Meropenem (EN)

Synoniemen

Laatst bijgewerkt:
vrijdag 26 augustus 2016 10:59:00

Indication:	Nosocomial pneumonia, bacterial meningitis, febrile neutropenia, Bacteremia associated with intravascular line (due to susceptible gram-negative bacilli, complicated infectious diseases of abdomen, complicated infections of skin and/or subcutaneous tissue[1], bronchopulmonary infections in cystic fybrosis
Sample material:	Plasma or serum[2]
Time of sampling:	During continuous infusion, or trough concentration (C_{trough})[3]
Storage conditions:	-80 ˚C (stable for three months)[4]
	Meropenem is not stable at room temperature[3] and stable for 24 hours at 4˚C[4]
Interpretation:	C_{trough}/MIC ≥ 5 [5,6]
	C_{ss} 8-12 mg/L (C_{ss}/MIC = 4-6)[7,8]

Inleiding

Meropenem is a bactericide ß-lactam antibiotic, that belongs to the carbapenems. It is active against gram-positive (ie, Enterococcus faecalis, Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae (penicillin-susceptible), Streptococcus pyogenes, Viridans group streptococci), gram-negative bacteria (ie, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria meningitidis, Pseudomonas aeruginosa, Proteus mirabilis), and anaerobic bacteria (ie, Bacteroides fragilis, Bacteroides thetaiotaomicron, Peptostreptococcus species), with significant stability to hydrolysis by beta-lactamases. It does not have activity against methicillin-resistant Staphylococcus aureus (MRSA) or methicillin-resistant Staphylococcus epidermidis (MRSE).

The EUCAST (European Committee on Antimicrobial Susceptibility Testing) clinical breakpoint for meropenem against most micro-organisms is 2 mg/L. In the treatment for meningitis, the clinical breakpoint has been set at 0.25 mg/L [9].

Meropenem exerts bactericidal activity by inhibiting cell wall synthesis by penetrating the cell wall of most gram-positive and gram-negative bacteria to reach penicillin-binding–protein (PBP) targets. Its strongest affinity is toward PBPs of Escherichia coli, Pseudomonas aeruginosa or Staphylococcus aureus.

Meropenem is not sensitive to serine ß-lactamases or to degradation by the enzyme dehydropeptidase-1 (DHP-1). Therefore, it is not necessary to administer a DHP-1-inhibitor like cilastatin. This high resistance to most bacterial beta-lactamases and good penetration of the drug through the outer microbial membrane contributes significantly to antimicrobial activity of meropenem.

Bactericidal concentrations are typically one to two times the bacteriostatic concentrations; with the exception of Listeria monocytogenes, against which lethal activity has not been observed.

Doseringsrichtlijnen

Adult[1]:	
Bacteremia associated with intravascular line: (due to susceptible gram-negative bacilli)	1 g IV every 8 hours
Bacterial meningitis:	2 g IV every 8 hours[10]
Febrile neutropenia:	1 g IV every 8 hours for at least 7 days
Infection of skin and/or subcutaneous tissue, complicated: caused by Pseudomonas aeruginosa:	500 mg IV every 8 hours; 1 g IV every 8 hours
Infectious disease of abdomen, Complicated:	1 g IV every 8 hours
Nosocomial pneumonia	1 g IV every 8 hours
Severe infections, in critically ill patients	Initial loading dose of 1-2 g IV, followed by continuous infusion dose depending on renal function and target C_{ss}[8]

Pediatric[11]:	
Bacterial meningitis (age > 1 month):	40 mg/kg (max 2 g) IV every 8 hours;
Infections: Postnatal age < 1 week Postnatal age 1 to 4 weeks Age > 1 month	 20 mg/kg IV every 12 hours 20 mg/kg IV every 8 hours 20 mg/kg (max 2 g) IV every 8 hours
Infections in cystic fibrosis (age > 1 month):	100 mg/kg/day IV as continuous infusion

Renal impairment[12]:	
Glomular filtration rate (GFR) 20-50 ml/min	500 mg-2 g IV every 12 hours
GFR 10-20 ml/min	500 mg-1 g IV every 12 hours or 500 mg IV every 8 hours
GFR < 10 ml/min	500 mg-1 g IV every 24 hours
Continuous ambulatory peritoneal dialysis (CAPD)	Dialysed. Dose as in GFR<10 mL/min
Intermittent haemodialysis (IHD)	Dialysed. Dose as in GFR<10 mL/min or 1-2 g post dialysis
Haemodiafiltration (HDF)/ High flux	Dialysed. Dose as in GFR<10 mL/min
Continuous arteriovenous/venovenous haemodiafiltration (CAV/VVHD)	Dialysed. 500 mg-1 g IV every 8 hours or 1 g IV every 12 hours
Continuous venovenous haemodialysis/haemodiafiltration (CVVHDF)	1 g IV every 12 hours

Table 1-3: Dosing schemes of meropenem in adult, pediatric patients and in renal impairment

Referentiewaarden

--

Spiegelafname

Sampling takes place at presumed steady-state concentration (reached after four doses or 24-48 hours after onset of treatment) after intermitting dosing.[3] In continuous infusion of meropenem, steady-state PK is reached after four to five half-lives after start treatment or after dose change.[3]

Matrices like peritoneal fluid, renal replacement therapy (RRT), dialysate, urine, pleural effusion, bronchoalveolar lavage fluid, bile and joint aspirate have been sampled, however, reference values for these matrices have not been established[3].

