Case series

Usage of Meropenem Continuous Infusion for treatment of Sepsis in Geriatric Patients in Trauma and Orthopaedics. A case series

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Abstract

Prolonged infusion of meropenem is recommended by guidelines for the treatment of sepsis. However, the use of prolonged infusions of meropenem is not registered by the FDA and is considered an off-label application. Also, some studies provide controversial data on the advantage of prolonged infusions over intermittent ones. It is known that age is an independent predictor of mortality in patients with sepsis and septic shock.

In this study, we evaluated the effectiveness of continuous infusion in geriatric trauma patients with sepsis.

This was a single-center case series of 7 geriatric trauma patients with sepsis who received continuous infusion of meropenem from November 2021 to March 2023. The objective of this study is to evaluate the feasibility and clinical impact of continuous infusion of meropenem in elderly with sepsis. Data including clinical findings, laboratory data, complications, and survival to hospital discharge were also collected. 7 patients (median age 71, 100% female) received continuous infusion of meropenem. All patients were septic prior to infusion. 1 patient transferred to another hospital and died during hospitalization, 6 survived to hospital discharge and 1 patient died after discharge. Multiresistant bacteria were observed in 2 patients.

Conclusion. The use of continuous infusion of meropenem can lead to clinical improvement, but do not decrease death rate.

Keywords: Sepsis, meropenem continuous infusion, geriatric trauma, SIRS, a case report.

Introduction

The use of continuous infusion of carbapenems in severe infections, including sepsis, is widely studied in the world. In particular, many studies have been conducted on the use of prolonged meropenem infusion in pediatric practice. Also, a large number of studies are being conducted separately on the topic of prolonged infusion of meropenem in adults. Most studies show the greatest effectiveness of using extended meropenem infusion, but there are studies in which there are no differences in effectiveness between bolus or extended meropenem infusion, depending on the expected results. In turn, the category of geriatric patients, as well as children, should be considered separately due to the presence of age-related features of drug metabolism.

According to the World Health Organization, by 2050 it is expected that the proportion of the world's inhabitants over 60 years of age will double and reach 22% [1]. Since aging is accompanied by changes in the immune response, this will lead to an increase in the growth of age-related diseases due to the increased susceptibility of the body to infections, cancer, cardiovascular and neurodegenerative diseases. Infections lead to an unregulated immune response and, consequently, dysfunction of vital organs. Worldwide,

sepsis affects 49 million people and leads to 11 million sepsis-related deaths [2]. According to the study Palomba H., et al., age was found to be an independent predictor of death in patients with sepsis and septic shock [3]. This phenomenon is probably associated with the peculiarities of the immune response in the elderly, a condition called immunosenescence. All over the world, studies are conducted on adults, starting at 18 years of age. In our opinion, this is possibly distorting the final data, since older people have their own age characteristics. And, therefore, isolated studies are needed that will be applicable to the elderly. In particular, this applies to antibiotic therapy in the treatment of sepsis. The new Surviving Sepsis Campaign Guideline recommends the use of prolonged infusions of meropenem in sepsis to maintain a therapeutic dose of the antibiotic in the blood [4]. Due to the characteristics of the immune response in the elderly, as well as slow metabolism and reduced kidney function, this approach to antibiotic therapy may be of particular concern.

This article highlights 7 clinical cases of continuous meropenem infusion for sepsis in geriatric trauma patients.

A series of clinical cases of pretension

This was a single center case series study conducted at the National Scientific Center of Traumatology and Orthopedics named after academician Batpenov N.D., in Astana, Kazakhstan, and was approved by the Local Ethics Committee of our institution. At the Center advanced, innovative technologies are used, including arthroplasty

and therapeutic and diagnostic arthroscopy of large joints, closed minimally invasive osteosynthesis technologies for fractures of the extremities, modern systems of surgical correction and fixation of the spine and other operations, including specialized care for elderly people with pathology of the musculoskeletal system.

