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Evaluation of Liquid Chromatography for Routine Quantification of Meropenem, Ceftazidime, and Piperacillin in Serum and Cerebrospinal Fluid

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Abstract

Critically ill patients often benefit from therapeutic drug monitoring (TDM) of -lactam antibiotics to reduce the risk of treatment failure. In this research, we created a rapid and easy-to-use high-performance liquid chromatography (HPLC) test for the detection of meropenem, ceftazidime, and piperacillin in human serum and for the quantification of meropenem in CSF.

Methods: An Atlantis® T3 5.0 m stationary phase was employed in this procedure. Mobile phase A was composed of 99.4 percent (m/m) water and 0.6 percent (m/m) formic acid (pH 2.30). Acetonitrile (93.6% m/m), water (6% m/m), and formic acid (0.4%) were the components of mobile phase B. Meropenem, ceftazidime, and piperacillin were all determined using a gradient elution technique. UV absorbance detection was performed at 309nm, 258nm, 235nm, and 260nm. An internal standard was included in the sample-preparation process, and acetonitrile/methanol was used to precipitate the proteins.

Results The method's linearity, specificity, accuracy, and precision were all studied. Antibiotic compounds and an internal standard were tested for their stability. Single run duration was 23 minutes, while meropenem retention time was 7.222 minutes. Quantification of meropenem was performed from the LOD (0.1mg/l in serum and CSF) to the ULOQ (100mg/l in serum and 25mg/l in CSF). High interindividual variability in serum and CSF meropenem levels was seen in routine analysis, with a mean CSF/serum ratio of 0.129 0.03. Meropenem, ceftazidime, and piperacillin all passed an external validation using the proposed technique with a score of 0.092.

The results of this experiment show that it is possible to examine relationships between meropenem dose, serum concentration, and CSF concentration. Serum from humans may also be tested for ceftazidime and piperacillin. To learn more about how deeply meropenem enters cerebrospinal fluid, researchers may conduct larger-scale experiments. The described methodology is useful for measuring the chemicals in serum and CSF and may be suggested for use.

Keywords: Meropenem, Ceftazidime, Piperacillin, Therapeutic drug monitoring, HPLC, validation, human serum, cerebrospinal fluid

Introduction

pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]the 4-methyl-7-oxo-1-azabicyclo[3.2.0] (Figure 1[1]) hept-2-ene-2-carboxylic acid has significant antibacterial action against both gram-positive and gram-negative bacteria, making it an ideal carbapenem derivative. It is a -lactam antibiotic, therefore it blocks cell wall formation by penetrating the bacterial cell wall [2]. It is utilized as a last-resort antibiotic in critical care units (ICUs) because of its high stability against beta-lactamases [3, 4]. When external ventricular drains (EVD) are utilized in the treatment of acute subarachnoid hemorrhage, intraventricular bleedings, or other acute cerebral pathologies, ventriculitis is a common consequence [5].

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Meropenem is often indicated for the treatment of such nosocomial infections. Since antimicrobial resistance is on the rise and there are few novel antimicrobials for clinical use, optimizing doses of already used drugs is crucial for achieving optimal therapeutic effects [3, 6, 7]. Therapeutic drug monitoring (TDM) of beta-lactam antibiotics is a common method for improving the efficacy of multiple antibiotic regimens. TDM is especially useful in intensive care units because it enables precise administration of medications for critically sick patients whose pharmacokinetics have been changed owing to organ failure at varying stages [8-10]. Critical care doctors have a number of challenges, but one of the biggest is ensuring that the right amount of antibiotic is present in the right tissues at the right time. The blood-CSF-barrier prevents meropenem from reaching its target area in ventriculitis [11]. Meropenem's penetration into CSF in individuals with ventriculitis has been shown to be very varied in recent studies [12, 13]. Additional evidence suggests that CSF concentrations below the minimal inhibitory concentration (MIC) [13] cannot be achieved with the conventional dose of meropenem (3 × 2g as intermittent infusion). Continuous infusion of beta-lactam antibiotics is recommended for preventing treatment failure by maintaining concentrations during the dose interval [14]. Furthermore, the highest recommended dose of meropenem (maximum 6g/24h [15]) may not be effective, necessitating higher-than-recommended dosing regimens [16]. Adequate CSF concentrations were achieved in all patients within 48 hours [16] using median starting doses of 8.8g/24h and TDM-guided dosage adjustment. Keeping ICUs supplied is a top priority, thus we

