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Optimal tigecycline dosage regimen is urgently needed: results from a pharmacokinetic/pharmacodynamic analysis of tigecycline by Monte Carlo simulation

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SUMMARY

Background: The number of reported cases of resistance to tigecycline is increasing. The aim of this study was to evaluate the current standard tigecycline dosage regimen from a pharmacokinetic/pharmacodynamic (PK/PD) perspective.
Methods: Pharmacokinetic parameters and microbiological data were analyzed by Monte Carlo simulation in an evaluation of effectiveness.
Results: Tigecycline exhibits excellent in vitro antimicrobial activity, however the standard tigecycline dosing regimen fails to achieve the best outcome in vivo for the common drug-resistant strains, including *Acinetobacter baumannii*, *Enterobacter spp*, and *Klebsiella pneumoniae*. This may result in a lack of response to tigecycline therapy or to a further increase in the resistance rate.
Conclusions: In the absence of new drugs on the horizon, rather than using a single fixed dosing regimen, tigecycline dosing needs to be optimized in order to achieve the desired successful clinical response and to prevent an escalation in drug resistance.

1. Introduction

Tigecycline, a novel intravenously administered glycylcycline antibiotic, was approved for the treatment of complicated intra-abdominal infections (cIAI) and complicated skin and skin-structure infections (cSSSI) in 2005 by the US Food and Drug Administration (FDA). This antibiotic has demonstrated an expanded spectrum of in vitro activity and clinical potency against Gram-positive and Gram-negative aerobic and anaerobic bacteria, as well as against antibiotic-resistant strains.[1–4] Tigecycline is also indicated for the treatment of community-acquired bacterial pneumonia.[5] More importantly, Kumarasamy et al.[6] have reported the presence of New Delhi metallo-β-lactamase 1 (NDM-1) among Gram-negative bacteria, and these bacteria are highly resistant to all antibiotics except tigecycline and colistin. Tigecycline has been regarded as the last resort to treat multidrug-resistant (MDR) bacteria and remains one of the important tools in the management of difficult-to-treat infections.

However, several failures of tigecycline therapy have occurred in recent years, as has been seen in ventilator-associated bacterial pneumonia (VAP) and other bacterial infections. These failures are likely due to the development of tigecycline resistance and perhaps to inadequate dosing. Since 2007, clinical resistance to tigecycline has been reported in many pathogens, including *Acinetobacter spp*, *Klebsiella spp*, *Enterobacter spp*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Serratia marcescens*, and the prevalence of tigecycline resistance has been found to vary worldwide over the years.[7–18] Thus, the use of the only constant tigecycline dosage regimen against a wide range of bacteria with variable minimum inhibitory concentrations (MIC) may be ineffective and lead to a further increase in antibiotic-resistant strains. (The standard, common dosage regimen for tigecycline for all of these pathogenic organisms is a 100-mg loading dose, followed by 50 mg every12 h for at least 5 days and not more than 14 days.[19])

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Therefore, a pharmacokinetic/pharmacodynamic (PK/PD) evaluation of the magnitude of efficacy of the empirical tigecycline dosage regimen for polymicrobial infections is needed. In a model of murine *Acinetobacter baumannii* pneumonia, tigecycline efficacy was predicted successfully by the relationship between the area under the free concentration–time curve and the MIC (*f*AUC/MIC).[20] In this study, the ratio of the 24-h area under the concentration–time curve and the MIC ($AUC_{(0-24)}$/MIC) was chosen as the PK/PD index for tigecycline, as this index is considered the most likely to be predictive of efficacy.[21]

In the present study, a Monte Carlo simulation was used to calculate the probability of attaining targeted pharmacodynamic exposure against a wide range of isolates with variable MICs from cIAI and cSSSI patients to evaluate the efficacy of the commonly used tigecycline dosage regimen from a PK/PD perspective. Based on this, we also compared different therapeutic schemes of tigecycline to investigate whether the standard dosage regimen achieves the optimal treatment.

2. Methods

The methodology included: (1) acquisition of pharmacokinetic parameters and microbiological information, (2) Monte Carlo simulation, and (3) forming an estimate of the probability of target attainment (PTA, defined as the probability that at least a specific value of a PK/PD index is achieved at a certain MIC) and calculation of the cumulative fraction of response (CFR, defined as the expected population probability of target attainment for a specific drug dose and a specific population of microorganisms).[22,23]

2.1. Pharmacokinetic parameters and microbiological information

The pharmacokinetic parameters of tigecycline were obtained from published studies.[24] The phase 1 studies were randomized, double-blind, single-center, and placebo-controlled. Pharmacokinetic studies were identified using the PubMed NLM search engine for the MEDLINE database. Studies were included if they evaluated clinically relevant dosing regimens and provided the means for the pharmacokinetic parameters of interest with the corresponding variability.