Table 1 - General data of the patients

№	Age (years)	Race	Diagnosis	Comorbidity	Height		Days in ICU	In-hospital days	Surgery	Outcome
1	79	Asian	Hip fracture	COVID-19 (IgG-positive), Diabetes mellitus 2 type, diabetic polyneuroangiopathy, diabetic nephropathy, Ischemic cardiac disease, arterial hypertension, Aorto-coronary shunt (2019), Cardiac insufficiency, Atherosclerosis of arteries of lower limbs, occlusion of trivial segments, chronic bronchitis	160	80	22	45	Closed lockable	Alive
2	66	Asian		Chronic ischemia of the brain of mixed genesis (hypertensive, atherosclerotic, vascular). Persistent residual effects of a stroke (from 2018) Left-sided spastic hemiplegia. Arterial hypertension. Iron deficient anemia	164	60	9	20		Alive
3	79		Hip fracture	Obesity, prediabetes, Arterial hypertension	170	98	17	22		Death after 10 days from discharge
4	86	Asian	Chest trauma. Closed fracture of 4 ribs	Chronic bronchitis, Brain ischemia, dementia, arterial hypertension	170	80	14	14		Alive
5	67	Asian		NA	165	45	62	62	Closed	Death in the hospital
6	65			Arterial hypertension Atrial fibrillation, paroxysmal form.	166	69	4	17		Alive
7	63	Asian		Rheumatoid arthritis, Chronical bronchitis, ischemic heart disease. Condition after myocardial infarction. Condition after stenting of the coronary arteries. Arterial hypertension	152	71	68	68		Alive

The study population was a convenient sample of patients because sepsis was associated with periprosthetic infection or trauma. Indications for participation in the study were patients over 60 years of age with a diagnosis of sepsis (q-SOFA scale over 2 points), contraindications for participation in the study were allergy or individual intolerance to the study drug, unfavorable prognosis by the SAPS II scale (over 65 points), individuals with concomitant acquired immunodeficiency syndrome (stage 3 according to the CDC).

The study patients received a continuous 24-hour infusion of meropenem (Santo, Shymkent, Kazakhstan), 500 mg of meropenem was diluted in 50 ml of NaCl 0.9% (10 mg/ml) and administered at a rate of 12.5 ml/h, taking into account kidney function. Dosage adjustment was made considering creatinine clearance. For ClCrea <50 ml/min. applied 2 g/day. Namely, 500 mg of meropenem was diluted in 50 ml (10 mg/ml) NaCl 0.9% and administred at a rate of 8.3 ml/h. The stability of the prepared antibiotic solution was ensured by preparing a completely new solution of the drug for every 4 hours. Such infusion methodic was recommended and described in the MERCY study protocol [5].

The main result of this study is a descriptive analysis of in-hospital and overall mortality of patients with sepsis in the intensive care unit, as well as an analysis of microbiological crops and appearance new multiresistant bacteria. Secondary outcomes included descriptive analysis of SOFA, CRP, leukocytes, number of days in intensive care, number of days in hospital.

Descriptive statistics were used to report study outcome data. Data was collected in password protected software and analyzed using commercial software (Microsoft Excel V16.43 20110804).

During the study period continuous infusion of meropenem were performed in 7 geriatric patients (Table 1). The median patient age was 72 years (Range 63–86) and 7/7 patients were female.1 patient died in the hospital. Two patients were found to have Pseudomonas aeruginosa 10^4 - 10^5 resistant to at least 3 antibiotics (Table 2). 6 patients survived to hospital discharge and 1 patient died after 10 days from discharge. Totally, 5 patients with sepsis survived.

