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EVALUATION OF PLASMA LEVELS OF MEROPENEM IN SEPTIC PATIENTS DURING EXTRACORPOREAL BLOOD PURIFICATION

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The relevance. Meropenem is a broad-spectrum carbapenem antibiotic widely used to treat patients with sepsis / septic shock. Critically ill patients are usually supported with one of the forms extracorporeal blood purification. However, data on the effect of various extracorporeal support techniques on the pharmacokinetics and pharmacodynamics of meropenem are insufficient or contradictory.

Aim: To evaluate the effectiveness of meropenem dosage regimens in the treatment of septic patients during extracorporeal blood purification.

Materials and methods. Plasma concentrations of meropenem were monitored in three critically ill patients with sepsis or septic shock. Patients were treated using various extracorporeal support techniques. Meropenem was used as empirical antibacterial mono- or complex therapy (1 g every 8 or 12 hours). Meropenem concentrations in plasma were determined by validated assay methods on Acquity ultraefficient liquid chromatography (UPLC) H-Class system.

Results. It is shown that the meropenem plasma concentration in critically ill patients changes significantly. It was found that the standard meropenem dosing regimens in patients with sepsis / septic shock during continuous hemodiafiltration do not ensure the achievement of the PK/PD target of 100% T > MIC for sensitive strains (MIC ⩽ 2 mg/L) and for intermediate resistance pathogens (2 ⩽ MIC < 8 mg/L). Continuous hemofiltration and selective adsorption of lipopolysaccharide have a less pronounced effect on the clearance of meropenem.

Conclusion. To increase the effectiveness of antibacterial therapy, it is necessary to conduct research aimed at developing protocols for dosing antibacterial drugs for the treatment of sepsis during extracorporeal blood purification.

Keywords: sepsis; antibacterial therapy; meropenem; hemodiafiltration; hemofiltration; lipopolysaccharide adsorption; plasma concentration.

ОЦЕНКА ПЛАЗМЕННОГО УРОВНЯ МЕРОПЕНЕМА У ПАЦИЕНТОВ С СЕПСИСОМ НА ФОНЕ ЭКСТРАКОРПОРАЛЬНОЙ ДЕТОКСИКАЦИИ

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List of abbreviations

HDF — hemodiafiltration; HF — hemofiltration; LPS sorption — selective adsorption of lipopolysaccharide; MIC — minimal inhibitory concentration; ICU — Intensive Care Unit; SSh — septic shock; PK — pharmacokinetics; PD — pharmacodynamics; SOFA — sepsis-related organ failure assessment.

Актуальность. Меропенем является антибиотиком из группы карбапенемов с широким спектром действия, наиболее часто применяемым для лечения пациентов с сепсисом/септическим шоком. В интенсивной терапии пациентов в тяжелом состоянии достаточно часто используют различные методики экстракорпоральной детоксикации. При этом данные о влиянии разных видов экстракорпоральной детоксикации на фармакокинетику и фармакодинамику меропенема недостаточны или противоречивы.

Цель — оценить эффективность стандартных схем дозирования меропенема при лечении пациентов с сепсисом на фоне экстракорпоральной детоксикации.

Материалы и методы. Проведен мониторинг остаточных концентраций меропенема в плазме крови трех пациентов с сепсисом/септическим шоком, находившихся на лечении в отделении реанимации и интенсивной терапии. В комплексной терапии пациентов применяли разные методы экстракорпоральной детоксикации. Меропенем был назначен в составе эмпирической антибактериальной моно- или комплексной терапии (по 1 г каждые 8 или 12 ч). Количественный анализ содержания антибактериального препарата в образцах плазмы крови пациентов проведен методом ультраэффективной жидкостной хроматографии при помощи хроматографа с диодной матрицей Acquity (США).

Результаты. Плазменный уровень меропенема у пациентов в критических состояниях отличается значительной вариабельностью. Стандартные схемы дозирования меропенема на фоне продленной гемодиафильтрации у пациентов с сепсисом/септическим шоком не обеспечивают достижения целевого значения параметров фармакокинетики и фармакодинамики — 100 % T > МПК не только для чувствительных штаммов (МПК ⩽ 2 мг/л), но и для патогенов с промежуточной устойчивостью (2 ⩽ МПК < 8 мг/л). Продленная гемофильтрация и селективная адсорбция липополисахарида также влияют на клиренс препарата, но менее выраженно.

Заключение. В целях повышения эффективности антибактериальной терапии необходимо проведение исследований, направленных на разработку протоколов дозирования антибактериальных препаратов для лечения сепсиса на фоне экстракорпоральной детоксикации в условиях отечественных стационаров.

Ключевые слова: сепсис; антибактериальная терапия; меропенем; гемодиафильтрация; гемофильтрация; селективная сорбция липополисахарида; плазменная концентрация.

Introduction

Despite the widespread increase in pathogenic microorganisms resistant to modern antibacterial drugs [1–4], one of the most effective and common representatives of the carbapenem group, meropenem continues to be widely used in the etiotropic treatment of sepsis, especially in patients in a severe disease state. This drug is included in most modern schemes of empirical antibiotic therapy for septic conditions with different localizations of infection focus. Meropenem is a broad-spectrum antibiotic with a high level of activity against gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter spp.*, and various anaerobes. Meropenem is a small, hydrophilic molecule with a molecular weight of 437.5 Da, a low volume of distribution (0.3 l/kg), and high degree of plasma protein binding (<2%). Drug elimination occurs mainly through the kidneys; approximately 30% of the meropenem administered to the body undergoes minor metabolism in the liver, and its half-life is 1 h [5].

