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Original Article

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Optimization of Linezolid Dosing Regimens for Treatment of Vancomycin-Resistant Enterococci Infection

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ABSTRACT

Background: Linezolid, an oxazolidinone antibiotic, is recommended for vancomycin-resistant enterococci (VRE). However, 100% free-drug concentration above the minimum inhibitory concentration (*f*T>MIC) and an area under the curve of free drug to MIC ratio (*f*AUC24/MIC) >100 were associated with favorable clinical outcome with less emerging resistance. A plasma trough concentration (C_{trough}) of linezolid ≥9 μg/mL was also related to hematologic toxicity. Thus, linezolid dose optimization is needed for VRE treatment. The study aimed to determine the *in vitro* linezolid activity against clinical VRE isolates and linezolid dosing regimens in critically ill patients who met the target pharmacokinetics/pharmacodynamics (PK/PD) for VRE treatment.
Materials and Methods: Enterococcal isolates from enterococcal-infected patients were obtained between 2014 and 2018 at Phramongkutklao Hospital. We used Monte Carlo simulation to calculate the probability of target attainment, and the cumulative fraction of response (CFR) of the free area under the curve to MIC ratio ($fAUIC_{24}$) was used to calculate the *f*AUC24/MIC 80 - 100 and *f*T/MIC >85 - 100% of the interval time of administration for clinical response and microbiological eradication as well as the C_{trough} ≥9 μg/mL for the probability of hematologic toxicity.
Results: For linezolid MIC determination, the MIC median (MIC_{50}), MIC for 90% growth (MIC_{90}), and range for linezolid were 1.5 μg/mL, 2 μg/mL, and 0.72 - 2 μg/mL, respectively. A dosing regimen of 1,200 mg either once daily or as a divided dose every 12 h gave target attainments of *f*AUC24/MICs >80 and >100, which exceeded 90% for MICs ≤1 and ≤1 μg/mL, respectively, with a rate of hematologic toxicity <15%. If the expected *f*T>MICs were >85% and 100%, a 1,200-mg divided dose every 12 h could cover VRE isolates having linezolid MICs ≤1 μg/mL and ≤0.75 μg/mL. Even 600 mg every 8 h and 1,200 mg as a continuous infusion gave a higher target attainment of *f*AUC24/MIC and a *f*T>MIC and the target CFR, but those regimens gave C_{trough} ≥9 μg/mL rates of 40.7% and 99.6%.
Conclusion: The current dosing of 1,200 mg/day might be optimal treatment for infection by VRE isolates with documented MICs ≤1 μg/mL. For treatment of VRE with a MIC of 2 μg/mL or to achieve the target CFR, the use of linezolid with other antibiotic combinations might help achieve the PK/PD target, provide better clinical outcome, and prevent resistance.

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Keywords: *Enterococcus faecium*; Minimum inhibitory concentration; Monte Carlo simulation; Thrombocytopenia

INTRODUCTION

Vancomycin-resistant enterococci (VRE; *Enterococcus faecium*) is an important pathogen in nosocomial infection worldwide. The ability of enterococci to acquire antibiotic resistance makes the treatment of enterococcal infections a difficult challenge [1, 2]. In 2017, the World Health Organization (WHO) designated VRE as a serious threat that required development of new drugs or strategies to prevent infections [3]. In Thailand, data from the National Antimicrobial-Resistance Surveillance Thailand, the prevalent rate of VRE in *E. faecium* as VRE isolates was found to be 8.1% in 2018 [4].

Typically, the major risk factors for VRE colonization include immunocompromised patients, hematologic malignancy, hematologic stem-cell transplantation, prolonged hospitalization, intensive care unit patients, comorbidities, close contact with patients with VRE infections or colonization, and prior vancomycin use [5, 6]. Generally, mortality has been found to be higher for VRE bacteremia than for vancomycin sensitive Enterococci bacteremia [7]. Moreover, the in-hospital and 30-day mortality rates were found to be 73.1% and 57.7%, respectively, for VRE infections [8].

