Using Monte Carlo Simulation to Evaluate Tigecycline Dosing Strategies for Bacteria with Raised Minimum Inhibitory Concentrations in Non-Critically Ill Patients

Brianna Kispal,[1,2] Pharmacy Student; Sandra A.N. Walker,[1,2*] BSc, BScPhm, ACPR, PharmD, FCSHP
[1]Sunnybrook Health Sciences Centre (SHSC), Department of Pharmacy Bayview Campus; [2]University of Toronto, Leslie Dan Faculty of Pharmacy
Underlined Author: Pharmacy student working under supervision of Sandra Walker at time of study; *Senior Author

BACKGROUND

- Worldwide, more than 700,000 patients die annually from infections caused by multi-drug resistant (MDR) pathogens (resistance to 3 or more potentially useful antibiotics), with millions more suffering from serious complications
- By 2050, it is estimated that 10 million patients will die annually as a consequence of antimicrobial resistance; a number which will surpass deaths due to cancer, diabetes, and automobile accidents
- *Acinetobacter baumannii* is one of the critical priority bacteria identified by the World Health Organization for which optimal antibiotic therapy is lacking and tigecycline may be an option for treatment
- Clinicians are often confronted with the challenge of appropriately choosing and dosing antibiotics for extensive drug-resistant pathogens based on limited clinical data and/or significant toxic effects, while trying to meet the pharmacokinetic-pharmacodynamic (PK-PD) targets that maximize bacterial killing and clinical cure
- Monte Carlo Simulation (MCS) is a recognized method for evaluating the probability of success with different antibiotic dosing strategies; where known PK-PD targets associated with improved clinical and microbiological outcomes are input as the surrogate marker for success
- With resistance to currently available antibiotics increasing, clinicians are forced to treat highly-resistant infections with relatively ineffective and/or toxic second-line agents, such as tigecycline or polymyxins

OBJECTIVE

To use MCS to evaluate different potential tigecycline dosing strategies to determine if safe dosing options could be identified that would attain practical numerical PK-PD target breakpoints for tigecycline ($AUC_{total,\ 0\text{-}24h}$ /MIC ≥ 4.5, 7, or 18) in normal volunteer and ward patients who were not on any dialysis mode, and did not have end-stage renal disease (ESRD) or hepatic dysfunction.

METHODS

Data Collection

- Medline (Ovid; 1946 – December 31, 2018) was conducted using the terms "tigecycline," "pharmacokinetic," "adult," and "human" to identify tigecycline pharmacokinetic (PK) and pharmacodynamic (PD) parameters (Figure 1)
- Studies were included if they evaluated clinically relevant tigecycline dosing regimens and provided mean PK variables of interest (at minimum 2 of: elimination rate constant (k^{-1}) or half-life ($t_{1/2}$), and volume of distribution (V_d) or clearance (CL)), with corresponding standard deviations (SD)
- Means and SDs for relevant PK parameters (k^{-1}, $t_{1/2}$, V_d, CL, and $AUC_{total,\ 0\text{-}24h}$) were extracted from eligible studies, and weighted mean and weighted SDs for each parameter were determined

Data Analysis

- Since there are no Clinical and Laboratory Standards Institute (CLSI) *Acinetobacter spp.* MIC breakpoints for tigecycline, CLSI recommends that the Food and Drug Administration breakpoints for susceptible (MIC ≤ 2 µg/mL), intermediate (MIC 4 µg/mL), and resistant (MIC ≥ 8 µg/mL) Enterobacteriaceae be used
- The weighted mean PK parameters from the eligible studies and a range of MICs were input to perform MCSs (Crystal Ball v11.1.2.4.000). MCS probability distributions (1 million iterations) for PK-PD target attainments of $AUC_{total,\ 0\text{-}24h}$/MIC ratios of ≥ 4.5, 7 and 18 and the number of times the steady state concentration (Css) was above the MIC were generated for several tigecycline dosing strategies
- The MCS inputs were a log-normal distribution for the weighted means of the one compartment model tigecycline k^{-1} ± SD and V_d ± SD, a normal distribution of the weighted mean ± SD for patient weight, and MIC inputs ranging from 0.06 to 18µg/mL
- MCS probability distributions for the PK-PD targets were determined for intermittent infusion dosing regimens of 50mg IV q12h, 75mg IV q12h, 100mg IV q12h, 125mg IV q12h, and 150mg IV q12h infused over 0.5 hours, and continuous infusion dosing regimens of 100mg and 300mg IV q24h infused over 24 hours
- A potentially successful regimen was defined as one in which the probability of attaining the target $AUC_{total,\ 0\text{-}24h}$/MIC was at least 80% at a given MIC for ward patients who were not on any dialysis mode and did not have ESRD or hepatic dysfunction

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Disclosure: No author has any conflict of interest related to this study.

