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Pharmacodynamic profiling of optimal sulbactam regimens against carbapenem-resistant *Acinetobacter baumannii* for critically ill patients

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ABSTRACT

Objective: To study the minimum inhibitory concentration (MIC) of sulbactam against carbapenem-resistant *Acinetobacter baumannii* (CR-AB) and to determine the dosage regimens reaching target time of free drug concentration remaining above the MIC (*fT*>MIC). **Methods:** Clinical isolates of CR-AB from patients admitted to Phramongkutklao Hospital, Thailand from January 2014 to December 2015 were obtained. The MIC of sulbactam for each CR-AB isolate was determined using the agar dilution method. Each sulbactam regimen was simulated using the Monte Carlo technique to calculate the probability of target attainment (PTA) and the cumulative fraction of response (CFR) in critically ill patients. PTA was defined by how likely a specific drug dose was to reach 40% and 60% *fT*>MIC. The CFR was the probability of drug dose covering the MIC range of CR-AB. Dosing regimens reaching above 80% of PTA and CFR, were considered as the optimal dosage for documented and empirical therapy, respectively. **Results:** A total of 118 CR-AB isolates were included in the study. The percentile at the fiftieth and ninetieth MIC of sulbactam were 64 and 192 μg/mL, respectively. For a MIC of sulbactam of 4 μg/mL, all dosage regimens achieved PTA target. However, only a sulbactam dosage of 12 g intravenous daily using 2-4 h infusion or continuous infusion that covered for isolates with a sulbactam MIC of 96 μg/mL, met the PTA or CFR targets. **Conclusions:** The MIC of sulbactam against CR-AB is quite high. The sulbactam dose of 12 g/day using prolonged infusion was required to achieve the target *fT*>MIC for CR-AB treatment.

1. Introduction

Acinetobacter baumannii (*A. baumannii*) is a Gram negative coccobacilli that can cause nosocomial infections, such as respiratory tract infection, bacteremia, urinary tract infections, post-surgical meningitis and intra-abdominal infections[1]. *A. baumannii* is an emerging carbarpemem-resistant pathogen, becoming a global threat[2]. Carbapenem-resistant *A. baumannii* (CR-AB) has several resistance mechanisms, including enzyme production, loss of

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porins, an efflux pump and a change of penicillin binding protein[3]. In Thailand, CR-AB is the most common causative pathogen of nosocomial pneumonia in tertiary care hospitals[4]. CR-AB has been reported to be the most prevalent pathogen in intensive care units in several studies[5,6]. In addition, colistin, sulbactam, and tigecycline are only major treatment options for CR-AB infection[7].

Colistin and tigecycline have good activity against CR-AB. Two studies in Thailand found more than 90% of CR-AB isolates were susceptible to colistin and tigecycline[8,9]. However, the pharmacokinetic properties and toxicities of colistin and tigecycline have limitations. Colistin poorly penetrates some tissues/organs and is nephrotoxic[10,11]. Tigecycline has a large volume of distribution resulting in a low serum concentration[12], so caution should be used in treating *A. baumannii* bacteremia with tigecycline[13]. Since 2013, the US Food and Drug Administration has warned increased risk of death among ventilator-associated pneumonia patients with MDR-AB treated with tigecycline[14,15].

Sulbactam is a β-lactamase inhibitor with activity against CR-AB. Sulbactam is not highly protein bound and penetrates most infected organs with adequate concentrations[16]. Sulbactam can be given in doses as high as 12 g daily without adverse reactions[17]. According to the 2016 guidelines recommended by the Infection Diseases Society of America/American Thoracic Society, sulbactam remains the drug of choice to treat MDR-AB pneumonia[18].

However, sulbactam is one of the β-lactam antibiotics. β-lactam antibiotics have augmented renal clearance and a large volume of distribution may cause inadequate tissue concentration[19]. Sulbactam shows a time-dependent bactericidal action at a percentage of the exposure time. When sulbactam is active, the free drug concentration remains above the minimum inhibitory concentration (*%fT*>MIC) in pharmacokinetic pharmacodynamic (PKPD) targets[20]. The Monte Carlo Simulation is a technique that randomly selects a pharmacokinetics parameter value from its distribution. That process is repeated many times to generate the pharmacokinetic parameter value incorporated with the structural pharmacokinetics model to predict the appropriate dosing regimen achieving the PKPD targets[21].