Linezolid, an oxazolidinone antibiotic, inhibits the 50S ribosomal subunit against several Gram-positive bacteria, especially resistant organisms, such as methicillin-resistant *Staphylococcus aureus*, vancomycin intermediate- (VISA) or -resistant *S. aureus* (VRSA), penicillin-resistant pneumococci, or VRE [9]. Pharmacodynamically, data from the Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program from 2004 to 2012 showed that the VRE isolates had minimum inhibitory concentration median (MIC_{50}) and minimum inhibitory concentration for 90% growth (MIC_{90}) linezolid values of 1 and 2 μg/mL, respectively, with nearly 99% of the susceptible rate [10]. Currently, linezolid has been approved by the US Food and Drug Administration (US FDA) for VRE treatment in blood, skin, and soft tissue infections, and pneumonia [11].

Several previous studies of pharmacokinetic/pharmacodynamic (PK/PD) targets for linezolid have been reported. A free-drug concentration above MIC (*f*T>MIC) >85 - 100% of the interval administration and an area under the curve of free drug and MIC ratio (*f*AUC24/MIC) of 80 - 100 have been associated with favorable clinical outcome and microbiological eradication with less emerging resistance [12-15]. Additionally, a plasma minimum concentration (C_{min}) of linezolid at steady state ≥9 μg/mL has also been associated with hematologic toxicity [16, 17]. Thus, determination of PK/PD targets for efficacy and safety are needed for dose optimization.

In critically ill patients, alteration of drug PK can occur, so optimal dosing of linezolid is of great concern. The occurrence of decreased protein binding, increased volume of distribution, and inhibited metabolism result in high inter-individual variability of linezolid plasma concentrations. These phenomena might prevent achieving PK/PD targets for efficacy, safety, and prevention of resistance. Therefore, the study aim was to determine the *in vitro* activity of linezolid against clinical VRE isolates and dosing regimens of linezolid in critically ill patients who met PK/PD targets for good efficacy, less hematologic toxicity, and prevention of emerging resistance.

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MATERIALS AND METHODS

1. Bacterial strains

Enterococcal isolates from patients with enterococcal infections were obtained between 2014 and 2018 at Phramongkutklao Hospital, a 1,200-bed university hospital in Bangkok, Thailand [18]. All clinical enterococcal isolates have to meet specific types of infection criteria in each organ/system that are based on the Centers for Disease Control (CDC) and Prevention/ National Healthcare Safety Network (NHSN) Surveillance Definitions [19]. Environmental active surveillance or colonization (CDC and NHSN definitions not met) or enterococcal isolates were excluded. Vancomycin resistance in the obtained enterococcal strains were proven by resistance to vancomycin (the isolates with an MIC ≥32 μg/ml to vancomycin) shown in broth micro-dilutions (standard vancomycin powder donated from Siam Pharmaceutical Co., Ltd., Bangkok, Thailand) based on the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [20]. The use of cultured organisms from clinical specimens was approved by the ethics review committee of the Royal Thai Army Medical Department, Bangkok, Thailand (No. Q017b/61).

2. Pharmacodynamic profiling of linezolid

In vitro linezolid activity against VRE isolates as the MIC (μg/mL) was evaluated by using E-test methods (Liofilchem, Teramo, Italy). The following CLSI incubation conditions were used: 35 - 37°C in ambient air for 16–18 h. The susceptibility breakpoint for linezolid was applied from the CLSI criteria as follows: susceptible (S) ≤2 μg/mL, intermediate (I) = 4 μg/mL, and resistant (R) ≥8 μg/mL [20].

3. Linezolid dosing simulations and PK and PD analysis

For simulated linezolid dosing regimens, the PK parameters from a previous study of critically ill patients were used [21]. Concentration versus time at steady state was described by using a two-compartmental model. A two-compartment model with PK parameters including the linezolid clearance 6.85 L/h (% coefficient of variation; %CV) (50.3%), intercompartmental clearance 9.09 L/h (14.9%), volume of the central compartment 39.6 L (22.7%), and volume of the peripheral compartment 26.3 L (41.8%) was used to describe the concentration-time course of linezolid [21].

