Extended infusion of meropenem and piperacillin in critically ill patients: a pharmacokinetic/pharmacodynamic analysis.

Poster 708

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Abstract

Introduction: Extended infusion of beta-lactams has been advocated as a viable method of optimizing antibiotic exposures in critically ill patients. Whilst simulation data exists, concentration-time data from critically ill patients are lacking.

Hypothesis: Compared to bolus infusion, extended infusion of piperacillin and meropenem changes the pharmacokinetics/pharmacodynamics in critically ill patients.

Methods: This was a prospective study in 20 critically ill patients without renal dysfunction. All patients received a loading dose (1g meropenem or 4g piperacillin), followed by an extended infusion (3h) of either antibiotic (1g meropenem or 4g piperacillin) every 6h for piperacillin and every 8 hours for meropenem. Serial plasma concentrations were obtained at 8 time points during and after the 3h infusion. Results were compared to data from bolus infusion obtained in previous studies

Results: Fifteen patients receiving piperacillin/tazobactam were included and 5 receiving meropenem. The mean age of the patients was 55y, mean APACHE2 and SOFA score on admission 18 and 8 respectively. Twenty-four-hour urinary creatinin clearances ranged from 39 to 304mL/min. In comparing both methods of administration, significant pharmacokinetic differences were observed in both meropenem and piperacillin groups for C_{max}, (higher in bolus group) and C_{min} (higher in extended infusion group). Considerable pharmacokinetic variability existed in each group for both drugs. Compared to bolus infusion, T>MIC using extended infusion was higher for both drugs: 98% (IQR 75-100%) compared to 58% (IQR 41-92%) for piperacillin and 81% (IQR 69-88%) compared to 50% (IQR 47-57%) for meropenem (assuming an MIC of 16mg/L and 2mg/L respectively.

Conclusions: This study confirms the conclusions of pharmacokinetic simulations, that extended infusion of beta-lactams in critically ill patients results in advantageous pharmacokinetic profiles by increasing the T>MIC for piperacillin and meropenem. In a significant sub-population of critically ill patients however, minimum T>MIC targets are not reached, even with extended infusion.

Introduction

- Beta-lactam antibiotics exhibit a time dependent pharmacodynamic profile
- The duration of antibiotic concentration exceeding the minimal inhibitory concentration (T>MIC) of the microorganism determines clinical efficacy
- In critically ill patients, antibiotic concentrations vary widely.
- Extended infusion of beta-lactams has been advocated as a viable method of optimizing beta-lactam antibiotic exposures in critically ill patients.
- Retrospective studies suggest overall improved outcomes
- Whilst simulation data exists, concentration-time data from critically ill patients are lacking.
- **The objective of this study** was to (**1) study the pharmacokinetics/pharmacodynamics of extended infusion** of meropenem and piperacillin in critically ill patients and (**2) compare it to a historical control group of intermittent bolus infusion**.

Methods

- This was a prospective study in 20 critically ill patients receiving either meropenem (Meronem, AstraZeneca) or piperacillin/tazobactam (Tazocin, Pfizer) according to the standard extended infusion protocol.
- All antibiotics were administered via a central venous catheter, and infused using a syringe pump.

Methods (continued)

- All but one patient received a standard loading dose (1g meropenem or 4g piperacillin), followed by an extended infusion (3h) of either antibiotic (1g meropenem or 4g piperacillin) every 6h for piperacillin and every 8 hours for meropenem. One patient received high dose meropenem (2g TID) according to the same scheme
- Exclusion criteria included renal dysfunction (defined as MDRD <80mL/min), age<18, absence of an arterial catheter and absence of informed consent from the patient or the legal representative of the patient.
- Data collected at baseline included admission diagnosis, severity of illness at admission (APACHE2 and SOFA score), degree of organ dysfunction at study inclusion (SOFA score), site of infection and causative microorganism.
- Serial plasma concentrations were obtained between 24-48 hours after the start of therapy at baseline (T0) and after 60 (T1), 120 (T2), 180 (T3), 210 (T4), 240 (T5), 270 (T6), 360 (T7) and 480 (T8) minutes for meropenem; at baseline (T0) and after 60 (T1), 120 (T2), 180 (T3), 210 (T4), 240 (T5), 270 (T6), 300 (T7) and 360 (T8) minutes for piperacillin.
- Renal function was evaluated using serum creatinine, and 24h creatinine clearance.
- Results were compared to data from bolus infusion obtained in previous studies [1, 2].
- Assuming a MIC of 16mg/L (piperacillin) and 2mg/L (meropenem), T>MIC was calculated and a 100% T>MIC was considered the optimal pharmacokinetic target.

