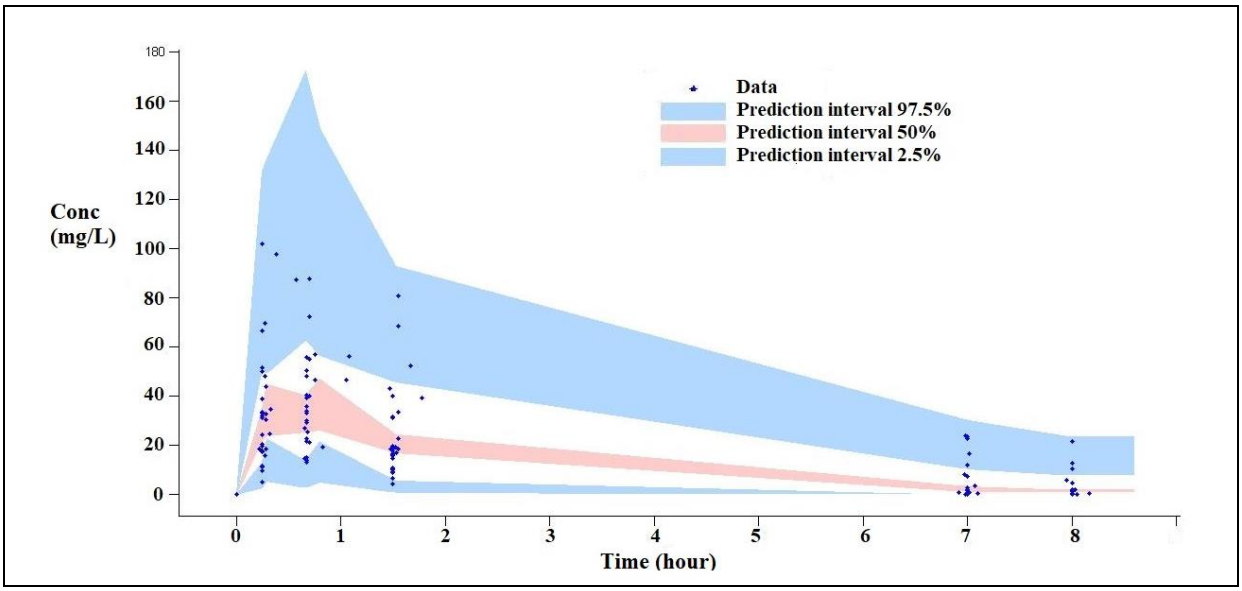


**Figure 3.** VPC plot.

## 4. DISCUSSIONS

Although the population pharmacokinetics of meropenem has been extensively studied, there are no reports in Vietnamese patients. In this study, a population pharmacokinetic model was developed to characterize meropenem pharmacokinetics in Vietnamese adult patients.

Sampling schedule was optimized with PFIM Interface 4.0, using parameters reported by Li *et al*[10]. Optimizing sampling schedule was not only helped minimize the number of samples, but also described adequately two-compartment pharmacokinetics characteristics of meropenem.

Indications for treatment with meropenem were all lower respiratory infections. The age range of patients who were enrolled in this study leaned toward the high end, with 73.3% patients with age greater than 60 years. In contrast, the distribution of creatinine clearance leaned to lower value than the normal value, with 43.3% patients with creatinine clearance below 50 mL/min whose needed to adjust dose.

A two-compartment model with zero order input and first order elimination showed best fit data in our study and this was consistent with many earlier pharmacokinetics studies of meropenem including not only traditional pharmacokinetic studies in healthy volunteers[5, 13-17], intra-abdominal infection[18], sepsis[19, 20], pediatrics[21-25] but also many population pharmacokinetics studies[7, 9, 10, 26-42]. However, there were some studies reporting one compartment model [8, 43-46] or three compartments model[47-49] that showed best fit to data . The reason for this difference in the number of compartment of the model among studies may be that the number of samples and the sampling timing were not similar[45], or specific characteristics of patients were different in such studies[47-49].

The exponential model to describe inter-individual variability and the combined additive and proportional model to describe residual variability were also consistent with many earlier population pharmacokinetic research.

In final model, there were two covariates explaining inter-individual variability of meropenem clearance (CL) but there were no any covariate explaining variability of Q, $V_c$ and $V_p$. The meropenem clearance was expressed as an exponential function including the creatinine clearance and vasopressor therapy:

$$CL\ (L/h) = 4.74 \times \exp(0.019 \times (CL_{CR} - 51\ mL/min)) \text{ if vasopressor was used}$$

and

$$CL\ (L/h) = 9.97 \times \exp(0.019 \times (CL_{CR} - 51\ mL/min)) \text{ if vasopressor was not used.}$$

The positive correlations between the CLCR and clearance of meropenem agreed with reports that meropenem elimination altered with the level of renal function[5, 50]. CLCR was also a significant covariate of meropenem clearance in many earlier population pharmacokinetics studies[7, 9, 10, 26-30, 33-36, 38, 41, 44, 46, 51]. In patients with median creatinine clearance (51 mL/min), CL (L/h) = 4.74 if vasopressor used and CL (L/h) = 9.97 if vasopressor not used. Meropenem clearance tended to be lower than value in healthy volunteers (12 – 17 L/h)[52] and was quite similar as estimates in a population pharmacokinetic in elderly with lower respiratory infection[35].

Vasopressors are clinically important agents that act at some of the most fundamental receptor and signal transduction systems in the body and they are often used in cases of patients with complicated clinical conditions[2, 53]. Since then, vasopressor therapy can lead to change pharmacokinetic of the drugs through alteration of the distribution and elimination and it is often considered as a covariate in population pharmacokinetic research[27, 43]. In our study, vasopressor therapy was identified as significant covariate and meropenem clearance in adult patients with vasopressor only half of that in patients without vasopressor. However, we did not find any research with similar results. It is necessary to have further studies to clarify this initial finding.

Volume of distribution at steady state was calculated as 20.94 L. This result was consistent with value in healthy volunteers (11 – 27 L)[5, 52]; and much lower than in burn, sepsis, severe sepsis, shock sepsis patients as reported in many earlier studies[8, 32, 33, 38, 44, 45]. The volume of distribution increases significantly in burn or sepsis patients due to pathophysiological mechanism and intensive fluid administration. The reason why the volume of distribution in our subjects was in the normal range was that our patients were focused on lower respiratory infection rather than patients with sepsis or burn, and the input-output fluid balance was well

controlled by treating clinicians. In earlier population pharmacokinetic analyses, body weight was the most significant covariate affecting volume of distribution but no correlation was found in our study[9, 10, 26, 27, 30, 32, 43, 46].

## 5. CONCLUSIONS

A population pharmacokinetics model of meropenem in Vietnamese adult patients was developed and validated using nonlinear mixed effect modeling analysis. It was shown that the clearance of meropenem depended on creatinine clearance and vasopressor therapy. The results of this study would be the premise for further studies of meropenem dosing optimization based on pharmacokinetic and pharmacodynamic principles.

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### Conflict of interest

None to declare

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### Ethical approval

Ethical approval was obtained from Phu Tho general hospital's ethics committee, according to certificate 01/CN-HDKH, December 28th, 2016. Written informed consent was obtained either from the patient or their appointed legal guardian.

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