Effects of uric acid, creatinine clearance, and infusion duration on the population pharmacokinetics of meropenem in critically ill patients

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Research

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Abstract

Background

Meropenem is a carbapenem antibiotic that has demonstrated excellent in vitro activity against gram-negative clinical Isolates and is commonly used in critically ill patients. This study aimed to describe the population pharmacokinetics (PPK) of meropenem and determine the optimal dosage in these patients.

Method:

We included 209 samples in 64 patients in this prospective study. PPK analysis and Monte Carlo dosing simulations were developed using Phoenix.

Results

A two-compartment model described the data adequately. Clearance (CL), volume (V), clearance of peripheral compartment (CL_2), volume of peripheral compartment (V_2) were 6.15 L/h, 2.83 L/h, 17.40L, and 17.48L, respectively. Creatinine clearance and uric acid were significant covariates. Patients with creatinine clearance of 60 ml/min or less and uric acid greater than 400 μmol/l could achieve the target > 90% under the minimum inhibitory concentration (MIC) of 8 mg/L, even with the administration dose of 500 mg/8 h with a 2-h infusion. Prolonging the infusion time significantly improved the therapeutic effect when MIC≥4. However, for the pharmacodynamic (PD) effects of 100% fT > MIC and 100% fT > 4MIC, no significant statistical difference was observed in critically ill patients.

Conclusions

Critically ill patients with lower creatinine clearance and higher uric acid levels were likely to need a lower dosage of meropenem. Prolonged infusion time were not appear to be beneficial for those who need a higher therapeutic target (100% fT > MIC,100% fT > 4 MIC) or with MIC＞4mg/L. Increasing dose or alternative therapeutic strategies may be required for critically ill patients with drug-resistant or severe infections. The study is of great significance to guide the rational use of meropenem in critically ill patients.

Trial registration:

The trial was registered in the China Clinical Trial (ChiCTR1900020672). Registered on 12 January 2019.

Key Points

This is the first time finding that uric acid level significantly impacts meropenem use. Ours is the first study to assess the achievement of various PK/PD targets (40% time free concentration above MIC (fT > MIC), 100% fT > MIC and 100% fT > 4MIC) with MIC values ranging from 1–8 mg/L in critically ill patients with severe pneumonia. During clinical empirical therapy, dose adjustment based on creatinine clearance and uric acid appears to be reasonable. Patients with a lower level of creatinine clearance and a high uric acid level tend to require lower dosages. There was significant clinical benefit from prolonged infusion time when MIC $\geq$ 4 mg/L. Increasing dose or alternative therapeutic strategies may be required for critically ill patients with drug-resistant or severe infections who require higher therapeutic targets.

Introduction

Severe pneumonia is a risk factor for in-hospital mortality[1–4]. In recent years, carbapenems have been widely used in patients and are considered the last line of defense in treating gram-negative bacterial infections [5–7]. Meropenem is a second-generation carbapenem antibiotic. Unlike the first generation, the 1-β methyl modification of the chemical structure enhances the stability of the drug to renal dehydropeptidase I [8, 9]. It is also a broad-spectrum antimicrobial used as empirical or directed therapy in critically ill patients. Meropenem shows time-dependent antibacterial activity and is characterized by linear pharmacokinetics in vivo; higher doses correspond to higher peak and trough concentrations [10, 11]. In healthy volunteers, the elimination half-life of meropenem in plasma was about 1 hour [12, 13].

Severe pathophysiological changes in critical illness can lead to dramatically altered antimicrobial pharmacokinetics (PK). In populations such as children, elderly, and obese, those with severe burns, those treated with continuous renal replacement therapy, and patients on extracorporeal membrane oxygenation, meropenem shows significant individual differences in plasma concentrations and pharmacokinetic parameters [14–18]. These effects are related to the time that the free concentration is maintained above the minimum inhibitory concentration (MIC) (fT > MIC), at least 40% [19]. Several clinical studies suggest that 100% fT > MIC in plasma is associated with better therapeutic effects [20–24]. Nevertheless, it remains unclear whether standard meropenem dosing regimens achieve this target in critically ill patients. Therefore, this study aimed to measure the meropenem PK in critically ill patients and determine the dose optimization strategy.

Materials And Methods

Study design and patients

This prospective study was conducted at the Department of Respiratory and Intensive Care Unit, the Second Xiang-ya Hospital of Central South University, between January and December 2019. The Ethics Committee of our hospital approved the study (number 2019-005) that was registered as a China Clinical Trial (ChiCTR1900020672).

Patients treated with meropenem and admitted to the Department of Respiratory and Critical Care Medicine were eligible. Written informed consent was obtained from all participants. Inclusion criteria were as follows: (i) severe lung infection; (ii) clear indications for the use of meropenem; (iii) the time of continuous medication exceeded two days; (iv) at least one steady-state plasma concentration could be obtained; (v) age > 18 years, and (vi) gram-negative bacilli were isolated from specimen culture. Exclusion criteria were as follows: (i) pregnancy and lactation; (ii) allergy to carbapenems; (iii) concomitant uses of sodium valproate; (iv) isolation of gram-positive cocci, viruses, or fungi before enrollment; and (v) incomplete dosing information or clinical data.