The features of the physicochemical properties of meropenem predetermine significant changes in the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug due to the use of extracorporeal detoxification techniques, which are one of the most effective and frequently used methods of intensive therapy for sepsis and septic shock (SSh), since the main determinants of increased drug clearance are the low molecular weight, high hydrophilicity, low volume of distribution, and predominance of the non-protein-bound fraction of the drug [6]. The fundamental PD parameter for assessing the microbiological activity of antibacterial drugs is the minimum inhibitory concentration (MIC), which is the lowest antibiotic concentration that inhibits the visible growth of a test microorganism *in vitro*. Achievement of target values of the PK/PD parameter, which is characterized by the antibiotic exposure time required for specific microorganism destruction for drugs with a time-dependent type of bactericidal activity, is of key importance when assessing the adequacy of the dosage regimen of antibacterial drugs. The main PK/PD parameter that determines the microbiological efficacy of drugs with this type of antimicrobial activity is the time during which the plasma concentration of their free (not bound to proteins) fraction exceeds the MIC for a specific microorganism (% T > MIC) [7].

Like all carbapenems, meropenem is a drug with time-dependent bactericidal activity. Studies

in vitro and in animal models have shown that the target value %T > MIC of carbapenems is 40% for complete eradication of most microorganisms. However, clinical trials suggest that longer exposure to antibiotics is required to treat severe infections in patients with sepsis or SSh. Thus, there is evidence of favorable outcomes in the treatment of critically ill patients with concentrations of beta-lactam antibiotics exceeding the MIC for a 100% dosing interval [8, 9]. Moreover, it is believed that the bactericidal efficacy of beta-lactams is maximally manifested when its minimum blood plasma concentration exceeds the MIC by a factor of 4–5 [10].

In recent years, foreign authors have been conducting PK studies of meropenem in critically ill patients in relation to the use of sustained procedures for renal replacement therapy [11, 12], but technical features of equipment and different types of filters, as well as different variations of the modes of sustained procedures of renal replacement therapy significantly complicate the interpretation of literature data and limit the possibilities of their application in a given medical institution. In addition, there are practically no data on the features of meropenem PK when using such procedures of extracorporeal detoxification as selective lipopolysaccharide adsorption (LPS sorption). In the national literature, the results of such studies are not presented.

Due to these circumstances, it is necessary to study the efficacy of meropenem in terms of the achievement of the target PK/PD parameter values needed to provide complete eradication of the pathogen for sepsis treatment in relation to extracorporeal detoxification in national hospitals.

The aim of the study was to evaluate the effectiveness of meropenem dosage regimens in the treatment of septic patients during extracorporeal blood purification.

Materials and methods

Patients' clinical state. The study included three patients who were treated in the intensive care unit (ICU) of the Nephrology and Efferent Therapy Clinic of S.M. Kirov Military Medical Academy (St. Petersburg), in whom the course of the underlying disease was complicated by the development of sepsis with organ dysfunction: sepsis-associated acute kidney injury and/or SSh, which served as the basis for the use of extracorporeal detoxification methods.

Patients' clinical state at the time of admission to the ICU and the development of their critical condition corresponded to a severe or extremely severe state, which was due to a number of factors: the course of the underlying disease, surgery, concomitant pathology, and age, as well as the development of purulent septic complications in the early postoperative period. Upon the development of a critical condition, all patients underwent a standard complex of intensive care, including the prescription of meropenem as part of empirical antibacterial mono- or complex therapy, respiratory support, infusion-transfusion therapy, nutritional support, and vasopressor support, (in the case of SSh development). One or more of the following methods of extracorporeal detoxification were used as part of combination therapy: hemofiltration (HF), hemodiafiltration (HDF), and LPS sorption. Table 1 shows the main clinical and laboratory parameters of the patients included in the study immediately before the start of extracorporeal detoxification.

According to the data presented in Table 1, all patients showed laboratory signs of the septic process and endogenous intoxication: leukocytosis, an increase in C-reactive protein and procalcitonin levels, and a decrease in blood plasma total protein, mainly due to a reduction in the size of the albumin fraction. In two patients, a significant increase in plasma creatinine and urea levels was reported, which indicated the development of acute kidney damage.

Antibacterial therapy included prescription of meropenem (Meropenem-Deco, Company Deco LLC, Russian Federation, in the dosage form "powder for intravenous infusion"). The dose, frequency, and mode of administration of meropenem were determined by the attending physician on the basis of data on its use in relation to extracorporeal detoxification available in the literature and presented in the leaflet.

Quantitative assessment of plasma meropenem levels in patients with sepsis

Five milliliters of the patient's blood was sampled into heparinized tubes and centrifuged to separate the plasma at +4°C and 1250 g for 15 min. The plasma was then frozen and stored in a freezer at −80°C until analysis.

