Short Communication *Science, Engineering and Health Studies 2020, 14(1), 1-7*

Optimal tigecycline dosage regimens in patients infected with carbapenem-resistant *Enterobacteriaceae*

Wichai Santimaleeworagun[1*], Weerayuth Saelim[1], Sudaluck Thunyaharn[2], Jatapat Hemapanpairoa[3] and Piraporn Juntanawiwat[4]

[1]*Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand*
[2]*Faculty of Medical Technology, Nakhonratchasima College, Nakhon Ratchasima 30000, Thailand*
[3]*Department of Pharmacy Practice and Pharmaceutical Care, Faculty of Pharmaceutical Sciences, Burapha University, Chonburi 20131, Thailand*
[4]*Division of Microbiology, Department of Clinical Pathology, Phramongkutklao Hospital, Bangkok 10400, Thailand*
[*]*Corresponding author: santimaleeworag_w@su.ac.th*

Received: May 20, 2019; Revised: August 22, 2019; Accepted: September 24, 2019

ABSTRACT

We aimed to evaluate the minimum inhibitory concentration (MIC) values of tigecycline for carbapenem-resistant *Enterobacteriaceae* (CRE) and to identify a potential regimen for achieving target values of the area under the curve from 0 to 24 h divided by MIC (AUIC) ≥10.1 and ≥6.9. CRE clinical isolates were first obtained from blood specimens from each patient admitted to Phramongkutklao Hospital, Thailand, from October 2017 to October 2018. Tigecycline MIC was assayed using broth microdilution method. The tigecycline dosage regimens for critically ill patients were simulated using the Monte Carlo technique. The tigecycline dose that met 90% of probability of target attainment (PTA) and cumulative fraction of response (CFR) was considered as an appropriate regimen. Sixty-one CRE isolates were included. MIC50, MIC90, and MIC range for tigecycline were 0.5, 1.0, and ≤0.25-4.0 μg/mL, respectively. Regarding AUIC ≥10.1 target, the dose of 150-200 mg/day achieved the PTA target for isolates with a MIC of 0.5 μg/mL. Whereas, for AUIC ≥6.9, a dose of 200 mg/day covered CRE with an MIC of 1.0 μg/mL. For CFR >90%, only a dose of 200 mg/day was capable of achieving the AUIC target of ≥6.9. None of the studied regimens yielded a CFR >90% for the AUIC target of ≥10.1. Tigecycline seems to be a possible treatment for CRE; however, tigecycline 200 mg daily may be optimized to cover the CRE isolates with a MIC ≤1 μg/mL.

Keywords: critically ill patients; gram-negative bacteria; Monte Carlo simulation; MIC

1. INTRODUCTION

Carbapenems, which are β-lactam antibiotics, are the best therapeutic choice for multidrug-resistant gram-negative pathogens, especially organisms producing extended-spectrum β-lactamase (ESBL) or Amp-C β-lactamase (AmpC) (Sheu et al., 2019). However, the increasing use of these antibiotics has led to carbapenem resistance. In 2017, the World Health Organization (WHO, 2017) announced a list of carbapenem-resistant pathogens, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, as the critical priority among

human-health-threatening conditions.

Carbapenem-resistant *Enterobacteriaceae* (CRE) are common pathogens in various infections, including bloodstream, urinary tract, intra-abdominal, lower respiratory tract, skin/soft tissue, and central nervous system infections. Therefore, antibiotic-resistant *Enterobacteriaceae* have a great impact on patient outcomes (Sheu et al., 2019). Falagas et al. (2014) performed a meta-analysis of attributable deaths defined as the difference between patients with CRE infections and those with carbapenem-susceptible *Enterobacteriaceae* (CSE) infections. The CRE-attributable mortality varied from 26% to 44%. Moreover, the patients who had CRE bacteremia exhibited death rates that were twice as those observed in patients who had CSE bacteremia.

