Karbapenemy v intenzivní péči

K. Urbánek

Ústav farmakologie

Lékařská fakulta Univerzity Palackého a Fakultní nemocnice Olomouc

Rozdělení

Skupina I **ertapenem,** panipenem, tebipenem

omezený účinek na G- nefermentující tyčky

Skupina II **imipenem, meropenem, *doripenem***

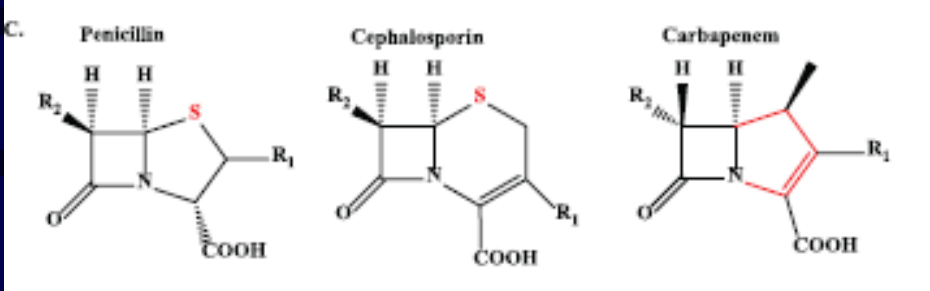
biapenem

dobrý účinek na G- nefermentující tyčky

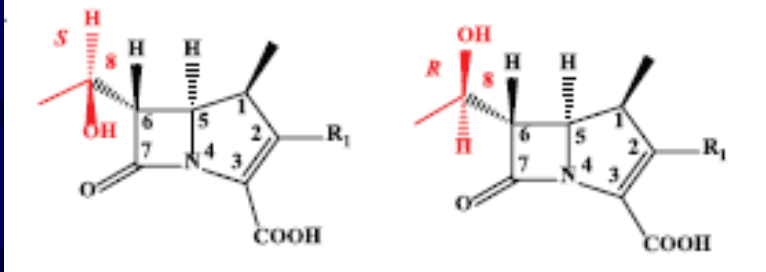
Skupina III není v praxi (tomopenem?)

účinek jako II rozšířený na MRSA

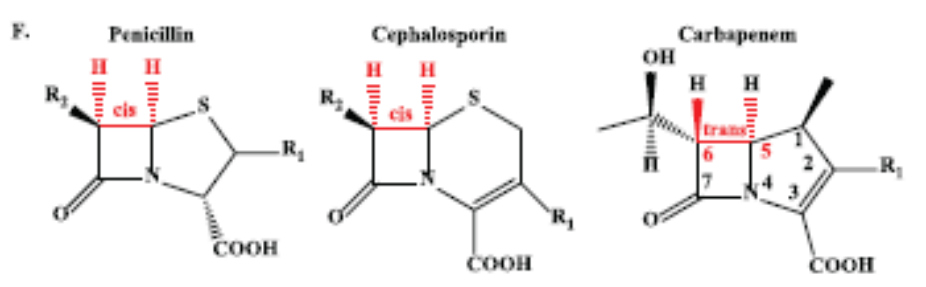
Chemická struktura



- C v pozici 1, dvojná vazba
  - Horší stabilita



- R pozice hydroxyethylové skupiny
  - Zesílení účinku



- Trans konfigurace na C5 a C6
  - Zesílení účinku

Farmakokinetika

Látka	Imipenem	Meropenem		Ertapenem
Distribuční objem	0,31	0,35		0,11
Vazba na proteiny	20 %	2 %		95 %
Biologický poločas	1	1		3,8
Interval dávkování	6 h	8 h		24 h

Farmakokinetika

Látka	Imipenem	Meropenem		Ertapenem
Dávka i.v. [g]	0,5	1		1
C_{max} [mg/l]	30-35	49-60		145-175
AUC [mg·h/l]	42	27-32		572
Exkrece močí (nezměněné) [%]	≈90 (60-70)	85-90 (70)		80 (40)