For PK and PD analysis, a 10,000-subject Monte Carlo simulation (Oracle Crystal Ball, Redwood City, CA, USA) was used to calculate the *f*AUC24/MIC >80 and >100, and the *f*T/ MIC >85% and 100% of the interval time of administration for clinical response [12, 22] and C_{min} ≥9 μg/mL for toxicity (increased occurrence of linezolid-related hematological toxicity) [16, 17]. The simulation was performed for various linezolid dosing regimens (600 mg intermittent intravenous administration every 12 - 24 h, continuous infusion of 1,200 mg, or 50 mg/hour). The probability of target attainment (PTA) was estimated for MICs of 0.25, 0.5, 0.75, 1, 1.5, and 2 μg/mL, and the cumulative fraction of response (CFR) was calculated as the sum of each %PTA against linezolid MIC distributions of VRE.

Dosing regimens that reached ≥90% of the PTA and CFR were highly recommended for documented therapy and empirical therapy against VRE infections, respectively. Dosing regimens that reached between 80 - 89% of the PTA and CFR were considered to be moderately recommended doses for documented therapy and empirical therapy, respectively.

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RESULTS

1. Pharmacodynamic profiling

All 49 clinical *E. faecium* strains were included. For linezolid MIC determination, the MIC_{50}, MIC_{90}, and range for linezolid were 1.5 μg/mL, 2 μg/mL, and 0.72 - 2 μg/mL, respectively. On the basis of a susceptible breakpoint for enterococci of ≤2 μg/mL, none of the studied VRE isolates were linezolid-resistant strains.

2. PK and PD analysis

The PTAs for each linezolid MIC value with a target of *f*AUC24/MIC >80 - 100 and *f*T>MIC of 85% and 100% at steady state are shown in **Table 1**. The dosing regimen of 1,200 mg either once daily or as a divided dose every 12 h given as a 0.5-hour infusion gave a target attainment of *f*AUC24/MIC >80, which exceeded 90% for a MIC ≤1 μg/mL. If the *f*AUC24/MIC target was expected to be >100, the dosing regimen of 1,200 mg either once daily or as a divided dose given as a 0.5-hour infusion also covered VRE isolates having linezolid MICs ≤1 μg/mL. Only 1,200 mg as a continuous infusion exceeded 90% of the PTA of *f*AUC24/MIC targets >80 and >100 for a MIC of 2 μg/mL.

Table 1. The percentage probability of target attainment for the different linezolid dosing regimens for critically ill patients at steady state with targets of $fAUC_{24}$/MIC and *f*T>MIC, with rates of hematologic toxicity

PK/PD target	Dosing regimen	Infusion time (hour)	Percentage of PTA (%)						C_{trough} ≥9 μg/mL (%)
			Linezolid MIC value (μg/mL) against VRE isolates						
			0.25	0.5	0.75	1	1.5	2	
$fAUC_{24}$>MIC									
80.0	600 mg q 12 h	0.5	100.0	99.9	99.3	97.1	84.6	66.1	14.3
	600 mg q 12 h	2	100.0	99.9	99.3	97.1	84.9	67.0	16.1
	600 mg q 12 h	3	100.0	99.9	99.4	97.3	85.2	66.1	17.1
	600 mg q 12 h	4	100.0	99.9	99.3	97.1	85.2	67.2	18.1
	1,200 mg q 24 h	0.5	100.0	99.9	99.4	97.0	84.5	65.8	7.0
	1,200 mg q 24 h	24	100.0	100.0	100.0	100.0	100.0	99.9	99.6
	600 mg q 8 h	0.5	100.0	100.0	99.9	99.7	96.7	90.0	40.7
100.0	600 mg q 12 h	0.5	99.9	99.8	97.8	92.0	70.8	48.2	14.3
	600 mg q 12 h	2	100.0	99.8	97.9	92.2	71.3	48.9	16.1
	600 mg q 12 h	3	100.0	99.8	97.9	92.4	71.1	49.0	17.1
	600 mg q 12 h	4	100.0	99.8	97.9	92.5	71.9	48.4	18.1
	1,200 mg q 24 h	0.5	100.0	99.8	97.8	91.8	70.5	47.5	7.0
	1,200 mg q 24 h	24	100.0	100.0	100.0	100.0	99.9	99.7	99.6
	600 mg q 8 h	0.5	100.0	100.0	99.8	98.6	91.7	78.6	40.7
*f*T>MIC									
85%	600 mg q 12 h	0.5	99.5	97.9	95.1	91.2	82.3	72.2	14.3
	600 mg q 12 h	2	99.7	98.5	96.5	93.3	85.3	76.7	16.1
	600 mg q 12 h	3	99.8	98.8	97.2	94.5	87.5	78.9	17.1
	600 mg q 12 h	4	99.9	99.1	97.7	95.7	90.0	81.8	18.1
	1,200 mg q 24 h	0.5	94.2	87.1	79.8	72.6	59.8	49.3	7.0
	1,200 mg q 24 h	24	100.0	100.0	100.0	100.0	100.0	100.0	99.6
	600 mg q 8 h	0.5	99.9	99.7	99.1	98.1	94.9	90.9	40.7
100%	600 mg q 12 h	0.5	98.9	96.5	92.1	87.4	76.6	66.3	14.3
	600 mg q 12 h	2	99.3	97.2	93.9	89.4	80.1	70.1	16.1
	600 mg q 12 h	3	99.4	97.8	94.9	91.1	82.3	72.5	17.1
	600 mg q 12 h	4	99.7	98.1	95.8	92.6	84.5	75.5	18.1
	1,200 mg q 24 h	0.5	89.8	80.0	70.8	62.8	49.7	39.2	7.0
	1,200 mg q 24 h	24	100.0	100.0	100.0	100.0	100.0	100.0	99.6
	600 mg q 8 h	0.5	99.9	99.5	98.7	97.4	93.5	88.7	40.7