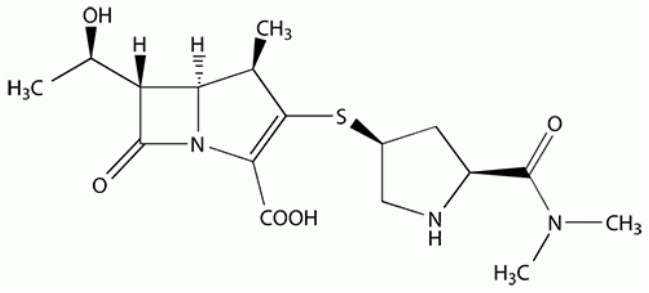

Figure 1: Structure of meropenem

describe a simple method to determinate meropenem in human serum and cerebrospinal fluid. The aim of this study is to demonstrate the development, validation and routine use of internal standard high-performance liquid chromatography assay for meropenem in human serum and cerebrospinal fluid. Additionally this method is able to determine ceftazidime andpiperacillin in human serum.

Materials and Methods

Antibacterial agents and other substances

We used meropenem powder for solution for injection/ infusion, commercially available from Dr. Friedrich Eberth Arzneimittel (Ursensollen, Germany), piperacillin/ tazobactam powder for solution for injection/infusion, commercially available from Fresenius Kabi Deutschland (Bad Homburg, Germany) and ceftazidime powder for solution for injection/infusion, commercially available from Dr. Friedrich Eberth Arzneimittel (Ursensollen, Germany). Also cefotaxime powder for solution for injection/infusion, commercially available from Fresenius Kabi Deutschland (Bad Homburg, Germany), cefazolin powder for solution for injection/infusion, commercially available from MIP Pharma GmbH (Blieskastel, Germany) and porcine serum from bio&sell GmbH (Feucht, Germany). Patient serum and patient cerebrospinal fluid were received from ICUs for TDM.

Solvents

We purchased formic acid, sodium hydroxide, methanol (HPLC grade) and acetonitrile (HPLC grade) from Th. Geyer GmbH & Co. KG (Renningen, Germany). Purified water was purchased from Fresenius Kabi Deutschland GmbH (Bad Homburg, Germany).

High-performance liquid chromatography (HPLC)

We used a high-performance liquid chromatography system by Shimadzu that contains a temperate autosampler, column oven and UV-Vis detector. Labsolution (Shimadzu, Germany) software was used to control the chromatographic system of the double internal standard based method. The stationary phase was Atlantis® T3 5µm, 15cm x 4,6mm Column (Waters Corpotation, Milford, MA, USA).

The mobile phase A contained water (99.4% m/m), formic acid (0.6% m/m) and was adjusted to pH 2.30 by the addition of 1M sodium hydroxide. The mobile phase B contained acetonitrile (93.6% m/m), water (6% m/m) and formic acid (0.4% m/m). We used a gradient elution method consisting of mobile Phase A and mobile phase B as seen in table 1.

The pump flow rate was 1.0ml/min. UV absorbance detection was used at 309nm (meropenem), 235nm (piperacillin), 258nm (ceftazidime), 260nm (cefotaxime) and 270nm (cefazolin). The column oven temperature was set to 20°C in routine. The method was running for 23min, the median retention times were 7.222min for meropenem, 17.541min for piperacillin, 6.704min for ceftazidime, 9.861min for cefotaxime and 12.105min for cefazolin at20°C.

Reference standards

To determine the content of the commercially available powders for solution for injection/infusion we used chemical reference substances (CRS). Meropenem trihydrate CRS (content 86.9%), piperacillin CRS (content 95.2%), ceftazidime CRS (content 85.5%), cefotaxime acid CRS (content 90.6%) and cefazolin (content 99.2%) were purchased from Sigma-Aldrich Chemie GmbH (Tauf kirchen,Germany).