Aktuální kazuistika

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Short communication

Decreased meropenem levels in Intensive Care Unit patients with augmented renal clearance: benefit of therapeutic drug monitoring

Uwe Tröger[a], Andreas Drust[a], Jens Martens-Lobenhoffer[a], Ivan Tanev[b], Rüdiger C. Braun-Dullaeus[b], Stefanie M. Bode-Böger[a,*]

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ABSTRACT

One of the first-line drugs for empirical antibiotic therapy in patients with hospital-acquired infections is meropenem. An often neglected problem in sepsis is that patients with a normal serum creatinine concentration (SCr) might display augmented renal clearance (ARC). Here we describe two cases of sepsis with subtherapeutic exposures with standard meropenem dosing in whom therapy could be optimised by therapeutic drug monitoring (TDM). A 37-year-old man with acute lymphatic leukaemia and sepsis had a normal SCr at the beginning of his Intensive Care Unit (ICU) stay but showed decreased SCr of between 30 μmol/L and 40 μmol/L during his stay. He failed to achieve effective plasma concentrations with the meropenem standard dose of 3 g/day. Estimated glomerular filtration rate revealed values between 120 mL/min and 160 mL/min. He required a high meropenem daily dosage of 12 g that was far above the approved maximum dose. A 66-year-old patient undergoing surgery of a pulmonary aspergilloma presented SCr persistently <50 μmol/L, indicating ARC between 120 mL/min and 150 mL/min. This patient required 8 g of meropenem to achieve effective plasma concentrations. TDM may represent an invaluable approach to optimising drug exposure of β-lactam antibiotics in patients with ARC in the ICU. Further trials are clearly needed to become better informed about empirical dosing regimens usable in the ICU setting with regard to the relevance of ARC. In the meantime, daily measurement of creatinine clearance as well as TDM can be used to identify patients who manifest ARC, thereby allowing drug therapy to achieve the therapeutic range.

- Dvě kazuistiky ARC – Augmented Renal Clearance
  - 120- 160 ml/min
  - Meropenem v dávce 1 g co 8 h nedosahoval PKPD cíle
- U 37-letého pacienta s ALL cíl dosažen při 12 g / den
- U 66-letého pacienta v sepsi po výkonu při 8 g /den

Aktuální kazuistika

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Optimal Meropenem Concentrations To Treat Multidrug-Resistant *Pseudomonas aeruginosa* Septic Shock

Fabio Silvio Taccone,[a] Frédéric Cotton,[b] Sandrine Roisin,[c] Jean-Louis Vincent,[a] and Frédérique Jacobs[d]

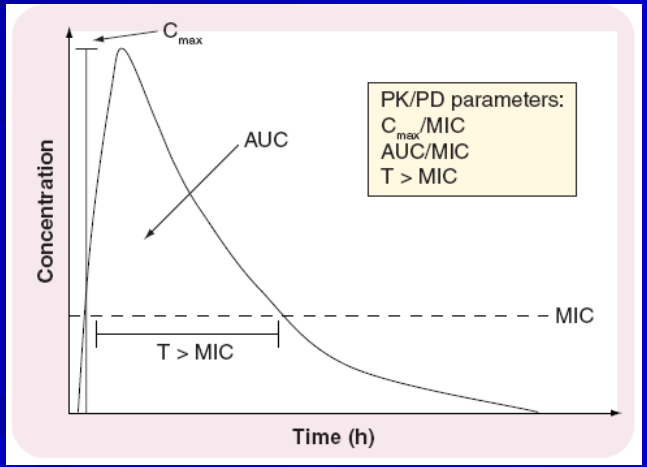
Department of Intensive Care, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[a]; Department of Clinical Biology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[b]; Department of Microbiology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[c]; and Department of Infectious Diseases, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[d]

A patient with septic shock due to extensively drug resistant (XDR) *Pseudomonas aeruginosa* was cured by optimizing the meropenem (MEM) regimen to obtain at least 40% of the time between two administrations in which drug levels were four times higher than the MIC of the pathogen. As the standard drug dose did not achieve these optimal concentrations, the MEM regimen was progressively increased up to 12 g/day (3 g every 6 h in a 3-h extended infusion), which eventually resulted in sepsis resolution. High MEM dosage may represent a valuable therapeutic option for infection due to multidrug-resistant (MDR) strains, and drug monitoring would allow rapid regimen adjustment in clinical practice.