Table 1 / Таблица 1

Clinical and laboratory data of septic patients before extracorporeal blood purification
Клинические и лабораторные показатели пациентов с сепсисом до проведения экстракорпоральной детоксикации

Parameter	Norm	Patients		
		M., 72 years old	K., 65 years old	P., 73 years old
Hemoglobin, g/l	120–150	112↓	113↓	119↓
Red blood cells, $\times 10^{12}$/l	3.5–5.0	3.72	3.57	3.91
White blood cells, $\times 10^{9}$/l	4.0–8.5	14.7↑	7.4	22.3↑
Platelets, $\times 10^{9}$/l	200–350	48↓	261	94↓
Erythrocyte sedimentation rate, mm/h	10–15	11	23↑	–
K^+, mmol/l	3.5–5.0	4.52	3.97	6.0↑
Na^+, mmol/l	135–145	133	142.1	140
Cl^-, mmol/l	94–108	–	104.4	108
pH	7.36–7.44	7.34	7.45	7.33
p_aO_2, mmHg	80–98	222.0↑	83.5	95.4
p_aCO_2, mmHg	34–48	34.4	29.8↓	42
BEecf (excessive buffer bases), mmol/l	–2.0–3.0	–8.4↓	–2.8↓	–2.8↓
Total protein, g/l	60–80	60	57↓	61.9
Albumin, g/l	40–50	26↓	22↓	34.7↓
Lactate, mmol/l	0.5–2.2	3.5↑	2.1	1.9
Glucose, mmol/l	4.2–6.4	6.8↑	5.9	13.6↑
Urea, mmol/l	6–8	19.4↑	7.7	22.6↑
Creatinine, μmol/l	60–120	306↑	69	220.5↑
Total bilirubin, μmol/l	3.4–17.1	106↑	15.6	15.9
C-reactive protein, mg/l	0–1	135.6↑	28.9↑	180.2↑
Procalcitonin, ng/ml	до 0.1	152.0↑	1.29↑	0.689↑

Quantitative analysis was performed by ultra-performance liquid chromatography on the basis of the Institute of the Federal Medical and Biological Agency in the laboratory of toxicological chemistry of organic compounds. Sample preparation was carried out as follows: One milliliter of blood plasma and 2 ml of acetonitrile were added to 9 ml Vacuette tubes. The samples were vortexed at 400 vibrations per min for 10 mins. The precipitated proteins were separated by centrifugation at 3550 g for 5 min. The supernatant was quantitatively transferred to 15 ml Falcon tube, and 5 ml of methylene chloride was added. Extraction of endogenous lipid compounds was carried out on a shaker at 400 vibrations per min for 10 min followed by centrifugation at 1278 g for 5 min. The aqueous layer was used to determine the meropenem concentration.

Chromatographic analysis was performed using a liquid ultra-performance chromatograph with an Asquity diode matrix (USA), verification

Table 2 / Таблица 2

Chromatographic elution mode for detection meropenem in patients' blood plasma
Режим хроматографического элюирования при определении содержания меропенема в плазме крови пациентов

Time, min	Ratio of mobile phase components		Flow rate, ml/min
	A, %	B, %	
0.0	92.5	7.5	0.25
5.0	77.5	22.5	0.25
6.0	77.5	22.5	0.25
6.5	92.5	7.5	0.25

Note. A — 0.1% trifluoroacetic acid; B — acetonitrile.

