Extended / Continuous Infusion Beta-lactams for Gram-Negative Infections

Intermittent intravenous administration of antibiotics has been the standard in clinical practice because of its many advantages including better utilization of available intravenous access, less concern about drug instability over time, and less compatibility concerns. Over the past several years, resistance has developed to a number of antibiotics and new agents are not currently available. It is necessary to optimize the pharmacokinetics-pharmacodynamics of currently available antibiotics for the management of severe infections due to resistant gram-negative pathogens. The use of extended / continuous infusions is particularly important for optimizing the time above the MIC with time-dependent killers (e.g. beta-lactams) to improve microbiologic and clinical cure.

Definitions

Intermittent intravenous administration	Infusion lasting 30-60 minutes
Extended intravenous administration	Infusion lasting 3-4 hours
Continuous intravenous administration	Continuous infusion over a 24 hour period at a fixed rate

Rationale

In vitro and animal studies have demonstrated that the amount of time in which the free or non–protein-bound drug concentration exceeds the MIC of the organism (fT>MIC) is the best predictor of bacterial killing and microbiologic response for beta-lactams[1]. The fT>MIC required for maximal bacterial effect varies for the different types of beta-lactams. Clinical pharmacokinetic-pharmacodynamic studies have shown that extended / continuous infusions of beta-lactams increase the chance of maintaining serum drug concentrations above the MIC of the pathogen over a 24 hour period. Furthermore, prospective and retrospective clinical trials have demonstrated higher clinical cure rates[2,3], shorter length of stay[4], and mortality benefits[4] with extended / continuous infusion beta-lactams vs. intermittent infusions.

Cephalosporins and penicillins require larger fT>MIC (>50%) to exhibit bactericidal activity. Therefore, it is reasonable to administer cefepime, ceftazidime, and piperacillin/tazobactam via either extended or continuous infusion. There is strong clinical data suggesting that for piperacillin/tazobactam, extended infusions over 4 hours is sufficient to maximize pharmacodynamic properties[4], and it is stable at room temperature for up to 24 hours. On the other hand, cephalosporins have been demonstrated to be less stable, especially at temperatures exceeding 25 ℃ and there is only clinical data supporting the use of continuous infusions for cephalosporins as opposed to extended infusions.

For carbapenems like meropenem, the fT>MIC required for bactericidal activity is only ~40% of the dosing interval. Additionally, meropenem is even more unstable at room temperature compared to cephalosporins. Per package labeling, the infusion should remain at room temperature for a maximum of 4 hours and in clinical trials, it has been demonstrated that extended infusions of meropenem over 3 hours is sufficient to maximize pharmacodynamic properties.

Recommendations

Maximizing the fT>MIC is critically important in the setting of serious infections caused by intermediate to resistant gram-negative pathogens. The target population for the utilization of extended / continuous infusion beta-lactams consists of patients with normal renal function with severe infections (e.g. bacteremia, nosocomial pneumonia, intra-abdominal infections) with the following organisms:

- Carbapenemase-producing *Enterobacteriacae*
- MDR-*Pseudomonas* spp
- MDR-*Acinetobacter* spp

Extended / continuous infusion beta-lactams should also be considered in cystic fibrosis patients with pulmonary infections due to resistant gram-negatives. Cystic fibrosis patients require higher doses of beta-lactams due to increased clearance of the beta-lactams.

Dosing Recommendations for Extended / Continuous Infusion Beta-lactams

	Type of Infusion	Dose / Freq (normal renal function)		Stability	Pharmacy / Nursing Instructions and Renal Dosage Adjustment
Cefepime	Continuous over 24 hours	6 g IV	q24h	Change infusion q12h	Give 2 g IV bolus loading dose over 30 minutes, followed by 6 g IV as continuous infusion over 24 hours (2 g IV over 8 hours, every 8 hours) CrCl >60 mL/min: 2 g IV q8h infused over 8 hours CrCl 30-60 mL/min: 2 g IV q12h infused over 12 hours CrCl <30 mL/min or HD/CVVHD: Use renally adjusted dose with intermittent infusion
Ceftazidime	Continuous over 24 hours	6 g IV	q24h	Change infusion q8h	Give 2 g IV bolus loading dose over 30 minutes, followed by 6 g IV as continuous infusion over 24 hours (2 g IV over 8 hours, every 8 hours) CrCl >50 mL/min: 2 g IV q8h infused over 8 hours CrCl 30-50 mL/min: 2 g IV q12h infused over 8 hours CrCl <30 mL/min or HD/CVVHD: Use renally adjusted dose with intermittent infusion
Piperacillin	Continuous over 24 hours	24 g IV	q24h	Stable for up to 24 hours	Give 4 g IV bolus loading dose over 30 minutes, followed by 24 g IV as continuous infusion over 24 hours (4 g IV over 4 hours, every 4 hours) CrCl >40 mL/min: 4 g IV q4h infused over 4 hours CrCl 20-40 mL/min: 4 g IV q6h infused over 6 hours CrCl <20 mL/min or HD/CVVHD: Use renally adjusted dose with intermittent infusion
Piperacillin / tazobactam	Extended over 4 hours	4.5 g IV	q6h	Stable for up to 24 hours	Give 4.5 g IV dose, and infuse over 4 hours as opposed to 30 minutes. CrCl >40 mL/min: 4.5 g IV q6h infused over 4 hours CrCl 20-40 mL/min: 3.375 g IV q6h infused over 4 hours CrCl <20 mL/min or HD/CVVHD: Use renally adjusted dose with intermittent infusion
	Continuous over 24 hours	20.25 g IV	q24h	Stable for up to 24 hours	Give 3.375 g IV bolus loading dose over 30 minutes, followed by 20.25 g IV as continuous infusion over 24 hours (3.375 g IV over 4 hours, every 4 hours) CrCl >40 mL/min: 3.375 g IV q4h infused over 4 hours CrCl 20-40 mL/min: 3.375 g IV q6h infused over 6 hours CrCl <20 mL/min or HD/CVVHD: Use renally adjusted dose with intermittent infusion
Meropenem	Extended over 3 hours	2 g IV	q8h	Stable for up to 4 hours	Give standard 2 g IV dose, and infuse over 3 hours as opposed to 30 minutes. CrCl >51 mL/min: 2 g IV q8h infused over 3 hours CrCl 26-50 mL/min: 1 g IV q8h infused over 3 hours CrCl <26 mL/min or HD/CVVHD: Use renally adjusted dose with intermittent infusion

References:

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2. Lorente L, Lorenzo L, Martin MM, Jimenez A, Mora ML. Meropenem by continuous versus intermittent infusion in ventilator associated pneumonia due to gram-negative bacilli. *Ann Pharmacother* 2006;40:219–23.
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