Table 2 - Cultures and antibioticotherapy

	Age	Sex	Cultures	Sensitivity	Received antibiotics	Outcome
1	79	F	Enterobacter aerogenes 10:5 / Klebsiella pneumoniae - 10:3	Amikacin - S Amoxicillin - S Cefepime - S Cefotaxime - I Ceftazidime - I Ceftazidime Avibactam - S Cefuroxime - R Ciprofloxacin - S Doripenem - S Imipenem in combination with beta-lactamase inhibitors - S Meropenem - S Tetracycline - S / Amikacin - S Amoxicillin - S Cefepime - I Cefotaxime - I Ceftazidime - I Ceftazidime Avibactam - S Cefuroxime - I Ciprofloxacin - S Imipenem in combination with beta-lactamase inhibitors - S Levofloxacin - S Meropenem - S	Cefalosporines 1-13 days Meropenem 14-21 Meropenem+Amikacin 21-3 Amikacin Ciprofloxacine	Alive
2	66	F	Pseudomonas aeruginosa 10^5	Amikacin S Ceftazidime S Ceftazidime Avibactam S Ciprofloxacin S Gentamicin S Imipenem in combination with beta-lactamase inhibitors S Levofloxacin S Meropenem S Tetracycline I Piperacillin in combination with beta-lactamase inhibitors S	Cefalosporines 1-3 days Meropenem 4-5 days Cef3+Levofloxacine 5-20 days	Alive
3	79	F	Candida Albicans 10^4	Clotrimazole S Fluconazole S Itraconazole S	Cefalosporines 1-3 days Meropenem 4-12 days Meropenem+Levofloxacine 14-22 days	Death after 10 days from discharge
4	86	F	Not found	-	Cef3+Levofloxacine Meropenem	Alive
5	65	F	Multiresistant Pseudomonas aeruginosa 10^5	Amikacin S Cefepime R Cefoperazone/sulbactam R Ceftazidime R Ciprofloxacin S Doripenem S Imipenem in combination with beta-lactamase inhibitors S Levofloxacin R Meropenem S Tetracycline R Piperacillin in combination with beta-lactamase inhibitors S Ticarcillin in combination with beta-lactamase inhibitors R.	Cef3+metronidazole 7 days Meropenem+levofloxacine 8-18 days Piperabactam (Ps.aureginosa) 19 Ciprofloxacine Imipinem+Cilostatin Fluimucil	Death in the hospital
6	65	F	Staphylococcus epidermidis 10^4	Amoksiklav S Ampicillin R Azithromycin R Cefazolin S Cefepime S Cefoxitin S Ceftriaxone S Gentamicin S Imipenem in combination with beta-lactamase inhibitors S Levofloxacin S Linezolid S Moxifloxacin S Vancomycin S	Cef 3 Levofloxacin Meropenem	Alive
7	63	F	Staphylococcus epidermidis / Multiresistant pseudomonas aeruginosa 10^4	Amoksiklav S Azithromycin S Cefazolin S Cefepime S Cefoxitin S Ceftriaxone S Gentamicin S Imipenem in combination with beta-lactamase inhibitors S Levofloxacin S Linezolid S Moxifloxacin S Sulfamethoxazole and trimethoprim S Vancomycin S Ampicillin in combination with beta-lactamase inhibitors R / Amikacin S Cefepime R Cefoperazone/sulbactam R Ceftazidime R Ciprofloxacin S Doripenem S in combination with beta-lactamase inhibitors S Levofloxacin R Meropenem S Tetracycline R Piperacillin in combination with beta-lactamase inhibitors S Ticarcillin in combination with beta-lactamase inhibitors R	Meropenem 7 days, Meropenem +Levofloxacin 8-14 days Vankomicin+Levofloxacin 15-25	Alive

As presented in the Table 1 the average length of ICU stay was 28 days (range 4-68 days), the average length of stay in hospital was 35 days (range 14-68 days). The table 3 highlights initial indicators of the patients. As showed in the Table 3, the average score on APACHE II scale was 10 points (range 6-15 points), The average score on SOFA scale was 3,85 points (range 2-8 points). Frailty index was calculated taking into account the injury, the average fraility score was 6,2 points (range 3-8).