In this work, pathogens in the cSSSI and cIAI patient populations were selected for analysis. Gram-positive pathogens isolated from the infection site of patients with cIAI and cSSSI included *S. aureus*, streptococci, and *Enterococcus spp*, among which *S. aureus* and streptococci were the predominant pathogens for cSSSI.[25] In addition, the isolated pathogenic Gram-negative and anaerobic bacteria included *A. baumannii*, *Citrobacter spp*, *Enterobacter spp*, *Escherichia coli*, *Klebsiella spp*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Shigella dysenteriae*, *S. marcescens*, and *Bacteroides fragilis*. The predominant pathogens for cIAI were *E. coli* and *B. fragilis*.[26] The MIC distributions of the selected Gram-positive and Gram-negative bacteria isolates were those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). According to EUCAST, the tigecycline MICs for these pathogens are mainly distributed between 0.004 and 16 mg/l. Data were obtained from the EUCAST MIC distribution website (http://www.eucast.org, last accessed April 10, 2013). The distributions are based on collated data from a total of more than 24 000 MIC distributions from worldwide sources. The distributions include MICs from national and international studies, including resistance surveillance programs (Alexander, BSAC, ECO-SENS, MYSTIC, NORM, and SENTRY), as well as MIC distributions from published articles, the pharmaceutical industry, veterinary programs, and individual laboratories. EUCAST interpretive breakpoints were used for evaluation of the efficacy of tigecycline.[27]

2.2. Monte Carlo simulation

The pharmacokinetic parameters were defined as the lognormal distribution obtained with a mean and a percentage coefficient of variance (CV%); in the case of the MIC, a discrete distribution ranging from 0.004 to 64 mg/l based on reported data was considered according to statistical criteria. A Monte Carlo

Table 1
Frequency distribution of tigecycline MICs for the selected Gram-positive and Gram-negative and anaerobic pathogens from the EUCAST MIC distribution website

		MIC (mg/l)													Susceptibility breakpoint (mg/l)
	n	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	
Gram-positive pathogens															
Staphylococcus aureus	1363				0.37	33.16	49.60	15.77	0.81	0.22	0.07				≤0.5, EUCAST
MRSA	286						9.09	76.22	14.34	0.35					≤0.5, FDA
Streptococcus agalactiae	308			10.06	18.83	18.18	49.03	3.90							≤0.25, EUCAST
Streptococcus anginosus	244		0.41	1.64	3.28	69.67	21.31	3.28	0.41						N/A
Streptococcus constellatus	97			1.03	3.09	86.60	7.22		2.06						N/A
Streptococcus pyogenes	419			16.23	16.23	52.27	14.32	0.72	0.24						≤0.25, EUCAST
Streptococcus intermedius	26	3.85	3.85		30.77	34.62	15.38	3.85	3.85	3.85					N/A
Enterococcus faecalis	1150			0.26	9.74	44.52	30.96	14.00	0.52						≤0.25, EUCAST
Enterococcus faecium	799			0.63	19.90	55.69	20.53	3.00	0.13	0.13					≤0.25, EUCAST
Gram-negative pathogens															
Escherichia coli	4237					2.08	31.65	46.50	15.55	3.42	0.52	0.19	0.07	0.02	≤1.0, EUCAST
Acinetobacter baumannii	299				0.67	8.03	11.37	17.06	21.07	20.74	17.06	4.01			≤2.0, FDA
Citrobacter freundii	215				2.79	1.40	11.16	46.05	26.05	8.84	2.79		0.93		≤1.0, EUCAST
Citrobacter koseri	203					0.99	18.72	60.59	17.73	1.48	0.49				≤1.0, EUCAST
Enterobacter cloacae	894						0.34	10.96	52.01	26.96	5.70	2.13	1.68	0.22	≤1.0, EUCAST
Klebsiella oxytoca	613						5.22	45.02	41.76	5.55	1.63	0.82			≤1.0, EUCAST
Klebsiella pneumoniae	1856					0.05	0.92	14.87	49.62	23.11	7.76	3.23	0.32	0.11	≤1.0, EUCAST
Proteus mirabilis	1197						0.17	0.33	2.26	17.71	28.74	36.93	13.62	0.25	N/A
Pseudomonas aeruginosa	944						0.11	0.53	0.85	1.69	2.22	12.39	38.98	43.22	N/A
Shigella dysenteriae	159					3.14	35.22	47.17	11.32	2.52	0.63				N/A
Serratia marcescens	257							1.56	21.40	63.81	11.28	1.17	0.78		≤1.0, EUCAST
Anaerobic pathogen															
Bacteroides fragilis	1663			0.18	0.12	6.37	5.05	13.89	19.36	24.53	18.64	4.75	4.03	3.07	≤4.0, FDA

MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*; N/A, not available.