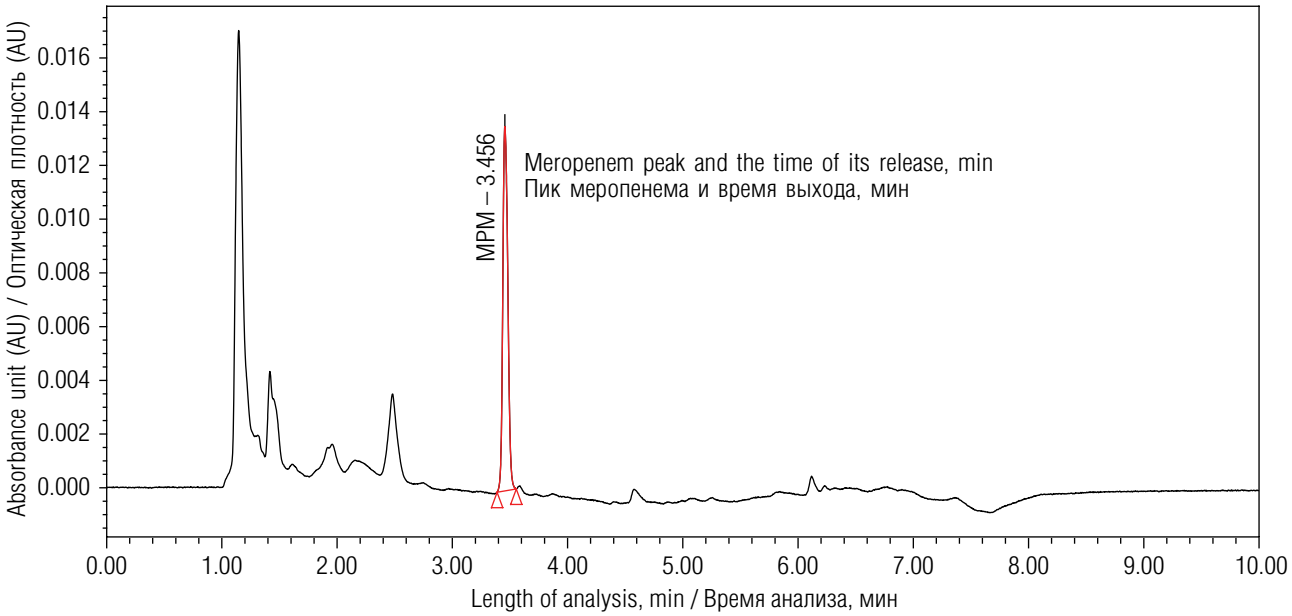

Fig. 1. Detection of meropenem in human blood plasma by ultraefficient liquid chromatography. MPM — meropenem
Рис. 1. Определение содержания препарата меропенем в плазме крови человека методом ультраэффективной жидкостной хроматографии. MPM — меропенем

certificate No. 242/9965-2019 dated December 17, 2019 on a Hypersil GOLD aQ column, 150 × 2.1 mm, 3 μm. Samples prepared for analysis in a volume of 5 μL were transferred into chromatographic vials, which were placed in the autosampler of the chromatograph and analyzed in gradient mode, the characteristics of which are presented in Table 2. The working wavelength of the UV detector was 311 nm.

The plasma meropenem concentration was determined using calibration characteristics and data processing software. In cases where the obtained value exceeded the upper limit of the corresponding calibration curve, the sample was diluted with water and reanalyzed. Fig. 1 shows the chromatogram of meropenem isolated from the blood plasma of one of the patients included in the study.

Among the isolates isolated from biomaterial samples from patients included in the study, *Klebsiella pneumonia* and *Acinetobacter baumannii* producing extended-spectrum beta-lactamases prevailed. However, in the context of the work, the data of microbiological analysis are not directly related to the results of the study aimed at determining the achievement of the target value PK/PD parameter when using meropenem, which is due to the empirical nature of antibacterial therapy. The parameters of the given PK/PD aim were formed based on the high probability of infection with the most common nosocomial strains.

Results and discussion

The efficacy of meropenem dosing regimens in the treatment of patients with sepsis under conditions of extracorporeal detoxification methods was assessed by therapeutic drug monitoring. Blood samples from patients were taken for meropenem assay immediately before the next administration of the drug (at the time of the expected lowest plasma antibiotic concentration). Taking into account the severity of the patients' state, we used 100% T > MIC as the target value of the PK/PD parameter at which the plasma level of the antibiotic during the entire interval between the next injections of the drug should exceed the MIC for the most common nosocomial strains. MIC values of meropenem were taken in accordance with the current recommendations of the European Committee for Antimicrobial Susceptibility Testing (EUCAST): the threshold MIC for susceptible microorganisms is 2 mg/L, and for bacteria with intermediate sensitivity (conditionally sensitive) it is 8 mg/L [13].

Data on the dosing regimen for meropenem, methods of extracorporeal detoxification used, and terms of biomaterial sampling for chromatographic analysis in the patients included in the study are presented in Table 3.

Patient M., 72 years old, diagnosis: acute pyelonephritis; nosocomial bilateral lower lobe polysegmental pneumonia; sepsis; SSh. Upon admission to the ICU, there was failure of four vital organs and systems, and the severity of multiple organ failure according to the SOFA scale was 17 points. Artificial ventilation of the

Table 3 / Таблица 3

Scheme of application of meropenem in septic patients during extracorporeal blood purification
Схема применения меропенема у пациентов с сепсисом на фоне экстракорпоральной детоксикации

Patient	Meropenem dosing regimen	Blood sampling schedule	Time from the start of antibacterial therapy, h
M., 72 years old	1 g every 12 h (30-min IV infusion)	Before meropenem administration in relation to HDF	16
		Before meropenem administration	26
		Before meropenem administration in relation to HDF	38
		Before meropenem administration	53
		Before meropenem administration, 30 mins after HDF	66
		Before meropenem administration	78
		Before meropenem administration in relation to HDF	90
		Before meropenem administration in relation to HDF	102
		Before meropenem administration in relation to HDF	114
		Before meropenem administration	126
K., 65 years old	1 g every 8 h (30-min IV infusion)	Before meropenem administration	14
		4 h after meropenem infusion; after the end of LPS-adsorption	19
		Before meropenem administration	22
P., 73 years old	1 g each 12 h (IV by drop infusion in 10 ml of isotonic sodium chloride solution)	Before meropenem administration in relation to HF	11
		Before meropenem administration; after HF	17
		5 h after meropenem infusion start, before HF	35

Note. HDF — hemodiafiltration; HF — hemofiltration; LPS-adsorption — selective lipopolysaccharide adsorption; IV — intravenous.

