Pharmacokinetics and Therapeutic Target Attainment of Meropenem in Pediatric Post-Liver Transplant Patients: Extended vs Intermittent Infusion

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ABSTRACT

Purpose. The aim of this study is to characterize the concentration-time profile, pharmacokinetics parameters, and therapeutic target attainment of meropenem in pediatric post-liver transplant patients according to the duration of infusion.

Methods. This is a prospective cohort of pediatric transplant recipients with preserved renal function receiving meropenem 40 mg/kg every 8 hours. The patients were stratified into 2 groups based on infusion duration: G1 (15 minutes of intermittent infusion) and G1 (3 hours of extended infusion). Two blood samples per child were collected during the same interval within 48 hours of starting the antimicrobial. Meropenem concentrations were determined by high-performance liquid chromatography with tandem mass spectrometry. Pharmacokinetic parameters were assessed using a noncompartmental analysis. The therapeutic target was defined as 100% of the time above the minimum inhibitory concentration.

Findings. Fourteen patients with 28 measured meropenem concentrations were included. Lower values of volume of distribution and meropenem clearance compared with other critically ill pediatric populations were found. All patients achieved the therapeutic target against gram-negative pathogens with a minimum inhibitory concentration of $\leq$8 mg/L. Patients receiving a 15-minute infusion had higher values of peak and trough concentrations, resulting in unnecessary increased total drug exposure when compared to patients receiving a 3-hour infusion ($P < .05$).

Conclusions. Meropenem at 120 mg/kg/d attained the therapeutic target against sensitive microorganisms in pediatric liver transplant recipients. The extended infusion should be preferred for patient safety. Because of the pharmacokinetic changes resulting from liver transplantation, individualized meropenem dosing regimens may be necessary.

MEROPENEM is a broad-spectrum β-lactam antibiotic frequently administered to critically ill patients for the treatment of severe infections, including those caused by multidrug-resistant (MDR) bacteria [1]. Liver transplant recipients present a high incidence of MDR colonization and infections because of immunosuppression, prolonged length of stay, multiple hospitalizations, medical procedures, invasive devices, frequent use of antibiotics, and the absence of an antimicrobial stewardship program on a daily basis [2].

A recent cohort study by Cies et al found that 95% of the critically ill children receiving β-lactams were outside of the recommended therapeutic range and required dose adjustments [3]. Unfortunately, few hospitals possess the capability to conduct high-performance liquid chromatography or mass

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spectrometry assays for real-time therapeutic drug monitoring of β-lactams [1]. Critically ill pediatric patients receiving liver transplantation present pathophysiological changes that significantly impact the pharmacokinetics and pharmacodynamics of antibiotics, but there is no data regarding meropenem pharmacokinetics after liver transplantation [4]. Therefore, these patients receive the generally recommended starting dose.

As with other β-lactam antibiotics, the bactericidal activity of meropenem is time-dependent, so microbiological and clinical results depend on the dosing interval that free drug concentrations remain above the pathogen's minimum inhibitory concentration (%fT> MIC) [5]. Recent guidelines suggest that 100% fT>MIC is a reasonable target for meropenem in critically ill patients [6,7]. Because of this time-dependent activity, it has been previously proposed that prolonging the duration of infusion or increasing the frequency of dosing increases the probability of target attainment of meropenem and results in better outcomes [8,9].

Our purpose was to characterize the concentration-time profile, pharmacokinetics parameters, and therapeutic target attainment of meropenem in pediatric post-liver transplant patients according to the duration of infusion.

MATERIAL AND METHODS

Study Design

This is a prospective cohort study conducted in the pediatric intensive care unit of a philanthropic hospital in São Paulo, Brazil, between February 2020 and October 2022. The study was approved by the local ethics committee. Caretakers of the children signed the informed written consent forms.

Participants

Pediatric patients (aged <18 years) in postoperative care of liver transplantation receiving meropenem were included in this study. Patients with renal impairment with an estimated creatinine clearance <50 mL/min using the Modified Schwartz equation [10] or receiving renal replacement therapy were excluded. Meropenem therapy started at 40 mg/kg every 8 hours, infused over 15 minutes (intermittent infusion) or 3 hours (extended infusion), according to the physician's decision. Therefore, the patients were stratified into 2 groups: G1, intermittent infusion (15 minutes), and G2, extended infusion (3 hours).