- Pacient v septickém šoku *P. aeruginosa*
- PKPD cíl T nad 4xMIC $\geq$ 40 % dávkového intervalu
- Cíl dosažen až při dávce 3 g co 6 h v 3 h infuzi

PK/PD charakteristika

- Účinek je závislý na čase
- C_{max} nemají zásadní význam
- Cílem dávkování je dosáhnout 40 - 100 % (?) dávkového intervalu koncentraci nad 4xMIC (?)
  - PAE může zajistit efekt i při suboptimálním dávkování
- Dosáhnout cíle lze
  - Zvýšením dávky
  - Prodloužením infúze
  - Kontinuálním podáním



Dávkování: prodloužené podání

- Prodloužené i.v. infúze
  - Imipenem
    - Studie s 2h i 3h aplikací, není registrováno
  - Meropenem
    - Studie s 3h aplikací, není registrováno
  - Doripenem
    - Studie i registrace 4h infúzí
- Kontinuální aplikace
  - Studie ukazují shodné dosažení PKPD cíle s prodlouženými infúzemi
  - Riziko nízké stability
  - Zřejmě nepřináší další výhody – je ekvivalentní prodloužené infuzi

Aktuální studie

Display Settings: Abstract — Send to:

Ann Pharmacother. 2013 Feb;47(2):170-80. doi: 10.1345/aph.1R523. Epub 2013 Jan 22.

Prolonged infusion antibiotics for suspected gram-negative infections in the ICU: a before-after study.

Arnold HM, Hollands JM, Skrupky LP, Smith JR, Juang PH, Hampton NB, McCormick S, Reichley RM, Hoban A, Hoffmann J, Micek ST, Kollef MH.

Author information

Abstract

BACKGROUND: ß-Lactam antibiotics demonstrate time-dependent killing. Prolonged infusion of these agents is commonly performed to optimize the time the unbound concentration of an antibiotic remains greater than the minimum inhibitory concentration and decrease costs, despite limited evidence suggesting improved clinical results.

OBJECTIVE: To determine whether prolonged infusion of ß-lactam antibiotics improves outcomes in critically ill patients with suspected gram-negative infection.

METHODS: We conducted a single-center, before-after, comparative effectiveness trial between January 2010 and January 2011 in the intensive care units at Barnes-Jewish Hospital, an urban teaching hospital affiliated with the Washington University School of Medicine in St. Louis, MO. Outcomes were compared between patients who received standardized dosing of meropenem, piperacillin-tazobactam, or cefepime as an intermittent infusion over 30 minutes (January 1, 2010, to June 30, 2010) and patients who received prolonged infusion over 3 hours (August 1, 2010, to January 31, 2011).

RESULTS: A total of 503 patients (intermittent infusion, n = 242; prolonged infusion, n = 261) treated for gram-negative infection were included in the clinically evaluable population. Approximately 50% of patients in each group received cefepime and 20% received piperacillin-tazobactam. More patients in the intermittent infusion group received meropenem (35.5% vs 24.5%; p = 0.007). Baseline characteristics were similar between groups, with the exception of a greater occurrence of chronic obstructive pulmonary disease (COPD) in the intermittent infusion group. Treatment success rates in the clinically evaluable group were 56.6% for intermittent infusion and 51.0% for prolonged infusion (p = 0.204), and in the microbiologically evaluable population, 55.2% for intermittent infusion and 49.5% for prolonged infusion (p = 0.486). Fourteen-day, 30-day, and inhospital mortality rates in the clinically evaluable population for the intermittent and prolonged infusion groups were 13.2% versus 18.0% (p = 0.141), 23.6% versus 25.7% (p = 0.582), and 19.4% versus 23.0% (p = 0.329).

