Training a Drug to Do New Tricks: Insights on Stability of Meropenem Administered as a Continuous Infusion

Microbiology Insights
Volume 11: 1–6
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1178636118804549

Veena Venugopalan[1], Kayihura Manigaba[2], Samuel J Borgert[2], Jessica Cope[2], Charles A Peloquin[1] and Kenneth P Klinker[1]

[1]Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL, USA. [2]Department of Pharmacy, University of Florida Health Shands Hospital, Gainesville, FL, USA.

ABSTRACT

BACKGROUND: The antibiotic armamentarium used to combat multi-drug resistant organisms (MDROs) include carbapenems. Continuous infusion (CI) dosing is frequently employed to maximize beta-lactam efficacy; however, use of meropenem CI has been limited due to concerns with product instability.

OBJECTIVE: The primary objective of this study was to quantify meropenem serum concentrations to reflect drug stability when administered as CI over 8- or 12-h exchanges. In addition, a stability experiment was performed to further establish meropenem integrity over 12 h. The secondary objectives were to assess the ability of meropenem to achieve target pharmacokinetic/pharmacodynamic (PK/PD) exposures relative to the minimum inhibitory concentration (MIC) of the pathogen, and to determine clinical cure.

METHODS: This was a retrospective, observational study on use of CI meropenem (infused either over 8- or 12-h) at a 1% concentration. The stability experiment was conducted on 1% meropenem at room temperature.

RESULTS: In 22 patients, a median meropenem daily dose of 6 g/day (range 2-6 g/day) resulted in a median serum concentration of 17.8 mg/L (interquartile range, 9.3-27.8 mg/L). In 95% of cases, meropenem delivered as CI resulted in free drug concentrations at or above the MIC of the pathogen for the entire dosing interval. Clinical cure was achieved in 80% of patients included in this review. The stability experiment revealed negligible drug degradation at the end of the 12-h dosing interval.

CONCLUSIONS: The data from this study provides compelling evidence for the use of meropenem as CI utilizing either a 12- or 8-h exchange process.

KEYWORDS: Drug stability, meropenem, continuous infusion, therapeutic drug monitoring, antibiotic exposure

RECEIVED: August 9, 2018. **ACCEPTED:** September 7, 2018.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Veena Venugopalan, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, P.O Box 100484, Gainesville, FL 32610, USA. Email: vvenugopalan@cop.ufl.edu

Background

Emergence of resistant bacteria threatens global public health. In the United States alone, nearly 2 million patients develop infections with multi-drug resistant organisms (MDROs) each year, resulting in approximately 23 000 deaths.[1] Carbapenem resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* are among those organisms listed by the World Health Organization that have a critical need for new therapies.[2] The medical community has used this global burden of antibiotic-resistant bacteria to leverage the urgent development of new treatments. In the interim, while awaiting replenishment of the anti-infective pipeline, there has been renewed interest in using modified dosing strategies to optimize currently available antimicrobials.

Carbapenems, like other beta-lactams, display time-dependent bactericidal activity. This means that for maximal efficacy, free-drug concentrations must be maintained higher than the minimum inhibitory concentration (MIC) for an adequate percentage of time in a dosing interval (%T>MIC).[3] In critically ill patients with lower respiratory tract infections, the ideal target concentration *f*C/MIC>5 (free unbound concentration to MIC ratio) to achieve clinical cure and microbiologic eradication.[4] Other data indicate that target steady-state beta-lactam concentrations four times above MIC are required to produce positive microbiological outcomes.[5] A common intervention in clinical practice, to improve MDRO management, is to maximize beta-lactam exposure by administering beta-lactams as a continuous infusion (CI). Data from previously published studies reveal that this infusion strategy can improve clinical cure rates while decreasing the likelihood of selecting resistant organisms.[6–9] Unfortunately, meropenem administration by CI has been limited due to stability concerns when administered over extended periods.[10] Several factors such as diluent used, infusion time, concentration, and temperature have been identified as contributors to meropenem degradation.[11]

At our institution, meropenem CI is achieved with either 8- or 12-h exchanges. We report our experience administering meropenem CI at room temperature in 22 patients. In this study, meropenem serum concentrations were measured to determine drug stability when CI was performed over 8-h or

12-h exchanges. Based on measured serum concentrations, achievement of target pharmacokinetic/pharmacodynamic (PK/PD) exposures relative to MIC as well as clinical cure were evaluated. In addition to the patient cases reviewed, a stability experiment was prospectively performed to further establish integrity of meropenem 1% solution at room temperature over a 12-h CI.

