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Optimizing Pharmacokinetic/Pharmacodynamics Principles & Role of Cefoperazone – Sulbactam

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Summary

Antimicrobial resistance is associated with adverse patient outcomes and increased resource utilization. With limited options of antibiotics in pipeline, the effective clinician in today's hospital environment must utilize all available laboratory and clinical data in the selection of the optimal antibiotic therapy for the critically ill patient. Antibiotics must be utilized in a manner that ensures not only a maximally favorable outcome for the individual patient but, also, the minimization of subsequent antimicrobial resistance. All antibiotic use has potential public health consequences and, in this way, differs from the use of all other classes of pharmaceutical agents. Present review focuses on the application of pharmacokinetic/pharmacodynamic principles and their role in the combination of Cefoperazone – sulbactam.

Key words: Pharmacokinetics, Pharmacodynamics, Cefoperazone, Sulbactam,

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Introduction

Antimicrobial resistance is strongly associated with adverse patient outcomes and increased resource utilization[1]. The effective clinician in today's hospital environment must utilize all available laboratory and clinical data in the selection of the optimal antibiotic therapy for the critically ill patient. Antibiotics must, however, be utilized in a manner that ensures not only a maximally favorable outcome for the individual patient but, also, the minimization of subsequent antimicrobial resistance[2]. Each antibiotic use, whether appropriate or inappropriate, affects the bacterial ecology by exerting selective pressure and thereby driving resistance. Thus, all antibiotic use has potential public health consequences and, in this way, differs from the use of all other classes of pharmaceutical agents.

Current understanding has allowed the development of a series of simple principles of antibiotic therapy for the critically ill patient. Perhaps the most important principle is the understanding that any delay in the initiation of adequate antibiotic therapy is potentially lethal. In addition, inappropriately prolonged antibiotic therapy may adversely affect both the individual patient and the more general bacterial ecology. Multiple studies have demonstrated that survival is significantly improved when the initial choice of antibiotics is "appropriate," defined as indicating that all isolated pathogens are susceptible to ⩾1 of the administered antibiotics[3]. Considered more broadly, however, both empirical and definitive antibiotic therapy, to be considered appropriate, require timely initiation, administration in appropriate dosages consistent with pharmacokinetic and pharmacodynamic (PK/PD) information, and appropriate alteration of therapy in response to clinical responses and microbiological data as they become available.

Pharmacokinetic and Pharmacodynamic (Pk/Pd) Principles in The Management of The Bacterial Infections

Following table describes the practices promoting the optimization of antimicrobial use in the intensive care unit setting. In addition to the strategies described in this review (Table 1), clinicians must insure that antibiotic administration satisfies minimal requirements, such as proper dosing, drug interval administration, monitoring drug levels, and avoiding harmful drug interactions[4].

Table 1 ***Practices promoting the optimization of antimicrobial use in the intensive care unit setting***[4]

- Provide adequate initial treatment of serious infections (e.g. pneumonia, bloodstream)
- Awareness of predominant causative pathogens
- Up to date unit-specific pathogen antibiograms
- Drainage of abscesses, empyema cavities, other infected fluid collections
- Removal of infected foreign bodies (e.g. central venous catheters)
- Monitor serum drug concentrations when appropriate to achieve therapeutic levels
- Minimize antibiotic pressures promoting resistance

- Avoid prolonged courses of empiric antibiotic therapy
- Consider de-escalation of antibiotics based on available microbiologic data and clinical course
- Use narrow spectrum antibiotics when supported by clinical situation and culture data
- Establish appropriate thresholds for prescribing antibiotics
- Develop predetermined criteria for the discontinuation of antimicrobial therapy

The appropriate dosage of antibacterial agents is essential in achieving both clinical and microbiologic success in the treatment of infections. By using *in vitro* experimental data and animal model outcome data, the pharmacokinetic-pharmacodynamic (PK-PD) parameters predictive of antibacterial effect have been elucidated. For time-dependent drugs such as β-lactams, the PK-PD parameter of interest is the percentage of time in a dosage interval for which drug concentrations remain above the minimum inhibitory concentration (MIC) of the infecting organism. For concentration-dependent drugs such as aminoglycosides, the PK-PD parameter of interest is the ratio of the area under the plasma concentration-time curve to the MIC. Recent studies using data on clinical and microbiologic outcomes from infected adults and children, combined with data on drug exposure, have confirmed the importance of these parameters and provided estimates of the PK-PD goals of therapy for various antibacterial agents. Application of these PK-PD principles allows rational dosage regimen selection, both for serious infections and for non-life-threatening community-acquired infections[5].