Sample preparation

We prepared samples by mixing 250µl patient serum or CSF with 50µl internal standard (cefotaxime

125mg/l and cefazolin 125mg/l) and 500µl acetonitrile/methanol (1:1) for precipitation. The samples were mixed for 10s and centrifuged at 10 000 RPM for 10min. 200µl of the supernatant were diluted with 460µl water and 50µl of this mixture was injected.

Results

Selectivity

Selectivity of the analytical method was proven using six individual sources of the appropriate blank matrix (human serum), which were individually analyzed and evaluated for interference. No relevant interference was detected but to prevent interference with the internal standard we decided to use a mixture of two internal standards. If there is an interference with cefotaxime we can use cefazolin to analyze the patient sample. Interference may occur in patients who received cefotaxime or cefazolin in earlier therapy regimes.

Carry-over

To prevent carry-over we injected blank samples after high concentration samples [17]. There was no carry-over detected in the blank samples.

Table 1: Gradient time program for HPLC

Time (min)	Solvent B concentration (%)
0.01	10
1	10
11	35
15	35
16	10
23	10

Lower limit of quantification

The lower limit of quantification is defined as the lowest concentration of analyte in a sample, which can reliably be quantified, with an acceptable accuracy and precision. LLOQ is aimed to be at least 5 times the signal of a blank sample [17]. For this analytical method, the LLOQ for meropenem is 0.1mg/l in serum and CSF, 0.2mg/l for ceftazidime in serum and 10mg/l for piperacillin in serum.

Calibration curve

For time-dependent drugs, the main parameter associated with therapeutic success is the percentage of time that the levels of antibiotics at the infection site exceed the minimum inhibitory concentration (%f T > MIC) of the pathogen [18]. Due to the clinically sensible breakpoint against the pathogenic *Pseudomonas spp*. at 2 mg/l [19] we defined the target concentration in CSF > 2mg/l. For meropenem levels in serum we defined target concentrations of 8 – 16mg/l (100% fT > 4x MIC - 100% fT > 8x MIC). Ceftazidime serum target concentrations 32 – 48mg/l (100% fT > 4x MIC - 100% fT > 6x MIC) and piperacillin serum target concentrations 64 – 96mg/l (100% f T > 4x MIC - 100% fT > 6x MIC) due to their MIC breakpoints against *Pseudomonas spp* [19].

According to the target concentration range a minimum of six calibration concentration levels were used for each method [17]. The LLOQ is defined being the lowest calibration standard and the highest calibration standard defines the upper limit of quantification (ULOQ) as seen in table 2 [17]. LLOQ is 0.1mg/l for meropenem in serum and liquor, the ULOQ is 100mg/l in serum and 25mg/l in CSF. LLOQ is 0.2mg/l for ceftazidime in serum; the ULOQ is 75mg/l in serum. LLOQ is 10mg/l for piperacillin in serum; the ULOQis 200mg/l in serum.

For the calibration standards, we used porcine serum and residual material of human CSF. To prepare the calibration standards we spiked 200µl matrix with 50µl antibiotic solution (target concentration level x5 mg/l). The following steps were performed analog the sample preparation. All calibration curves analysis used freshly spiked samples. The correlation between mean area ratio and concentration ratio was strong for all calibration curves (R^2 >0.9999).

Accuracy

The accuracy describes the closeness of the determined value obtained by the method to the nominal concentration of the analyte. Accuracy was assessed on samples spiked with known amounts of the analyte. These samples were spiked independently from the calibration standards and were analyzed against the calibration curve. For the validation of the accuracy, we analyzed LLOQ, low, medium and high concentration samples. The mean concentration within a value of 15% from the nominal values is commonly considered acceptable, except for the LLOQ, which is acceptable within 20% of the nominal value [17]. The accuracy was demonstrated with all mean concentrations between 88.56% and 100.82% of the nominal value.