Color codes: Strongly recommended dose based on ≥90% PTA or ≥90% CFR.
Moderately recommended dose based on 80 - 89% PTA or 80 - 89% CFR.
*f*AUC, free area under the curve; MIC, minimum inhibitory concentration; *f*T, time of free drug concentrations; PK/PD, pharmacokinetics/pharmacodynamics; PTA, probability of target attainment; VRE, vancomycin-resistant enterococci; C_{trough}, trough concentration; q, every; h, hour; CFR, cumulative fraction of response.

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Table 2. Cumulative fraction of response (%) of linezolid for various dosing regimens that met each pharmacokinetic/pharmacodynamic target

Dosing regimens	Infusion time (hour)	CFR (%)				C_{trough} ≥9 μg/mL (%)
		AUC/MIC		*f*T>MIC		
		≥80	≥100	85%	100%	
600 mg q 12 h	0.5	80.1	66.5	80.3	74.9	14.3
600 mg q 12 h	2	80.6	67	83.7	78.2	16.1
600 mg q 12 h	3	80.7	67	85.7	80.4	17.1
600 mg q 12 h	4	80.8	67.2	87.9	82.7	18.1
1,200 mg q 24 h	0.5	79.9	66.1	58.5	48.4	7.0
1,200 mg q 24 h	24	99.9	99.8	100	100	99.6
600 mg q 8 h	0.5	94.7	88.2	94.1	92.5	40.7

Color codes: Strongly recommended dose based on ≥90% PTA or ≥90% CFR.
Moderately recommended dose based on 80 - 89% PTA or 80 - 89% CFR.
CFR, Cumulative fraction of response; AUC, area under the curve; MIC, minimum inhibitory concentration; *f*T, time of free drug concentrations; C_{trough}, trough concentration; h, hour; mg, milligram; q, every; PTA, probability of target attainment.

For a PK/PD target of *f*T>MIC, the regimen of a 1,200-mg divided dose every 12 h as a 0.5-hour infusion reached the target attainment of *f*T>MIC >85%, which exceeded 90% for a MIC of ≤1 μg/mL. If the expected *f*T>MIC was 100%, the dosing regimen of a 1,200-mg divided dose every 12 h as a 0.5-hour infusion could cover VRE isolates having a linezolid MIC ≤0.75 μg/mL. For the prolonged infusion over 3 - 4 h, the dosing regimen of a 1,200-mg divided dose every 12 h exceeded 90% of the PTA for a *f*T>MIC of 100% at a MIC of 1 μg/mL. Only 1,200-mg as a continuous infusion exceeded 90% of the PTA for a *f*T>MIC target > 85% and 100% at a MIC of 2 μg/mL.

The dosing regimen of 1,200 mg either once daily or as a divided dose every 12 h as a 0.5 - 4 h infusion gave a hematologic toxicity rate (as a C_{trough} ≥9 μg/mL) <20%. Whereas the dosing regimen of 600 mg every 8 h and 1,200-mg as a continuous infusion had hematologic toxicity rates of 40.7% and 99.6%, respectively.

