MEROPENEM PHARMACOKINETICS IN CHILDREN: SERIES OF CASES

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ABSTRACT

Daily doses of antibiotics recommended for children are based on studies in healthy adult volunteers, so this study aimed to describe the pharmacokinetic/pharmacodynamic characteristics of meropenem in children and to verify whether plasma concentrations were within the range therapy. This is a series of cases, which included 4 children, aged 02-12 years old using meropenem dose empirical, 8/8h in 75% of children. The study was conducted in a pediatric hospital from March 2016 to March 2017. Only one child had the result of the culture of biological material recorded in medical records at the time of collection. We observed high inter-patient variability of pharmacokinetic parameters, however plasma concentrations of meropenem were effective in 100% of the study population considering the parameter 40%*f* T>CIM to CIM of 0.25μg/mL.

Keywords: Antibacterials. Meropenem. Children. Pharmacokinetics.

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INTRODUCTION

In children with bacterial infections, the selection of the antibiotic and the appropriate dose allows the management of treatment efficacy. The daily doses of antibiotics recommended for children are based on studies in healthy adult volunteers and it is known that the plasma concentrations of antibiotics in critically ill children can easily change due to rapid changes in physiology, body size and clinical status.[1-4]

Meropenem is a broad-spectrum carbapenem antibiotic and currently one of the main treatment options in severe infections.[1,3] Shows dependent time activity, and the pharmacodynamic parameter that predicts clinical results is the time that the plasma concentration remains above the minimum inhibitory concentration, and free fraction of 98%.[3-4] In pediatric populations its use is widespread, although studies on its pharmacokinetics and pharmacodynamics in this population are still scarce.[1,4]

In critically ill patients plasma concentrations of meropenem demonstrate high pharmacokinetic variability, with the efficacy of meropenem treatment being evaluated as a challenge, since no methods are available to rapidly assess the success or failure of the dosages used.[1-4]

In Brazil, the monitoring and adjustment of doses of antibiotics in children is not routinely performed, and the lack of this service not only compromises care, but also information related to the antimicrobial resistance pattern in children, as resistance is not well defined to carbapenems and, if related to concentrations, dose, pharmacokinetics, among other factors.[4-5] Therefore, this study aimed to describe the pharmacokinetic/pharmacodynamic characteristics of meropenem in children in a pediatric hospital and to verify whether the plasma concentrations of meropenem were within the therapeutic range.

MATERIAL AND METHODS

This study was approved by the Research Ethics Committee Involving Human Beings, CAE 44803815.700005545 of the Federal University of São João del Rei- Centro-Oeste Campus. It is a series of cases from medical records and collection of blood samples. The study was conducted at a large pediatric hospital, located in Belo Horizonte, Minas Gerais. The samples were all patients who consented to participate in the study from March 2016 to March 2017. Patient data information was collected only after approval by the Ethics Committee, and all the data of the participants involved were identified only with numbers, guaranteeing the anonymity of each patient's data. Both legal guardians and children, when possible, were invited to participate in the study, signing an Informed Consent Form (ICF) and the Term of Assent. Four children, both genders aged between 2 and 12 years old, using meropenem for at least five half-lives were included in the study. Burned children and children undergoing renal replacement therapy were excluded.

From the children's charts included in this study, the variables were obtained and transcribed to a database in *excel*: age, gender, date of birth, weight, height and body mass index (BMI), date of hospitalization, hospitalization unit, start of treatment, pharmacological therapy, antimicrobial infusion time, surgeries, central and peripheral venous catheters, intra-arterial puncture, mechanical ventilation and laboratory tests: serum creatinine, results of cultures of biological material: blood, urine, secretions and results of minimum inhibitory concentrations (CIM) for meropenem.

The height of the children, as well as the BMI, when not available in medical records was estimated from the anthropometric data available at the National Center for Health Statistics from the Center for Disease Control and Prevention (CDC, 2017).[6]

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The other variables of interest were obtained through equations: renal *clearance* (*Cl*), pharmacokinetic profile: volume of distribution (Vd), clearance constant (Kel), antimicrobial half-life ($T_{1/2}$), *clearance* of the antimicrobial and vale.