Precision

The precision of the analytical method describes the closeness of repeated individual measures of analyte in the same sample. Precision can be expressed as the relative standard deviation (RSD). Precision of the analytical method should be demonstrated for the LLOQ, low, medium and high sample concentrations. The RSD value should not exceed 15% for the low, medium and high concentration samples, except for the LLOQ, which should not exceed 20% [17]. Precision was demonstrated for every antibiotic substance with all RSD values ranging between 0.64% and 12.95%.

Stability

The low stability of meropenem in aqueous solutions or biological fluids is often reported in literature [20-22]. Even transport between clinic and laboratory is difficult due to the limited stability [21]. To detect stability, we analyzed the degradation of meropenem, ceftazidime and piperacillin under relevant conditions. Therefore, we evaluated the stability of meropenem in

spiked porcine serum and CSF after sample preparation at 5°C. This simulates the conditions in our autosampler and no relevant degradation was detected over 15h as seen in figure 2. Additionally we analyzed the stability of meropenem, ceftazidime and piperacillin in biological matrix.

We spiked human serum with a mixture of all three antibiotics and measured the concentrations at the beginning, after 24h and 48h. One sample was stored at 5°C, one in the freezer at -32°C and one at ambient temperature 25°C. The concentrations at 25°C decreased very fast compared to the samples at 5°C and -32°C as shown for meropenem

Table: 2 Antibiotic concentration levels used for the calibration curves. Every calibration sample contains 25mg/l internal standard (cefotaxime and cefazolin).

Conc. Level	Meropenem serum	Meropenem CSF	Ceftazidime serum	Piperacillin serum
#1	0.1 mg/l	0.1 mg/l	0.2 mg/l	10 mg/l
#2	0.2 mg/l	0.2 mg/l	0.5 mg/l	25 mg/l
#3	0.5 mg/l	0.5 mg/l	1 mg/l	50 mg/l
#4	1 mg/l	1 mg/l	2.5 mg/l	100 mg/l
#5	5 mg/l	2.5 mg/l	5 mg/l	160 mg/l
#6	12.5 mg/l	5 mg/l	10 mg/l	200 mg/l
#7	25 mg/l	10 mg/l	20 mg/l	not used
#8	50 mg/l	25 mg/l	30 mg/l	not used
#9	100 mg/l	not used	50 mg/l	not used
#10	not used	not used	75 mg/l	not used

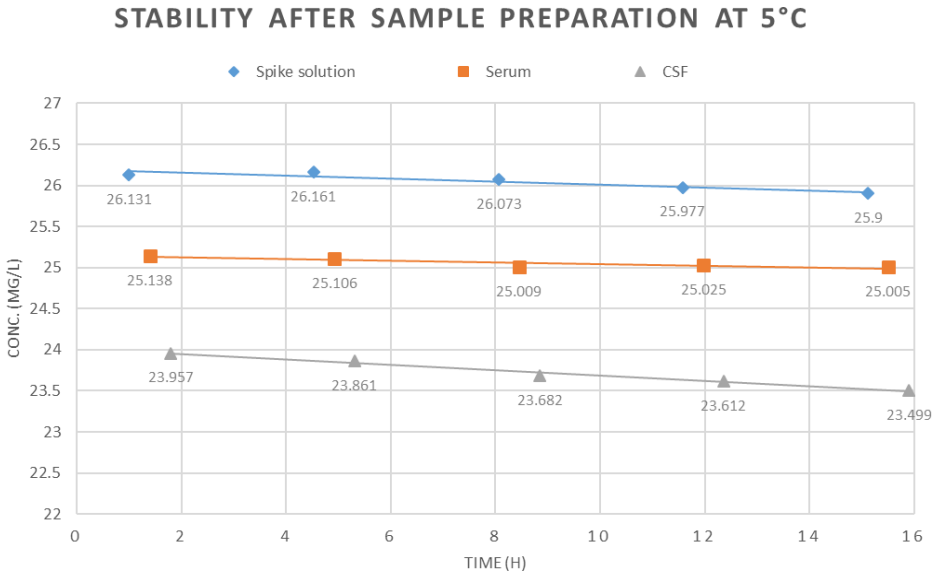

Figure 2: Stability of meropenem in porcine serum and CSF after sample preparation at 5°C.