The relationship between antibacterial exposure and to therapy is dependent on two factors[5]:

(i) free (unbound) drug concentrations at the site of infection; and
(ii) the sensitivity of the infecting pathogen(s) to the drug.

The sensitivity of the pathogen to the drug is most easily identified by the minimum inhibitory concentration (MIC). The impact of drug concentrations is more complex. Depending on the agent's antibacterial mechanism of activity, one of three PK-PD measures is usually predictive of effect:

(i) the duration of time (T) the drug concentrations remain above the MIC of the drug to the pathogen (T > MIC);
(ii) the ratio of the maximal drug concentration (Cmax) to the MIC of the pathogen (Cmax **:** MIC);
(iii) the ratio of the area under the plasma concentration-time curve from time 0 to 24 hours to the MIC of the pathogen (AUC24 **:** MIC).

Table 2 ***Pattern of bactericidal effect in vitro and pharmacokinetic-pharmacodynamic (PK-PD) measures correlating with efficacy***[5]

Antimicrobial	Pattern of effect based on *in vitro* studies	PK-PD measure(s) associated with efficacy
Aminogylcosides	Concentration dependent	AUC : MIC, C_{max} : MIC
β-Lactams		
penicillins	Time dependent	T > MIC
cephalosporins	Time dependent	T > MIC
carbapenems	Time dependent	T > MIC
monobactams	Time dependent	T > MIC
Clindamycin	Time dependent	AUC : MIC
Glycopeptides/lipopeptides		
daptomycin	Concentration dependent	AUC : MIC, C_{max} : MIC
oritavancin	Concentration dependent	T > MIC, C_{max} : MIC
vancomycin	Time dependent	AUC : MIC
Macrolides/ketolides		
azithromycin	Time dependent	AUC : MIC
clarithromycin	Time dependent	AUC : MIC
telithromycin	Concentration dependent	AUC : MIC
Metronidazole	Concentration dependent	AUC : MIC, C_{max} : MIC
Oxazolidinones		
linezolid	Time dependent	AUC : MIC
Quinolones	Concentration dependent	AUC : MIC, C_{max} : MIC
Tetracyclines		
doxycycline	Time dependent	AUC : MIC
tigecycline	Time dependent	AUC : MIC

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum concentration; **MIC** = minimum inhibitory concentration; **T > MIC** = time drug concentrations are above the minimum inhibitory concentration.

The importance of the T>MIC in per cent of dosing interval or as the cumulative per cent over 24 h, being above a value of 40-50%, has been shown in experimental animal studies and by the bacteriological cure rate of otitis media in a study by Craig and Andes. These authors reviewed a series of studies that used beta- lactam or macrolide treatment of otitis media and where treatment effect was measured by culture of secretions collected from the infected ears. They could demonstrate a clear dose-effect relationship between T>MIC, as estimated from population kinetics, and frequency of bacteriological cure with a maximum of 90% cure achieved with a T>MIC around 50%[18].

Cefoperazone-sulbactam and the PK-PD Principles

As a class, Beta-lactam antibacterials have also been the subject of PK-PD optimization of dosage regimens. Early work in the field, using retrospective analysis of published literature, identified T > MIC as the PK-PD parameter most predictive of outcome for the Beta-lactam antibacterials (penicillins, cephalosporins, and carba- penems)[5,6,7].Although intermittent administration remains the norm in most centers, for practical reasons, the utility of continuous infusion (or extended infusions) has been advocated for sever- al Beta-lactams, including cefepime, piperacillin/tazobactam, penem, and ceftazidime, in certain situations[8,9,10,11].