Meropenem analysis is performed using HPLC with UV-detection (HPLC-UV) and (ultra performance) liquid chromatography - tandem mass spectrometry ((UP)LC-MS/MS)[3].

Interpretatie resultaten

The aim of β-lactam TDM is to provide doses of antibiotic that maintain unbound (f) β-lactam concentrations above bacterial MICs over a desired percentage of the dosing period (% $fT_{>MIC}$)[3,13]. For meropenem, the free concentration is approximated by the total concentration, due to its low protein binding (2%).

Ariano et al. observed an 80% clinical response rate if >75% $T_{>MIC}$ (p=0.01)[13]. Numerous studies have demonstrated that antibiotic plasma concentrations—especially those of hydrophilic antibiotics, such as β-lactams—are variable and unpredictable in ICU patients[14–16]. Increased volume of distribution, elimination rate from the circulation through the kidney or the use of extracorporeal circuits contribute to this phenomenon, which has important implications[14]. In these patients, it has been advocated to maintain C_{trough} > MIC for the entire dosing interval (C_{trough} > MIC), which implicates a 100% $T_{>MIC}$[7].

Due to its time-dependent activity in the treatment of severe infection, meropenem effectivity may be maximized by continuous infusion[7,8,17]. Target steady-state concentrations (C_{ss}) between 8 and 16 mg/L have been proposed[7,8]. This is based on the clinical breakpoint for meropenem against Enterobacteriaceae of 2 mg/L and the desire to maintain a C_{ss}/MIC ratio of 4–6[7,8]. In the article of Pea et al, useful dosing nomograms based on CLCr to target meropenem Css at 8, 12 and 16 mg/L in critically ill patients are presented[8].

TDM of meropenem should be considered In critically ill or neutropenic patients or in patients who might have variable pharmacokinetics due to augmented or decreased renal function or renal replacement therapy[18].

Toxiciteit

A toxic dose has not been established with carbapenem antibiotics [1]. β-lactam antibiotics have a relatively safe therapeutic profile, but there have been reports of neurotoxicity. C_{trough}> 16 mg/L (C_{trough}/MIC > 8, Clinical breakpoint for *Pseudomonas aeruginosa* = 2mg/L) seems to be a predictive factor for worsening of the neurological status of septic ICU patients [24]. Additionally, patients treated with high dosages of meropenem for > 14 days were more likely to develop liver dysfunction [25].

Achtergrondinformatie

--

Interacties

--

PK parameters

Pharmacokinetics

Absorption:	**Not applicable. Meropenem is administered intravenously.**
Distribution:	Protein binding of meropenem is approximately 2%[1]. Meropenem achieves concentrations that match or exceed those required to inhibit most susceptible bacteria in most body fluids and tissues including cerebrospinal fluid. Peak concentrations in body fluids were mostly achieved in 1 hour following IV infusion[1]. Volume of distribution (Vd): Table 5.
Metabolism:	There is one (inactive) metabolite of meropenem.[1] There are no genotypes known to influence the kinetics of meropenem. Meropenem is well tolerated in patients with hepatic disease, adjustments to dosage are not necessary.[19]
Excretion:	The kidneys are the primary route of clearance of meropenem. The clearance of meropenem from plasma correlates with the CrCl. Meropenem undergoes both filtration and tubular secretion. There is no accumulation of repeated doses of meropenem 500 mg every 8 hours, or 1 gram every 6 hours in patients with normal renal function. Approximately 70% (50% to 75%) of a meropenem dose administered intravenously is recovered unchanged in the urine over 12 hours[1]. Extra-renal 20-25%, this may increase to 50% in patients with creatinine clearance (CrCl) < 20 ml/min. Elimination half-life ($T_{1/2}$): Table 5.

Table 4: ADME information.

Population	Vd	Cl (L/h)	$T_{1/2}$ (h)	Ref
Adults	12 - 20 L	11-18	1	[1]
Adults obese (mean BMI 65.5 kg/m^2)	25.1 ± 9.1 L	8.1 ± 2.6	2.8 ± 1.4	[20]
Hospitalized patients				[21]
CrCl 91.5 ± 17.3 ml/min	29.3 ± 8.7 L	10.7 ± 2.6	2.5 ± 0.9	
CrCl 52.1 ± 8 ml/min	23.8 ± 8.1 L	6.4 ± 2.2	3.4 ± 1.3	
CrCl 35.1 ± 11.6 ml/min	28.7 ± 8.6 L	3.7 ± 0.7	6.1 ± 1.4	
Endstage renal failure			6-13.7	[12]
			3.4-20	[1]
CVVH/ CVVHD	0.35 L/kg		5.2	[22]
Pediatric patients 3 months to 2 years			1,5	[1]
Preterm neonates (27 to 32 weeks gestational age, 21 days postnatal age)	0.74 L/kg		3.4	[23]

Table 5: Pharmacokinetic parameters.