(figure 3). The same degradation progress was detected for ceftazidime and piperacillin. At 25°C the value 90% of start concentration was passed within the first 24h and at 5°C after 48h. At -32°C the value 90% of start concentration was not passed within 48h. Consequently, we concluded to freeze thecollected patient samples and analyze them within 24h after collection.

Quality control samples

We performed quality control samples to show our system und methods work as we expect on days with analysis of unknown samples. Therefore, high and low concentration samples were prepared out of antibiotic (meropenem + ceftazidime + piperacillin) and internal standard (cefotaxime
+ cefazolin) stock solution with porcine serum. The low concentration sample was spiked with 4mg/l meropenem, 16mg/l ceftazidime and 34mg/l piperacillin. The high concentration sample was spiked with 16mg/l meropenem, 65mg/l ceftazidime and 137mg/l piperacillin. We defined the acceptable concentration range of the measured antibiotics with ±7% and the acceptable area range of internal standard with ±7.5% due to the recommendation of the EMA guideline on bioanalytical method validation[17]. They recommend ranges of ±15% but we decided to define closer limits with
±7% and ±7.5%.

External validation

To verify the performance of the method an external validation assay was passed. This assay was offered by INSTAND (Gesellschaft zur Förderung der

Qualitätssicherung in medizinischen Laboratorien e.V., Düsseldorf). The achieved certificate is valid for 12 months and proves that two samples with unknown concentration of meropenem, ceftazidime and piperacillin were analyzed correctly within acceptable limits. The results are shown in table 3.

Routine analysis

The method we described here is routinely used in our laboratory to determine meropenem levels in human sera and CSF. Within the setting described above, we measured 64 pairs of simultaneous collected human serum and CSF samples from critically ill patients on intensive care units. The serum levels of meropenem ranged between 5.4mg/l up to 49.3mg/l (mean 18.6mg/l ± 7.6mg/l, median 16.4mg/l). The CSF levels of meropenem ranged between 0.3mg/l up to 17.9mg/l (mean 2.6mg/l ± 2.6mg/l, median 1.9mg/l). For our measurements, the mean CSF/serum ratio was 0.129 ± 0.092. Patient characteristics and dosage regimes are collected in table 4.

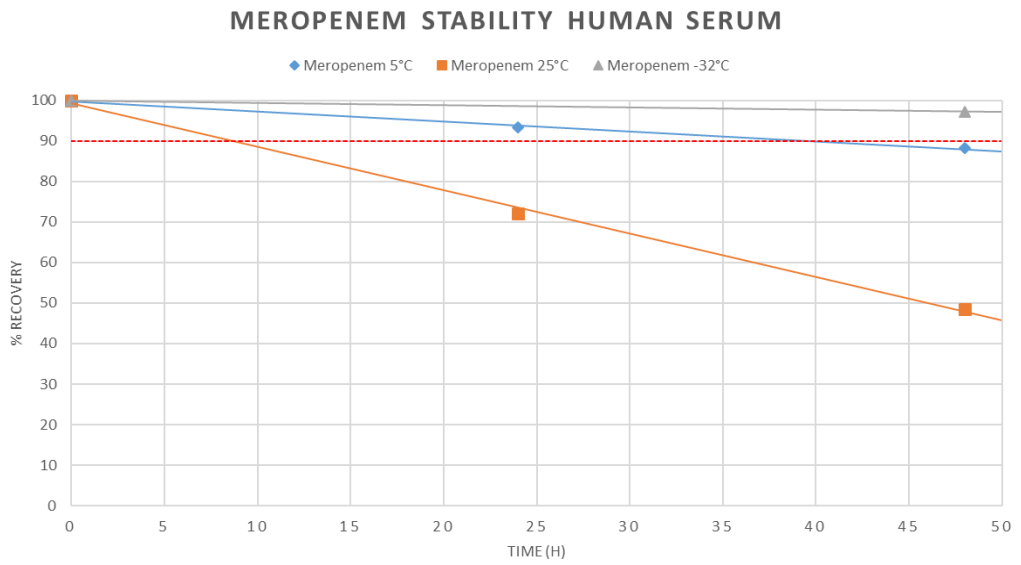

Figure 3: Degradation of meropenem in human serum at 5°C, 25°C and -32°C over 48h