CONCLUSIONS: Routine use of prolonged infusion of time-dependent antibiotics for the empiric treatment of gram-negative bacterial infections offers no advantage over intermittent infusion antibiotic therapy with regard to treatment success, mortality, or hospital length of stay. These results were confirmed after controlling for potential confounders in a multivariate analysis.

PMID: 23341160 [PubMed - indexed for MEDLINE]

- 503 pacientů s meropenememem, pip/tazo nebo cefepimem
- Srovnání 30 min a 3 h infúzí
- Žádný rozdíl v úspěchu léčby, mortalitě, délce hospitalizace

Dávkování:
renální insuficience

Látka	CL_{Kr} [ml/min]	Dávka [mg]	Dávkovací interval [hod]
Imipenem	31-70	500	6-8
	21-30	500	8-12
	6-20	250	12
Meropenem	26-50	500-1000	12
	10-25	250-500	12
	<10	250-500	24
Ertapenem	<30	500	24

Dávkování:
umělé eliminační metody

- Intermitentní hemodialýza
  - Doporučení pro imipenem 250 mg co 12 h, vždy po dialýze
  - Pro meropenem 500 mg co 24 h po dialýze
  - U AKI spíše vyšší dávkování
- Kontinuální eliminační metody
  - Doporučení pro imipenem i meropenem 500 mg co 12 h
  - Vysoká účinnost eliminace, zachovaná diuréza
    - Spíše normální dávkování

Fish DN et al. Pharmacokinetics and pharmacodynamics of imipenem during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother. 2005; 49(6):2421-8.

Aktuální studie

Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: A multicentre pharmacokinetic study*

Darren M. Roberts, PhD; Jason A. Roberts, PhD; Michael S. Roberts, PhD; Xin Liu, PhD; Priya Nair, FCICM; Louise Cole, PhD; Jeffrey Lipman, MD; Rinaldo Bellomo, MD; on behalf of the RENAL Replacement Therapy Study Investigators

Objectives: In critically ill patients receiving continuous renal replacement therapy, we aimed to assess the variability of antibiotic trough concentrations, the influence of effluent flow rates on such concentrations, and the incidence of suboptimal antibiotic dosage.

Design: Prospective, observational, multicenter, pharmacokinetic study.

Setting: Four tertiary intensive care units within the multicenter RENAL randomized controlled trial of continuous renal replacement therapy intensity.

Patients: Twenty-four critically ill adult patients with acute kidney injury receiving ciprofloxacin, meropenem, piperacillin/tazobactam, or vancomycin during continuous renal replacement therapy.

Interventions: We obtained trough blood samples and measured antibiotic concentrations.

Measurements and Main Results: We obtained data from 40 dosing intervals and observed wide variability in trough concentrations (6.7-fold for meropenem, 3.8-fold for piperacillin, 10.5-fold for tazobactam, 1.9-fold for vancomycin, and 3.9-fold for ciprofloxacin). The median (interquartile range) trough concentrations (mg/L) for meropenem was 12.1 (7.8–18.4), 105.0 (74.4–204.0)/3.8 (3.4–21.8) for piperacillin/tazobactam, 12.0 (9.8–16.0) for vancomycin, and 3.7 (3.0–5.6) for ciprofloxacin. Overall, 15% of dosing intervals did not meet predetermined minimum therapeutic target concentrations, 40% did not achieve the higher target concentration, and, during 10% of dosing intervals, antibiotic concentrations were excessive. No difference, however, was found between patients on the basis of the intensity of continuous renal replacement therapy; this effect may have been obscured by differences in dosing regimens, time off the filter, or altered pharmacokinetics.