Methods

This was a retrospective evaluation of adult patients receiving meropenem CI from November 2016 to November 2017. Patients were excluded if they were <18 years of age or if they did not have serum meropenem concentrations obtained during treatment.

Meropenem was reconstituted in sterile water for injection and prepared in normal saline to a final concentration of 1% (eg, 1.5 g in 150 mL or 3 g in 300 mL). Prepared meropenem was then placed in empty 250 or 500 mL PVC bags. All solutions were refrigerated at an average temperature of 4°C prior to administration. Timing of meropenem serum concentrations was performed at variable points at the discretion of the provider. For each sample, an aliquot of 4 mL of blood was drawn into non-heparinized tubes, which were centrifuged at 1000 g for 10 minutes, and the resulting plasma stored at −80°C. Serum concentrations of meropenem were measured in the Infectious Diseases Pharmacokinetics Lab (IDPL) at the University of Florida, using a validated ultrahigh pressure liquid chromatography assay with triple quadrupole mass spectroscopy (LC-MS-MS). The assay was developed in house, and it was validated according to the FDA Guidance on Bioanalytical Methods.[12] Meropenem-d6 was used as the internal standard. The standard curve ranged from 2.0 to 100 mg/L. The overall validation precision across all standards was 2.8% to 8.7%. For saline samples, a saline standard curve was used.

Continuous infusion (CI) was achieved by infusing each meropenem dose over 8 or 12 h using Alaris™ pump modules. None of the patients received loading doses prior to initiation of CI. Total drug concentrations were measured in this study. For meropenem, the literature reports about 2% protein binding. Because the fraction of protein binding is relatively low, correction of total drug concentrations is not necessary.[13] Target PK/PD ratios assessed in this study were free drug concentration maintained above MIC of the known or suspected pathogen throughout the entire dosing interval (100%$fT \geq$MIC) or free drug concentration maintained above a concentration fourfold higher than the MIC of the known or suspected pathogen throughout the entire dosing interval (100%$fT \geq$4xMIC).

The primary objective of this study was to quantify meropenem serum concentrations to reflect drug stability when administered as CI over 8- or 12-h exchanges. The secondary objectives were to assess the ability of meropenem to achieve target PK/PD exposures relative to the MIC of the offending pathogen and to determine clinical cure with therapy. Clinical cure was defined as resolution of clinical signs and symptoms of infection at the end of treatment. Patients without clinical response or those requiring additional or alternative antibacterial therapy were considered clinical failures.

In addition to the clinical cases reviewed, a stability experiment was prospectively performed to further establish integrity of meropenem 1% solution at room temperature over 12 h. Meropenem 1 g/100 mL (1%) solution was prepared by constituting 1 g vial with sterile water and transferring the contents of the vial to a 100 mL PVC bag of 0.9% sodium chloride. Meropenem samples from the bag were collected hourly over 12 h and frozen. Subsequently, the samples were assayed using the methodology described above, comparing the results to a standard curve prepared with saline.