Based on the standard recommendations for meropenem use, the conventional dosage regimen was 500 mg/8 h or 1000 mg/8 h, two times/8 h, and continuous infusion for 30 min, 1 h or 2 h. From the electronic medical record information system, we recorded demographic information, clinical data, and laboratory test results using a standardized data collection form on the day of serum sampling. The endogenous creatinine clearance rate was calculated using the Cockcroft-Gault formula[25, 26].

According to the MICs of bacteria to meropenem in our hospital, various meropenem MICs (1, 2, 4, and 8 mg/L) were evaluated using the following PK/PD targets: 40% fT MIC, 100% fT MIC, and 100% fT 4MIC [23, 24].

Sampling and assays

Meropenem serum concentrations were measured using automatic two-dimensional high-performance liquid chromatography (Demeter Instrument Co., Ltd., Hunan, China). The first-dimensional chromatographic column was an Aston SNCB (4.6 × 50 mm, 5 μm), and the second-dimensional chromatographic column was an Aston SBN (4.6 × 200 mm, 5 μm) [27, 28]. There was an excellent linear relationship between peak area and the concentration range of 0.78 to 58.52 μg/mL. The lower limit of detection and the lower limit of quantification were 0.04 μg/mL and 0.1 μg/mL, respectively. The intra-day precision, inter-day precision, and accuracy were 1.21%–2.58%, 0.83%–1.80%, and 100.51%–101.69%, respectively. The extraction recovery of the high, medium, and low concentrations were 99.47%, 97.77%, and 97.23%, respectively.

Pharmacokinetic study

The PK model of meropenem in critically ill patients was developed using Phoenix NLME software (Version 8.1, Pharsight, A Certara Company, USA). Serum meropenem concentrations were fitted to a two-compartment model using the logarithmic additive residual. The first-order conditional estimation-extended least-squares method was used to estimate model parameters. The goodness of fit and visual predictive check (VPC) were used to evaluate the model. Objective function values (OFV) were used to compare the model fit. Covariates were retained in the model if the additional covariates were significant at a P-value of 0.01 (△OFV > 6.635). VPC was used to evaluate the goodness of fit [12, 29-32].

Probability of target attainment.

We use Monte Carlo simulations (n = 3,000) to determine the probability of target attainment (PTA) with different significant covariates. Meropenem doses of 500 mg, 1,000 mg, and 2,000 mg given intravenously every 8 h (q8h) with a duration of 0.5 h, 2 h, and 4h were simulated at different levels of selected covariates. The PTA was calculated after three days of therapy. The MIC at which PTA was equal to 90% was derived to enable a numeric comparison among the regimens [16, 18, 33]. MIC values were selected for the most common value of pathogenic bacterias such as *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae,* and *Acinetobacter baumannii* obtained from our hospital. PTA was calculated for single doses of 500 mg,1000 mg, and 2000 mg. The therapeutic target adopted the effect of 40% fT > MIC, 100% fT > MIC, and 100% fT > 4MIC [19, 23, 24].

Statistical analysis.

Continuous variables are expressed as means (standard deviations [SD]) or medians (interquartile ranges) depending on the normality of distribution. Enumeration data were expressed as absolute numbers and relative frequencies. The Kolmogorov–Smirnov, and Shapiro–Wilk tests were used to test for normality. A two-sided P-value of < 0.05 was considered statistically significant. One-way analysis of variance was used to test the differences in selected significant covariate groups. All analyses were performed using IBM SPSS Statistics version 25 (IBM, New York, NY). Figures were generated using Phoenix NLME and Graphpad Prism version 8 (San Diego, CA, USA).

Results

Demographic and clinical data of study patients

Sixty-four patients were enrolled in this prospective study. A total of 210 meropenem plasma samples were obtained; 73.43% of the patients were male, with an average weight of 62.5 kg. The average age was 63.5 years, and the mean Acute Physiology and Chronic Health Evaluation (APACHE) score was 17.2. More details about the demographic and clinical characteristics are shown in Table 1.

Meropenem sensitivity test was performed in 71.86% of the patients, most of whom had more than one kind of pathogen. A total of 80 meropenem MIC values were collected, 53.75% of which were above 8 mg/L. The detection rate of *A. baumannii* was the highest (21 [26.3%]). Notably, the MIC values for this pathogen were above 8 mg/L, suggesting resistance to meropenem. Notably, 45 (56.3%) of the gram-negative bacteria were multi-drug-resistant. Microbiological data and distributions of MICs are displayed in Table 2.