Thus, the aim of this study is to determine the pharmacodynamics of sulbactam by determining its MIC. It also aims to develop a potential dosage regimen to achieve PKPD targets using the probability target of attainment (PTA) and the cumulative fraction of response (CFR) for CR-AB treatment of critically ill patients.

2. Materials and methods

2.1. Bacterial isolates

The study was conducted at Phramongkutklao Hospital in Bangkok, Thailand, a 1 200-bed tertiary care center, from January 2014 to December 2015. All clinical isolates of CR-AB obtained from patients were included in the study. Each isolate was grown in tryptic soy broth containing 20% glycerol and kept at -70 ℃ until used.

2.2. Determination of multidrug-resistant isolates

CR-AB was identified using the disk diffusion test and defined as resistance to carbapenems [imipenem (10 μg) or meropenem (10 μg)][22]: the other antibiotics used during this test were: aminoglycosides [gentamicin (30 μg) or amikacin (30 μg)], antipseudomonal penicillins [piperacillin/tazobactam (100 μg/10 μg)], cephalosporins [ceftazidime (30 μg) or cefepime (30 μg)], sulfa drugs [trimethoprim-sulfamethoxazole (1.25 μg/23.75 μg)] and fluoroquinolones [ciprofloxacin (5 μg)]. The methods used followed the Clinical and Laboratory Standards Institute, guidelines, version 2017[23]. Isolates with a clear zone ⩾11 mm to colistin (5 μg) were interpreted as susceptible.

2.3. MIC determination of sulbactam

The MIC of sulbactam was determined using the agar dilution method with Müller-Hinton agar (Oxiod) plates. The serial sulbactam (Wago, Japan) concentrations were freshly prepared between 1 and 1 024 μg/mL. A quality control strain, *Escherichia coli* ATCC 25922 (Department of Medical Sciences Culture Collection, Bangkok, Thailand) was used[23]. This study investigated MIC range, MIC50, and MIC90 of sulbactam against CR-AB. MIC range was defined as a list; the MIC value was just the difference between the largest and smallest values. MIC50 and MIC90 values were defined as the lowest concentration of sulbactam at which 50% and 90% of the isolates were inhibited, respectively.

2.4. Pharmacokinetic pharmacodynamic model study

All pharmacokinetic parameters obtained from published studies of critically ill patients were collected[24,25]. The concentration versus time was studied using a two-compartment model for critically ill patients and a one-compartment model for critically ill patients who received continuous renal replacement therapy. The pharmacokinetic and pharmacodynamic properties of sulbactam were represented by the percentage of free drug time above the MIC during the interval time (*%fT* >MIC). The PKPD goal was defined as 40% to 60% *fT*>MIC which was the good outcome related to the efficacy[20]. Dosage simulations were conducted using various dosages per day and dosage intervals at durations of infusion.

2.5. Monte Carlo Simulation

The PKPD investigation was conducted using a 10 000-subject Monte Carlo Simulation (Oracle Crystal Ball Classroom Faculty Edition-Oracle 1-Click Crystal Ball 201, Thailand). The Monte Carlo Program used to calculate *% fT*>MIC for intravenous dosage regimens of sulbactam depended on the linear pharmacokinetic behavior of the agent.

The PTA was defined by how likely a specific drug dose reached a target PKPD index (*fT*>MIC)[26]. In the present study, a target PKPD index was 40% and 60% *fT*>MIC. The CFR was the probability of drug dose covering a specified bacterial population[26]. Our bacterial population was the MIC of sulbactam among CR-AB isolates obtained from patients.

CFR was calculated by the cumulative fraction of proportional bacteria of each sulbactam MIC multiplied by PTA of each sulbactam MIC. Dosing regimen that reached above 80% of PTA and CFR was considered the optimal dosage for documented therapy and empirical therapy, respectively.

This study was approved by the institutional review board of the Royal Thai Army Medical Department and Phramongkutklao Hospital, Bangkok, Thailand (approval No. Q014h/59 issued on 24 November 2016).