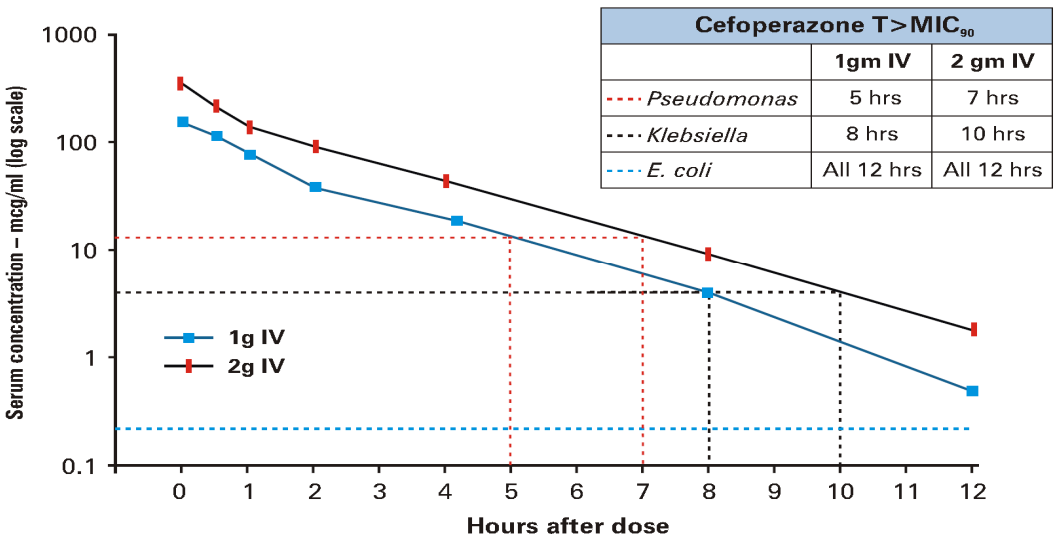
Extended or continuous infusions represent one of the simplest ways to maximize T > MIC. However, given the inherent issues when evaluating differing regimens in an infectious disease setting, the superiority of a continuous infusion regimen has been shown in limited studies such as one study of the treatment of febrile neutropenic patients treated with cefamandole[12]. Although these investigators did not attempt to quantify the T > MIC for the intermittent or continuous cefamandole regimens, this study is often cited as evidence of the importance of PK-PD target attainment for Beta- lactams.
Another interesting concept of optimizing t> MIC can be explained for cefoperazone-sulbactam.

Cefoperazone is a cephalosporin with a broad spectrum of activity whereas sulbactam inhibits hydrolysis of penicillins and cephalosporins by β-lactamases[13].

Cefoperazone is known to have dose dependent increase in the serum concentrations. It was administered in the dose of 1 and 2 gram intravenously every 12 hours and the serum concentrations were plotted against time. *(Graph 1)*. It was observed that there was a linear increase in the concentration when cefoperazone was administered in the dose of 2 gram iv as compared to 1 gram iv.[13] Minimal inhibitory concentration (MIC) values for *Pseudomonas*, Klensiella & E. coli were plotted to find out the duration for which concentration remained above MIC_{90} (t>MIC).[14]

As shown in the graph, t>MIC was 7 hrs with 2 gram dose for *Pseudomonas spp.* as compared 5 hrs observed with 1 gram dose. Similarly for Klebsiella it was 8 hrs with 1 gram dose as compared to the 10 hours observed with 2 gram dose[13,14].
As it can be observed from the graph, one way of optimizing the dose could be by giving a higher dose which would result in t> MIC for higher time. This concept needs to be validated in larger, prospective randomized clinical trials.

Graph 1: Cefoperazone: Serum concentration versus hours after dose



In infection models and in clinical studies, inhibition of growth is likely if the drug concentration exceeds the MIC for at least 40% of the dosing interval, and a maximal bacteriological response is predicted if the drug concentration exceeds the MIC for at least 60–70% of the dosing interval[15]. This would be maximized if the dose of cefoperazone is increased.

Maximum sulbactam that can be administered per day is 4 grams. Recommended cefoperazone dose varies from 6 to 8 grams though in severe infections dosages of up to 16 gram of cefoperazone daily have been given without complication in patients with normal renal status[16,17].

Based on the dose recommended, it may be important to increase the dose of Cefoperazone to optimize t>MIC in severe infections which may result in greater microbial clearance based on the principles mentioned above. This can be achieved by using Cefoperazone-sulbactam 2:1 where higher dose of cefoperazone will prove beneficial.

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