Table 3 - Initial assessment of the patients

	Age	Sex	APACHE II	SOFA	Creatinine Clearance	Frailty Score
1	79	F	11	3	61 mL/min	5
2	66	F	6	2	62 mL/min	4
3	79	F	10	5	54 mL/min	8
4	86	F	9	4	36 mL/min	8
5	65	F	15	8	149 mL/min	8
6	65	F	8	2	91 mL/min	3
7	63	F	12	3	61 mL/min	8

Discussion

The prevalence of elderly patients with severe sepsis and septic shock continues to grow rapidly worldwide. And in the near future, this may lead to a significant increase in the demand for ICU bed days among the elderly population, as older patients have a longer length of stay in the ICU compared to younger people due to presence of comorbidities, age-related changes in immune responses [6].

In this study, we applied the method of continuous infusion of meropenem in the treatment of sepsis in geriatric patients (>60 years) with trauma in order to assess the clinical course of sepsis in these patients, as well as to evaluate clinical outcomes.

Prescribing antibiotics in elderly patients can be challenging. A proportional increase in body fat relative to skeletal muscle in the elderly may lead to an increase in the volume of distribution. With age, there is a decrease in the total size and number of nephrons, tubulointerstitial changes, thickening of the glomerular basement membrane, and intensification of glomerulosclerosis. This age-related histological appearance is often described as nephrosclerosis. Decreased clearance of the drug may be the result of a natural decline in renal function with age, even in the absence of renal insufficiency. Reduced clearance prolongs the half-life of drugs and leads to increased plasma concentrations of drugs in the elderly [7].

A decrease in the detoxification function of the liver contributes to the development of a pro-inflammatory condition, in which weakness may develop.

Because inflammation also suppresses drug metabolism, drugs given to frail older adults according to disease-specific guidelines may be subject to decreased systemic clearance, leading to adverse drug reactions, further deterioration of function, and increased polypharmacy, exacerbating rather than improving the state of frailty [8].

It has long been recognized that beta-lactam antibiotics show a time-dependent effect on bacterial eradication. Long-term infusions of beta-lactam antibiotics achieve the target pharmacodynamic efficacy more effectively than short infusions. Thus, a prolonged infusion strategy may improve microbiological and clinical cure, especially when pathogens exhibit higher minimum inhibitory concentrations (MICs) [9-10]. But studies suggests that long-term or continuous infusions of carbapenems are associated with similar mortality rates as conventional intermittent infusions but may have other benefits such as clinical cure and microbiological success, as evidenced by limited data [11-13].

In a single-center, randomized, open-label study in 240 adult ICU patients, administration of meropenem as a continuous infusion resulted in similar mortality (16 percent) and clinical cure rates that were not statistically different (83 vs. 75 percent) compared with intermittent infusion, but rates microbiological success (90% versus 78%) was higher and ICU stay and duration of therapy were shorter with continuous infusion [14].

In a meta-analysis involving 632 patients with severe sepsis, the authors concluded that continuous administration of beta-lactam antibiotics was associated with a reduction in hospital mortality [15]. But Joel M Dulhunty et al. in a multicentre study of 432 patients with sepsis with a mean age of 64 years, state that, there was no difference in outcomes between β-lactam antibiotic administration by continuous and intermittent infusion [16]. Perhaps these results are related to the average age of participants. After all, age is known to be an independent predictor of mortality in patients with severe sepsis [17,18].

In this study, we describe our experience of using meropenem continuous infusion in geriatric trauma patients with sepsis. Since several Population Pharmacokinetics studies of Meropenem in adults indicate that meropenem must be administered by prolonged infusion in order to achieve microbiological success and subsequent clinical cure [19,20].