Currently, the treatment choices for CRE infections are very limited. Tigecycline has been considered as therapeutic option. To assess tigecycline susceptibility among *Enterobacteriaceae*, the SENTRY Surveillance Program collected 12, 869 *Enterobacteriaceae* isolates in 2016. Tigecycline had an *in vitro* activity against *Enterobacteriaceae* isolates with a MIC50/90 of 0.25/1 μg/mL and a susceptible rate (MIC breakpoint ≤2 μg/mL) of 97.8%. Moreover, tigecycline had a good activity against CRE isolates, with a MIC50/90 of 0.5/2 μg/mL and a susceptible rate of 98.0% (Pfaller et al., 2018).

The high tigecycline dosage regimens proposed recently seem to have favorable clinical outcomes for CRE treatment. Ni et al. (2016) showed that the ICU mortality in patients who used high-dose tigecycline was lower than that detected in patients who received standard-dosage regimens. Similarly, the results reported by Geng et al. (2018) showed significantly longer survival times in the group that received high-dose tigecycline to treat carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection. A previous population pharmacokinetics study showed that a higher tigecycline dose seemed to be necessary for the treatment of gram-negative bacteria in critically ill patients because of the altered pharmacokinetics of tigecycline (Xie et al., 2017).

The Monte Carlo Simulation is a technique that selects a value of a pharmacokinetics parameter randomly from its distribution to incorporate it with the structural pharmacokinetics, to predict the appropriate dosing regimen for achieving the target pharmacokinetic/pharmacodynamic (PK/PD) index (Roberts et al., 2011). Thus, we aimed to determine the pharmacodynamics of tigecycline by assessing its MIC. Furthermore, we attempted to develop a potential regimen including a high tigecycline dosage to achieve PK/PD targets using probability target of attainment (PTA) and cumulative fraction of response (CFR) for treatment of CRE in critically ill patients.

2. MATERIALS AND METHODS

2.1 Bacterial strains

Clinical CRE strains were isolated from patients who were admitted to Phramongkutklao Hospital, which is a 1200-bed university hospital located in Bangkok, Thailand, during the October 2017 to October 2018 period. CRE isolates were not susceptible to at least one of the carbapenems (imipenem, meropenem, or doripenem), according to the criteria of CRE from the Clinical and Laboratory Standards Institute (2018). *Proteus mirabilis* and indole-positive proteae strains were not included because of an intrinsically high MIC (Pfaller et al., 2018). All clinical isolates of CRE were firstly obtained from blood specimens from each patient. The institutional review board approved the research protocol with a waiver for informed consent [No. Q003b/62 Exp].

2.2 Determination of minimum inhibitory concentration

The MIC of tigecycline was assayed by automated

susceptibility testing (Thermo Scientific™ Sensititre™ ARIS™ 2X Instrument) based on the broth microdilution method (Chew et al., 2017). The MIC of tigecycline in each strain was interpreted as the number of susceptible isolates, MIC50, MIC90, and MIC range. Because no CLSI breakpoints are available for tigecycline, the Food and Drug Administration (FDA) breakpoints (≤2 μg/mL) were applied in this study.

2.3 Monte Carlo simulation

The pharmacokinetic parameters of critically ill patients were obtained from previous studies reported by Borsuk-De Moor et al. (2018). The concentration versus time in each patient was simulated based on a two-compartment model with the mean of PK parameters (% coefficient of variation; % CV); tigecycline clearance, 22.1 (17.3%); volume of distribution of the central compartment, 162 (19.2%); volume of distribution of the peripheral compartment, 87.9 (38.7%); and intercompartmental clearance, 69.4 (fixed at 0%) (Borsuk-De Moor et al., 2018).

The PK/PD investigation was simulated by replication of 10,000 subjects by Monte Carlo Simulation (Oracle Crystal Ball version 201).