Results

- Fifteen patients receiving piperacillin/tazobactam were included and 5 receiving meropenem. The mean age of the patients was 55y, mean APACHE2 and SOFA score on admission 18 and 8 respectively. Twenty-four-hour urinary creatinine clearances ranged from 39 to 304mL/min. Details are in table 1.
- When comparing extended infusion with bolus infusion (historical controls), significant pharmacokinetic differences were observed in both meropenem and piperacillin groups for C_{max}, (higher in bolus group) and C_{min} (higher in extended infusion group)(table 2).
- Considerable pharmacokinetic variability existed in each group for both drugs. Compared to bolus infusion, T>MIC using extended infusion was higher for both drugs: 98% (IQR 75-100%) compared to 58% (IQR 41-92%) for piperacillin and 81% (IQR 69-88%) compared to 50% (IQR 47-57%) for meropenem (assuming an MIC of 16mg/L and 2mg/L respectively)(Figure 1 and2).

Table 1. Patient characteristics data in the table are reported as median (interquartile range).

	Meropenem (n=5)	Piperacillin (n=15)	All patients (n=20)
Age	54 (35-64)	60 (52-73)	57 (51-71)
BMI	27.8 (21.8-30.1)	25.4 (24.2-27.8)	25.6 (24.2-28.0)
APACHE2 admission	14 (9-21)	19 (14-22)	19 (14-22)
SOFA admission	9 (4-10)	9 (4-12)	9 (4-11)
SOFA inclusion	5 (3-11)	7 (3-9)	6 (3-9)
Baseline serum creatinin (mg/dL)	0.50 (0.42-0.66)	0.67 (0.49-0.81)	0.65 (0.49-0.79)
24h creatinin clearance (mL/min)	164 (123-244)	125 (94-189)	132 (105-188)

Results (continued)

Table 2. Steady-state pharmacokinetic parameters for meropenem and piperacillin by either bolus infusion or extended infusion. Data are reported as median (interquartile range)

	Meropenem		Piperacillin	
	Extended infusion	**Bolus infusion**	**Extended infusion**	**Bolus infusion**
C_{max} (mg/L)	17.0 (12.6 – 21.9)	85.2 (66.7 – 140.3)	76.2 (57.7 – 92.6)	215.9 (149.0 – 251.6)
C_{min} (mg/L)	0.6 (0.3 – 1.4)	0.0 (0.0 – 0.0)	14.7 (4.2 – 24.3)	5.9 (2.7 – 13.1)
AUC0-8 (mg.h/L)	59.6 (41.5 – 77.5)	70.1 (61.4 – 70.6)	281.6 (176.3 – 344.2)	223.1 (148.9 – 375.0)
AUMC0-8 (mg.h²/L)	183.5 (111.8 – 227.6)	67.4 (59.3 – 79.4)	808.9 (431.6 – 916.9)	330.3 (198.9 – 674.2)
CL (L/hr)	16.7 (12.9 – 24.1)	14.3 (14.2 – 16.3)	13.2 (10.2 – 22.7)	14.4 (8.9 – 20.5)
MRT	2.9 (2.7 – 3.0)	1.2 (0.9 – 1.3)	2.7 (2.6 – 2.8)	1.3 (1.1 – 1.6)
K_{el} (h-1)	0.7 (0.6 – 0.7)	0.7 (0.6 – 0.8)	0.6 (0.4 – 095)	0.4 (0.4 – 0.5)
Vd (L/kg)	0.28 (0.25-0.40)	0.27 (0.21-0.39)	0.28 (0.22 – 0.36)	0.44 (0.28 – 0.55)
T1/2 (h)	1.0 (1.0 – 1.1)	1.1 (0.9-1.2)	1.2 (0.8 – 1.8)	1.6 (1.3 – 1.7)

Legend: C_{max} – observed maximum concentration during sampling period; C_{min} – observed minimum concentration during sampling period (for continuous infusion is steady state concentration; C_{ss}); AUC_{0-8} – area under the concentration-time curve during 8-hour dosing period; $AUMC_{0-8}$ - area under the moment curve during 8-hour dosing period; MRT – mean residence time; Cl – total clearance; K_{el} – elimination rate constant; $T_{1/2}$ – elimination half-life; Vd – volume of distribution during terminal phase

Figure 1. Meropenem concentrations

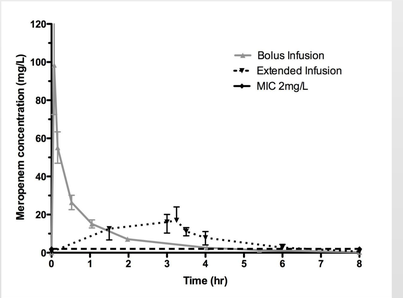
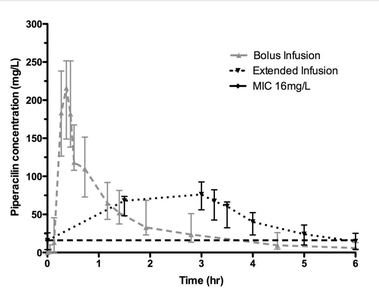


Figure 2. Piperacillin concentrations



Conclusions

- Extended infusion of beta-lactams in critically ill patients results in advantageous pharmacokinetic profiles by increasing the T>MIC for piperacillin and meropenem.
- In a significant sub-population of critically ill patients however, minimum T>MIC targets for are not reached, even with extended infusion.

References.

1. Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Crit Care Med 2009, 37(3):926-933.
2. Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. J Antimicrob Chemother 2009, 64(1):142-150.