Pharmacokinetic model

A total of 210 meropenem plasma concentrations were included in the population analysis. The meropenem PPK was best described by a two-compartment linear model with first-order elimination. A stepwise method was used to determine all the covariates that may affect the pharmacokinetic parameters. For covariates, we selected gender, age, body weight, APACHE score, Cockcroft-Gault CLCR

(CG-CLCR), white blood cell, red blood cell, platelets, hemoglobin, alanine aminotransferase, aminotransferase, albumin, urea nitrogen, and uric acid. Inflammatory indicators were also included in the covariate selection. Despite various covariates having relationships with the estimated clearance, they were not included in the final model. Uric acid was finally found to be closely connected to meropenem V2 and CL. CG-CLCR was closely connected to CL. These two factors for meropenem V2 and CL improved the model fit best. When they were added to the model, the log-likelihood value from the previous model was significantly improved ($P < 0.01$). The covariate model was as follows: **see equations 1 - 4 in the supplementary files section.**

In these equations, CG-CLCR was calculated using the Cockcroft-Gault equation; tvCL is the typical value of meropenem clearance, CL is the population parameter of meropenem clearance, tvV is the typical value of volume in the central compartment, is the population parameter estimate for the volume of the peripheral compartment, and CL, V, , and are the inter-individual random effects of the parameter.

The parameters for the basic and final covariate model are shown in Table 3. Individual and population predicted serum meropenem concentrations vs. observed concentrations are shown in Fig. 1. The distribution of conditional weighted residuals is presented in Fig. 2. The values of conditional weighted residuals were between -2 to 2. Both plots indicated the fitting advantages of the final model. The final covariate model was used for Monte Carlo dosing simulations.

Simulations

Monte Carlo simulations and meropenem probabilities of target attainment for various CG-CLCR values, uric acid values, dosage regimens, and MICs with a duration of 0.5 h, 2 h, and 4 h are presented in an additional file. Details are shown in Additional file 1-3. MIC values listed in the tables were chosen according to the sensitivity of pathogenic bacteria to meropenem at our hospital. We found that at the lowest dosage (500 mg/q8h), patients with uric acid levels of > 400 mol/L can achieve an optimal PTA (of 40% fT > MIC for isolates with MICs of 8 mg/L with a duration of 4 h. However, those with uric acid levels > 40 mol/L and CG-CLCR of 120 ml/min could not achieve optimal PTA (of 40% fT>MIC for isolates with MICs of 1 mg/L, even with the highest dosage of 2000 mg/8h with a duration of 0.5 h. Moreover, the numbers of targeted PTA for the three infusion time groups were 55.56%, 62.96%, and 77.78%, respectively. These findings suggest that to achieve an optimal PTA, a prolonged infusion time, higher dose, or alternative administration protocol is needed for this cohort. Notably, patients with uric acid levels of 800 μmol/L and CG-CLCR of 30 ml/min can achieve optimal PTA (for all targeted therapeutic effects, including 100% fT > 4MIC for isolates with MICs of 8 mg/L using a dosage of 2000 mg/8h with infusion durations of 2 h and 4 h. The low uric acid group of 40 mol/L failed to achieve the PK/PD target of 100% fT>MIC and 100% fT>4MIC for all the simulated dosing regimens. In general, high levels of CG-CLCR and low levels of uric acid were associated with lower PTA. Detailed influences of creatinine and uric acid on PTA are shown in Fig. 3. Patients with high creatinine clearance rates were

likely to have lower PTA (P = 0.003), while those with high levels of uric acid were likely to have higher PTA (P < (Fig. 3).

We analyzed the PTA obtained from the simulation result and found that the infusion times of 2 h and 4 h appeared to have a higher PTA value than 0.5 h on average (P = 0.047, Fig. 4). However, the number of targeted PTA ( ) showed no significant difference among the three groups (P = 0.6847). Given this surprising result, various MICs and therapeutic targets were analyzed. The results are presented in Fig. 5. We found that the duration of infusion affected the improvement of PTA (Fig. 5). For the target of 40% fT MIC, PTA was significantly different among the three groups of simulated data when MIC < mg/L (P < 0.05). Under these circumstances, PTA could be improved by prolonged infusion time. The difference in PTA was close to significant when MIC was 4 mg/L (P = 0.0568). Notably, the P-value of the three groups was 0.234 for the target of 40% fT MIC when MIC was 8 mg/L This finding suggests that, for drug-resistant bacteria with high MICs, prolonged infusion time does not improve PTA level. There was no significant difference in PTA among the three groups for the targets 100% fT MIC and 100% fT 4MIC, even though MIC was 1 mg/L.

Discussion

I We developed a PPK model of meropenem in patients with severe pulmonary infection. In the previous literature, correlations of antibiotic CL with creatinine clearance were often reported. To the best of our knowledge, our study is the first to determine that uric acid is a significant covariate describing the pharmacokinetic parameters of meropenem. Supplementary Tables S1–S3 display the PTAs for all simulated dosage regimens using 40% fT > MIC, 100% fT > MIC, and 100% fT > 4MIC pharmacodynamic (PD) thresholds, respectively. According to further PTA analysis, we observed that higher levels of CG-CLCR and lower levels of uric acid were associated with the lower achievement of PK/PD targets for critically ill patients. Many studies found that the characteristics of meropenem pharmacokinetics could be described in different populations using a two-compartment model, which is consistent with the results of our study [16, 17, 34-36]. Adela et al. found that the administration of 2000 mg/8 h of meropenem as a continuous infusion allowed higher serum meropenem concentrations [35]. Similar results were found in other studies of meropenem [14, 16, 34, 35, 37].