Population pharmacokinetic studies of meropenem in elderly patients are few and research is mainly focused on investigating the optimal dosage regimen of meropenem. Thus, in China, there were 284 measurements of meropenem serum concentrations in 75 patients (aged 63–95 years). CLCR and the APACHE II score have a significant effect on the pharmacokinetics of meropenem. In patients with lower respiratory tract infections (LRTI), a cut-off value of 76% for %T>MIC can be used to optimize the meropenem dosing regimen for clinical success [21]. In other prospective single-center open-label randomized controlled trial with 79 elderly patients with an LRTI, authors concluded that strategy for meropenem dosing based on a population PK/PD model can improve clinical response and avoid overtreatment in elderly patients with an LRTI [22]. But both PK studies of the optimal dosing regimen for meropenem were conducted using intermittent infusion.

Only in one PK study with participation of 178 elderly patients continuous infusion of meropenem was used. Usman M, Frey OR, Hempel G. concluded that an

extended infusion of 1000 mg q8h can be considered for empirical treatment of infections in elderly patients when CLCR is ≤ 50 mL/min. A continuous infusion of 3000 mg daily dose is preferred if CLCR > 50 mL/min. However, a higher daily dose of meropenem would be required for resistant strains (MIC>8 mg/L) of bacteria if CLCR is >100 mL/min [23].

In the first few days, elderly patients have an improvement in the respiratory system after application of continuous mode meropenem infusion, possibly due to an increase in the alveolar concentration of meropenem, but in some patients this effect was short-lived. These patients subsequently required intensification of antibiotic therapy. Studies show that administration of meropenem by continuous infusion maintains higher concentrations in the subcutaneous tissue and plasma, and thus better penetrates the lung tissue compared with intermittent bolus administration [24, 25]. For instance, the PROMESSE study performed in 55 critically ill patients with severe pneumonia treated with 1 g/8 h reported a statistically higher AUC penetration ratio in the extended infusion group (3 h) compared to the intermittent group [mean (SD) 29 (± 3) % vs 20 (± 3) %(P = 0.047) [26].

In recently published MERCY randomised clinical trial with participation of 607 individuals' authors concluded that continuous administration of meropenem did not improve the composite outcome of mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28 [27].

In a systematic review with meta-analysis of randomized trials comparing short and prolonged infusion of beta-lactams infusion authors recommended provide further studies in specific subgroups of patients according to age, sepsis severity, degree of renal dysfunction, and immunocompetence are warranted [28].

Prolonged beta-lactam infusions have both advantages and disadvantages. The disadvantages of the prolonged method of infusion include the presence of constant intravenous access, the compatibility of the drug with other administered drugs, and the issue of the stability of the prepared solution. The instruction for branded meropenem (Merrem) notes that meropenem prepared for infusion in normal saline is stable for 1 hour at room temperature and up to 15 hours refrigerated. For meropenem (Santo, Shymkent, Kazakhstan) used in patients, no such information is available.

This case series study has several limitations, including the absence of comparison groups, limited data collecting.

In this article, we present the use of continuous meropenem infusion in geriatric patients with trauma or periprosthetic infection. Despite the using of continuous infusion of meropenem in these patients, mortality among patients remained high.

Conclusions

Therefore, after analyzing the usage of continuous infusion of meropenem in 7 geriatric patients, we concluded that continuous infusion mode can lead to the clinical improvement in the respiratory status of patients. Since our study has the following limitations in the form of a lack of therapeutic drug monitoring, we focus only on the clinical picture of patients. Further development of strategies for optimal dosing of meropenem and administration by continuous infusion in geriatric patients possibly will increase clinical cure rates and decrease demand in ICU bed-days.

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Түйіндеме

Меропенемнің үздіксіз инфузиясы сепсисті емдеуге арналған нұсқауларда ұсынылады. Дегенмен, меропенемнің ұзартылған инфузиясын қолдану азық-түлік және дәрі-дәрмек басқармасы (FDA) тарапынан мақұлданбаған және «белгіден тыс» пайдалану болып саналады. Сонымен қатар, кейбір зерттеулер үзіліссіз инфузияларға қарағанда үзіліссіз инфузиялардың пайдасы туралы қарама-қайшы дәлелдерді береді. Жас сепсис пен септикалық шокпен ауыратын науқастардағы өлімнің тәуелсіз болжаушысы екені белгілі.