Results

Twenty-two patients receiving meropenem CI were included in this review. Of these cases, 17 received meropenem CI as 12-h exchanges, while 5 received 8-h exchanges (Table 1). The median age of the cohort was 44 years (interquartile range, IQR 27-63). This was a non-obese group (median body mass index, BMI, of 24 kg/m^2, IQR 20-30), with all patients having normal renal function at the time of initiation of meropenem CI. Most patients (68%) were located in an intensive care unit. Most common clinical syndromes managed with CI therapy were pneumonia (41%), bacteremia (32%), and genitourinary tract infections (9%). Vitek-2 (bioMérieux, Durham NC) and E-test were used to determine antibiotic susceptibilities based on 2017 Clinical and Laboratory Standards Institute (CLSI) M100-S10 breakpoints for carbapenems. Where the MIC was unavailable or no pathogen was identified, surrogate MIC values for *P. aeruginosa* were used for analysis. The pathogen implicated in 16 (75%) cases was *P. aeruginosa*, two of which carried a MDR phenotype based on in vitro susceptibilities.

A median daily meropenem dose of 6 g/day (range 3-6 g/day) resulted in an overall median serum concentration of 17.8 mg/L (IQR 9-28.8 mcg/mL) (Table 2). Median meropenem concentrations during 8-h exchanges (15 mg/L, IQR [8.5-23]) did not vary greatly from those measured during 12-h exchanges (20.4 mg/L, IQR [9.5-29]). The median meropenem sampling time from the start of the infusion was 35.6 and 29.6 h during 8 and 12-h exchanges. For CI, steady state is achieved in 4 to 5 half-lives, which in the case of meropenem is about 4 to 5 h. Based on this, all meropenem concentrations obtained are steady state. Current CLSI clinical susceptibility breakpoints for meropenem against *Enterobacteriaceae* and *P aeruginosa* are ≤1 and ≤2 mg/L, respectively. When assessing target concentration attainment, CI resulted in 100%$fT \geq$MIC in 95% (18), with 74% (14) achieving 100%$fT \geq$4xMIC (Table 3). Clinical cure was achieved in 80% (16) of patients. In general, CI meropenem was considered safe and no adverse events were noted. One patient died within 30 days of completing meropenem therapy. Death was not related to infection in this case.

Table 1. Baseline demographics.

VARIABLE	N = 22		
Age (years), median (IQR)	44 (27-63)		
Male, n (%)	16 (73)		
ICU, n (%)	15 (68)		
Weight (kg), median (IQR)	69 (62-79)		
BMI (kg/m^2), (IQR)	24 (20-30)		
Charlson Comorbidity Index, median (IQR)	2 (1-4)		
Serum creatinine (μmol/L), median (IQR)[a]	0.7 (0.6-0.9)		
Meropenem daily dose (g), median (IQR)	6 (3-6)		
Meropenem CI, n (%)			
8-h exchange	5 (23)		
12-h exchange	17 (77)		
Primary infection site, n (%)			
Respiratory	9 (41)		
Abdominal	1 (4)		
Blood	7 (32)		
Urinary	2 (9)		
Other	3 (14)		
CNS (2)			
Skin (1)			
Pathogens, n = 29 (%)[b]			
Pseudomonas spp.	16 (55)		
Enterobacteriaceae	5 (17)		
Other[c]	6 (21)		
No pathogen isolated	2 (7)		
Hospital length of stay (days), median (IQR)	28 (15-53)		
Duration of treatment (days), median (IQR)	9 (5-15)		
Time to meropenem concentration from start of first meropenem infusion, median (IQR) (h)			
8-h exchange	35.6 (12.5-55.5)		
12-h exchange	29.6 (12.4-53.3)		
Susceptibilities of pathogens, n (%)	Susceptible	Intermediate	Resistant
Pseudomonas aeruginosa (n = 16)	9 (56)	5 (19)	2 (13)
Enterobacteriaceae (n = 5)	4 (80)	0 (0)	1 (20)
Meropenem minimum inhibitory concentration, median (IQR)			
P aeruginosa (n = 16)	2 (1-4)		
Enterobacteriaceae (n = 5)	0.2 (0.12-0.25)		

Abbreviations: CI, continuous infusion; CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range.
[a]Day 1 of therapy.
[b]Six patients with polymicrobial infections.
[c]Others: *Achromobacter xylosoxidans*, methicillin-resistant *Staphylococcus aureus, Candida krusei*, microaerophilic *Streptococcus* sp.