Data collection included patient age, weight, height, primary diseases, date of surgical procedure, postoperative day (defined as the period between the transplantation day and the first day of vancomycin monitoring), mechanical ventilation, vasoactive drugs, concomitant drugs, graft weight to recipient weight, serum albumin, aspartate aminotransferase, alanine aminotransferase, urea, serum creatinine, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, direct bilirubin, hemoglobin, hematocrit, platelet count, lactate, C-reactive protein, white blood count, prothrombin time, partial thromboplastin time, and fibrinogen.

Meropenem Dosing and Quantification

Two blood samples per child were collected during the same interval within 48 hours of starting the antimicrobial. The first samples were collected at least 1 hour after infusion, whereas the second samples were collected within 1 hour before the next dose.

The collected blood samples were promptly transported to the laboratory for immediate processing. After centrifugation (at 1100g for 8 minutes), the resulting serum was preserved at a temperature of -20°C until further laboratory analysis. Serum concentrations of meropenem were determined using a high-performance liquid chromatography-tandem mass spectrometry method previously validated for the simultaneous detection of piperacillin and meropenem. Briefly, the samples and internal standards were processed with acetonitrile and water as extractor solution and protein precipitant, followed by high-performance chromatographic separation with gradient elution of mobile phase A (2 mM ammonium acetate) and phase B (acetonitrile), both phases with 0.1% formic acid. The mass/charge transitions were monitored and detected by mass spectrometry using the Acqwity model (triple quadrupole/liquid chromatography of ultra-efficiency) from Waters. The intra-day and inter-day precision and relative errors were <10%, with plasma recovery within the acceptable limits of 80% to 120% and no significant matrix effects. The lower limit of detection was 0.27 μg/mL for meropenem. This method has been successfully applied in therapeutic monitoring studies of meropenem and piperacillin in septic burn patients [11].

Pharmacokinetic and Pharmacodynamic Analysis

Noncompartmental pharmacokinetic analysis was performed on patients' individual drug concentrations using PKanalix (MonolixSuite 2019R1, Lixoft, France). Pharmacokinetic variables included predicted peak and trough, elimination rate constant, biological half-life, meropenem clearance, and volume of distribution. The therapeutic target was defined as maintaining the drug concentration above MIC for the entirety of the dosing interval (100%fT> MIC), considering the highest values established by the Clinical and Laboratory Standards Institute for antipseudomonal activity: sensible (MIC $\leq$ 2 mg/L) and intermediate (MIC = 4 mg/L) [12].

Statistical Analysis

The statistical analysis of the study data was conducted using GraphPad Prism 7.0 software (GraphPad Software). Categorical data are presented as absolute frequencies (N) and percentages (%). Continuous demographic data, as well as the pharmacokinetics, are expressed as medians (IQR). Statistical comparisons between groups were performed using the Mann−Whitney U test or Fisher exact test, with significance defined as $P < .05$.

RESULTS

Study Population

Nineteen patients receiving meropenem after liver transplantation were considered. However, 5 patients were excluded because they had renal impairment before receiving meropenem. Accordingly, 14 patients with 28 measured meropenem concentrations were included. The median age of the studied population was 16 months. The main primary disease requiring liver transplantation was biliary atresia (63%). The predominant infection was bacteremia (29%), followed by pulmonary (7%) and abdominal (7%) infections. Among the cohort, 8 patients (57%) exhibited clinical manifestations consistent with sepsis, lacking a definitively localized site of infection at the

Table 1. Characteristics of Pediatric Post-Liver Transplant Patients at the Beginning of Meropenem Monitoring, n = 14