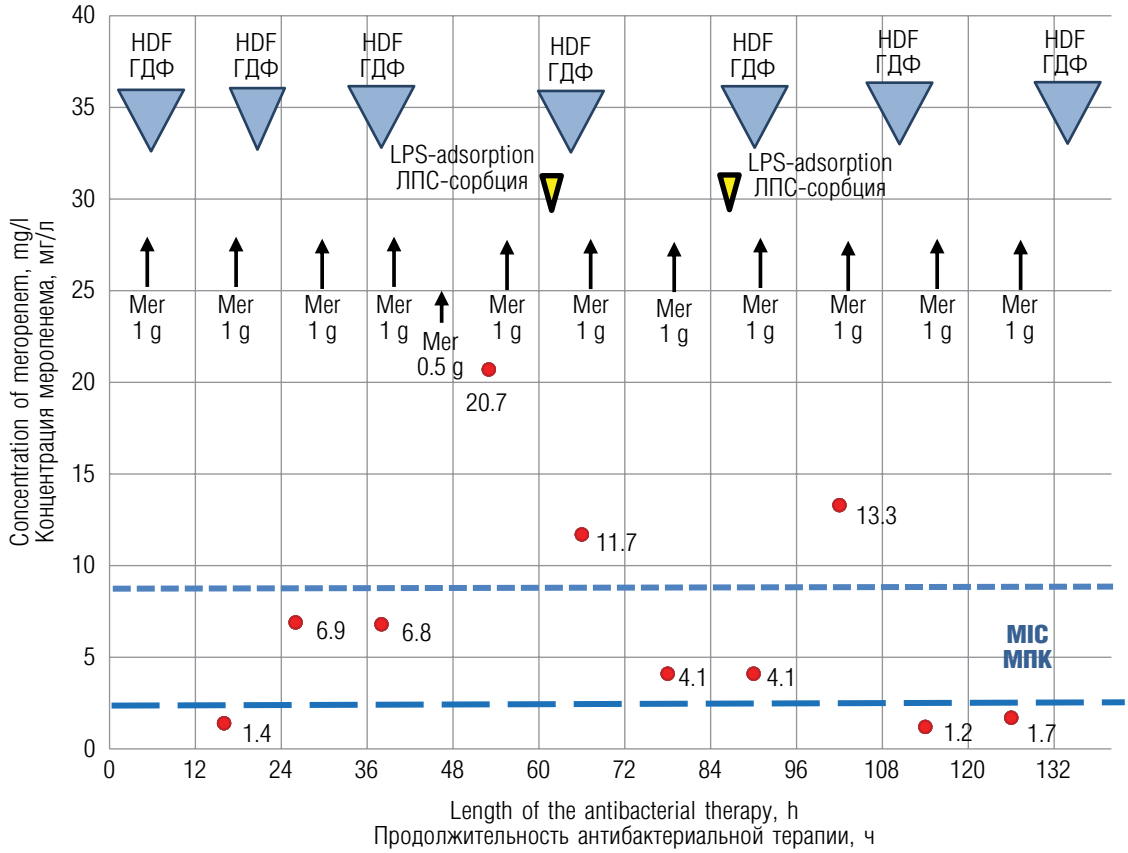

Fig. 2. The concentration of meropenem (Mer) in the blood plasma of patient M. during extracorporeal blood purification. HDF — continuous hemodiafiltration; LPS-adsorption — selective lipopolysaccharide adsorption; MIC — minimal inhibitory concentration

Рис. 2. Содержание меропенема (Mer) в плазме крови пациента М. на фоне экстракорпоральной детоксикации. ГДФ — продленная гемодиафильтрация; ЛПС-сорбция — селективная адсорбция липополисахарида; МПК – минимальная подавляющая концентрация

lungs was performed from the date of admission for 9 days; vasopressor support was performed with norepinephrine 0.5–0.1 μg/kg per min for 8 days. As an antibacterial therapy, meropenem was prescribed 1 g every 12 h (twice a day) by 30-min infusion, for a course of 6 days, and vancomycin 1 g by infusion once a day for 6 days. Renal replacement therapy was started on the day of admission to the ICU clinic of Nephrology and Efferent Therapy. During a 6-day stay in the ICU, patient M. underwent six HDF sessions lasting 10 h and one 7 h session. The HDF dialyzer parameters were as follows: blood flow rate — 250 ml/min, dialysate delivery rate — 600 (500; 800) ml/min, replacement rate — 40–60 ml/min; and mean ultrafiltration volume — 1200 ml. HDF was performed using an ELISIO 19H high-permeability hemofilter (Nipro, Japan). On treatment days 3 and 4, two LPS sorption sessions (120 and 140 min) were carried out using Alteco LPS Adsorber column (Alteco, Sweden) with a blood flow rate of 100 ml/min, 12 and 14 l of blood were processed. During treatment in the ICU, the patient's state improved: sepsis, SSh, and multiple organ failure were arrested; cerebral, renal, and hepatic functions were restored; and compensation for homeostasis disorders was achieved. The patient was discharged from the clinic to continue outpatient treatment.

Fig. 2 shows schematically the dosage intervals of meropenem in relation to sessions of sustained HDF and LPS sorption in patient M. as well as the trough drug concentrations based on the results of chromatographic analysis. The data show that the blood plasma meropenem concentration in patient M. before the next infusion of the antibiotic was characterized by significant variability during the entire course (6 days). The median value of plasma concentrations at the end of each meropenem dosing interval was 5.45, the minimum was 1.2 mg/L, and the maximum was 20.7 mg/L.