Table 3: Results of the external validation by INSTAND

Substance	Sample	Unit	Measured conc.	Target conc.	Lower limit	Upper limit	Deviation	Result +/-
Ceftazidime	1	mg/l	0	0	0	2.50		+
	2	mg/l	3.80	4.08	2.86	5.30	-6.9%	+
Meropenem	1	mg/l	58.9	63.2	44.2	82.2	-6.8%	+
	2	mg/l	46.1	48.3	33.8	62.8	-4.6%	+
Piperacillin	1	mg/l	14.6	17.4	12.2	22.6	-16.1%	+
	2	mg/l	120	132	92.4	172	-9.1%	+

Table 4: Patient characteristics and dosage regimes

No. of patients	30
Gender (No. M/no. F)	19/11
Mean age (yr)	53.0
Mean body weight (kg)	80.3
No. of serum/CSF pair	64
Mean serum conc. (mg/l)	18.7 ± 7.6
Mean CSF conc. (mg/l)	2.6 ± 2.6
Mean CSF/serum ratio	0.129 ± 0.092
Dose continuous 8000mg/24h	14
Dose continuous 6000mg/24h	46
Dose continuous 4000mg/24h	2
Dose continuous 3000mg/24h	1
Dose continuous 2000mg/24h	1
Mean dose continuous /24h (mg)	6.3 ± 1.1
Indication ventriculitis	14
Indication meningitis	2
Indication subarachnoid hemorrhage	1
Indication brainstem abscess	2
Indication shunt infection	3
Indication unknown	8

Discussion

The developed assay is reproducible, accurate, precise, and linear across the range of the calibration curves. The preparation of our samples is quick and simple. The HPLC assay time of 23min is acceptable for the processing ofsamples for routine TDM.

Previous studies described large interindividual variability in the concentrations of meropenem in plasma and CSF[13]. A reduced distribution into CSF has been documented for β-lactams, especially carbapenems, due to their hydrophilic nature [23, 24]. Additionally results were published on whether meropenem plasma concentrations simply used as a surrogate parameter of CSF concentrations may lead to under dosing [25]. These results are in line with Blassmann et al. who is reporting a median CSF/plasma penetration of 9% in 21 neurocritical care patients with ventriculitis [13]. We measured serum and CSF levels at the same time during continuous infusion of meropenem; this gave us also the chance to calculate the CSF/serum ratio and for our 64 pairs of serum and CSF levels the mean ratio was 0.129 ± 0.092. Compared to the non β-lactam antibiotic linezolid with a reported CSF/serum ratio of 0.71 ± 0.16 [26], meropenem has a very poor CNS penetration. Our data from routine analysis with a mean CSF/serum ratio of 12.9% support the data from Blassmann et al. and suggest a high interindividual variability of serum levels, CSF levels and the CSF/serum ratio due to large standard deviations. If these analysis are compared with reported CSF penetration of between 21 and 39% in patients with bacterial meningitis [27, 28], it is suspected that dosing regimens for meropenem in patients with meningitis cannot be extrapolated to patients with ventriculitis.

Our data contains two patients with proven or suspected meningitis in which the measured CSF/serum ratio are higher than the mean CSF/serum ratio (13.7% and 23.3% compared with mean 12.9%). It is likely, that drug penetration in inflamed meninges is greater than in patients with non- inflamed. Consequently, in critically ill patients with CNS infections, the standard dosing regimen of meropenem with 6g daily does not predictively achieve optimal plasma and CSF concentrations in all patients. Results like these push the need for TDM of meropenem in plasma and in CSF to avoid either the risk of dose-dependent toxicity or that of treatment failure. The development of meropenem-induced toxicity is significantly affected in patients with a high serum meropenem concentration. The threshold concentrations for which there is 50% risk of developing a neurotoxicity event is described with meropenem c_{min} = 64.2mg/l and a nephrotoxicity event with c_{min} = 44.45mg/l [29].