Table 2. Primary and secondary objectives.

VARIABLE	N = 22
Meropenem serum concentration (mg/L), median (IQR)	
Overall	17.8 (9-28.8)
8-h exchange	15 (8.5-23)
12-h exchange	20.4 (9.5-29)
PK/PD ratio, n (%)	
Total patients with isolated pathogen (n = 19)	
100%*f*T⩾MIC	18 (95)
100%*f*T⩾4xMIC	14 (74)
Clinical cure, n (%)[a]	16 (80)
30-day mortality, n (%)	1 (4.5)

Abbreviations: *f*C, MIC-free drug concentration to MIC ratio; IQR, interquartile range; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.
[a]Two patients were lost to follow-up post discharge and were excluded for clinical cure analysis.

Table 3. PK/PD target attainment.

PATIENT[a]	DAILY DOSE (G)	8- OR 12-H CI EXCHANGE	MIC (mg/L)	MEROPENEM CONCENTRATION (mg/L)	PK/PD TARGET ACHIEVED	
					100%FT⩾MIC ACHIEVED	100%FT⩾4XMIC ACHIEVED
1	6	12	2	20.4	Yes	Yes
3	6	8	1	15.2	Yes	Yes
4	4	12	2	8.4	Yes	Yes
5	2	12	4	23.4	Yes	Yes
6	6	12	1	55.5	Yes	Yes
7	3	12	2	3.4	Yes	No
8	3	12	2	22.0	Yes	Yes
9	6	8	3	14.7	Yes	Yes
10	6	12	4	6.35	Yes	No
12	6	8	0.125	7.8	Yes	Yes
13	6	12	0.25	20.4	Yes	Yes
14	6	12	2	24.7	Yes	Yes
15	6	12	4	31.8	Yes	Yes
16	6	12	1	13.4	Yes	Yes
17	6	12	32	38.1	Yes	No
18	6	12	2	12.3	Yes	Yes
19	6	12	64	28.9	No	No
20	3	8	1	9.3	Yes	Yes
22	6	12	4	10.6	Yes	No

Abbreviations: CI, continuous infusion; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; 100%*f*T⩾MIC, 100% probability time of free drug concentration is above MIC; 100%*f*T⩾4xMIC, 100% probability time of free drug concentration is four times above MIC.
[a]Three patients did not have a pathogen isolated.

Table 4. Meropenem stability experiment.

MEROPENEM 1% IN 0.9% SODIUM CHLORIDE AT 25°C		
TIME (H)	CONCENTRATION (mg/L)	% CONCENTRATION COMPARED WITH TIME ZERO
0	98.7	–
4	96.6	99.8
8	95.1	96.4
12	95.3	97.4

Regarding results from the meropenem stability experiment, the concentration at hour 12 was 95.3 mg/L, which is 97.4% of the concentration at time zero (Table 4). The observed variation in drug concentration is attributed to normal assay variability compared with standards and quality controls for validation. Therefore, we concluded that there was negligible meropenem degradation at the end of a 12-h infusion period when meropenem is prepared at a 1% concentration and maintained at room temperature.

Discussion

In an era of growing antimicrobial resistance, carbapenems have become one of our last lines of defense against MDROs. Unfortunately, due to instability concerns with meropenem, clinicians have been reluctant to extend infusions beyond 3 h. In the present study utilizing an 8- or 12-h bag change policy together with CI strategy, we observed meropenem concentrations at or well above the MIC breakpoint demonstrating drug stability. Furthermore, we were able to establish clinical cure in most study patients, underscoring the benefits of maximizing antibiotic exposure on treatment.