The renal *clearance* was estimated using the formula of Schawartz*et al.* (1976)[7], according to equation (eq.1):

$$CLcr=(Hxk)/Scr \quad [1]$$

H: Height (cm);

Scr: Serum creatinine (mg/dL);

K: constant related to age group and gender:

k: 0.45	Children <1 year old
k: 0.55	Children (1-12 years old) and female adolescents
k: 0.70	Teenage boys

The efficacy prediction parameter for meropenem considered for this study was the percentage of time in which the free drug fraction remained above the CIM, 40%*f*T>CIM[8] e 100%*f*T>CIM.[9]

The concentration in %*f*T>CIM of meropenem was determined from the equation (eq.) below: (eq.2)10

where:

Kel = clearance constant;

ln C1 = natural logarithm of the plasma concentration of the first collection;

ln C2= natural logarithm of the plasma concentration of the second collection;

T1 = time of first collection;

T2 = time of the second collection in relation to the value;

Cmin = minimum concentration (value)

Tmin=time to reach the minimum inhibitory concentration, according to the dose frequency administered (8/8h).

τ = dose range

CIM = minimal inhibitory concentration

Determination of antimicrobial half-life T1/2 (eq.3):

$$T1/2= 0.693/Kel \quad [3]$$

Volume of distribution (eq.4).

$$Vd=dose*(e^{-KT})/vale*(1-e^{-KT}) \quad [4]$$

Antimicrobial clerance (eq.5)

$$CL=Vd*Kel \quad [5]$$

The dose adjustment estimate for meropenem was performed using the equation suggested by Winter (2004)10 eq.6, maintaining an interval of 8 hours between doses, considering CIM of 1μg/mL and 4μg/mL, in 40 and 100% *f*T>CIM.

Dose estimation according to Winter (2004)[10] eq.6

Css desired = (Desired dose x Css current) / Current dose [6]

where:

C^{ss}: Concentration at steady state.

CIM changes were obtained from results from cultures of biological material (blood, urine, secretions) provided by the hospital infection control service (SCIH). The CIM results for meropenem provided by the hospital laboratory ranged from 0.25 and 1μg/mL.

The results of cultures of biological material of each child (isolated bacterium) were obtained through record in medical records.

The administration of meropenem, empirical dose, was performed according to recommendations of the local SCIH. Respecting the interval of five biological half-lives, two blood samples were collected on the third day of treatment with meropenem at different times, with a minimum interval of two hours between the collections, through a venous catheter and / or arterial catheter already existing in children (2mL/collection in Vacutainer/Sodium EDTA bottle) and duly identified. The samples were centrifuged (Centrifuge Excelsa Baby® I 206), for 15 minutes at 3500 rpm, 500 μL of plasma was withdrawn and stored in eppendorf tapered tubes with 500μL of 10% solution of MOPS (3-[N-morpholin]-propanesulfonicacid, J.T. Baker®) to preserve the stability of meropenem.

The samples were frozen at -80oC until the moment of the analysis. The quantification of the drug in biological matrix was performed by high performance liquid chromatography (HPLC) using SHIMADZU model LC 10A chromatograph (Kyoto, Japan). For the quantification of serum meropenem in plasma, a methodology developed and validated previously by Santos *et al* was used. (2011)[5], considering the free fraction of 98%2 the final concentration was calculated for the free drug from this ratio.

RESULTS AND DISCUSSION

During the study period, from March 2016 to March 2017, four pediatric patients, aged 12; 2; 11.8 and 5.6 years old respectively were included. Weight 27.5 (median) 21.1-35.6 (IQ) kg, height 127 (median) 103-131 (IQ) cm, using meropenem. 50% (2) of the participants were hospitalized in the intensive care unit (ICU), in mechanical ventilation and in vasoactive drug use, and another 50% (2) in the ward. The individual characteristics of these children were expressed through the median, interquartile, minimum and maximum values, table 1.

Table 1-Anthropometric data and individual characteristics of the children included in the study (n=04).

Children	INDIVIDUAL CHARACTERISTICS						
(n=04)	SEX (F/M)	AGE (years)	WEIGHT (Kg)	HEIGHT (cm)	BMI (kg/m2)	SCr (mg/dL)	Clcr (mL/min.)
#1	F	12	31	149	13.96	0.67	122.31
#2	F	2	12.600	85	16.63	0.42	111.3
#3	M	11.8	60	144	28.63	0.45	176
#4	M	5.6	24	110	19.88	0.19	378.1
Median	-	8.7	27.5	127	18.23	0.43	149.10
Interquartile 25% -75%	-	4.7-9.4	21.1-35.6	103-131	15.9-28.9	0.35-0.43	119.5-226.5
Vmin./Vmax.	-	2/12	31/90	85/149	13.9/28.9	0.16/0.67	111.3/378

Abbreviations: Scr: creatinine. Cl: clerance. F: female. M: male. Vmin: Minimum value. Vmax: maximum value

Serum meropenem concentrations obtained from blood samples, using the method developed by Santos *et al.* (2011)5, as well as the results obtained from the meropenem pharmacokinetic (PK) analysis were described in Table 2.