We found that the duration of infusion had a complex effect on the improvement of PTA. It was significant only when using the traditional target of 40% fT > MIC with MIC < 4 (Fig. 4). For the PD effects of 100% fT > MIC and 100% fT > 4MIC, no significant statistical differences were discovered. This finding suggests that, for patients with sensitivity to meropenem and mild infection, prolonging the infusion time can improve the therapeutic effect (MIC < 4). By contrast, those with meropenem-resistance or severe infections (who require a higher therapeutic target) had no significant clinical benefit from prolonged infusion time. *A. baumannii* and *K. pneumoniae* generally have high MICs. Therefore, higher dosages are needed to achieve the targeted therapeutic effect. However, Mohd et al. conducted an observational study of 211 patients receiving piperacillin/tazobactam and meropenem and found that administration of meropenem by prolonged infusion in critically ill patients was beneficial. Several studies showed similar

results and encouraged extended infusions because this maximizes the likelihood of achieving target blood concentrations[35, 37-40].

The reason for this distinction is most likely that few studies have compared the differences in therapeutic responses of 100% fT > MIC,100% fT > 4MIC, and 40% fT > MIC caused by infusion time; we did so and identified the distinction. It is worth noting that De Waele et al. mentioned that, in a significant subpopulation of critically ill patients with normal renal function, a 100% fT>MIC target is not reached, even with 3-hour extended infusions. This finding agrees with our results.

We also assessed the achievement of different PK/PD target (40% fT > MIC,100% fT > MIC and 100% fT > 4MIC) under MIC values ranging from 1 mg/L to 8 mg/L. The effect of meropenem dosage and infusion duration was also assessed. In particular, patients with creatinine clearance of 60 ml/min or less and uric acid greater than 400 μmol/L can achieve the target of PTA 90% under the MIC of 8 mg/L, even with the administration dose of 500 mg/8 h with a 2-h infusion (Additional file 2). This finding suggests that 500 mg/8 h is sufficient for critically ill renal failure patients with high uric acid levels.

Although the correlation of antibiotic CL with creatinine clearance has been widely reported [11, 12, 16], this study represents the first finding of uric acid having a significant impact on meropenem use. We also found that patients with lower creatinine clearance and high uric acid levels tend to require lower dosages. Our findings suggest that dose adjustment based on these two factors appears to be reasonable.

However, our study also has some limitations. First, the sample size is small, and it is only a single-center study. Second, adverse effects and the influence of plasma concentration were not assessed. Therefore, actual tissue concentrations are unknown [41, 42]. Measurements of concentrations in the epithelial lining fluid of the lung are needed in further studies [35, 43]. In addition, most of the samples were collected at the trough concentration time; this may affect the fitting of the model and intraindividual variability during the treatment period that could not be measured [41, 44].

Nevertheless, our study still provides essential information about the optimized dosage regimen of meropenem in critically ill patients. During empirical therapy of severe pneumonia caused by gram-negative bacteria, clinicians should consider both the achievement of clinical cure and the prevention of drug resistance. Therapeutic drug monitoring is one of the best means to achieve precision therapy.

Conclusions

Lower CG-CLCR and higher uric acid levels were likely to achieve higher exposure in serum and associate with lower PTA. The dose of 500 mg/8 h may be necessary to achieve an optimal coverage in critically ill patients for all susceptible isolates (MIC≤8mg/L) in patients with high uric acid levels associated with severe renal injury. Moreover, for those with drug-resistant or severe infections (MIC>4mg/L and critically ill patients who need a higher therapeutic target (100% fT > MIC,100% fT > 4 MIC), prolonged infusion time does not appear to be beneficial. Increasing dose or alternative therapeutic strategies may be

required for critically ill patients with drug-resistant or severe infections who need a higher therapeutic target.

Declarations

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Authors' contributions

YZ and YWX conceived of the study, and participated in its design. YCZ and MY made substantial contributions to data collection, sample and data analysis, and drafting of the manuscript. HL gave some advice on interpretation of the data. FW contributed in the part of therapeutic drug monitoring. BKZ, DXX and FY made contributions in revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethics approval was obtained from the local ethics committee (he Second Xiang-ya Hospital of Central South University; approval No. 2019-005). It was also registered in the China Clinical Trial (No. ChiCTR1900020672). Written informed consent was obtained either from the patient or their appointed legal guardian.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; CG-CLCR: creatinine clearance rate calculated by the equation of Cockcroft-Gault; fT>MIC: Percentage of time remaining concentration above MIC; ICU: Intensive care unit; MDR: Multidrug-resistant; MIC: Minimal inhibitory concentration; attainment; OFV: the objective function values; △OFV: change of the objective function values; PD: Pharmacodynamic; PK: Pharmacokinetic; PPK: Population pharmacokinetic; PTA: Probability of target.