Prior to this assessment, several research groups have provided evidence supporting alternative meropenem dosing strategies to ensure optimal exposure. Kuti et al[14] evaluated the pharmacokinetic properties and stability of meropenem in adult cystic fibrosis patients randomized to receive meropenem 125 or 250 mg/h (equivalent to 3 or 6 g daily dose) as a CI over 12 h. Meropenem was infused using portable infusion pumps, which were stored between freezer packs to maintain drug at a cooled temperature. Stability analysis revealed that none of the antibiotic cassettes sampled had a 12- to 16-h concentration <90% or >110% of the respective concentration at hour 0, establishing drug stability for the dosing interval. In addition, CI meropenem provided serum concentrations greater than the MICs for meropenem susceptible pathogens. Our study revealed similar findings in that target concentration attainment with CI resulted in *f*C:MIC≥1 in 95%. In addition, we also determined that in 74% of patients *f*C:MIC≥4. This is an extremely valuable finding particularly in clinical scenarios involving bacterial pathogens with elevated MICs where treatment options are limited and reliance on optimal dosing is crucial.

The effect of drug concentration and temperature on meropenem integrity was evaluated in two studies. In the first study by Manning and colleagues, meropenem prepared to a final concentration of either 1% or 2% was placed in elastomeric pumps and refrigerated.[15] The antibiotic was then assigned to "room temperature" or "cooled" (placed in a cooler bag with an ice brick). Meropenem recovery from the elastomeric devices over a 24-h period was profiled. Drug exposure was presented as the maximum deliverable dose (MDD). Study data revealed greater than 95% MDD of 1% meropenem at 24 h in the uncooled device. The 2% meropenem concentration in uncooled conditions yielded the lowest MDD (87%) at 24 h. The second study by Berthoin and colleagues studied the stability of meropenem at concentrations varying from 1 to 9 g/mL following 12 h of incubation at temperatures of 25°C and 37°C.[10] The greatest concentration of meropenem (mean of 90%) recovered following 12 h of incubation was with 1 g/100 mL concentration maintained at 25°C. Consistent with other published data, results of our stability experiment reveal minimal degradation of drug at 1% concentration under room conditions.

Beyond establishing stability, therapeutic drug monitoring of meropenem is a valuable tool in achieving the desired PK/PD index. A recent study evaluated the impact of real-time PK/PD optimization of high-dose CI meropenem on clinical outcome of patients receiving combination antimicrobial therapy for the treatment of infections due to *Klebsiella pneumoniae* carbapenemase producing *Klebsiella pneumoniae* (KPC-kp).[16] Meropenem CI was achieved by replacing infusion bags every 6 to 8 h. Greater than 50% of the KPC-Kp isolates (16 out of 30) were deemed resistant to meropenem. The mean doses of meropenem CI ranged from 1.7 to 13.2 g/day. The resultant steady-state concentrations achieved ranged from 15.6 to 143 mg/L. Clinical cure in this study was achieved in 73% of the total patient cohort and in 50% of those with meropenem-resistant isolates. These investigators concluded that optimization of CI meropenem dosing through therapeutic drug monitoring is valuable in achieving positive treatment outcomes.

We recognize that there are limitations to this study. First, we did not measure temperature within patient rooms. To simulate real-world conditions, we tested meropenem concentrations when infused at normal room temperature, under natural light and humidity. Also, we did not examine drug stability within elastomeric pumps. While previously published data support stability in these devices when infused over extended

periods, our results cannot be directly extrapolated to outpatient antibiotic infusion delivery devices. Finally, for the purposes of this study, we assumed 2% protein binding for meropenem which is based on published data. We acknowledge that antibiotic protein binding in critically ill patients can be highly variable due to numerous factors such as hypoalbuminemia, renal, and hepatic insufficiency.[17] Wong et al.[13] report meropenem protein binding of 12.1% (CI 6.6%-17.6%) in an observational study evaluating beta-lactam therapeutic drug monitoring in intensive care unit patients. If unbound meropenem concentrations in the present study were corrected based on 12% protein binding as previously mentioned, the median serum concentration would drop to 15.7 mg/L. Despite this overall reduction in unbound drug, 95% of patients would still achieve free drug concentrations above the MIC of the pathogen for the entire dosing interval. Remarkably, even when adjusting for higher protein binding, our results reveal minimal impact on overall meropenem exposure.