Table 2–Pharmakinetic parameters (PK) of meropenem.

Children	Pharmacokinetic Parameters					
(n=04)	Cmax (µg/ml)	Cmin (µg/ml)	t(1/2)ß (h)	CLT (mL/min)	Kel (h-1)	Vd(L/kg)
#1	1.7	1.4	9.91	4.92	0.09	3.04
#2	16.1	11.3	5.44	1.29	0.17	0.43
#3	40.8	21.2	2.94	0.60	0.32	0.11
#4	1.5	1.3	3.39	6.95	0.28	1.47
Median	8.9	6.3	4.41	3.10	0.23	0.95
Interquartile 25% -75%	-	-	3.27-4.67	1.20-4.07	0.15-0.29	0.35-1.08
Vmin./Vmax.	1.3/40.8	1.3/21.2	2.94/9.91	0.60/6.95	0.09/0.32	0.11/3.04

Abbreviations: Cmax/Cmin(µg/ml) maximum and minimum concentration observed.T(1/2)biological half-life. CLT: clerance total. Vd: volume of distribution. Kel: Clearance constant. PK: pharmacokinetic parameter. Vmin: minimum value. Vmax: maximum value.

Regarding the pharmacodynamic profile (PD) it was verified that for meropenem, considering CIM 0.25 and 1µg/mL, obtained from results of cultures of biological material of the local laboratory, with 100%*f*T>CIM,75% of the children maintained plasma concentrations within the therapeutic target PK/PD. For CIM 4µg/mL, with 100%*f*T>CIM, 50% of the children had plasma concentrations within the target. On the other hand, for parameter 40%*f*T>CIM, coverage was 100% for the CIM of 0.25µg/mL and 75% for CIMs of 1 and 4µg/mL, according to table 3.

Table 3 - Pharmacodynamic profile (PD) of the population studied for meropenem (n=4).

Children (n=4)	Culture results	%fT>CIM		
		0.25 µg/mL	1 µg/mL	4 µg/mL
#1	Not isolated	50%	30%	10%
#2	Pseudomonas sp.	100%	100%	100%
#3	BGN.	100%	100%	100%
#4	Not isolated	100%	100%	75%
Median		100	100	87.5
Interquartile		87.5-100	82.5-100	58.7-100
V.min/V.max		50/100	30/100	10/100

Abbreviations: BGN: Gram-negative bacillus.

Three children used meropenem, with 60 minutes infusion, and were diagnosed with severe infections requiring empirical therapy. Only one child #4 (25%) was in protocol for bacterial decolonization using meropenem infusion for 180 minutes. The individual characteristics of each child were used to calculate the adjusted dose. The empirical dose used, and the adjusted dose estimate are described in Table 4.

Table 4 - Empirical daily dose regimen of meropenem *versus* adjusted dose estimate by Winter (2004) (n=4).

Cases (n=4)	Prescribed Empirical Dosage			Dose Adjustment Suggestion				
	Dose (mg/kg)	Interval between doses (h)	Infusion time (min.)	Dose (mg)	CIM 1µg/mL 40 % fT>CIM (µg/mL)	CIM 1µg/mL 100 % fT>CIM (µg/mL)	CIM 4µg/mL 40 % fT>CIM (µg/mL)	CIM 4µg/mL 100 % f>CIM (µg/mL)
#1	20mg/kg	8/8	60	620mg	291	464.88	1166	1859
#2	20mg/kg	8/8	60	252mg	14.8	34.7	59	138
#3	16.7mg/kg	8/8	60	1000mg	22.2	106.9	88	427
#4	40mg/kg	8/8	180	960mg	107	418.0	428	1672
Median	20	-	60	790	64.6	262.5	258	1050
Interquartile 25%-75%	19.1-25	-	60-90	528-970	20.3-75.2	88.8-301	81-300	355-1205
Vmin./Vmax	16.7/40	-	60/180	252/1000	14.8/291	34.7/464	59/1166	138/1859

Abbreviations: %fT>CIM: percentage of time above the minimum inhibitory concentration. *Considering an interval between doses of 8 hours, CIM between 1 and 4 µg/mL and 40 and 100% fT>CIM.