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Figures

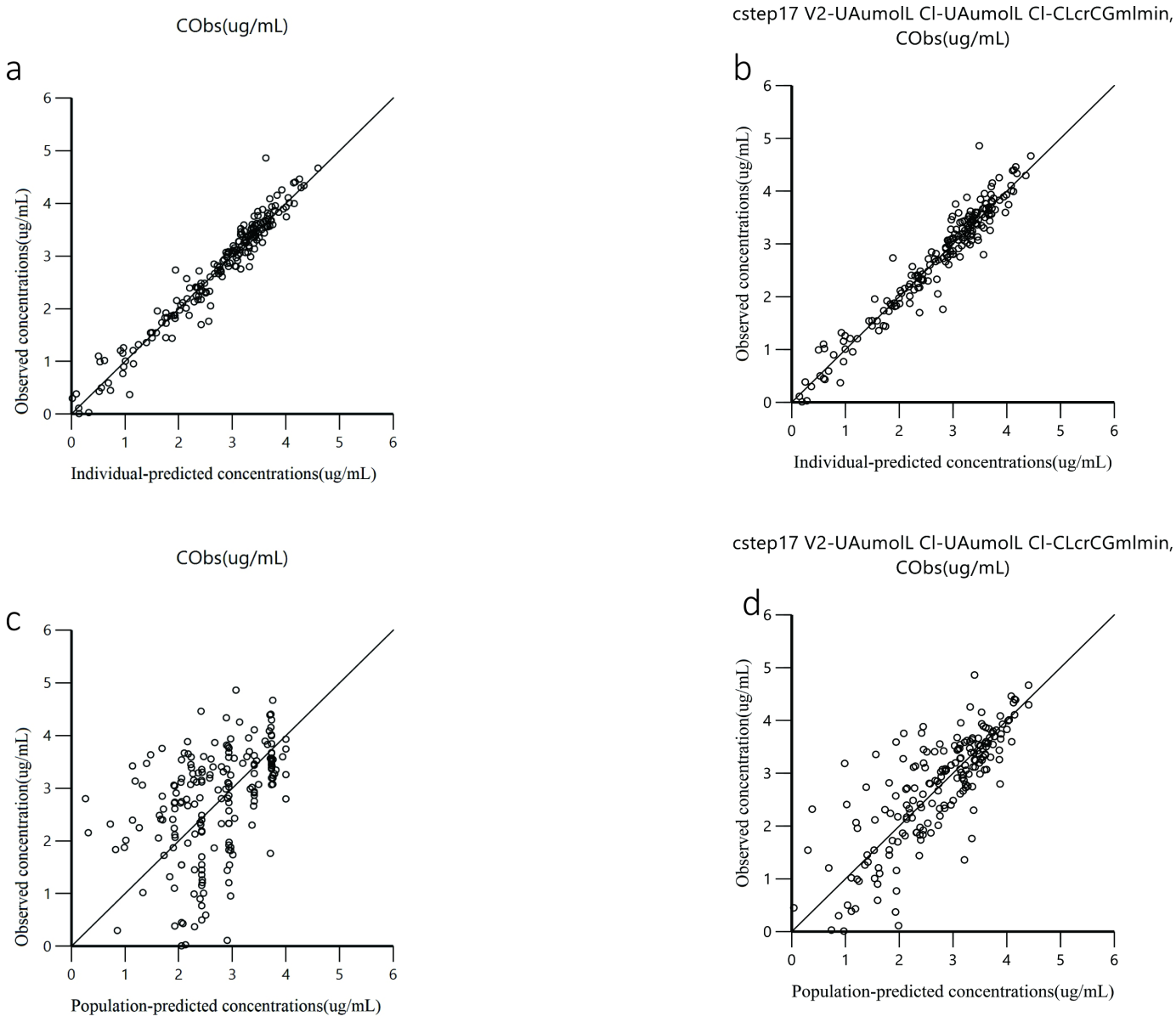

Figure 1

Scatter plots of DV-PRED and DV-IPRED in basic model and final model Individual (a and b) and population (c and d) predicted meropenem concentrations vs observed concentrations of meropenem for the basic model (a and c) and the final model (c and d).