RESULTS

Figure 1. Study Selection

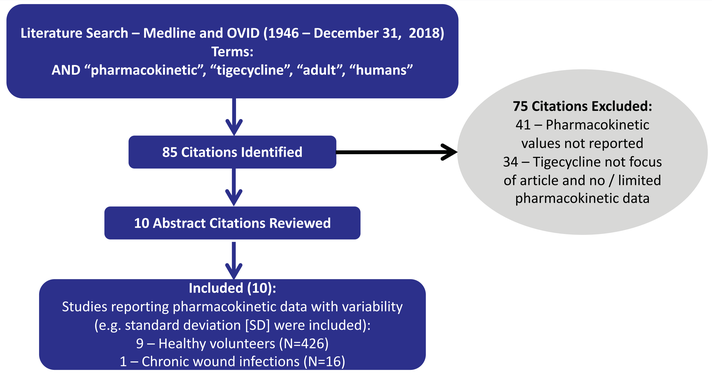
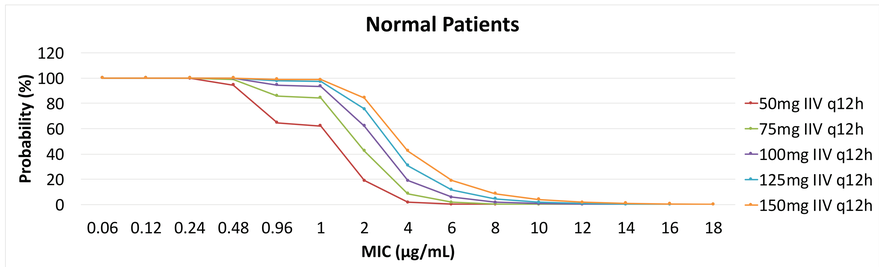


Table 1. Summarized Weighted Results

Parameter	Healthy Subjects (N=442, # studies = 10)
Patient weight kg (n=199)	80.37 ± 7.11
Elimination rate constant (k) hr^{-1} (n=397)	0.0296 ± 0.0150
Volume of distribution (V_d) L/kg (n=307)	8.70 ± 3.44
Clearance (CL) L/hr/kg (n=307)	0.29 ± 0.06
Biliary Excretion (%) (n=12)	58.60 ± 0.04
Urinary Excretion (%) (n=44)	20.25 ± 0.03
Pharmacokinetic Parameters for Multiple Dose Tigecycline 50mg iv q12h (N=171, # studies = 6)*	
Peak concentration ($C_{max,ss}$) mg/L (n=163)	3.40 ± 5.61
Trough concentration ($C_{min,ss}$) mg/L (n=60)	3.25 ± 3.15
Peak time (T_{max}) hr (n=110)	2.46 ± 2.25
Mean Area Under the Concentration Curve ($AUC_{total,\ 0\text{-}24h}$) mg*hr/L (n=144)	59.77 ± 106.83

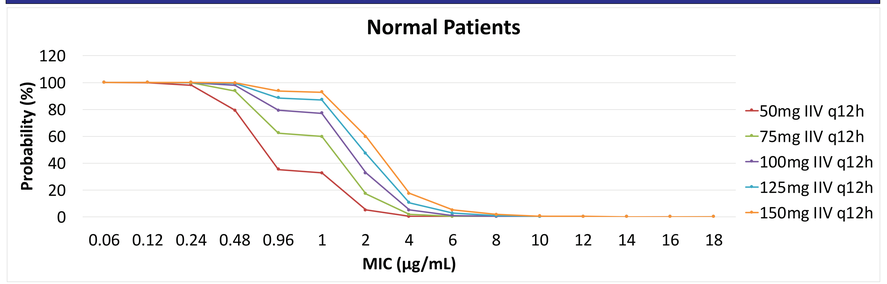
* Data reflect total plasma or serum concentrations