For CFR analysis, none of the linezolid dosing regimens except for 600 mg every 8 h and 1,200-mg continuous infusion had a CFR of any targets of *f*AUC24/MIC (>80 or >100) and *f*T>MIC (>85% and 100%) exceeding 90% (**Table 2**).

DISCUSSION

The linezolid PK properties show that linezolid is well-absorbed from the gastrointestinal tract, with a bioavailability of 100%. This drug penetrates various organs, such as the biliary tract system, colon, bloodstream, skin/soft tissue, and bone, as well as the central nervous system with adequate concentrations [23]. Additionally, linezolid is one of two drugs approved by the US FDA for VRE infection, with clinical and microbiologic cure rates of 78% and 85%, respectively [24].

In the linezolid MIC determination, all of the studied VRE isolates were susceptible to linezolid and exhibited MIC_{50} and MIC_{90} at 1.5 and 2 μg/mL. Our findings of the susceptibility of VRE to linezolid agreed with those reported in previous studies [25, 26]. Chen et al. determined the *in vitro* activity of linezolid against VRE isolates, linezolid MIC_{50} and MIC_{90} values were equal to 2 μg/mL [25]. Similarly, Houri et al. investigated linezolid activity, and linezolid resistance was not found at an MIC_{90} for VRE of 2 μg/mL [26]. However, there were no strains in the VRE isolates that were not susceptible to linezolid in our study. Linezolid resistance has been documented worldwide but the prevalence rate is very low (<1%) [27].

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Thus, linezolid, as a last resort antibiotic for treatment of VRE infection, has to be closely monitored, and the dosing regimen should be optimized to reduce emerging resistance [14, 15].

This is the first study using Monte Carlo simulation to determine optimal linezolid dosage regimens focusing on the balance between efficacy and safety including various infusion time (short infusion, prolonged infusion, and continuous infusion) and various PK/PD targets (*f*AUC24/MIC and *f*T>MIC) against VRE. From our findings, the regimen of 1,200-mg infused 0.5 h either once daily or as a divided dose every 12 h as the current recommended dosing regimen reached the target attainment of *f*AUC24/MIC >80, *f*AUC24/MIC >100, and *f*T>MIC 85% at a MIC of ≤1 μg/mL and a *f*T>MIC of 100% at a MIC of ≤0.75 μg/mL. Only the 1,200-mg as a continuous infusion exceeded 90% of the PTA of all *f*AUC24/MICs (>80 and >100) and *f*T>MIC (>85% and 100%) targets at a MIC of 2 μg/mL. Moreover, none of the linezolid dosing regimens except for 600 mg every 8 h and 1,200-mg continuous infusion had a CFR of any targets of *f*AUC24/MIC and *f*T>MIC exceeding 90%.

From the previous PK studies published by Taubert et al. [28] and Adembri et al. [29] simulating linezolid dosing regimens, the continuous infusion allowed more patients to achieve the *f*AUC24/MIC and *f*T>MIC than intermittent administration. However, the continuous-infusion regimen and dosing regimen of 600 mg every 8 h had very high rates of potential hematologic disorders. Our findings support previous studies that the increased doses or administered by a standard dose with continuous infusion were shown to be inappropriate because of putting patients at a high risk of hematologic disorder [28, 29]. This adverse effect has to be concerned in clinical practice. Once thrombocytopenia is occurred during linezolid therapy, the patients received more platelet transfusions and had higher intensive care unit mortality rates [30]. Although a very limited data to support the effect of continuous infusions related more at risk for adverse events, the hematologic toxicity rate between continuous infusions and intermittent administration has to be clinically evaluated.

According to the current recommended regimen (600 mg every 12 h), this dosage tends to end in treatment failure and development of linezolid resistance. Sub-optimal PK/PD indices on the development of linezolid resistance have been described by Boak et al. who found that the tendency toward emerging resistance is greater when the linezolid concentration is maintained near its MIC of the VRE isolates and cannot reach the target of an AUC/MIC >100 [31]. Thus, linezolid dosing regimens with an AUC/MIC >100 and a *f*T>MIC of 100% have been associated with better clinical outcome and resistance prevention [31]. Unfortunately, in this study, the most studied isolates (81.6%) have had linezolid MICs >1 μg/mL. Thus, the linezolid dose of 1,200 mg/day did not reach an AUC/MIC >100 and a *f*T>MIC of 100% for VRE at a MIC >1 μg/mL.