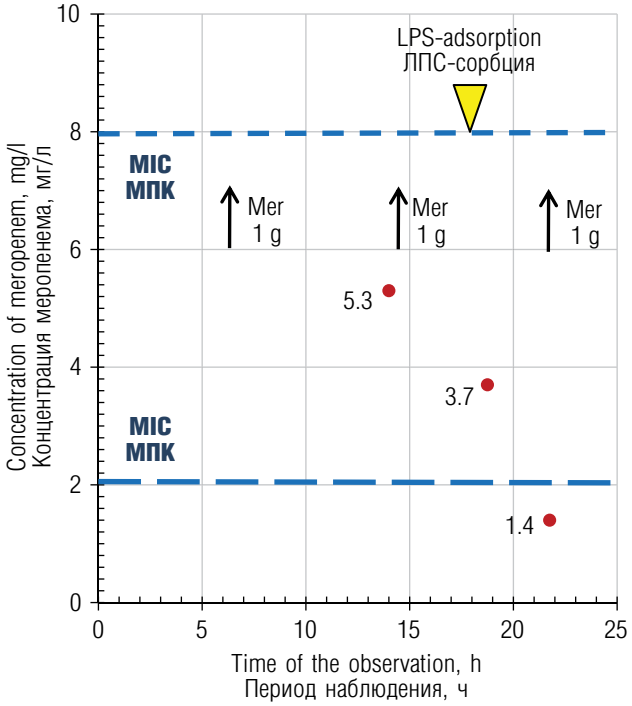

Рис. 3. Содержание меропенема (Mer) в плазме крови пациентки К. при проведении селективной адсорбции липополисахарида (ЛПС-сорбция)

Fig. 3. The concentration of meropenem (Mer) in the blood plasma of patient K. receiving selective lipopolysaccharide adsorption (LPS-adsorption)

The results of determination of trough plasma meropenem concentrations in patient M. in relation to daily administration of prolonged HDF showed that this parameter was less than 2 mg/L and did not reach the threshold MIC value for drug-sensitive strains of pathogenic microorganisms in 3 of 10 samples. In four other cases, the meropenem concentration was within 2–8 mg/kg, which is evidence of the possibility of complete eradication of sensitive pathogens with the selected antibiotic dosage regimen but, at the same time, the potential inconsistency of its use for the treatment of sepsis caused by bacteria with intermediate sensitivity to this drug. Only in three cases did the meropenem concentration correspond to the achievement of the target PK/PD values. It is clear that HDF sessions contributed to meropenem clearance. In particular, the maximum value of the trough drug concentration (20.7 mg/L) was noted in the case when the next infusion of the antibiotic was carried out after the end of the HDF procedure lasting 10 h. It was not possible to assess the effect of LPS sorption on the clearance of meropenem in patient M., since the procedure was used in relation to sustained HDF.

Patient K., 65 years old, diagnosis: severe sepsis, unspecified. The severity of the disease state was explained by SSh development due to immunosuppressive therapy of the underlying disease (myasthenia gravis). Antibiotic therapy was carried out in the following regimen: meropenem 1 g every 8 h (3 times a day) by infusion for 30 mins, for a course of 7 days. Vasopressor support with norepinephrine 0.13 μg/kg per min was used to correct hemodynamic disorders in SSh development. LPS sorption was carried out for 120 min using an Alteco LPS Adsorber column (Alteco, Sweden) with a blood flow rate of 100 ml/min; 12 liters of blood were processed. On day 9 of the patient's stay in the ICU, there was a positive trend in the form of stabilization of hemodynamic parameters and SSh arrest. Three blood plasma samples were taken for a meropenem assay (see Table 3). Data on the meropenem concentration in these samples as well as the timing of antibiotic administration and LPS sorption are shown in Fig. 3.

The absence of significant decrease in renal function in patient K. caused a rather high natural clearance of the drug, which explains the relatively low concentration of meropenem in the first plasma sample (5.3 mg/L) taken immediately before administration of the next antibiotic dose outside of extracorporeal detoxification (see Fig. 3). Despite the fact that this value of the blood drug concentration does not allow us to count on the achievement of the target PK/PD values for strains with intermediate sensitivity to meropenem ($2 < MIC \leq 8$ mg/L), the chosen dosing regimen turned out to be potentially effective for the treatment of sepsis caused by pathogens sensitive to meropenem (MIC ≤2 mg/L). The next two blood samples to determine drug concentration were taken after LPS sorption; the second sample was taken immediately after the end of the procedure. Although only 4 h passed after the next injection of meropenem, the concentration of the drug in this case was significantly lower than that in the previous sample (3.7 mg/L), which may indicate antibiotic elimination from the systemic circulation during LPS sorption probably due to adsorption the drug on the column. This assumption confirms the result obtained in the analysis of the third sample: the meropenem concentration 2 h after LPS sorption before the next administration of the drug was 1.4 mg/L, which did not allow us

to count on the achievement of the target values of the PK/PD parameter, even for strains sensitive to the drug. Thus, the dosage regimen of meropenem used for the treatment of this patient (1 g 3 times a day), which, according to the leaflet, should provide a high efficiency of antibiotic therapy, can be insufficient in combination with LPS sorption.