Furthermore, optimized dosing strategies like administration of higher than standard dosages or administration by continuous infusion should be taken into consideration. Continuous infusion has been demonstrated to improve PK/PD target attainment in various further studies of time-dependent antibiotics [30-32]. Recommended daily doses for meropenem are 6g in adults [5]. High initial meropenem doses (median 8.8g/24h by continuous infusion) together with dose adjustments according to TDM ensured sufficient CSF concentrations in all patients according to Tiede et al [16] Consistent evidence is now available showing that therapeutic drug monitoring and guided individual dose optimization of meropenem is justified and feasible in clinical practice to reduce underexposure, improve tolerability and possibly response to therapy [16].

We have demonstrated meropenem, ceftazidime and piperacillin to be stable in human serum up to 48h in frozen condition at -32°C. This is important because it was shown that meropenem was unstable when stored at temperatures above 4°C [20-22]. Furthermore, meropenem, ceftazidime and piperacillin were stable after treatment with acetonitrile/ methanol. Accordingly, the prepared samples can be assayed under storage conditions of 5°C within 24h period and no relevant loss of meropenem, ceftazidime or piperacillin was detected.

Conclusion

In the present study, we developed a simple method for the quantification of meropenem in human serum and CSF. The developed method could be easily and quickly performed and enabled the quantification of meropenem in patient samples for routine TDM. In the future, this method can be used to evaluate the serum and CSF concentrations of meropenem in critically ill patients. Consequently, meropenem dosage regimes should be tailored to individual patients. This is essential because our data suggests that there is a high variability in serum concentrations, CSF concentrations and CSF/serum ratios.

Furthermore, the developed method creates the chance to study CSF penetration of meropenem because the simplest way to study the entry of drugs into the CNS is to measure drug concentrations in the CSF during a continuous drug infusion[33]. Additionally, this method enables to quantify ceftazidime and piperacillin concentrations in human serum. Our investigation was limited due to the lack of information about clinical outcomes of the patients and the lack of microbiological analysis. In conclusion, our results are in line with other studies that showed a high variability of serum and CSF levels of meropenem, and future studies can be performed using the method described above.

References

1. Carbonate, Sodium, and Meropenem. Life Science Retailer: Biomol GmbH. Retrieved on March 8, 2022.
2. (2) Papp-Wallace KM, Endimiani A, Taracila MA, and Bonomo RA. The Past, the Present, and the Future of Carbapenems. Reference: Antimicrobial Agents and Chemotherapy 55, no.
3. Streit, F.; Perl, T.; Schulze, M.H.; Binder, L. Principles and practice of individualized beta-lactam treatment. Lab Med 40, no. 4 (2016): 385–397.
4. Antibiotics in critically sick patients: a comprehensive study of the pharmacokinetics. 4. Gonçalves-Pereira J,

Póvoa P.

