CASE REPORT

Meropenem pharmacokinetics during relapsing peritonitis due to ESBL-producing Enterobacteriaceae in a liver transplant recipient

Kensuke Shoji1 | Jumpei Saito2 | Yusuke Oho2 | Shotaro Matsumoto3 | Satoshi Aoki3 | Akinari Fukuda4 | Seisuke Sakamoto4 | Mureo Kasahara4 | Edmund Capparelli5 | Isao Miyairi1,6

1Division of Infectious Diseases, Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo, Japan
2Department of Pharmacy, National Center for Child Health and Development, Tokyo, Japan
3Division of Critical Care Medicine, National Center for Child Health and Development, Tokyo, Japan
4Organ Transplantation Center, National Center for Child Health and Development, Tokyo, Japan
5Division of Host-Microbe Systems and Therapeutics, UC San Diego, La Jolla, CA, USA
6Department of Microbiology, Immunology, and Biochemistry, University of Tennessee Health Science Center, Memphis, TN, USA

Abstract
We report on an 8-year-old girl with Wilson disease who developed three episodes of peritonitis due to extended-spectrum beta-lactamase-producing Escherichia coli after liver transplantation. Massive ascites were thought to account for low meropenem concentrations with standard dosing. Extending the infusion achieved higher troughs, greater time above minimum inhibitory concentration.

KEYWORDS
liver transplantation, meropenem, pediatrics, pharmacokinetics, prolonged infusion

Correspondence
Kensuke Shoji, Division of Infectious Diseases, Department of Medical Subspecialties, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.
Email: shoji-k@ncchd.go.jp

Funding information
This study was supported by a grant from the Japanese Society of Pediatric Infectious Diseases and National Center for Child Health and Development (NCCHD 30-31) awarded to KS.

This study was partly presented at the 9th Asian Congress of Pediatric Infectious Diseases held at Fukuoka, Japan on November 12, 2018.
1 | INTRODUCTION

Multidrug-resistant (MDR) Enterobacteriaceae is a major clinical problem worldwide. It is known that the prognosis for infections due to MDR Enterobacteriaceae is worse than infections due to non-MDR strains.\(^1\) Meropenem, classified as a carbapenem, is a first-line antibiotic for the majority of MDR Enterobacteriaceae infections, including extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae infections. Meropenem therapy has been associated with better outcomes compared to other broad-spectrum antibiotics.\(^2\)

Meropenem is a time-dependent antibiotic, and its efficacy is dependent on the time above minimum inhibitory concentration (TMIC). In general, achieving a TMIC ≥ 40% is considered a sufficient pharmacodynamic (PD) target for meropenem. However, a recent study indicated that achieving a higher TMIC, such as 50%-100% TMIC, was associated with favorable outcomes for severe infections in critically ill patients.\(^3\)

There are several factors that might change the pharmacokinetics (PK) after solid organ transplantation (SOT), such as hemodynamic change due to surgery, blood loss, massive ascites, and inflammation. These changes might alter meropenem PK, resulting in different dosing requirements to maintain sufficient TMIC for severe bacterial infections due to MDR Enterobacteriaceae infection after SOT. However, there are no data regarding meropenem PK after liver transplantation (LT).

We present a case of bacterial peritonitis due to ESBL-producing \textit{Escherichia coli} in a pediatric LT recipient who had massive ascites. The patient experienced multiple relapses of peritonitis during the first four months post-transplantation despite standard dosing and adequate duration of meropenem therapy.