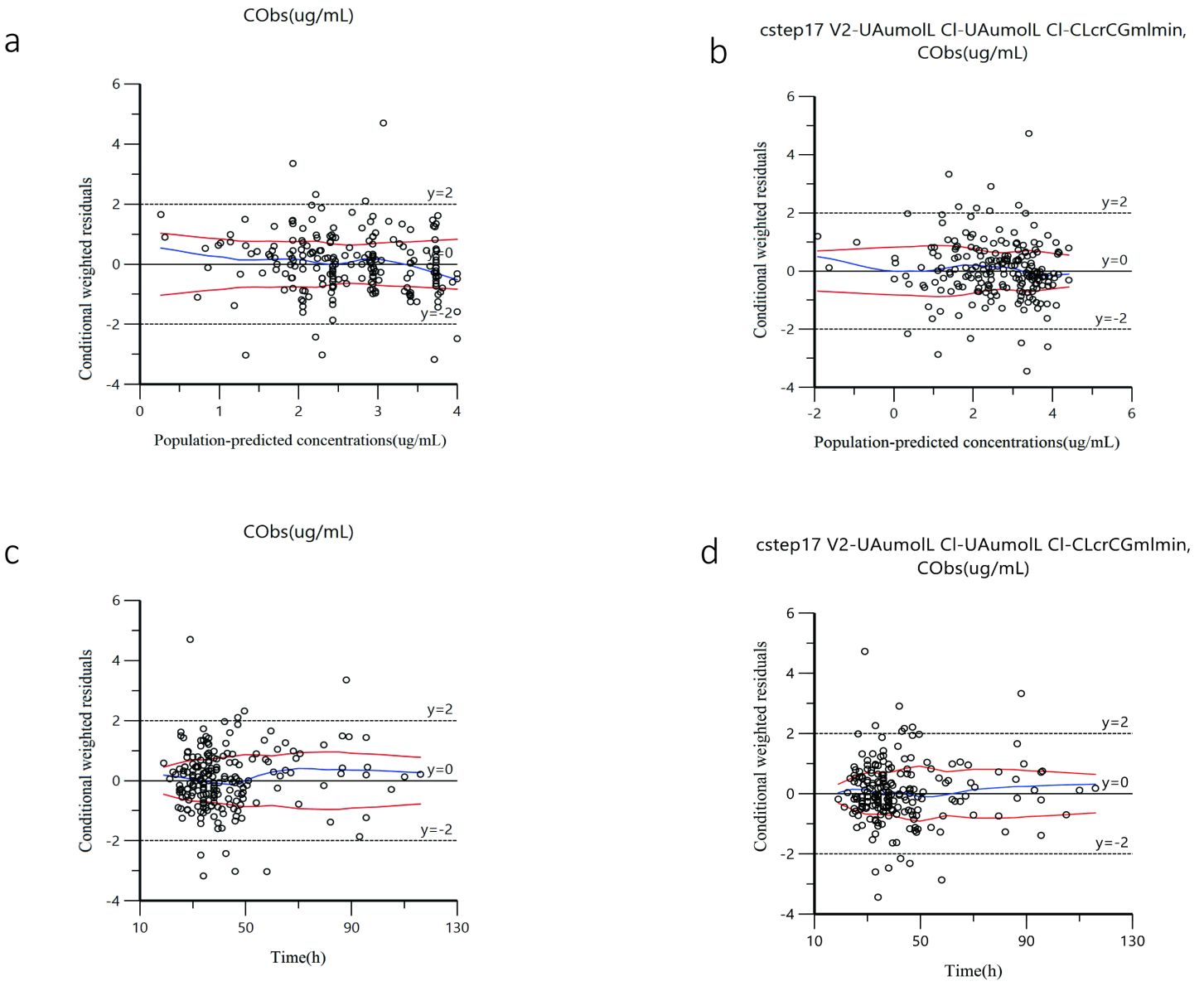

Figure 2

Scatter plots of conditional weighted residuals in basic model and final model The distribution of conditional weighted residuals for the basic model (a and c) and the final model (b and d). The conditional weighted residuals versus population-predicted concentrations (a and b) and time (c and d).

