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Original Article

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Optimizing the Dosing Regimens of Tigecycline against Vancomycin-Resistant Enterococci in the Treatment of Intra-abdominal and Skin and Soft Tissue Infections

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No conflicts of interest.

ABSTRACT

Tigecycline was previously considered to have activity against vancomycin-resistant *Enterococcus* (VRE) isolates, but the optimal dose was not clarified. Thus, this study assessed the *in vitro* activity of tigecycline against clinical VRE isolates to determine its optimal regimens for complicated intra-abdominal (cIAIs) and complicated skin/soft tissue infections (cSSTIs). We used Monte Carlo simulation to calculate the probability of target attainment (PTA) and the cumulative fraction of response for the ratio of the free area under the curve to the minimum inhibitory concentration (MIC) ($fAUIC_{24}$), which were 17.9 and 6.9 for treating cSSTIs and cIAIs, respectively. All clinical isolates were *Enterococcus faecium*. Only a maintenance dose of 200 mg/day tigecycline gave the target attainment of $fAUIC_{24}$ >17.9, and PTA exceeded 90% for MIC ≤0.38 μg/mL. Meanwhile, this dose gave the target attainment of $fAUIC_{24}$ >6.9, and PTA exceeded 90% for MIC ≤1 μg/mL. All simulated tigecycline dosing regimens met the $fAUIC_{24}$ targets more than 90% of the cumulative fraction of response. Despite its apparent efficacy, a daily tigecycline dose of 200 mg is recommended for VRE isolates with MICs of ≤0.38 μg/mL and ≤1 μg/mL for treating cSSTIs and cIAIs, respectively.

Keywords: Dosing regimen; Minimum inhibitory concentration; Monte Carlo simulation; Tigecycline; Vancomycin-resistant Enterococcus

INTRODUCTION

Vancomycin-resistant *Enterococcus* (VREs) are recognized as important nosocomial pathogens worldwide [1]. According to data from the National Healthcare Safety Network (NHSN) in 2009 and 2010, one-third of enterococcal infections in the hospital were resistant to vancomycin. Additionally, VREs represented the second most common causative pathogens

Infection & Chemotherapy

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in the United States [2]. However, a report by the European Antimicrobial Resistance Surveillance Network in 2018 across 30 European countries recorded a prevalence of VREs of only 4%, but the rate ranged from less than 1 to 40% across countries [3]. In Thailand, the prevalence of VREs among *Enterococcus faecium* isolates from hospitals nationwide was 8.1% in 2018 [4]. Among enterococcal species, *E. faecium* is intrinsically more resistant to antibiotics including vancomycin [1].

Importantly, VRE infections frequently occur because of their colonization in the human gastrointestinal tract and persistence in the healthcare environment [1]. Among patients who acquire nosocomial VRE infections, the in-hospital and 30-day mortality rates are 73.1 and 57.7%, respectively [5].

Initially, penicillin and ampicillin are the preferred treatment options for β-lactam–susceptible Enterococci. Once resistance to penicillin arises, vancomycin is selected. Because of increasing vancomycin use, the prevalence of vancomycin resistance among *Enterococcus* species is increasing, resulting in few antibiotic options. However, at the time of this writing, quinupristin/dalfopristin, lipoglycopeptides (*e.g.*, oritavancin, dalbavancin), oxazolidinones (*e.g.*, linezolid), daptomycin, and tigecycline were stated to have activity against VRE isolates [6].

Tigecycline, a glycylcycline antimicrobial derived from minocycline, exerts activity against VREs by inhibiting the 30S ribosomal subunit, thereby blocking protein synthesis. Kresken et al. performed a global investigation of *in vitro* tigecycline activity. Tigecycline was extremely active against VRE isolates collected in 2006 - 2014, with a 90% minimum inhibitory concentration (MIC_{90}) of less than 0.25 μg/mL and an overall susceptibility rate of 99% [7]. Despite its excellent activity against VREs, the use of tigecycline is mainly limited by its pharmacokinetic properties. Because of its high volume of distribution, its serum concentrations are inadequate for treating bloodstream infections. Conversely, its extensive distribution in certain organs such as the intra-abdominal system and soft tissue makes this drug desirable for treating relevant infections involving VREs [1, 8]. Therefore, tigecycline can be attractive treatment choice for complicated intra-abdominal infections (cIAIs) and complicated skin/soft tissue infections (cSSTIs) caused by VRE.