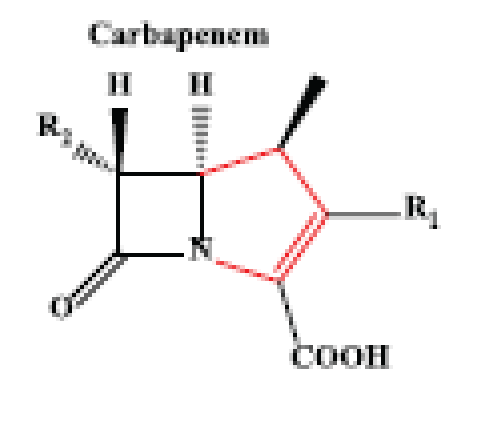
Conclusions: There is significant variability in antibiotic trough concentrations in critically ill patients receiving continuous renal replacement therapy, which did not only appear to be influenced by effluent flow rate. Here, empirical dosing of antibiotics failed to achieve the target trough antibiotic concentration during 25% of the dosing intervals. (Crit Care Med 2012; 40:1523–1528)

Key Words: antibiotic; critically ill patient; dialysis; pharmacodynamics; pharmacokinetics; therapeutic drug monitoring

- 24 nemocných s různými ATB při AKI a CRRT
- Empirické dávkování dle doporučení
- V 15 % dávkových intervalů nebylo dosaženo minimálních koncentrací, ve 40 % maximálních v 10 % bylo předávkování

Stabilita

- Ve formě prášku pro přípravu roztoků velmi vysoká
- V roztoku nízká
  - Závisí na teplotě, i na koncentraci (meropenem)
  - Ve fyziologickém roztoku při teplotě 15-25 °C
    - meropenem 6 hodin
    - imipenem 4 hodiny (cilastatin nedegraduje)
    - ertapenem 6 hodin
  - V 5% glukóze
    - meropenem 1 hodinu
    - Ostatní asi o 1/3 kratší než ve FR



Ředění a inkompatibility

- Imipenem
  - Ředění FR a 5 % glukózou
  - Inkompatibilní s laktátem, bikarbonátem, midazolamem, flukonazolem
- Meropenem
  - Ředění FR a 5 % glukózou
  - inkompatibilní s kalcium glukonátem, diazepamem, zidovudinem, doxycyklinem a ondansetronem
- Ertapenem
  - Ředění pouze FR, ne v glukóze

Interakce

- Nejsou ve fázi distribuce (vazba na albumin)
- Nejsou na CYP 450 ani P-glykoproteinu (?)
- Potenciálně významné interakce
  - Valproát
    - Snížení plazmatických koncentrací VPA
    - Zvýšené riziko křečí
  - Teofylin
    - Zvýšený výskyt křečí při konkomitantní léčbě
    - Více meropenem, méně imipenem/cilastatinem a ertapenemem
    - Zřejmě farmakodynamická interakce (?)

Park MK et al. Reduced valproic acid serum concentrations due to drug interactions with carbapenem antibiotics: overview of 6 cases. Ther Drug Monit. 2012 Oct;34(5):599-603.