The PK/PD properties of tigecycline were represented by the area under the curve from 0 to 24 h divided by the MIC (AUIC). The optimal PK/PD targets for pneumonia (Xu et al., 2019) and intra-abdominal infections (Passarell et al., 2008) were defined as an AUIC ≥10.1 and ≥6.9, respectively. Dosage simulations were performed using various dosages per day and different dosage intervals.

PTA was defined by the manner in which a studied regimen reached the AUIC targets, whereas CFR was the probability of the tigecycline dosage covering the MIC of tigecycline among the CRE isolates obtained from patients (Asín-Prieto et al., 2015). Dosage regimens that reached a PTA and CFR >90% were considered to be the optimal dosage against CRE infections.

3. RESULTS

3.1 Determination of the MIC of the CRE isolates

During the study period, 61 clinical non-repeated strains of CRE obtained from blood cultures were collected. The CRE isolates included 51 isolates of *Klebsiella pneumoniae*, seven isolates of *Escherichia coli*, and three isolates of *Enterobacter* spp.

The MIC50, MIC90, and MIC range for tigecycline against the 61 CRE isolates were 0.5, 1.0, and ≤0.25-4.0 μg/mL, respectively. Among all the isolates studied here, 96.7% were susceptible to tigecycline (Figure 1).

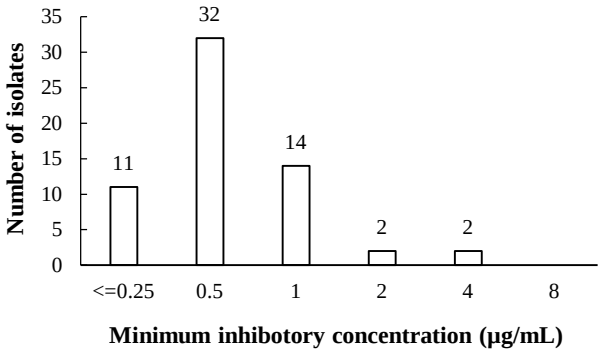

Figure 1 Minimum inhibitory concentration (MIC) of tigecycline against the carbapenem-resistant *Enterobacteriaceae* isolates studied here

3.2 Probability target of attainment

The PTA values for the different tigecycline regimens at specific MICs with AUIC targets of ≥10.1 and ≥6.9 are listed in Table 1. Among critically ill patients who needed AUIC ≥10.1, the loading dose of 150-200 mg with a maintenance dose of 150-200 mg/day alone achieved the PTA target for isolates with a MIC up to 0.5 μg/mL. However, a tigecycline loading dose of 200 mg followed by a maintenance dose of 200 mg/day, which covered isolates with a tigecycline MIC of 1.0 μg/mL, met the PTA at AUIC ≥6.9. None of the tigecycline dosage regimens reached the PTA target for CRE isolates with a MIC ≥2 μg/mL.

Table 1 The probability of target attainment (PTA) for different tigecycline doses at specific MICs, with targets of AUIC at ≥10.1 and ≥6.9

AUIC target	Loading dose	Maintain dose	PTA (%) in each tigecycline MIC					
			0.25	**0.5**	**1**	**2**	**4**	**8**
≥10.1	100 mg	50 mg q 12 h	99.99	28.61	0	0	0	0
	200 mg	100 mg q 24 h	99.99	30.13	0	0	0	0
	150 mg	75 mg q 12 h	100	96.51	1.33	0	0	0
	150 mg	150 mg q 24 h	100	96.84	1.62	0	0	0
	200 mg	100 mg q 12 h	100	99.97	28.85	0	0	0
	200 mg	200 mg q 24 h	100	100	30.67	0	0	0
≥6.9	100 mg	50 mg q 12 h	100	95.2	0.93	0	0	0
	200 mg	100 mg q 24 h	100	95.4	1.28	0	0	0
	150 mg	75 mg q 12 h	100	100	50	0	0	0
	150 mg	150 mg q 24 h	100	100	50.54	0.01	0	0
	200 mg	100 mg q 12 h	100	100	95.43	0.96	0	0
	200 mg	200 mg q 24 h	100	100	95.61	0.26	0	0

3.3 Cumulative fraction of response

Using a CFR >90% for AUIC ≥6.9, only two tigecycline regimens met the targets: a loading dose of 200 mg with a maintenance dose of either 100 mg every 12 h or 200 mg every 24 h (Table 2). However, none of the tigecycline regimens studied here gave a CFR >90% for an AUIC target ≥10.1.