5. Critical Care 15 (2011): R206, beta-lactams.
6. Infectious Diseases Society of America's 2017 Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Authors: Tunkel AR, Hasbun R, Bhimraj A, et al. The latest issue of Clin Infect Dis is 64 (2017): e34-e65.
7. Nicolau DP, Furtado GH, Nicolau JA, Briceno DF, and Villegas MV. Using Gram-negative bacteria often found in Colombian samples, evaluate the pharmacodynamic profile of intravenous antibiotics. 15 (2011), issue of the Braz J Infect Dis: 413–419.
8. Seventh, Pascale R., M. Giannella, M. Bartoletti, P. Viale, and F. Pea. Infections caused by strains of Enterobacteriaceae resistant to carbapenems may be treated with meropenem. Expert Review of Anti-Infective Therapy. 17:819-827 (2019).
9. Antibiotic dosage in critically unwell patients. J Antimicrob Chemother 66 (2011): ii25-ii31. McKenzie, C.
10. Nicolau D, Mabilat C, Gros MF, et al. Antibiotics: diagnostic and medical requirements for therapeutic drug monitoring. Europe Journal of Clinical Microbiology and Infectious Diseases 39 (2020): 791-797.
11. Cojutti P, Della Siega P, Pea F, et al. Infections caused by KPC-producing Klebsiella pneumoniae may be more successfully treated if high-dose continuous-infusion meropenem is optimized for pharmacokinetics and pharmacodynamics in real time. International Journal of Antimicrobial Agents 49, no. 3 (2017): 255-258.
12. Kumta, N., J.A. Roberts, J. Lipman, W.T. Wong, G.M. Joynt, and M.O. Cotta. Cerebrospinal Fluid Antibiotic Pharmacokinetic Data from Non-Inflamed Critically Ill Patients: A Systematic Review. e01998-20, Antimicrobial Agents and Chemotherapy 65 (2020).
13. Twelfth Place: Mader MMD, Czorlich P, König C, et al. Treatment of patients with intrathecal meropenem and vancomycin in a retrospective study of their efficacy against ventriculitis. 2099-2105 Acta Neurochir (Wien) 160 (2018).
14. Uwe Blassmann, Andreas Roehr, Oliver R. Frey, et al. Meropenem's ability to enter the central nervous system: a prospective observational study in patients in neurocritical care with confirmed or suspected ventriculitis. Care Critically, 20, 343 (2016).
15. Alffenaar JWC, Bassetti M, Abdul-Aziz MH, et al. A Position Paper on Antimicrobial Therapeutic Drug Monitoring in Adults in Critical Care. ICU Medicine 46 (in 2020): 1127-1153.
16. Inc. RLS 15. Patient Information Service for Meronem® 500mg and 1000mg Tablets. Retrieved on March 8, 2022.
17. To cite this chapter: Tiede C, Chiriac U, Dubinski D, et al. Cerebrospinal
18. Meropenem and Vancomycin Concentrations in Ventriculitis Patients' Fluids Obtained Using TDM-Guided Continuous Infusion. 1421 Antibiotics 10 (2020).
19. Agency for European Medicines. Bioanalytical method validation guidelines. Posted on the internet (2015).
20. Steffens NM, ES Zimmerman, SM Nichelle, BR Brucker. 18. Review of the literature on the subject of therapeutic drug monitoring and the usage of meropenem in clinical practice. Not Available in J Clin Pharm Ther.
21. Antibiotic doses and clinical thresholds according to EUCAST. Available 12 July (2021).
22. Twenty members of the Kipper, Anier, Leito, Karjagin, Oselin, and Herodes teams
23. K. A Comparison of Several Sample Preparation Methods and an Analysis of Meropenem Stability for the Rapid Determination of Meropenem in Biological Fluids Using LC. Chromatographia 70:1423 (2009).
24. Bode- Böger SM, Tröger U, Martens-Lobenhoffer J, Monastyrski D, and Bode- Böger. Meropenem's stability in plasma compared to that in dried blood spots (DBS). 279-284 in the 2019 edition of J Pharm Biomed Anal.
25. 22. Jamieson, C.; Allwood, M.C.; Stonkute, D.; Wallace, A.; Wilkinson, A.S.; Hills, T. The effects of buffering on meropenem's stability after reconstitution and the difficulties of ensuring compliance with the NHS Yellow Cover Document for outpatient continuous infusions were the focus of this study. 27 (2020):e53-e57 in the European Journal of Hospital Pharmacy.
26. Antibacterials in cerebral fluid: a clinical pharmacokinetics study. Di Paolo A, Gori G, Tascini C, Danesi R, Del Tacca M. Pages 511-542 in Clin Pharmacokinet, Volume 52, 2013.
27. Thiel A, Prange HW, Sörgel F, Kinzig-Schippers M, Nau R, and Lassek C. Meropenem distribution and clearance in cerebrospinal fluid of patients with hydrocephalus treated by external ventricular drainage. Journal of Antimicrobial Chemotherapy 42 (1998): 2012–2016.
28. Therapeutic drug monitoring for antibacterials in cerebral fluid. 25. Lonsdale DO, Udy AA, Roberts JA, Lipman J.