2 | CASE

An eight-year-old (29.9 kg) girl underwent deceased-donor LT due to Wilson disease. She received ampicillin and cefotaxime as perioperative prophylactic antibiotics for 2 days. Immunosuppression after LT consisted of tacrolimus and methylprednisolone. After LT, massive ascites (up to 79 L over 7 days) developed, possibly due to small size graft and/or hepatic vein stenosis. On postoperative day (POD) 43, fever (maximum 40.0°C) and abdominal pain developed. The peripheral white blood cell count was elevated to 35,530/µL with 85% neutrophils. Total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine, albumin, and C-reactive protein levels were 4.18 mg/dL, 3.03 mg/dL, 50 U/L, 39 U/L, 0.34 mg/dL, 2.8 g/dL, and 5.45 mg/dL, respectively. Renal function was normal with an estimated glomerular function rate of 130 mL/min/1.73 m\(^2\). Ascites cell count was elevated at 1775/µL with 75% neutrophils and Gram staining revealed gram-negative bacilli. Bacterial peritonitis was suspected, and piperacillin/tazobactam was initiated. Two days later (POD 45), exploratory laparotomy detected abdominal abscess and intensive peritoneal lavage was performed. MDR Enterobacteriaceae was isolated from the original ascites sample, and antibiotics were switched to meropenem (60 mg/kg/d) and gentamicin (5 mg/kg/d) every 24 hours. The isolate was identified as ESBL-producing \textit{E. coli} (meropenem MIC ≤ 1.0 µg/mL), and gentamicin was discontinued. The dosing of meropenem was increased to 120 mg/kg/d every 8 hours (60-minute infusion) on day 3 of treatment because of suspected underdosing due to massive ascites. The antibiotic dose was based on the patient’s total weight. The patient’s condition improved gradually, and meropenem was stopped after completion of 2 weeks of therapy (POD 59). However, fever, abdominal pain, and leukocytosis in blood (33 650/µL with 82% neutrophils) and ascites (3800/µL with 90% neutrophils) were observed 6 days after finishing the first course of meropenem-based antibiotic therapy. Relapse of bacterial peritonitis was suspected, and meropenem (120 mg/kg/d every 8 hours, 60-minute infusion) was reinitiated. The peritoneal drainage tube was replaced, and ascites culture was performed. The culture revealed ESBL-producing \textit{E. coli} with the same antibiotic susceptibility pattern, confirming the diagnosis of relapsed peritonitis. The patient’s condition improved after initiation of the second course of meropenem-based antibiotic therapy. During this episode, normalization of ascites cell count was confirmed, and 3 weeks of meropenem therapy was completed. However, peritoneal abscess and peritonitis due to ESBL-producing \textit{E. coli} relapsed again 12 days after completion of antibiotic therapy (POD 101). Meropenem was reinitiated at 120 mg/kg/d every 8 hours. This time, meropenem was administered using a prolonged (3 hours) infusion to achieve a longer time above MIC. Meropenem was continued for 4 weeks, but peritoneal effusion still persisted. Therefore, antibiotics were continued, but meropenem was switched to cefmetazole to reduce overall exposure to carbapenem antibiotics. Disappearance of abdominal abscess was confirmed by CT scan and abdominal ultrasound. Cefmetazole was stopped after 4 weeks of therapy and no relapse was observed thereafter. The amounts of pleural fluid and ascites were high with 4-6 L/d throughout these three episodes.

2.1 | Method for meropenem pharmacokinetic analysis

Remnant serum samples were scavenged for meropenem concentration determinations. These samples were analyzed using a validated liquid chromatography method with tandem mass spectrometric detection (LC/MS/MS).\(^4\) This LC/MS/MS method for determination of meropenem concentration
was validated and met the requirements for specificity, sensitivity, linearity, recovery, precision, accuracy, and dilution integrity according to the European Medicines Agency guidelines. The PK data were fit to a two-compartment model using the program WinBUGS version 1.4.3 (https://www.mrc-bsu.cam.ac.uk/software/bugs) to estimate the pharmacokinetic parameters in this patient. A previously validated and published pediatric population PK model of meropenem was provided as the PK parameter and variance priors for this analysis.5 This retrospective study was approved by the institutional review board at our hospital (NCCHD-1328).

2.2 | Result of meropenem pharmacokinetic analysis

During each of the three peritonitis episodes, multiple serum meropenem concentrations were measured. The sampling timing and modeled meropenem concentration-time profile are shown in Figure 1. Meropenem was administered as 40 mg/kg/dose every 8 hours, 60-minute infusions in the first and second episodes and the same dose but 3-hour infusions in the third episode. The PK and PD parameters in each episode are shown in Table 1. The modeled troughs were higher in the third episode with 3-hour infusions than in the first and second episodes with 60-minute infusions (0.82, 0.08, and 0.027 µg/mL, respectively). The estimated total meropenem clearance (CL) values were 0.44–0.47 L/kg/h, and the estimated volumes of distribution at steady-state (Vdss) were 0.43–0.59 L/kg.

The calculated TMIC (for meropenem MIC = 1 µg/mL) was highest (92.5%) in the third episode with prolonged infusion compared to 65.0% and 77.5% in the first and second episodes with 60-minute infusions.

3 | DISCUSSION

We encountered a case of relapsing peritonitis due to ESBL-producing E. coli in a pediatric LT recipient with massive ascites despite standard therapy that achieved a TMIC greater than 50%. Prolonged infusion of high-dose meropenem was necessary to achieve a TMIC near 95%.
Severe infection due to MDR Enterobacteriaceae has been reported in immunocompromised patients including solid organ recipients, which leads to poor prognosis. Prompt initiation of appropriate antibiotics is essential in this situation. Meropenem has been shown to be clinically superior compared with other antibiotics; therefore, it has been used as a first-line antibiotic for ESBL infections. Additionally, identification of the infectious focus is essential for treatment of bacterial infection. In general, removal of the focus by surgical debridement or drainage is recommended in patients with apparent source of infection such as an abscess. The guideline for treatment of secondary peritonitis recommends prompt initiation of antibiotics and surgical intervention when possible. From this perspective, this case received standard therapy for secondary peritonitis. However, the peritonitis relapsed in spite of standard therapy. Therefore, we suspected underexposure of meropenem due to alteration of the PK profile in the post-transplant condition.