3. Results

3.1. Characteristics and antimicrobial susceptibilities of CR-AB

One hundred eighteen isolates of CR-AB were collected during the study period. Seventy-one percent of the isolates were from blood, 17% from the skin and soft tissue, 6% from intra-abdominal specimens, and 6% from other sources. Seventy-seven percent of the isolates were obtained from sterile sites. Using the disk diffusion method, most CR-AB isolates (90%) in our study were found to be resistant to gentamicin, amikacin, piperacillin/tazobactam, ceftazidime, cefepime, and ciprofloxacin, making them extensively drug-resistant *A. baumannii*. Of all the study isolates, 100% were susceptible to colistin and 91.7% were susceptible to tigecycline.

3.2. Minimum inhibitory concentrations of study isolates

The MIC range, MIC50, and MIC90 for sulbactam against studied isolates were 8 to >1 024 μg/mL, 64 μg/mL, and 192 μg/mL, respectively. Each MIC value of sulbactam included 8 μg/mL (0.8%), 16 μg/mL (5.1%), 32 μg/mL (11.9%), 64 μg/mL (42.4%), 80 μg/mL (15.3%), 96 μg/mL (5.1%), 128 μg/mL (7.6%), 192 μg/mL (5.1%), 256 μg/mL (0.8%), 512 μg/mL (3.4%), and >1 024 μg/mL (2.5%).

3.3. PTA

The PTA for the different sulbactam regimens at specific MICs, with targets of 40% *fT*>MIC and 60% *fT*>MIC is shown in Figures 1A and 1B for critically ill patients. Figures 1C and 1D indicate PTA among critically ill patients with CRRT. Among critically ill patients, for pathogens with a MIC of 4 μg/mL, all dosage regimens achieved the PTA target. However, only a sulbactam dosage of 12 g intravenous daily using 2-4 h infusion or continuous infusion that covered for isolates with a sulbactam MIC of 96 μg/mL, met the PTA at 40% and 60% *fT*>MIC. None of all sulbactam dosage regimens reached the PTA target for critically ill patients with CRRT.

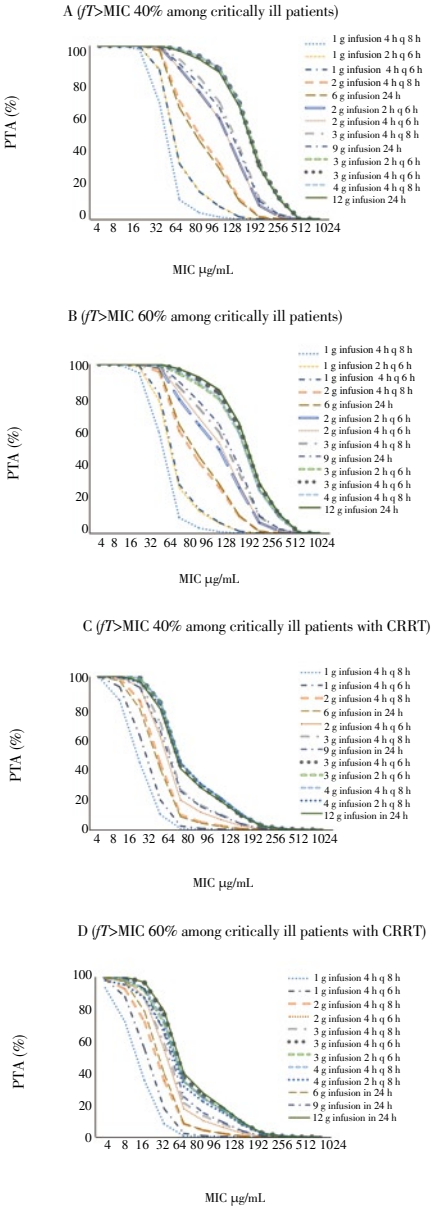

Figure 1. PTA for different sulbactam regimens at specific MICs, with targets of 40% *fT*>MIC and 60% *fT*>MIC.

A: *fT*>MIC 40 % among criticaly ill patients; B: *fT*>MIC 60 % among criticaly ill patients; C: *fT*>MIC 40 % among criticaly ill patients with CRRT; D: *fT*>MIC 60 % among criticaly ill patients with CRRT.