To date, linezolid and quinupristin/dalfopristin are the only approved antibiotics for VRE infections [6]. However, thrombocytopenia caused by linezolid use is common, with a reported prevalence of up to 12% [9]. Moreover, quinupristin/dalfopristin is not available in certain countries including Thailand. Therefore, this study examined the *in vitro* activity of tigecycline against clinical VRE isolates and the optimal dosing regimens of tigecycline in critically ill patients for achieving pharmacokinetic (PK)/pharmacodynamic (PD) targets in patients with VRE-associated cIAIs and cSSTIs.

MATERIALS AND METHODS

1. Bacterial strains

Enterococcal isolates were collected from patients based on the definition of infection in each organ/system by the Centers for Disease Control and Prevention (CDC)/NHSN surveillance definitions [10]. This study performed from 2014 to 2018 at Phramongkutklao Hospital, a medical school hospital in Bangkok, Thailand. We excluded enterococcal isolates collected

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via environmental surveillance or from patient specimens that did not meet the CDC/NHSN definitions. Each isolate was grown in skim milk and kept at -70°C until used [5]. This study was approved by the ethics review committee of the Royal Thai Army Medical Department, Bangkok, Thailand (No. Q017b/61).

2. Tigecycline susceptibility testing

All included enterococcal isolates were identified as VREs using broth microdilution methods (standard vancomycin powder donated from Siam Pharmaceutical Co., Ltd., Bangkok, Thailand) per the manufacturer's recommendations. The incubation condition was 35°C in ambient air for 24 h for accurate detection. The tested enterococcal strains with MIC ≥ 32 μg/mL for vancomycin were considered VREs [11].

Tigecycline susceptibility was determined using E-test methods (Liofilchem, Teramo, Italy). This study investigated MIC range, MIC_{50}, and MIC_{90} of tigecycline against VRE. MIC range was defined as the smallest and largest MIC values. MIC_{50} and MIC_{90} values were defined as the lowest concentration of tigecycline at which 50% and 90% of the isolates were inhibited, respectively. According to no the Clinical and Laboratory Standards Institute susceptibility interpretation, the susceptible breakpoint ≤ 2 g/mL was applied in this study [7].

3. PK/PD analysis of tigecycline

In the context of critically ill patients and more participants in the study, the PK parameters from a population PK study of tigecycline in 37 patients with sepsis and septic shock in intensive care unit were applied [12]. A two-compartment model with PK parameters (clearance 22.1 L/h, intercompartmental clearance 69.4 L/h, volume of the central compartment 162 L, and volume of the peripheral compartment 87.9 L) was used to describe the concentration-time course of tigecycline.

To simulate the concentration-time course of tigecycline, a 10,000-subject Monte Carlo simulation (Oracle Crystal Ball) was used to calculate area under the curve (AUC). AUC is the area under the plot of plasma concentration of drug against time after drug administration. The AUC was calculated by using the trapezoidal rule. The AUC_{24} was the areas under the curve over 24 hours calculated for steady-state on day 7 of tigecycline administration. The PK/PD targets of tigecycline were represented as the AUC_{24}/MIC ratio. The optimal ratio of the free area under the curve to MIC ($fAUIC_{24}$) targets for exposure-response analyses of clinical efficacy in the treatment of cSSTIs and cIAIs were defined as ≥17.9 and ≥6.9, respectively [13, 14]. The simulated tigecycline dosing regimens included a loading dose of 100 - 200 mg followed by a maintenance dose of 100 - 200 mg administered as 1 - 2 doses per day. The probability of target attainment (PTA) was defined by how likely a specific drug dose reached a target PK/PD index [15]. PTA was estimated at MICs of 0.06, 0.09, 0.12, 0.19, 0.25, 0.38, 0.5, 0.75, 1, 1.5, and 2 μg/mL. The cumulative fraction of response (CFR) was the probability of drug dose covering a specified bacterial population [15]. The CFR was calculated using below equation

$$\sum_{i=1}^{n} \text{PTA}\, i \times Fi$$

where *i* indicates the MIC value ranked from lowest to highest MIC, PTA*i* is the PTA of each MIC value, and *Fi* is the fraction of the VRE population in each MIC value.