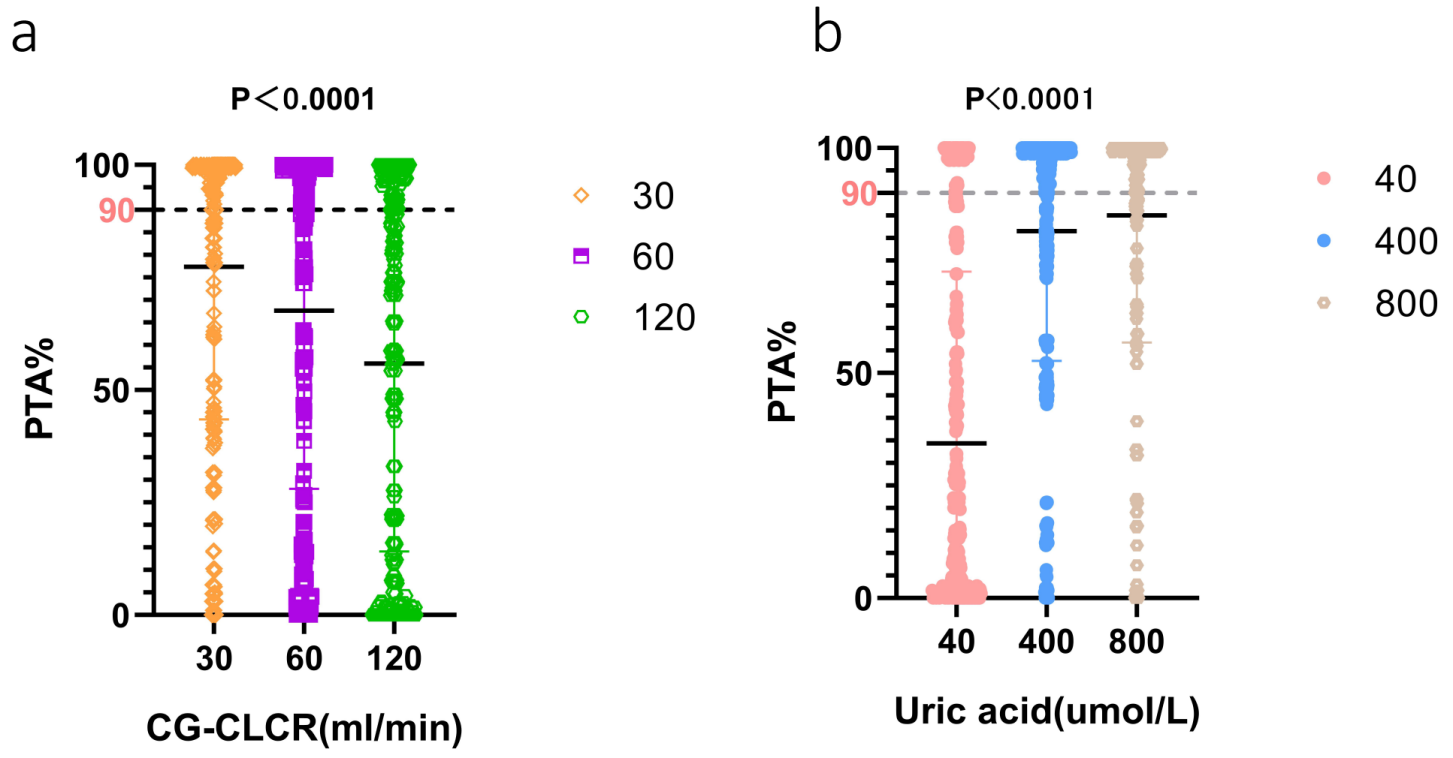

Figure 3

The effect of CGCL-CR and uric acid to PTA. Distinctions of PTA in different CG-CLCR (a) and uric acid (b) group based on the simulated data.

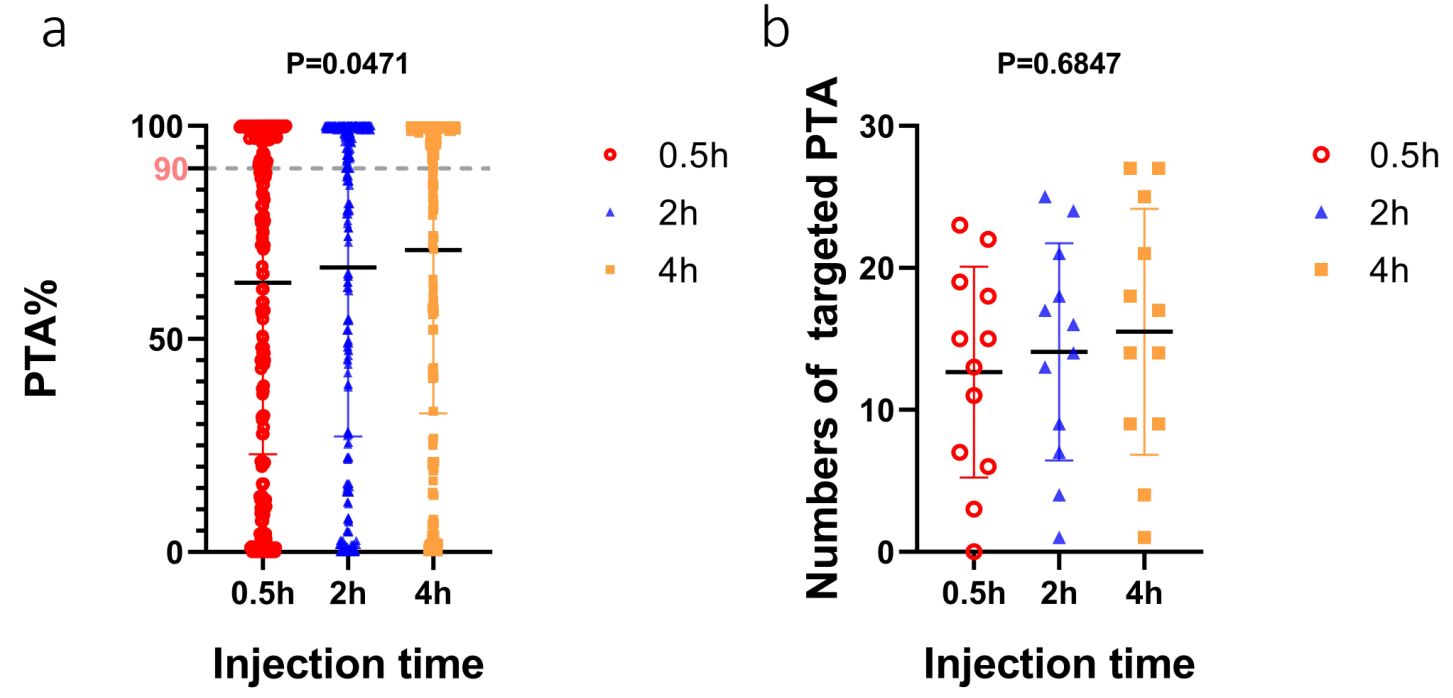

Figure 4

The effect of injection time to PTA Distinctions of PTA (a) and the number of achieved targeted PTA≥90% (b) in different injection time (0.5h, 2h and 4h) group.