Table 2 Cumulative fraction of response of tigecycline with targets of AUIC among various drug regimens

Loading dose	Maintain dose	Cumulative fraction of response (%)	
		at AUIC ≥ 10.1	**at AUIC ≥ 6.9**
100 mg	50 mg q 12 h	33.04	68.19
200 mg	100 mg q 24 h	33.84	68.37
150 mg	75 mg q 12 h	68.97	81.97
150 mg	150 mg q 24 h	69.21	82.09
200 mg	100 mg q 12 h	77.10	92.43
200 mg	200 mg q 24 h	77.53	92.48

4. DISCUSSION

Carbapenems remain the antibiotics of choice to treat multidrug-resistant gram-negative bacteria, especially ESBL or AmpC-producing *Enterobacteriaceae* Nevertheless, the development of resistance is mediated by carbapenemase production or porin loss associated with ESBL or AmpC expression. Therefore, tigecycline is currently defined as a drug of last resort against CRE (Kaewpoowat and Ostrosky-Zeichner, 2015) and carbapenem or colistin resistant *A. baumannii*

(Lertsrisatit et al., 2017).

We found that the MIC50 and MIC90 values and the susceptible rate of tigecycline against CRE were 0.5 μg/mL, 1.0 μg/mL, and 96.7%, respectively. Pfaller et al. (2018) collected several CRE isolates from Thailand and showed that the composite values of MIC50/MIC90 from various parts of the Asia/Pacific region were 0.5/2.0 μg/mL, with a susceptible rate of 93.1%. Recently, Prawang et al. (2019) revealed that the MIC50/MIC90 value of carbapenem-resistant *Klebsiella pneumoniae* isolates with colistin resistance was 1/1 μg/mL, with a susceptible rate of 100%. Thus, the MIC50/MIC90 and susceptible rate obtained in the present study were similar to those reported previously.

The pharmacokinetic properties of tigecycline indicate that it has a large volume of distribution, which assures good penetration into different tissues, e.g., the biliary tract system, colon, and skin/soft tissue. Unfortunately, suboptimal tigecycline concentrations have been detected in the serum and pulmonary epithelial lining fluid (Giamarellou and Poulakou, 2011). This unfavorable tigecycline level was evident in a previous meta-analysis indicating that the presence of baseline bacteremia, especially among patients with ventilator-associated pneumonia, was a significant factor for mortality (McGovern et al., 2013). However, the lack of therapeutic choices in the antimicrobial resistance era has prompted clinicians to use either high-dose tigecycline or combination therapy to treat CRE infections.

Our findings revealed that only high-dose tigecycline regimens, such as a loading dose of 150-200 mg with a maintenance dose of 150-200 mg/day, reached the PTA target for isolates with a MIC of 0.5 μg/mL. Moreover, only tigecycline regimens consisting of a loading dose of 200 mg with a maintenance dose of 200 mg/day met a CFR >90% for an AUIC target ≥6.9. Thus, based on our simulated PK/PD profile, high-dose tigecycline therapy is important for the treatment of CRE infections.

The benefits of high-dose tigecycline for the treatment of CRE were evidenced previously. Ni et al. (2016) performed a meta-analysis to evaluate the benefit of high-dose tigecycline regimens in treating CRE infections. The ICU mortality rate was significantly lower in patients who were treated with high-dose tigecycline regimens. Similarly, a retrospective study of the ventilation-associated pneumonia (VAP) group reported by De Pascale et al. (2014) showed that treatment using a high tigecycline dosage regimen (100 mg every 12 h) was a significant factor for the clinical cure of this disease.