Variables	Value		*P* Value
	G1, n = 7	G2, n = 7	
Demographic data			
Sex ratio (men/women), n	4/3	4/3	> .5
Age (mo), median (IQR)	14 (8-84)	25 (13.5-38.5)	> .5
Weight (kg), median (IQR)	8.6 (8-19)	11.3 (6.5-13.9)	> .5
Height (cm), median (IQR)	68 (66-113)	85 (68.5-89.3)	> .5
Clinical data, median (IQR)			
Serum albumin (g/dL)	3.9 (3.6-4.2)	3.4 (3-3.6)	> .5
Alanine aminotransferase (U/L)	195 (155-227)	332 (201-370.5)	> .5
Aspartate aminotransferase (U/L)	84 (78-222)	198 (132-214)	> .5
Urea (mg/dL)	49 (27-55)	30 (15.5-44)	> .5
Serum creatinine (mg/dL)	0.2 (0.2-0.3)	0.2 (0.2-0.2)	> .5
Creatinine clearance (mL/min/1.73 m^2)	164 (160-170)	175.6 (145.6-209.9)	> .5
Graft weight to recipient weight (%)	2.8 (2-3.2)	2.8 (2-3.6)	> .5
Gamma-glutamyltransferase (U/L)	25 (23-44.5)	81 (31.5-104.5)	> .5
Alkaline phosphatase (U/L)	89 (56.5-121.5)	119 (114-181)	> .5
Total bilirubin (mg/dL)	5.2 (4.7-8.7)	6.8 (3.9-10.5)	> .5
Direct bilirubin (mg/dL)	3.6 (2.8-6.2)	5.6 (3-7.9)	> .5
Hemoglobin (g/dL)	9.8 (9.2-10.2)	8 (7.4-8.7)	> .5
Lactate (mg/dL)	9 (8.5-25.5)	10 (8.5-12.5)	> .5
C-protein reactive (mg/dL)	3 (2.2-4.4)	3.5 (2-4.9)	> .5
White blood count $\times 10^3/mm^3$	5.5 (4.1-6.1)	5.6 (3.2-7.4)	> .5
Platelet $\times 10^3/mm^3$	32 (26-73)	50 (42.5-85)	> .5
Prothrombin time (s)	25.6 (21.8-37.2)	19.8 (19.1-25)	> .5
Partial thromboplastin time	38.7 (35-74.3)	38.6 (34-47.4)	> .5
Fibrinogen (mg/dL)	153 (130-169.25)	154 (135-163.5)	> .5
Postoperative day	2 (1.5-3)	2 (1-3)	> .5
Mechanical ventilation, n (%)	4 (57%)	0 (0%)	> .5
Vasoactive drug, n (%)	1 (14%)	0 (0%)	> .5
Concomitant administration of tacrolimus, n (%)	4 (57%)	2 (29%)	> .5
Site of infection			
Bacteremia	2 (28%)	2 (28%)	> .5
Pulmonary	1 (14%)	0 (0%)	> .5
Abdominal	0 (0%)	1 (14%)	> .5
Unknown	4 (57%)	4 (57%)	> .5

commencement of meropenem therapy. Seven patients received meropenem with a 15-minute infusion (G1), and 7 patients received a 3-hour extended infusion (G2). Table 1 summarizes the characteristics of the patients at the beginning of therapeutic monitoring. All analyses were performed within 5 days of transplantation. There was no difference between the groups regarding the clinical and demographic characteristics. Eleven patients (78%) presented augmented renal clearance (creatinine clearance >130 mL/min/1.73 m^2). During the study period, no adverse reactions to meropenem were registered.

Therapeutic Drug Monitoring and Pharmacokinetics

Table 2 shows the pharmacokinetic profile of meropenem in G1 and G2. Patients who received intermittent infusion had higher values of peak and trough concentrations, resulting in greater total exposure to meropenem (area under the curve) when compared with patients who received extended infusion ($P < .05$). Patients showed a wide inter-individual variation of meropenem concentration-time profile (Fig 1). In all patients, the therapeutic target of 100% *f*T>MIC was attained against gram-negative pathogens with MIC ≤8 mg/L.

DISCUSSION

This is the first study describing meropenem pharmacokinetics in pediatric patients after liver transplantation. The pharmacokinetic parameters were described both for patients receiving label-recommended infusion duration and for patients receiving extended infusion. Regardless of the infusion duration, all patients achieved the therapeutic target of 100% *f*T>MIC against pathogens with MIC up to 8 mg/L.