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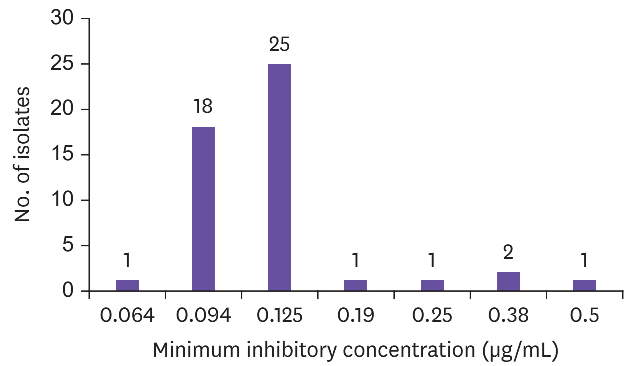

Figure 1. Minimum inhibitory concentrations of tigecycline against the studied vancomycin-resistant *Enterococcus faecium* isolates (n = 49).

Our bacterial population was the MIC of tigecycline among VRE isolates obtained from patients. CFR was calculated as the sum of each PTA against the tigecycline MIC distributions of VREs. Dosing regimen that reached above 90% of PTA and CFR was considered the optimal tigecycline dosage for documented therapy and empirical therapy, respectively.

RESULTS

1. *In vitro* activity of tigecycline

Forty-nine clinical VRE isolates were obtained, all of which were *E. faecium.* MIC_{50}, MIC_{90}, and the MIC range for tigecycline were 0.125, 0.19, and 0.064 – 0.5 μg/mL, respectively. No isolate was resistant to tigecycline (**Fig. 1**).

2. PK/PD analysis

The PTA for the ratio of the free AUC to MIC ($fAUIC_{24}$) for tigecycline dosing regimens is shown in **Table 1**. For $fAUIC_{24}$ >17.9, all studied tigecycline regimens exceeded 90% at MIC ≤0.19 μg/mL. Only the maintenance dose of 200 mg/day tigecycline achieved $fAUIC_{24}$ >17.9, and PTA exceeded 90% for MIC ≤0.38 μg/mL. Conversely, no regimen achieved a 90% PTA of $fAUIC_{24}$ >17.9 when MIC ≥0.5 μg/mL (**Table 1**).

Table 1. The probability of target attainment for the different tigecycline regimens at steady state with each target of $fAUIC_{24}$

Dosing regimen		Percentage of probability of target attainment (%)								
Loading dose (mg)	Maintenance dose (mg)	Tigecycline MIC value against VRE isolates (μg/mL)								
		0.06	0.09	0.12	0.19	0.25	0.38	0.5	1	2
$fAUIC_{24}$ >17.9										
100	50 mg q 12 h	100	100	100	96.1	56.1	1.1	0	0	0
200	100 mg q 24 h	100	100	100	96.3	56.5	1.5	0	0	0
150	75 mg q 12 h	100	100	100	100	99.5	53.3	6.5	0	0
150	150 mg q 24 h	100	100	100	100	99.5	54.1	7.2	0	0
200	100 mg q 12 h	100	100	100	100	100	96.4	55.3	0	0
200	200 mg q 24 h	100	100	100	100	100	96.3	56.7	0	0
$fAUIC_{24}$ >6.9										
100	50 mg q 12 h	100	100	100	100	100	100	95.2	0.9	0
200	100 mg q 24 h	100	100	100	100	100	100	95.4	1.3	0
150	75 mg q 12 h	100	100	100	100	100	100	100	50	0
150	150 mg q 24 h	100	100	100	100	100	100	100	50.5	0
200	100 mg q 12 h	100	100	100	100	100	100	100	95.4	1
200	200 mg q 24 h	100	100	100	100	100	100	100	95.6	0.3

$fAUIC_{24}$, ratio of the free area under the curve to MIC; MIC, minimum inhibitory concentration; VRE; vancomycin-resistant *enterococcus*.

Infection & Chemotherapy

Table 2. Cumulative fraction of response (%) of tigecycline with various dosing regimens met each pharmacokinetic/pharmacodynamic targets

Loading dose (mg)	Maintenance dose (mg)	Cumulative fraction of response (%)	
		$fAUIC_{24}$ >6.9	$fAUIC_{24}$ >17.9
100	50 mg q 12 hr	99.9	93
200	100 mg q 24 hr	99.9	93
150	75 mg q 12 hr	100	96.2
150	150 mg q 24 hr	100	96.2
200	100 mg q 12 hr	100	98.9
200	200 mg q 24 hr	100	99

$fAUIC_{24}$, ratio of the free area under the curve to minimum inhibitory concentration.