Because there are no linezolid dosing regimens for VRE with MICs >1 μg/mL, clinicians have been prompted to use combination therapy to reduce the MIC of linezolid, resulting in greater opportunities of expected PK/PD indices. Hemapanpairoa et al. determined the *in vitro* effect of combined antimicrobials against 16 VRE clinical isolates. A synergistic (two-fold or greater linezolid MIC reduction) or additive effect (one-fold MIC reduction) was found in all studied VRE isolates treated with linezolid plus fosfomycin, whereas a fourfold or greater MIC reduction was observed for linezolid plus gentamicin concentrations of 2 μg/mL and 4 μg/mL at 83.3% and 91.6% of studied VRE isolates, respectively [8]. Additionally, the studied regimen of a 3 - 4 h infusion of 600 mg every 12 h increased the opportunity to reach 90% of the PTA of a *f*T>MIC 100%, with the same rate of potential hematologic disorders,

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for a MIC of 1 μg/mL when compared with the same dose but as a 0.5-h infusion. Thus, the beneficial additive benefit or synergism of a linezolid combination and 3 - 4-h infusion might be necessary to reach the PTA and CFR targets, especially for VRE isolates with MICs >1.5 - 2 μg/mL. However, prospective clinical studies of our recommended linezolid dosing and antibiotic combination are needed to assess the benefits of treatments for VRE infections.

Besides the use of antibiotic combination for VRE treatment at a MIC of 2 μg/mL in order to increase the opportunities of expected PK/PD indices, the other effective antibiotics has to be considered in this situation. Daptomycin, a lipopeptide antibiotic, is a potentially interesting therapeutic option for treating VRE infections. The previous meta-analysis indicated similar the clinical cure, relapse rate, and overall mortality between patients receiving daptomycin and those treated with linezolid [32]. However, the loading and maintenance doses of 8 - 12 mg/kg/day have to be used for optimal treatment [33].

For limitation in our study, first, we used the pharmacokinetic parameters of linezolid from study published by Meagher et al. [21] but the population pharmacokinetics in critically ill patients for linezolid in Asian population was not available. Moreover, there is limited data published with regards to comparing pharmacokinetic parameters for linezolid across ethic populations. Thus, the impact of different pharmacokinetic parameters and the application of our findings to other populations had to be concerned. Second, we gathered only 49 VRE isolates; however, our isolates were from a 5-year period. The minimum numbers of isolates and the isolates of the VRE were from MIC distributions at a single hospital which might be dissimilar when taken from other settings. Third, thrombocytopenia does not develop in all patients exposed to the linezolid C_{trough} ≥9 μg/mL [17]. The presence of other factors such as age, serum creatinine, baseline platelet count, and concomitant medications as independent enhance patient risk for hematologic toxicity [16, 34]. Lastly, we used the total clearance of linezolid for simulating the concentrations versus time at steady state whereas a good model for linezolid clearance prediction consists of renal clearance predicted by linear model and nonrenal clearance by using Michaelis-Menten model. Our findings of suggested linezolid regimens might not be applicable for patients with reduced renal clearance because the increased plasma linezolid concentrations caused saturation of the Michaelis-Menten pathway and a further decrease in the nonrenal clearance [21].

In conclusion, linezolid showed good activity against VRE, and we observed no resistant strains. However, a larger number of VRE isolates in Thailand must be analyzed to confirm the activity of linezolid. Finally, the current dosing of 1,200 mg/day might be an optimal treatment regimen for VRE infections with MICs ≤1 μg/mL for documented therapy whereas, the standard dose of 600 mg infused in 4 h every 12 h might be considered as optimal regimen for empirical treatment against VRE infection. Therefore, the use of linezolid combined with other antibiotics and prolonged infusion times have potential for achieving PK/PD targets, better clinical outcomes, and to prevent emergence of resistance.