In this cohort, composed of 2 groups (G1 and G2), the median half-life varied between 1.8 and 2.7 hours. Meropenem is known for its short half-life, and the biological half-life value in this investigation is similar to the values described in children and adults [13,14]. The median volume of distribution ranged from 0.08 to 0.17 L/kg, slightly below previously reported values for meropenem of 0.4 L/kg in pediatric patients with clinically stable conditions and 0.2 L/kg in critically ill children

Table 2. Pharmacokinetic Parameters of Meropenem in Pediatric Liver Transplant Recipients Receiving 15-Minute Infusion (G1) or 3-Hour Extended Infusion (G2), n = 14

Variable	Value Intermittent Infusion, n = 7	Value Extended Infusion, n = 7	*P* Value*
Therapeutic drug monitoring data, median (IQR)			
Initial daily dose (mg/kg)	115.4 (112.7-122.5)	119.5 (114.8-127.9)	> .05
k_{el} (h^{-1})	0.256 (0.220-0.310)	0.384 (0.245-0.420)	> .05
$T_{1/2}$ (h)	2.7 (2.2-3.2)	1.8 (1.7-2.9)	> .05
CL_{mer} (mL/min/kg)	0.39 (0.16-0.40)	0.97 (0.84-1.29)	< .05
V_d^{ss} (L/kg)	0.06 (0.04-0.13)	0.17 (0.12-0.33)	< .05
Peak (mg/L)	389.7 (326.8-888.4)	154.9 (102.4-174.7)	< .05
Trough (mg/L)	79.1 (58.9-94.1)	24.2 (13.2-34.6)	< .05
AUC_{24} (mg/h/L)	5318.5 (4578.1-12023.9)	2041.9 (1643.7-2303.1)	< .05
Patients who reach the therapeutic target against MIC, n(%)			
1 mg/L	7 (100%)	7 (100%)	
2 mg/L	7 (100%)	7 (100%)	
4 mg/L	7 (100%)	7 (100%)	
8 mg/L	7 (100%)	7 (100%)	

AUC, 24-hour area under the curve-time curve; CL_{mer}, meropenem clearance; K_{el}, elimination rate constant; MIC, minimum inhibitory concentration; $T_{1/2}$, biological half-life; Vd^{ss}, volume of distribution.

* Mann-Whitney *U* test or Fisher exact test (significant at *P* <.05).

[13,15]. All patients in our study had slow meropenem clearance (<3 mL/kg/min), with a median of 0.39 to 0.97 mL/min/kg. Nevertheless, Cies et al found a median meropenem clearance of 6.5 mL/kg/min in 9 critically ill young children (aged 1 to 9 years) [16]. Blumer et al and Du et al suggest an estimated clearance range of 3 to 6 mL/min/kg [13,17]. Wang et al reported an even higher median of 7.2 mL/kg/min in 57 critically ill infants and children (aged 1 month to 14.4 years) [18]. A tendency for younger patients to have lower clearance was observed, probably because of the natural process of development of renal function during the first 2 years of life. Therefore, besides our median ages between 1 and 2 years, the unique patient characteristics from our cohort (eg, post-liver transplantation) may have also contributed to the lower meropenem clearance found.

Maimongkol et al reported that patients receiving the usual dose of meropenem of 20 mg/kg with 30 minutes of infusion are at high risk of subtherapeutic levels [19]. The most commonly described strategies for enhancing target attainment involve increasing the dose or frequency of drug administration, as well as extending the duration of infusion [8]. Population pharmacokinetics analysis also suggested that higher doses may be necessary to ensure antimicrobial coverage against pathogens with MIC near the clinical breakpoint [13,18]. In our cohort, the maximum approved