Patient P., 73 years old, diagnosis: ischemic coronary disease, effort angina Functional Class II; essential hypertension Stage III; type 2 diabetes mellitus with absolute insulin deficiency. Complications of the underlying disease: nosocomial left-sided polysegmental pneumonia; pulmonogenic sepsis. The patient underwent treatment at the Therapeutic Clinic for Advanced Training of Doctors No. 1 of S.M. Kirov Military Medical Academy. Due to the progression of clinical and laboratory signs of acute kidney damage and treatment failure on day 7, the patient was transferred to the ICU of the Nephrology and Efferent Therapy Clinic. Indications for renal replacement therapy were identified: severe overhydration, hypervolemia, oliguria, hyperazotemia, and uremia. A 7-h HF was performed with an ultrafiltration volume of 4000 l (Elisio 19H filter, blood flow rate 150 ml/min, replacement rate 30–50 ml/min); insulin therapy, cardiotropic, neurotropic, anticoagulant, and symptomatic therapy were continued. Meropenem was prescribed at dose of 1.0 g intravenously in 100 ml of isotonic sodium chloride solution every 12 h; the total duration of antibiotic therapy was 7 days. Three blood plasma samples were taken for chromatographic analysis (see Table 3). The data on the plasma meropenem level at sustained HF combined with 4-time administration of the antibiotic are shown in Fig. 4.

A significantly higher level of blood plasma meropenem in the patient P. with the dosage regimen of 1 g every 12 h was noted in comparison with patients M. and K., which confirms the literature data on the significant modification of PK antibiotic in the development of sepsis-associated pathophysiological disorders [14, 15]. Due to the 7-h HF session, the plasma meropenem level in patient P. decreased from 25.3 to 8.7 mg/L, while at the end of the dosing interval without the use of this procedure of renal replacement therapy, the plasma concentration of meropenem reached 43.5 mg/L, significantly exceeding the target values of the MIC for pathogens with intermediate sensitivity. Nevertheless, despite the treatment, the patient's state progressively worsened, multiple organ (cerebral, respiratory, cardiovascular, and renal) failure developed and progressed. On treatment day 8 in the ICU, a fatal outcome occurred.

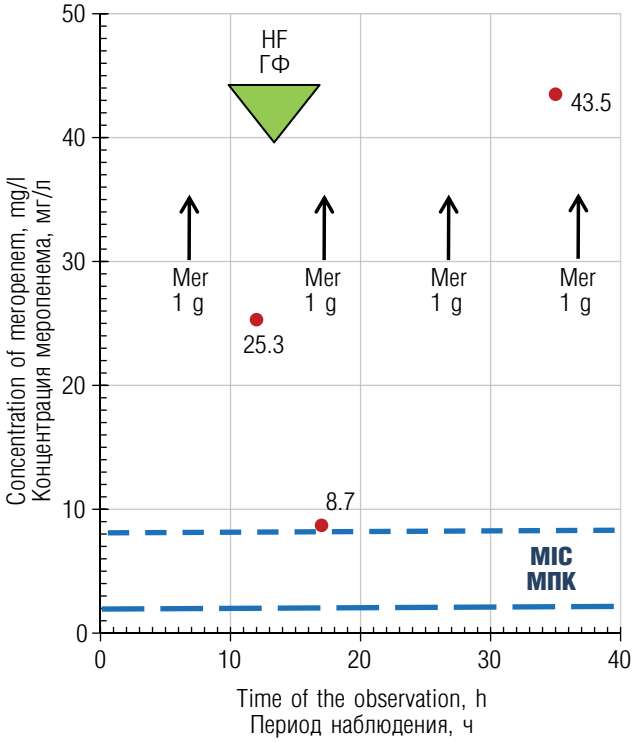

Fig. 4. The concentration of meropenem (Mer) in the blood plasma of patient P. during continuous hemofiltration (HF)

Рис. 4. Содержание меропенема (Mer) в плазме крови пациентки П. при проведении продленной гемофильтрации (ГФ)

It is important to note that, despite significant progress in understanding the pathophysiological and genetic aspects of the septic process development, improvement of medical technologies and clinical, laboratory and microbiological diagnostics, treatment of patients with sepsis does not lead to a significant decrease in mortality. Sepsis is one of the 10 leading causes of hospital mortality, and mortality in patients with purulent septic complications remains at a consistently high level (approximately 33%), increasing to 60% in patients with SSh [16]. The main effective method of etiotropic treatment of bacterial sepsis is antibiotic therapy; its adequacy is of key importance for reducing the mortality of septic patients [17]. Sepsis in ICU patients is the main reason for the use of extracorporeal detoxification procedures [18] represented

by various modifications of renal replacement therapy (hemodialysis, HF, and HDF) and sorption procedures (LPS sorption and sorption of cytokines) and allowing elimination of and wide range of inflammatory mediators and microbial toxins from the bloodstream. Removal of toxic substances when using methods of renal replacement therapy is based on two mechanisms: diffusion and convection. The main mechanism of mass transfer in hemodialysis is diffusion, which is the movement of solutes usually of low molecular weight through the hemofilter membrane along the concentration gradient. Hemofiltration allows the removal of larger molecules due to a convention mechanism: the movement of solutes through the hemofilter membrane is carried out when pressure is applied. In the HDF method, both mechanisms of mass transfer are involved, which generally leads to a greater clearance of substances.