Бұл зерттеуде біз травматология және ортопедиядағы сепсиспен ауыратын гериатриялық науқастарда үздіксіз инфузияның тиімділігін бағаладық.

Бұл 2021 жылдың қарашасынан 2023 жылдың наурызына дейін үздіксіз инфузиялық меропенемді қабылдаған сепсиспен ауыратын 7 гериатриялық жарақат алған пациенттерді қамтитын бір орталықты жағдайлар сериясы болды. Бұл зерттеудің мақсаты сепсиспен ауыратын егде жастағы емделушілерде меропенемді үздіксіз инфузиялаудың орындылығын және клиникалық әсерін бағалау болып табылады. Клиникалық нәтижелерді, зертханалық параметрлерді, асқынуларды және ауруханадан шыққанға дейін тірі қалуды қамтитын деректер де жиналды. Барлығы 7 пациент (орташа жасы 71 жас, әйелдер 100%) меропенемнің үздіксіз инфузиясын алды. Барлық науқастар инфузия алдында септикалық болды. Бір науқас басқа ауруханаға ауыстырылды, онда науқастың өлімі кейіннен тіркелді, 6 науқас ауруханадан шыққанға дейін аман қалды, 1 науқас ауруханадан шығарылғаннан кейін қайтыс болды. 2 науқаста көп дәріге төзімді бактериялар байқалды.

Қорытынды. Меропенемнің үздіксіз инфузиясын қолдану клиникалық жақсартуға әкелуі мүмкін, бірақ өлімді төмендетпейді.

Түйін сөздер: Сепсис, меропенемнің үздіксіз инфузиясы, гериатриялық жарақат, жүйелі қабыну реакциясының синдромы, жағдай туралы есеп.

Использование непрерывной инфузии меропенема для лечения сепсиса у гериатрических пациентов в травматологии и ортопедии. Серия клинических случаев

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Резюме

Длительная инфузия меропенема рекомендована руководством для лечения сепсиса. Однако применение пролонгированных инфузий меропенема не зарегистрировано Управлением по контролю качества пищевых продуктов и лекарственных средств (FDA) и считается применением "не по инструкции". Кроме того, в некоторых исследованиях приводятся противоречивые данные о преимуществе длительных инфузий над прерывистыми. Известно, что возраст является независимым предиктором смертности у пациентов с сепсисом и септическим шоком.

В данном исследовании мы оценили эффективность непрерывной инфузии у гериатрических пациентов с сепсисом в травматологии и ортопедии.

Это была одноцентровая серия случаев, включающая 7 гериатрических травматологических пациентов с сепсисом, которые получали непрерывную инфузию меропенема с ноября 2021 по март 2023 года. Цель данного исследования - оценить целесообразность и клиническое воздействие непрерывной инфузии меропенема у пожилых пациентов с сепсисом. Также были собраны данные, включая клинические результаты, лабораторные показатели, осложнения и выживаемость до выписки из стационара. 7 пациентов (средний возраст 71 год, 100% женщин) получали непрерывную инфузию меропенема. Все пациенты были септическими до начала инфузии. Один пациент переведен в другую больницу, где далее была зарегистрирована смерть пациента, 6 пациентов выжили до выписки из больницы, и 1 пациент умер после выписки. Мультирезистентные бактерии наблюдались у 2 пациентов.

Выводы. Использование непрерывной инфузии меропенема может привести к клиническому улучшению, но не снижает смертность.

Ключевые слова: Сепсис, непрерывная инфузия меропенема, гериатрическая травма, ССВО, клинический случай.