This is one of the few studies conducted in Brazil evaluating meropenem concentrations in children. Current evidence on the PK/PD efficacy of meropenem in children is scarce,1,4-5 generating apprehension regarding dose adjustment in this population. Cconsidering the parameter of efficacy suggested by Pai, Cojutti and Pea (2015),9 100%*f*T>CIM in 75% of the children were found effective concentrations, this result was like the study by Kongthavonsakul *et al.* (2016),4 the author evaluates PK/PD concentrations and parameters in 14 children with severe infections.

There was great inter-patient variability in relation to the studied pharmacokinetic parameters. These pharmacokinetic variabilities may be associated with differences in age, physiological characteristics such as volume of distribution, biological half-life, renal clerance and clinical condition.[1,4-5] To Santos *et al.*, (2011)[5] in their study evaluating only one burned child, observed differences in pharmacokinetic parameters at two different moments of evaluation, indicating that these alterations in the parameters are related to clinical status, changes in the degree of hydration, serum protein concentrations, creatinine clearance, presence of lesions, mechanical ventilation and the use of vasoactive drugs. As in the study of Kongthavonsakul *et al.* (2016)[4] the interindividual variability in relation to pharmacokinetic parameters did not occur due to age, but due to the physiological changes of the severe clinical picture, since many of these children had some organic dysfunction, indicating the need for therapeutic monitoring and dose individualization in populations pediatric patients.

Abbreviations: %*f*T>CIM: percentage of time above the minimum inhibitory concentration. *Considering an interval between doses of 8 hours, CIM between 1 and 4 μg/mL and 40 and 100% *f*T>CIM.

There are no records at the time of collecting on renal changes or other organic dysfunctions that could affect the pharmacokinetic parameters found, however, child #1 presents sickle cell anemia, was hemotransfused multiple times, which could explain $t_{(1/2)}$ß e Vd increased, and the therapeutic target did not reach the other parameters evaluated. For Kongthavonsakul *et al.*, (2016)[4] most children infected in pediatric wards have some form of organic dysfunction.

Regarding infusion of meropenem in this study when compared to similar studies performed in children as in the study of Kongthavonsakul *et al.* (2016)[4] the authors reported better effectiveness of meropenem and therapeutic target range in continuous infusions. In our study only in one child was indicated continuous infusion, with superior dosage, in application of decolonization protocol.

It is important to note that only one child had recorded the species of the bacterium isolated, for the others, now of collection of the blood sample, the bacterium causing the infection was unknown, this is a relevant data for PK/PD analysis. The therapeutic target assessment was performed based on the local epidemiological profile considering the CIM variations of 0.25, 1 and 4μg/mL.

Regarding the ideal dose of meropenem, dose estimation was suggested according to Winter (2004),10 since a population model for dose adjustment is not available in Brazil. According to the results obtained through the adjusted dose estimate, it is suggested that meropenem doses should be reduced in 100% of the cases considering CIM of 1μg/mL and the parameter 100%*f*T>CIM, and reduced in 50% of the cases considering CIM of 4μg/mL and the parameter 100%*f*T>CIM. However, this information should be interpreted with caution, since CIM results were not available for 75% of the cases, and the author uses an equation for nonspecific dose calculation and the reduction could reduce the effectiveness found, as well such as predisposition to bacterial resistance at lower concentrations than required. As an example we can mention child #4, an obese child, using a dose suggested for adults, since pharmacokinetic studies are rare in obese children and, according to Hites *et al.* (2013)1 pharmacokinetic studies in obese subjects are essential to avoid risk of underdosage or overdosage, so in this case the dose suggested by Winter (2004)10 could not be taken as the ideal reference for application of dose adjustment for meropenem.

This study was limited by the number of children included and some data not available on the chart at the time of the evaluation, such as record of results of cultures of biological material and CIM, which could imply other conclusions in the presented results. However, these results are important in evaluating and encouraging the implementation of therapeutic monitoring services and instigates the need for further studies to explore the pharmacokinetics of meropenem in children to provide an optimal dose regimen.

CONCLUSION

Given the paucity of pharmacokinetic data of meropenem in children for comparison purposes, we observed that despite the high inter-patient variability of pharmacokinetic parameters, plasma concentrations of meropenem were within the therapeutic range, guaranteeing the therapeutic efficacy of the drug considering the parameter 40%*f* T>CIM to CIM of 0.25μg/mL.

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Contributors:

GSCA collected, interpreted study data and performed article writing. FMDC conducted the critical review of the article. CS coordinated the study project, contributed to the analysis and interpretation of the data and performed the critical review of the article. All authors are responsible for the article information and have approved the final version for publication.

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