Figure 2. Probability of $AUC_{total,\ 0\text{-}24h}$ /MIC target attainment of at least 4.5 relative to MIC with a variety of Tigecycline intermittent infusion dosing regimens



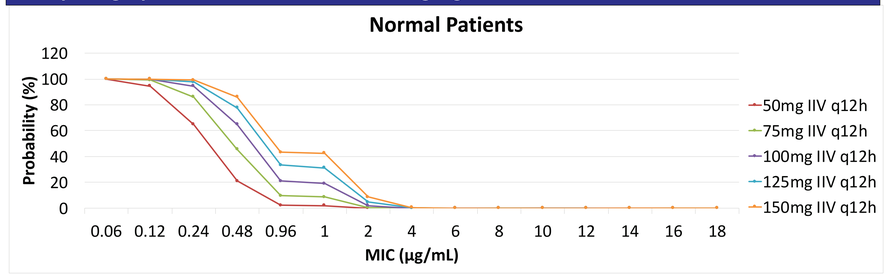
$AUC_{total,\ 0\text{-}24h}$, area under the total tigecycline concentration time profile from 0 to 24 hours
IIV, intermittent infusion over 0.5h
MIC, minimum inhibitory concentration

Figure 3. Probability of $AUC_{total,\ 0\text{-}24h}$ /MIC target attainment of at least 7 relative to MIC with a variety of Tigecycline intermittent infusion dosing regimens



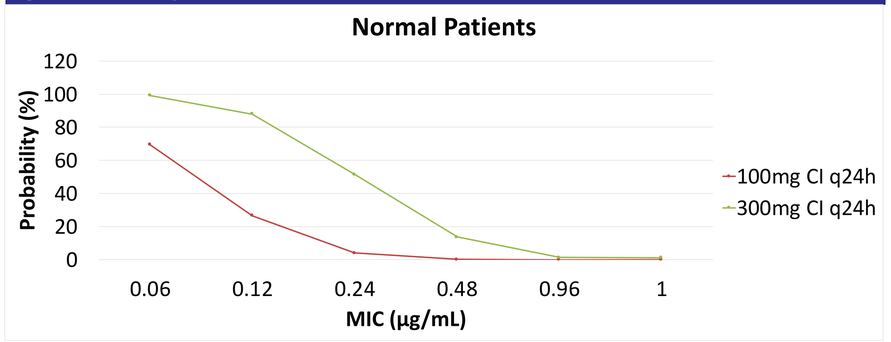
$AUC_{total,\ 0\text{-}24h}$, area under the total tigecycline concentration time profile from 0 to 24 hours
IIV, intermittent infusion over 0.5h
MIC, minimum inhibitory concentration

Figure 4. Probability of $AUC_{total,\ 0\text{-}24h}$ /MIC target attainment of at least 18 relative to MIC with a variety of Tigecycline intermittent infusion dosing regimens



$AUC_{total,\ 0\text{-}24h}$, area under the total tigecycline concentration time profile from 0 to 24 hours
IIV, intermittent infusion over 0.5h
MIC, minimum inhibitory concentration

Figure 5. Probability the Css is at least 3 times above the MIC



CI, continuous infusion without a loading dose; Css, steady state concentration; MIC, minimum inhibitory concentration

DISCUSSION and CONCLUSION

- Intermittent infusion tigecycline 150mg IV q12h for ward patients with resistant gram-negative bacteria up to a MIC of 0.48µg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 18, up to a MIC of 1µg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 7, and up to a MIC of 2µg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 4.5 may be appropriate

Limitations:

- Findings may not be generalizable to other patient populations
- Interpatient pharmacokinetic variability may increase the risk of error in calculated weighted PK values
- North American data were used to estimate encountered *Acinetobacter spp.* in institutions
- To conclude, resistant gram-negative bacteria infections that are associated with a tigecycline MIC ≥ 0.48µg/mL may require treatment with alternate antibiotics, based on failure to attain PK-PD tigecycline targets