CrCl: Creatinine clearance, Vd: volume of distribution, Cl: Clearance, $T_{1/2}$: half-life

Populatiemodellen

--

Literatuur

1. Anon. Micromedex® 2.0, (electronic version). Thomson Reuters (Healthcare), Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com (cited: 09/24/2015).

2. Carlier M, Stove V, Wallis SC, *et al.* Assays for therapeutic drug monitoring of β-lactam antibiotics: A structured review. *Int J Antimicrob Agents* 2015; **46**: 367–75.

3. Wong G, Brinkman A, Benefield RJ, *et al.* An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J Antimicrob Chemother* 2014; **69**: 1416–23.

4. Elkhaïli H, Niedergang S, Pompei D, Linger L, Leveque D, Jehl F. High-performance liquid chromatographic assay for meropenem in serum. *J Chromatogr B Biomed Appl* 1996; **686**: 19–26.

5. Roberts JA, Abdul-Aziz MH, Lipman J, *et al.* Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 2014; **14**: 498–509.

6. Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. *Antimicrob Agents Chemother* 2007; **51**: 1725–30.

7. Pai MP, Cojutti P, Pea F. Pharmacokinetics and pharmacodynamics of continuous infusion meropenem in overweight, obese, and morbidly obese patients with stable and unstable kidney function: a step toward dose optimization for the treatment of severe gram-negative bacterial infectio. *Clin Pharmacokinet* 2015; **54**: 933–41.

8. Pea F, Viale P, Cojutti P, Furlanut M. Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. *Antimicrob Agents Chemother* 2012; **56**: 6343–8.

9. Anon. Eucast. Available at: www.eucast.org.

10. Tunkel AR, Hartman BJ, Kaplan SL, *et al.* Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; **39**: 1267–84.

11. Anon. Kinderformularium. Available at: www.kinderformularium.nl.

12. Ashley C, Currie A eds. *The Renal Drug Handbook*. Third. Radcliff Pulbishing Ltd; 2011.

13. Ariano RE. Pharmacokinetics and Pharmacodynamics of Meropenem in Febrile Neutropenic Patients with Bacteremia. *Ann Pharmacother* 2005; **39**: 32–8.

14. De Waele JJ, Carrette S, Carlier M, *et al.* Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. *Intensive Care Med* 2014; **40**: 380–7.

15. Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. *J Antimicrob Chemother* 2009; **64**: 142–50.

16. Taccone FS, Laterre P-F, Dugernier T, *et al.* Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. *Crit Care* 2010; **14**: R126.

17. Mattioli F, Fucile C, Del Bono V, *et al.* Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients. *Eur J Clin Pharmacol* 2016; **72**: 839–48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27048201. Accessed June 28, 2016.

18. Roberts JA, Paul SK, Akova M, *et al.* DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current -Lactam Antibiotic Doses Sufficient for Critically Ill Patients? *Clin Infect Dis* 2014; **58**: 1072–83.

19. Thyrum PT, Yeh C, Birmingham B, Lasseter K. Pharmacokinetics of meropenem in patients with liver disease. *Clin Infect Dis* 1997; **24 Suppl 2**: S184–90.

20. Kays MB, Fleming MR, Cheatham SC, Chung EK, Juenke JM. Comparative pharmacokinetics and pharmacodynamics of doripenem and meropenem in obese patients. *Ann Pharmacother* 2014; **48**: 178–86.

21. Cheatham SC, Kays MB, Smith DW, Wack MF, Sowinski KM. Steady-state pharmacokinetics and pharmacodynamics of meropenem in hospitalized patients. *Pharmacotherapy* 2008; **28**: 691–8.

22. Giles LJ, Jennings AC, Thomson AH, Creed G, Beale RJ, McLuckie A. Pharmacokinetics of meropenem in intensive care unit patients receiving continuous veno-venous hemofiltration or hemodiafiltration. *Crit Care Med* 2000; **28**: 632–7.

23. van Enk JG, Touw DJ, Lafeber HN. Pharmacokinetics of meropenem in preterm neonates. *Ther Drug Monit* 2001; **23**: 198–201.

24. Beumier M, Casu GS, Hites M, *et al.* Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients. *Minerva Anestesiol* 2015; **81**: 497–506.

25. Yagi Y, Okazaki M, Higaki H, Nakai M, Hirata A, Miyamura M. Outcome evaluation of an intervention to improve the effective and safe use of meropenem. *Int J Clin Pharm* 2014; **36**: 648–56.

Colofon

This guideline has been constituted by Marieke G.G. Sturkenboom, PharmD, PhD, and Anton G.T. Terwisscha van Scheltinga, PharmD, PhD, under the auspices of Analytical and Toxicology Committee (CAT) of the Dutch Association of Hospital Pharmacists (NVZA), July 2016

Bijlage

Revisie