Whereas all studied tigecycline regimens exceeded 90% PTA of $fAUIC_{24}$ >6.9 for MIC ≤0.5 μg/mL, only the maintenance dose of 200 mg/day achieved $fAUIC_{24}$ >6.9, and PTA exceeded 90% for MIC ≤1 μg/mL. No regimen achieved 90% PTA of $fAUIC_{24}$ >6.9 at MIC ≥ 2 μg/mL (**Table 1**).

Concerning the CFR against the studied VRE isolates, all simulated tigecycline dosing regimens met $fAUIC_{24}$ >17.9 and $fAUIC_{24}$ >6.9 more than 90% of the time (**Table 2**).

DISCUSSION

Antibiotic resistance among enterococci represents a clinical challenge given the small number of available anti-Enterococcal agents. However, the principle treatment for enterococcal infections depends on the source of infection control, optimized dosage regimens, and antibiotic combinations [8].

Our results illustrated that all VRE isolates were sensitive to tigecycline (MIC susceptible breakpoint, ≤2 μg/mL), in line with previous findings. Previously, Zhang et al. reported that vancomycin-resistant *E. faecium* isolates collected in North America and Latin America from 2012 to 2016 had a tigecycline susceptibility rate at 98.9% [16]. Similarly, Sader et al. collected VRE clinical isolates in North America, Latin America, Europe, and the Asia-Pacific region, revealing that 99.5% of VRE strains were susceptible to tigecycline [17]. Finally, in the tigecycline *in vitro* surveillance in Taiwan study, a prospective surveillance of 219 VRE isolates, the tigecycline susceptibility rate was 98.6% [18].

Despite its good activity against VREs in both the present and previous studies [16-19], tigecycline only has bacteriostatic effects on enterococcal isolates at any concentration exceeding the MIC [20]. Not surprisingly, antibiotics such as cell wall-targeting agents (*e.g.*, penicillin, ampicillin, vancomycin) or ribosomal inhibitors (linezolid) also usually exhibit bacteriostatic activity against most enterococcal isolates [21]. Because of the limited efficacy of monotherapy, synergistic combinations are often warranted for complex infections with high inoculum and deep locations [8]. Thus, synergistic effects might be useful for optimizing the use of tigecycline in the treatment of VRE infection. A synergistic or additive effect was previously reported for fosfomycin combined with tigecycline in 83.3% of tested VRE strains [5].

Because of the scant clinical data regarding treatment efficacy against VRE infections, clinicians have relied on alternative regimens extrapolated from PK/PD indices. Based on our simulated PK/PD profiles, high-dose tigecycline therapy (maintenance dose of 200 mg/day) is appropriate for the empirical treatment of VRE-associated cIAIs and cSSTIs. When the MIC of a VRE isolate is known, an equal or lower tigecycline dose for documented therapy might

ic Infection & Chemotherapy

be appropriate based on the achievement of >90% PTA for each $fAUIC_{24}$ target. However, due to a larger volume of distribution and a higher clearance of tigecycline from Borsuk-De Moor et al. study [12] that were used for PK simulation in the present study, with the same tigecycline MIC value, the PTA of $fAUIC_{24}$ value in our study seemed to be lower than those of the previous study [22].

Importantly, our simulated tigecycline dose used different $fAUIC_{24}$ targets for cIAIs and cSSTIs. If patients have such infections and bacteremia, the use tigecycline is contraindicated because of the inadequate plasma concentration [6]. This unfavorable tigecycline level was documented by a meta-analysis indicating that patients with baseline bacteremia had a higher risk of mortality [23]. Daptomycin as alternative option is clinically used for VRE treatment by using the loading and maintenance doses with 8 mg/kg/day determined to be optimal and safe [19]. Lastly, this study only suggested the possible dose of tigecycline to meet the current PK/PD target. Updated PK/PD targets for the treatment of cIAIs and cSSTIs, especially those associated with VRE infection, and prospective clinical studies of our recommended dosing are required to confirm the benefits of tigecycline against VRE infections.

In conclusion, the present study suggested that tigecycline might be a potential treatment for cSSTIs and cIAIs due to VRE infection. However, to achieve PK/PD targets for better clinical outcomes, tigecycline should be used at a daily dose of 200 mg to cover VRE isolates with MIC ≤0.38 μg/mL and MIC ≤1 μg/mL for treating cSSTIs and cIAIs, respectively.

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