3.4. CFR

Using a CFR >80%, only 4 drug regimens were determined to be appropriate for sulbactam: 3 g infused over 2 h given every 6 h, 3 g infused over 4 h given every 6 h, 12 g infused over 24 h given every 24 h and 4 g infused over 4 h given every 8 h (Table 1). However, none of the studied regimens gave a CFR >80% among patients with

CRRT.

Table 1

Cumulative fraction of response of sulbactam with various drug regimens (%).

Dosage regimen	Infusion time (h)	Critically ill		Critically ill with CRRT	
		40% *fT*>MIC	60% *fT*>MIC	40% *fT*>MIC	60% *fT*>MIC
1 g/6 h	2	32.79	28.81	7.69	6.29
	4	32.57	30.46	7.38	6.71
2 g/6 h	2	71.62	65.77	24.12	20.12
	4	71.36	68.60	23.21	21.23
3 g/6 h	2	84.84	80.96	40.58	33.84
	4	84.80	83.06	39.64	36.06
4 g/8 h	2	84.51	79.64	40.27	31.34
	4	84.88	81.65	40.60	34.22
9 g/6 h	24	74.29	74.29	26.83	26.82
12 g/6 h	24	83.87	83.86	37.87	37.87

4. Discussion

CR-AB is the leading causative pathogen presenting the high mortality rate (73.3%) among critically ill patients[27]. Colistin is the agent most commonly used to treat MDR-AB and extensively drug-resistant *A. baumannii*[28]. In our study, all isolates were susceptible to colistin. However, colistin has nephrotoxicity and poor tissue penetration that limits its usefulness[10,11]. Sulbactam has been purported be a good option to treat CR-AB[29].

With our study, MIC50, and MIC90 values of sulbactam against CR-AB were 64 μg/mL and 192 μg/mL, respectively. In Thailand, two studies performed at Siriraj Hospital[30] and at Queen Sirikit National Institute[31] showed values of MIC50/MIC90 at 32/32 and 16/89.6 μg/mL, respectively. However, unlike other related studies conducted in Thailand, the MIC50 and MIC 90 in the present study presented higher than ever before. These distinguished MIC results might be explained because almost CR-AB isolates in our study comprised extensively drug-resistant *A. baumannii* and more than one half of isolates (60%) was obtained from critically ill patients at the ICU ward of a university-affiliated hospital.

Generally, the pharmacokinetics of sulbactam among critically ill patients differed from the general population in the aspects of volume of distribution (Vd). The reported Vd values in Thai healthy volunteers were 3.69 liters[32] while among critically ill patients, Vd of sulbactam were 14.56 liters[24]. The larger Vd values among critically ill patients effect lower serum sulbactam levels. The inadequate sulbactam concentration might be resolved by using a higher sulbactam dose and prolonged or continuous infusion as in our recommended dose of sulbactam at 12 g daily regimens. Our suggestion was similar to the results from reporting that 12 g of sulbactam daily could be achieved at the desired PTA[24].

Sulbactam is unavailable as a single agent in Thailand. Only sulbactam in combination with cefoperazone or ampicillin is available. A sulbactam dose of 12 g daily in a combination form with cefoperazone or ampicllin might result in adverse drug reactions. Thus, patients complying with a high dose of sulbactam should be closely monitored. However, several related studies have indicated that sulbactam in combination with colistin, fosfomycin or imipenem could reduce the MIC of sulbactam against CR-AB[33–35]. Thus, the beneficial synergism of a sulbactam combination might be necessary toward the increasing PTA and CFR targets.

Our study has some limitations. First, the isolates of the CR-AB were from MIC distributions at a university-affiliated hospital which might be dissimilar when taken from other types of hospital. Second, our simulation used plasma pharmacokinetics and not tissue pharmacokinetics. Lastly, this study only suggested the probable dose of sulbactam to achieve the PKPD index. Further clinical studies are needed to determine the most beneficial dosage regimens.

In conclusion, the present study shows the MIC of sulbactam against CR-AB is quite high. However, sulbactam could be maximized in a dosage as high as 12 g daily with prolonged or continuous infusion, especially in treatment of critically ill patients.

Conflict of interest statement

We declare that there is no conflict of interest.

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