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REFERENCES

1. Reyes K, Bardossy AC, Zervos M. Vancomycin-resistant enterococci: epidemiology, infection prevention, and control. Infect Dis Clin North Am 2016;30:953-65.
PUBMED | CROSSREF
2. Ahmed MO, Baptiste KE. Vancomycin-resistant enterococci: a review of antimicrobial resistance mechanisms and perspectives of human and animal health. Microb Drug Resist 2018;24:590-606.
PUBMED | CROSSREF
3. World Health Organization (WHO). WHO publishes list of bacteria for which new antibiotics are urgently needed: Available at: http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/. Cited 27 Febuary 27 2017.
4. National Antimicrobial Resistant Surveillance Center. Thailand. Antibiogram 2018. Available at: http://narst.dmsc.moph.go.th/. Cited 20 Febrary 2019.
5. Rice LB. Emergence of vancomycin-resistant enterococci. Emerg Infect Dis 2001;7:183-7.
PUBMED | CROSSREF
6. O'Driscoll T, Crank CW. Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management. Infect Drug Resist 2015;8:217-30.
PUBMED
7. Prematunge C, MacDougall C, Johnstone J, Adomako K, Lam F, Robertson J, Garber G. VRE and VSE bacteremia outcomes in the era of effective VRE therapy: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016;37:26-35.
PUBMED | CROSSREF
8. Hemapanpairoa J, Changpradub D, Thunyaharn S, Santimaleeworagun W. Vancomycin-resistant enterococcal infection in a Thai university hospital: clinical characteristics, treatment outcomes, and synergistic effect. Infect Drug Resist 2019;12:2049-57.
PUBMED | CROSSREF
9. Ager S, Gould K. Clinical update on linezolid in the treatment of Gram-positive bacterial infections. Infect Drug Resist 2012;5:87-102.
PUBMED
10. Mendes RE, Hogan PA, Streit JM, Jones RN, Flamm RK. Zyvox® Annual Appraisal of Potency and Spectrum (ZAAPS) program: report of linezolid activity over 9 years (2004-12). J Antimicrob Chemother 2014;69:1582-8.
PUBMED | CROSSREF
11. Senior K. FDA approves first drug in new class of antibiotics. Lancet 2000;355:1523.
PUBMED | CROSSREF
12. Dong H, Xie J, Chen L, Wang T, Sun J, Zhao Y, Dong Y. Developments in the pharmacokinetic/pharmacodynamic index of linezolid: a step toward dose optimization using Monte Carlo simulation in critically ill patients. Int J Infect Dis 2014;22:35-40.
PUBMED | CROSSREF
13. Theuretzbacher U. Pharmacokinetic and pharmacodynamic issues for antimicrobial therapy in patients with cancer. Clin Infect Dis 2012;54:1785-92.
PUBMED | CROSSREF
14. Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 2003;42:1411-23.
PUBMED | CROSSREF
15. Tsuji BT, Bulitta JB, Brown T, Forrest A, Kelchlin PA, Holden PN, Peloquin CA, Skerlos L, Hanna D. Pharmacodynamics of early, high-dose linezolid against vancomycin-resistant enterococci with elevated MICs and pre-existing genetic mutations. J Antimicrob Chemother 2012;67:2182-90.
PUBMED | CROSSREF
16. Cattaneo D, Orlando G, Cozzi V, Cordier L, Baldelli S, Merli S, Fucile S, Gulisano C, Rizzardini G, Clementi E. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with gram-positive infections. Int J Antimicrob Agents 2013;41:586-9.
PUBMED | CROSSREF
17. Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother 2012;67:2034-42.
PUBMED | CROSSREF

18. Santimaleeworagun W, Hemapanpairoa J, Changpradub D, Thunyaharn S. Optimizing the dosing regimens of tigecycline against vancomycin-resistant enterococci in the treatment of Intra-abdominal and skin and soft tissue infections. Infect Chemother 2020;52:345-51.
PUBMED | CROSSREF

19. Centers for Disease Control and Prevention (CDC). National Healthcare Safety Network (NHSN) patient safety component manual: Identifying Healthcare-associated Infections (HAI) for NHSN surveillance. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf. Cited 20 Febuary 2019.

20. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing: Twenty-ninth informational supplement. Wayne, PA: CLSI; 2019;282.