Nežádoucí účinky: křeče

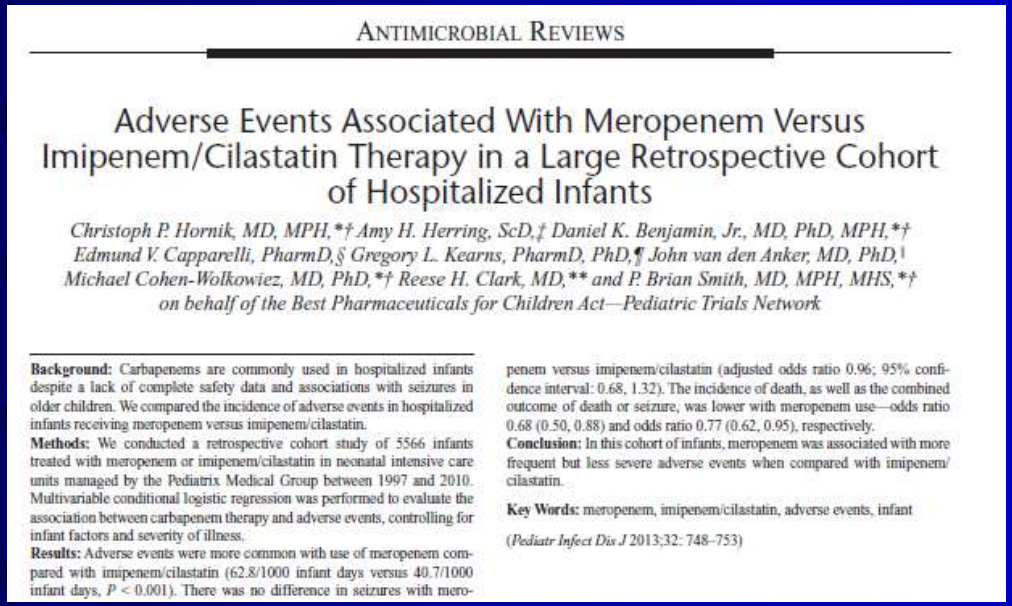
- Incidence
  - Imipenem/cilastatin 3-33 %
  - Ostatní do 1 %
- Mechanismus vzniku
  - GABA antagonismus
  - NMDA agonismus
- Terapie
  - benzodiazepiny

TABLE 10–5 Risk Factors for Drug-Induced Seizures

- Cancer
- Compromised blood–brain barrier
- Concomitant use of central nervous system stimulant drugs
- History of epilepsy or seizures
- Impaired metabolism of hepatically metabolized potentially seizure-inducing drugs in patients with liver disease
- Impaired elimination of renally eliminated potentially seizure-inducing drugs in patients with kidney disease

Miller AD et al. Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates, and clinical considerations. Pharmacotherapy. 2011 Apr;31(4):408-23.

Aktuální studie



ANTIMICROBIAL REVIEWS

Adverse Events Associated With Meropenem Versus Imipenem/Cilastatin Therapy in a Large Retrospective Cohort of Hospitalized Infants

Christoph P. Hornik, MD, MPH,† Amy H. Herring, ScD,‡ Daniel K. Benjamin, Jr., MD, PhD, MPH,*† Edmund V. Capparelli, PharmD,§ Gregory L. Kearns, PharmD, PhD,¶ John van den Anker, MD, PhD,‖ Michael Cohen-Wolkowiez, MD, PhD,*† Reese H. Clark, MD,** and P. Brian Smith, MD, MPH, MHS,*† on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network*

Background: Carbapenems are commonly used in hospitalized infants despite a lack of complete safety data and associations with seizures in older children. We compared the incidence of adverse events in hospitalized infants receiving meropenem versus imipenem/cilastatin.

Methods: We conducted a retrospective cohort study of 5566 infants treated with meropenem or imipenem/cilastatin in neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2010. Multivariable conditional logistic regression was performed to evaluate the association between carbapenem therapy and adverse events, controlling for infant factors and severity of illness.

Results: Adverse events were more common with use of meropenem compared with imipenem/cilastatin (62.8/1000 infant days versus 40.7/1000 infant days, $P < 0.001$). There was no difference in seizures with meropenem versus imipenem/cilastatin (adjusted odds ratio 0.96; 95% confidence interval: 0.68, 1.32). The incidence of death, as well as the combined outcome of death or seizure, was lower with meropenem use—odds ratio 0.68 (0.50, 0.88) and odds ratio 0.77 (0.62, 0.95), respectively.

Conclusion: In this cohort of infants, meropenem was associated with more frequent but less severe adverse events when compared with imipenem/cilastatin.

Key Words: meropenem, imipenem/cilastatin, adverse events, infant

(*Pediatr Infect Dis J* 2013;32: 748–753)

- Retrospektivní, kohorta 5556 dětí s IMI a MER
- Signifikantně vyšší výskyt NÚ pro meropenem
- Žádný rozdíl pro výskyt křečí (OR 96 %)
- Nižší mortalita u meropenemu

Děkuji za pozornost!