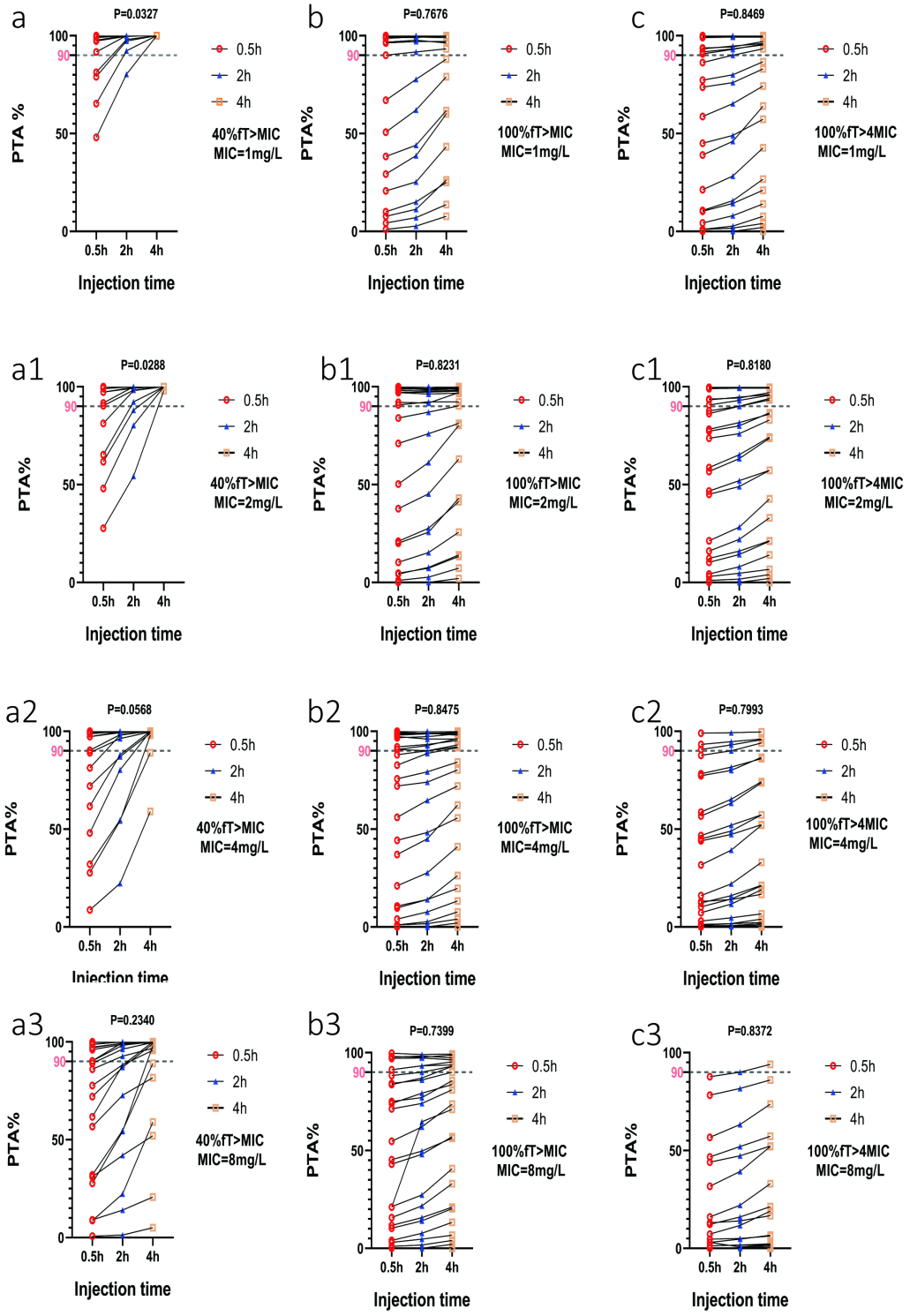

Figure 5

The effect of infusion time to PTA under different MICs. Distinctions of injection time (0.5h, 2h and 4h) on simulated PTA value in MIC=1mg/L (a,b,c), MIC=2mg/L(a1,b1 and c1), MIC=4mg/L(a2,b2 and c2) and MIC=8mg/L(a3,b3 and c3) groups, respectively. Distinctions of injection time (0.5h, 2h and 4h) on

simulated PTA value for PK/PD target of 40% fT>MIC (a,a1,a2 and a3), 100% fT>MIC(b,b1,b2 and b3) and 100% fT>4MIC(c,c1,c2 and c3), respectively.

Supplementary Files

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