Generally, CRE treatment requires the use of antibiotic combinations to improve clinical outcomes (Ni et al., 2016). In particular, our simulated PK/PD profile showed that only high-dose tigecycline could reach the AUIC target of ≥6.9 with the exception of ≥10.1. Thus, the beneficial synergism of a tigecycline combination, such as imipenem-tigecycline or tigecycline-colistin (Dundar et al., 2018), might be necessary to increase PTA and CFR targets by reducing the tigecycline MIC against CRE isolates.

Our study had several limitations. First, this was the first report of tigecycline susceptibility in Thailand. However, the CRE isolates were from a university hospital, which might be dissimilar from other types of medical settings. Second, based on current knowledge, our tigecycline simulation used the two AUIC targets of CRE for pneumonia and intra-abdominal infections; thus, the suggested tigecycline regimens to treat infections of other organs remain debatable. The AUIC targets of either ≥10.1 or ≥6.9 for pneumonia and intra-abdominal infection, respectively, were based on gram-positive and gram-negative bacteria that were not specified as CRE isolates. The determination of the best tigecycline PK/PD index for CRE infection warrants further examination. Last, this study only suggested the probable dose of tigecycline that is necessary to achieve the PKPD index. Prospective

clinical studies are needed to determine the clinical outcomes and assess the safety profile of high-dosage regimens.

5. CONCLUSION

Our study showed that tigecycline might be a potential therapeutic option for CRE infection. However, only one PK/PD target with AUIC ≥6.9 was identified; tigecycline may be optimized for use at a dosage as high as 200 mg daily, to cover CRE isolates with a MIC ≤1 μg/mL.

REFERENCES

Asín-Prieto, E., Rodríguez-Gascón, A., and Isla, A. (2015). Applications of the pharmacokinetic/ pharmacodynamic (PK/PD) analysis of antimicrobial agents. *Journal of Infection and Chemotherapy*, 21(5), 319-329.

Borsuk-De Moor, A., Rypulak, E., Potrec, B., Piwowarczyk, P., Borys, M., Sysiak, J., Onichimowski, D., Raszewski, G., Czuczwar, M., and Wiczling, P. (2018). Population pharmacokinetics of high-dose tigecycline in patients with sepsis or septic shock. *Antimicrobial Agents and Chemotherapy*, 62(4), e02273-17.

Chew, K. L., La, M. V., Lin, R. T. P., and Teo, J. W. P. (2017). Colistin and polymyxin B susceptibility testing for carbapenem-resistant and *mcr*-positive *Enterobacteriaceae*: Comparison of sensititre, MicroScan, Vitek 2, and Etest with broth microdilution. *Journal of Clinical Microbiology*, 55(9), 2609-2616.

Clinical and Laboratory Standards Institute. (2018). *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Eight Informational Supplement*. Pennsylvania: Clinical and Laboratory Standards Institute (CLSI).

De Pascale, G., Montini, L., Pennisi, M., Bernini, V., Maviglia, R., Bello, G., Spanu, T., Tumbarello, M., and Antonelli, M. (2014). High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. *Critical Care*, 18(3), R90.

Dundar, D., Duymaz, Z., Genc, S., Er, D. K., Irvem, A., and Kandemir, N. (2018). *In-vitro* activities of imipenem-colistin, imipenem-tigecycline, and tigecycline-colistin combinations against carbapenem-resistant *Enterobacteriaceae*. *Journal of Chemotherapy*, 30(6-8), 342-347.

Falagas, M. E., Tansarli, G. S., Karageorgopoulos, D. E., and Vardakas, K. Z. (2014). Deaths attributable to carbapenem-resistant *Enterobacteriaceae* infections. *Emerging Infectious Diseases*, 20(7), 1170-1175.