Conclusions

Meropenem CI is an ideal method for administration without compromising drug stability. From this investigation, we were able to establish the stability of meropenem CI exchanged every 8 or 12 h at room temperature. Taken together, these results highlight the value of meropenem CI in the management MDROs given the ability to optimize antibiotic exposure. Further studies with larger patient populations are warranted to correlate meropenem CI strategy with patient outcomes. Consideration should also be given to meropenem CI as practical approach for outpatient antibiotic therapy. Stability studies in ambulatory infusion devices such as elastomeric pumps are required to support this in clinical practice.

Author Contributions

VV, KM, CAP, and KPK made significant contributions to the concept and design of the research, interpretation of data, and preparation of the manuscript. JC and SJB revised the manuscript and approved final version for publication.

Ethical Approval

Approved by Institutional IRB.

ORCID iD

Kenneth P Klinker https://orcid.org/0000-0002-0318-7099

REFERENCES

1. Centers for Disease Control. Antibiotic/antimicrobial. https://www.cdc.gov/drugresistance/index.html. Accessed July 23, 2017.
2. Tacconelli E, Magrini N. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. World Health Organization. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1>. Accessed February 27, 2017.
3. Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. *Clin Infect Dis*. 2008;47:S32–S40.
4. Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. *Antimicrob Agents Chemother*. 2007;51:1725–1730.
5. Osthoff M, Siegemund M, Balestra Abdul-Aziz MH, Roberts JA. Prolonged administration a β-lactam antibiotics—a comprehensive review and critical appraisal. *Swiss Med Wkly*. 2016;146:w14368.
6. Abdul-Aziz MH, Lipman J, Akova M, et al.; DALI Study Group. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetics/pharmacodynamic and patient outcomes? an observation from the Defining Antibiotic Levels in Intensive Care Unit Patient (DALI) cohort. *J Antimicrob Chemother*. 2016;71:196–207.
7. Fehér C, Rovira M, Soriano A, et al. Effect of meropenem administration in extended infusion on the clinical outcome of febrile neutropenia: a retrospective observational study. *J Antimicrob Chemother*. 2014;69:2556–2562.
8. Chytra I, Stepan M, Benes J, et al. Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. *Crit Care*. 2012;16:R113.
9. Abdul-Aziz MH, Lipman J, Mouton JW, et al. Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. *Semin Respir Crit Care Med*. 2015;36:136–153.
10. Berthoin K, Le Duff CS, Marchand-Brynaert, et al. Stability of meropenem and doripenem solutions for administration by continuous infusion. *J Antimicrob Chemother*. 2010;65:1073–1075.
11. Smith DL, Bauer SM, Nicolau DP. Stability of meropenem in polyvinyl chloride bags and an elastomeric infusion device. *Am J Health Syst Pharm*. 2004;61:1682–1685.
12. *Guidance for Industry: Bioanalytical Method Validation*. Silver Spring, MD: US Department of Health and Human Services, Center for Drug Evaluation and Research, Center for Veterinary Medicine, 2018. https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf.
13. Wong G, Briscoe S, Adnan S, et al. Protein binding of β-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? *Antimicrob Agents Chemother*. 2013;57:6165–6170.
14. Kuti JL, Nitingale CH, Knauft RF, et al. Pharmacokinetic properties and stability of continuous-infusion meropenem in adults with cystic fibrosis. *Clin Ther*. 2004;26:493–501.
15. Manning L, Wright C, Ingram PR, et al. Continuous infusions of meropenem in ambulatory care: clinical efficacy, safety, and stability. *PLoS ONE*. 2014;9:e102023.
16. Pea F, Siega P, Cojutti P, et al. Might real-time pharmacokinetic/pharmacodynamic optimization of high-dose continuous-infusion meropenem improve clinical cure in infections caused by KPC-producing Klebsiella pneumoniae? *Int J Antimicrob Agents*. 2017;49:255–258.
17. Schleibinger M, Steinbach CL, Topper C, et al. Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients. *Br J Clin Pharmacol*. 2015;80:525–533.