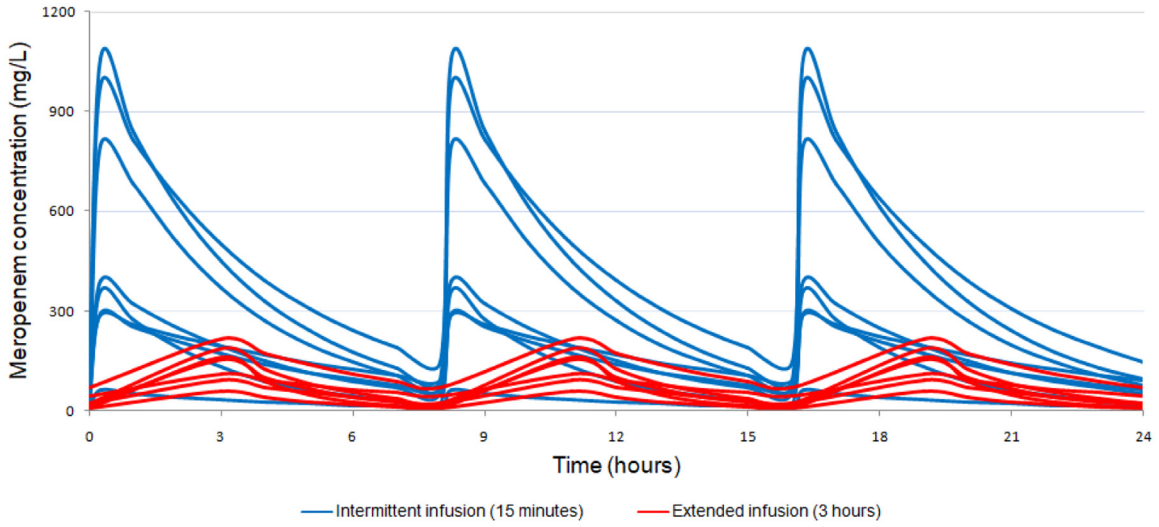

Fig 1. Individual plasma-concentration–time curves of meropenem at steady state of 14 pediatric liver transplant recipients; 40 mg/kg every 8 hours infused over 15 minutes or over 3 hours.

dose of meropenem (120 mg/kg/d) for children was sufficient to attain the therapeutic target against sensitive microorganisms regardless of infusion duration, probably because our patients had low clearance.

In the present study, the main difference found between patients who received extended infusion and intermittent infusion was that those with intermittent infusion had significantly higher peak values and unnecessarily increased total drug exposure. Some evidence suggests a dose dependence between β-lactam exposure and neurotoxicity [20]. A previous cohort study of hospitalized patients found that meropenem trough concentrations higher than 64 mg/L may increase 50% the incidence of neurotoxicity [21]. Because the efficacy of β-lactams does not depend on peak concentration, in critically ill patients with a high risk of MDR infection, such as transplant recipients, for whom higher doses are required, it is intuitive to recommend the prolonged or continuous infusion strategies to avoid unnecessarily high peaks of meropenem for a patient's safety, although a clear superior limit of concentration has not yet been established and require further investigation.

The wide inter-individual variation of the meropenem concentration-time profile supports the need to individualize meropenem dosing. A recent guideline proposes that the implementation of therapeutic drug monitoring with real-time dosing optimization of meropenem would benefit patients with highly variable and unpredictable pharmacokinetics or those at risk of being infected with a pathogen that has an MIC near or above the susceptibility breakpoint [6]. However, several obstacles currently hinder the widespread integration of beta-lactam therapeutic drug monitoring into clinical practice. These include inadequate awareness among health care providers, insufficient evaluation of cost-effectiveness, and limited availability of bacterial susceptibility information [1].

This study is subject to certain limitations, notably its single-center design and relatively small sample size. Because most of the patients were aged <2 years, caution should be used when extrapolating results to older patients. Additionally, it was not the purpose of this study to investigate the correlation of therapeutic target attainment with clinical or microbiologic outcomes, and we were unable to track the complete clinical course of all patients because of their transfer to another medical facility. Nevertheless, our study still provides essential information about the clinical pharmacokinetics and drug disposition of meropenem in pediatric post-liver transplant patients.

CONCLUSIONS

In pediatric patients after liver transplantation, meropenem at 120 mg/kg/d was sufficient to attain the therapeutic target against sensitive microorganisms regardless of infusion duration; however, the 3-hour extended infusion should be preferred for patients' safety because it avoids unnecessarily high peaks of meropenem. The wide inter-individual variation of the meropenem concentration-time profile supports the need to individualize meropenem dosing.

DECLARATION OF COMPETING INTEREST

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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