The use of renal replacement therapy procedures predetermines removal of the wide range of drugs from the bloodstream, including antibacterial drugs, which can lead to the decrease of antibiotic therapy efficacy. The modern literature presents a significant number of international studies devoted to the study of antibacterial drugs PK including meropenem during the renal replacement therapy while their results are quite contradictory. The dosage regimens recommended by different authors differ significantly, which is largely due to the significant variability of the types and parameters of renal replacement therapy, mass transfer devices and composition of pathogenic microflora in hospitals in different countries [18–22]. In addition, data on changes in the PK of clinically significant antibacterial drugs with the use of LPS sorption in the modern literature are extremely limited.

The reason for the difficulties in drawing up informative recommendations for dosing antibiotics is the presence of many factors that determine the PK and PD parameters of antibacterial drugs in combination with extracorporeal detoxification. The most significant of them include physicochemical properties of antibiotics, the characteristics of the patient's state and factors directly related to extracorporeal detoxification: its duration and characteristics of mass transfer devices including the composition of the material, surface area and pore size of the hemofilter/dialyzer. Other variables such as blood and dialysate and/or substitute flow rates, cut-off points, and the sorption capacity of the hemofilter membrane may also contribute. In particular, the use of hemofilters with high- and ultra-high-permeability membranes and a high rate of ultrafiltration can provide better removal of substances with a large molecular weight [23].

Optimizing antibiotic therapy in critically ill patients with concomitant renal replacement therapy is challenging. As you know, ultimately antibiotic therapy is reduced to maintaining the optimal concentration of the antibiotic at the site of action. In particular, with sepsis, it is necessary to maintain a sufficient level of antibiotic in the focus of the septic process for the complete eradication of the pathogen. This is especially important for drugs with a narrow therapeutic index since an elevation of the dosage increases the risk of developing toxic effects, and a decrease in the concentration of antibacterial drug to subtherapeutic values can lead to a decrease in clinical efficacy and the emergence of pathogenic microorganism resistance. At the same time, most of recommendations on the dosage regimen of antibacterial drugs indicated in the leaflets were developed on the basis of results obtained after administration of a single dose of antibiotic in non-critical patients on intermittent hemodialysis. As for sustained methods of renal replacement therapy, which in recent years have led the treatment of SSh in critically ill patients with acute kidney injury, clinical recommendations are often based on the results of studies conducted with the participation of healthy volunteers or heterogeneous groups of patients, which significantly limits their practical significance. In addition, the data on the clearance of antibacterial drugs used in the development of recommendations for dosing drugs in critically ill patients, including those with acute renal injury are rather limited and quickly become obsolete due to technological improvement and extension of the possibilities of renal replacement therapy. As a result, the dosing of antibacterial drugs in critically ill patients with acute and chronic renal failure using different methods and regimens of sustained renal replacement therapy may not lead to the achievement of therapeutic concentrations of antibiotics.

A way out of this situation can be the development of protocols based on PK and PD

clinical studies of antibiotics in combination with extracorporeal detoxification. This method is based on the analysis of the dynamics of plasma concentration levels of drugs, carried out after treatment, with further extrapolation of the results to a similar population of patients. This approach is widely used by international authors. Another way to solve the problem is to use real-time monitoring of the blood concentration of antibacterial drugs. At the same time, as the data presented in this work show, it is possible to obtain the necessary information without resorting to the procedure of multiple sampling of biomaterial, by assessing the trough concentrations of antibacterial drugs at certain control points. For a more detailed understanding of the regularities of meropenem PK in the blood of patients with sepsis/SSh using various methods, modes and parameters of extracorporeal detoxification, it is advisable to conduct further studies.

Taking into account the expansion of the capabilities of domestic hospitals observed in recent years in terms of the use of various methods of extracorporeal detoxification in the intensive care of sepsis and SSh, on the one hand, as well as a decrease in the sensitivity to antimicrobial drugs of most causative agents of nosocomial infections and the emergence of new mechanisms of their resistance, on the other, the relevance of studies on optimizing the dosage of antibacterial drugs is increasing significantly, but solving this problem requires the participation of a wide range of specialists.

Conclusion

As a result of the study, a significant variability in the plasma level of meropenem was noted in patients in severe and extremely severe state with sepsis/septic shock who were treated in the intensive care units and intensive care of the clinics of S.M. Kirov Military Medical Academy. The inclusion of extracorporeal detoxification procedures in the treatment regimens for septic patients increased the clearance of meropenem, which did not always make it possible to exceed the minimum inhibitory concentration of meropenem for causative agents of nosocomial infections in 100% of the dosing interval. The most significant modifying effect on the plasma content of meropenem was exerted by prolonged hemodiafiltration, and a less pronounced decrease in the antibiotic level was observed during LPS sorption and hemofiltration.

In order to increase the effectiveness of antibacterial therapy, it is necessary to conduct studies aimed at developing protocols for dosing antibacterial drugs for the treatment of sepsis in combination with extracorporeal detoxification in national hospitals.

Additional information

Conflict of interest. The authors declare no conflict of interest.

Compliance with ethical standards. The studies were carried out in compliance with the ethical principles of medical studies in humans as a subject provided in the World Medical Association Declaration of Helsinki (2013 version) and in accordance with Good Clinical Practice in the Russian Federation, approved by Order No. 200 and dated April 01, 2016 of the Ministry of Health of the Russian Federation. The research project was approved at the meeting of Independent Ethics Committee under S.M. Kirov Military Medical Academy (Mins No. 221 dated April 23, 2019).

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