Several PK changes might occur after LT. LT recipients often experience large amounts of ascites or pleural fluid due to graft rejection, low albumin level, and alternation of blood flow. These changes lead to larger volumes of distribution for water-soluble antibiotics. Body fluids, such as ascites, contain water-soluble drugs that are often wasted through the drainage tube, leading to larger CL. In addition, inflammation due to transplantation or infection might lead to higher CL due to augmented renal clearance. Since the majority of beta-lactam antibiotics including meropenem are highly water-soluble, these medications are highly affected by PK changes due to transplantation. According to the PK analysis, the estimated total meropenem CL and the Vdss were approximately up to 1.4-fold and 1.7-fold higher, respectively, than in a reported population PK study in Japanese pediatric patients. Therefore, we considered that massive ascites and the patient’s various symptoms might affect meropenem PK parameters.

Prolonged infusion was performed in this case, and higher TMIC was achieved. It is well known that prolonged or continuous infusion of antibiotics is effective to achieve higher TMIC. The clinical efficacy of prolonged or continuous infusion of antibiotics is still debatable. However, a recent meta-analysis showed prognostic improvement in severe patients receiving prolonged infusions. The optimal TMIC in immunocompromised patients is still not well-defined, but recent data supports that the higher TMICs, including up to 100%, may be associated with better clinical outcomes. In our case, while causality is still unclear, relapsing ESBL peritonitis was successfully treated by prolonged infusion with higher TMIC. Further investigations with a large number of patients are needed to clarify the clinical impact of prolonged infusion of antibiotics in pediatric immunocompromised patients with severe infection due to multidrug-resistant organisms.

**ACKNOWLEDGMENT**

We would like to thank the medical editors from the Department of Education for Clinical Research of the National Center for Child Health and Development for editing this manuscript.

**CONFLICT OF INTEREST**

All authors do not have any potential, perceived, or real conflict of interest.

**AUTHOR CONTRIBUTIONS**

KS contributed to conceptualizing and designing the study and drafted the manuscript. JS and YO also contributed to conceptualizing and designing the study, data collection, PK analysis and revising the manuscript. SM, SA, AF, SS, and MK contributed to data collection and revising the manuscript. EC and IM contributed to the conceptualization and design of the study, revised the manuscript, and supervised the study. All authors approved the final manuscript as
submitted and agree to be accountable for all aspects of the work.

ORCID

Kensuke Shoji https://orcid.org/0000-0002-7164-0262

REFERENCES

1. Lautenbach E, Patel JB, Bilker WB, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. Clin Infect Dis. 2001;32:1162-1171.
2. Tamma PD, Han JH, Rock C, et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis. 2015;60:1319-1325.
3. Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014;58:1072-1083.
4. Carlier M, Stove V, Roberts JA, Van de Velde E, De Waele JJ, Verstraete AG. Quantification of seven β-lactam antibiotics and two β-lactamase inhibitors in human plasma using a validated UPLC-MS/MS method. Int J Antimicrob Agents. 2012;40:416-422.
5. Du X, Li C, Kuti JL, Nightingale CH, Nicolau DP. Population pharmacokinetics and pharmacodynamics of meropenem in pediatric patients. J Clin Pharmacol. 2006;46:69-75.
6. Aguiar EB, Maciel LC, Halpern M, et al. Outcome of bacteremia caused by extended-spectrum β-lactamase-producing Enterobacteriaceae after solid organ transplantation. Transplant Proc. 2014;46:1753-1756.
7. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the surgical infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133-164.
8. Shimamoto Y, Fukuda T, Tanaka K, Komori K, Sadamitsu D. Systemic inflammatory response syndrome criteria and vancomycin dose requirement in patients with sepsis. Intensive Care Med. 2013;39:1247-1252.
9. Ikawa K, Morikawa N, Ikeda K, Miki M, Kobayashi M. Population pharmacokinetics and pharmacodynamics of meropenem in Japanese pediatric patients. Infect Chemother. 2010;16:139-143.
10. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis. 2018;18:108-120.

How to cite this article: Shoji K, Saito J, Oho Y, et al. Meropenem pharmacokinetics during relapsing peritonitis due to ESBL-producing Enterobacteriaceae in a liver transplant recipient. Clin Case Rep. 2019;7:2169–2173. https://doi.org/10.1002/ccr3.2398