21. Meagher AK, Forrest A, Rayner CR, Birmingham MC, Schentag JJ. Population pharmacokinetics of linezolid in patients treated in a compassionate-use program. Antimicrob Agents Chemother 2003;47:548-53.
PUBMED | CROSSREF

22. Barrasa H, Soraluce A, Usón E, Sainz J, Martín A, Sánchez-Izquierdo JÁ, Maynar J, Rodríguez-Gascón A, Isla A. Impact of augmented renal clearance on the pharmacokinetics of linezolid: Advantages of continuous infusion from a pharmacokinetic/pharmacodynamic perspective. Int J Infect Dis 2020;93:329-38.
PUBMED | CROSSREF

23. Falagas ME, Vardakas KZ. Benefit-risk assessment of linezolid for serious gram-positive bacterial infections. Drug Saf 2008;31:753-68.
PUBMED | CROSSREF

24. Narayanan N, Rai R, Vaidya P, Desai A, Bhowmick T, Weinstein MP. Comparison of linezolid and daptomycin for the treatment of vancomycin-resistant enterococcal bacteremia. Ther Adv Infect Dis 2019;6:2049936119828964.
PUBMED | CROSSREF

25. Chen KH, Huang YT, Liao CH, Sheng WH, Hsueh PR. In vitro activities of tedizolid and linezolid against Gram-positive cocci associated with acute bacterial skin and skin structure infections and pneumonia. Antimicrob Agents Chemother 2015;59:6262-5.
PUBMED | CROSSREF

26. Houri H, Kazemian H, Sedigh Ebrahim-Saraie H, Taji A, Tayebi Z, Heidari H. Linezolid activity against clinical Gram-positive cocci with advanced antimicrobial drug resistance in Iran. J Glob Antimicrob Resist 2017;10:200-3.
PUBMED | CROSSREF

27. Bender JK, Cattoir V, Hegstad K, Sadowy E, Coque TM, Westh H, Hammerum AM, Schaffer K, Burns K, Murchan S, Novais C, Freitas AR, Peixe L, Del Grosso M, Pantosti A, Werner G. Update on prevalence and mechanisms of resistance to linezolid, tigecycline and daptomycin in enterococci in Europe: Towards a common nomenclature. Drug Resist Updat 2018;40:25-39.
PUBMED | CROSSREF

28. Taubert M, Zander J, Frechen S, Scharf C, Frey L, Vogeser M, Fuhr U, Zoller M. Optimization of linezolid therapy in the critically ill: the effect of adjusted infusion regimens. J Antimicrob Chemother 2017;72:2304-10.
PUBMED | CROSSREF

29. Adembri C, Fallani S, Cassetta MI, Arrigucci S, Ottaviano A, Pecile P, Mazzei T, De Gaudio R, Novelli A. Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion. Int J Antimicrob Agents 2008;31:122-9.
PUBMED | CROSSREF

30. Kim HS, Lee E, Cho YJ, Lee YJ, Rhie SJ. Linezolid-induced thrombocytopenia increases mortality risk in intensive care unit patients, a 10 year retrospective study. J Clin Pharm Ther 2019;44:84-90.
PUBMED | CROSSREF

31. Boak LM, Li J, Rayner CR, Nation RL. Pharmacokinetic/pharmacodynamic factors influencing emergence of resistance to linezolid in an in vitro model. Antimicrob Agents Chemother 2007;51:1287-92.
PUBMED | CROSSREF

32. Zhao M, Liang L, Ji L, Chen D, Zhang Y, Zhu Y, Patel K. Similar efficacy and safety of daptomycin versus linezolid for treatment of vancomycin-resistant enterococcal bloodstream infections: a meta-analysis. Int J Antimicrob Agents 2016;48:231-8.
PUBMED | CROSSREF

33. Mercuro NJ, Davis SL, Zervos MJ, Herc ES. Combatting resistant enterococcal infections: a pharmacotherapy review. Expert Opin Pharmacother 2018;19:979-92.
PUBMED | CROSSREF

34. Dai Y, Jiang S, Chen X, Han L, Zhang C, Yu X, Zhang X. Analysis of the risk factors of linezolid-related haematological toxicity in Chinese patients. J Clin Pharm Ther 2021;46:807-13.
PUBMED | CROSSREF