Geng, T. T., Xu, X., and Huang, M. (2018). High-dose tigecycline for the treatment of nosocomial carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: A retrospective cohort study. *Medicine (Baltimore)*, 97(8), e9961.

Giamarellou, H., and Poulakou, G. (2011). Pharmacokinetic and pharmacodynamic evaluation of tigecycline. *Expert Opinion on Drug Metabolism & Toxicology*, 7(11), 1459-1470.

Kaewpoowat, Q., and Ostrosky-Zeichner, L. (2015). Tigecycline: A critical safety review. *Expert Opinion on Drug Safety*, 14(2), 335-342.

Lertsrisatit, Y., Santimaleeworagun, W., Thunyaharn, S., and Traipattanakul, J. (2017). In vitro activity of colistin mono and combination therapy against colistin-resistant *Acinetobacter baumannii*, mechanism of resistance, and clinical outcomes of patients infected with colistin-resistant *A. baumannii* at a Thai university hospital. *Infection and Drug Resistance*, 10, 437-443.

McGovern, P. C., Wible, M., El-Tahtawy, A., Biswas, P., and Meyer, R. D. (2013). All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials. *International Journal of Antimicrobial Agents*, 41(5), 463-467

Ni, W., Han, Y., Liu, J., Wei, C., Zhao, J., Cui, J., Wang, R., and Liu, Y. (2016). Tigecycline treatment for carbapenem-resistant *Enterobacteriaceae* infections: A systematic review and meta-analysis. *Medicine (Baltimore)*, 95(11), e3126.

Passarell, J. A., Meagher, A. K., Liolios, K., Cirincione, B. B., Van Wart, S. A., Babinchak, T., Ellis-Grosse, E. J., and Ambrose, P. G. (2008). Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. *Antimicrobial Agents and Chemotherapy*, 52(1), 204-210.

Pfaller, M. A., Huband, M. D., Streit, J. M., Flamm, R. K., and Sader, H. S. (2018). Surveillance of tigecycline activity tested against clinical isolates from a global (North America, Europe, Latin America and Asia-Pacific) collection (2016). *International Journal of Antimicrobial Agents*, 51(6), 848-853.

Prawang, A., Santimaleeworagun, W., Changpradub, D., Thunyaharn, S., and Puttilerpong, C. (2019). *In vitro* antibiotic synergy colistin-resistant *Klebsiella pneumoniae*. *The Southeast Asian Journal of Tropical Medicine and Public Health*, 50(4), 703-707. [in Thai]

Roberts, J. A., Kirkpatrick, C. M., and Lipman, J. (2011). Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. *Journal of Antimicrobial Chemotherapy*, 66(2), 227-231.

Sheu, C. C., Chang, Y. T., Lin, S. Y., Chen, Y. H., and Hsueh, P. R. (2019). Infections caused by carbapenem-resistant *Enterobacteriaceae*: An update on therapeutic options. *Frontiers in Microbiology*, 10, 80.

World Health Organization. (2017). WHO publishes list of bacteria for which new antibiotics are urgently needed. [Online URL:http://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed] accessed on April 17, 2019.

Xie, J, Roberts, J. A., Alobaid, A. S., Roger, C., Wang, Y., Yang, Q., Sun, J., Dong, H., Wang, X., Xing, J., Lipman, J., and Dong, Y. (2017). Population pharmacokinetics of tigecycline in critically ill patients with severe infections. *Antimicrobial Agents and Chemotherapy*, 61(8), e00345-17.

Xu, Y., Jin, L., Liu, N., Luo, X., Dong, D., Tang, J., Tang, J., Wang, Y., You, Y., Liu, Y., Chen, M., Yu, Z., Hao, Y., and Gu, Q. (2019). Evaluation of the ratio of the estimated area under the concentration-time curve to minimum inhibitory concentration (estimated AUIC) as a predictor of the outcome for tigecycline treatment for pneumonia due to multidrug-resistant bacteria in an intensive care unit. *International Journal of Antimicrobial Agents*, 82, 79-85.