A pharmacodynamic simulation to evaluate tigecycline in treatment of nosocomial pneumonia caused by multidrug-resistant *Acinetobacter baumannii*

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Abstract: The shortage of effective antibiotics against multidrug-resistant *Acinetobacter baumannii* (MDR-Ab) has posed great threat to the public health. But the advent of tigecycline gives us new hope. The goal of our research was to assess the clinical efficacy of tigecycline at different doses by using a pharmacokinetic/pharmacodynamic (PK/PD) model which can incorporate pharmacokinetic data of tigecycline from patients with pneumonia and MICs of MDR-Ab from a tertiary hospital. A 10000-patient Monte-Carlo Simulation based on the PK/PD model was conducted to calculate the probability of target attainment (PTA) and the cumulative fraction of response (CFR) of tigecycline. 97% isolates displayed susceptibility and 3% were tigecycline-intermediate strains and the values of MIC ranged from 0.125 to 4μg/ml. A CFR of 61.62% was predicted for tigecycline at current dosage (50 mg q12h). When the dosage was increased, the predicted CFRs for 75 mg q12h, 100 mg q12h, 125 mg q12h, 150 mg q12h were 81.00%, 89.86%, and 94.57%, 96.77%, respectively. Despite presented higher susceptibility, the CFR obtained was not optimal at current dosage. A higher CFR indicating a better clinical efficacy can be gained by the increased dosage.

Keywords: *Acinetobacter baumannii*, bacteria resistance, tigecycline, pharmacology, pneumonia.

INTRODUCTION

Acinetobacter baumannii, a non-fermentative Gram-negative bacillus, has emerged as a major cause of nosocomial infection (Towner, 2009). It has remarkable ability to develop resistance against all available antibiotic classes and the occurrence of outbreaks caused by multidrug resistant *A. baumannii* (MDR-Ab) has been continuously reported (Perez *et al*., 2007). In Asia, it was responsible for 13.6% of nosocomial pneumonia and nearly 82% strains were MDR-Ab (Chung *et al*., 2011). Colistin has been considered as a last resort for dealing with these organisms, but the increasing resistance rate and significant nephrotoxicity and neurotoxicity limit its wider application (Cai *et al*., 2012; Spapen *et al*., 2012).

The advent of tigecycline which has appealing in vitro activity against MDR or extensive drug-resistant (XDR) Gram-negatives gives us new hope (Rose and Rybak, 2006; Cheng *et al*., 2005). The Food and Drug Administration (FDA) has approved it in treatment of complicated intra-abdominal infections, complicated skin and soft tissue infections, and community-acquired bacterial pneumonia. It is also frequently prescribed in nosocomial pneumonia, bacteremia and sepsis/septic shock caused by MDR-pathogens because of lacking other active and safety antimicrobial agents (Giamarellou and Poulakou, 2009; Gamarellou, 2010). However, some questions and concerns of these off-label uses such as dosage of the drug, low concentrations in serum and epithelial lining fluid (ELF) still remains unsettled (Arnold *et al*., 2011).

Therefore, a comprehensive assessment of tigecycline is paramount for guiding rational uses, especially from the pharmacokinetic (PK) and pharmacodynamic (PD) points (Cooper *et al*., 2011). Monte-Carlo simulation, a stochastic analysis incorporating the PK and PD parameters can evaluate the clinical/microbiological response of a certain antibiotics with high rationality and accuracy prior to multiple studies in the same population and money can be saved by generating the similar data (Kuti *et al*., 2008). Further to this, the outputs of simulations are relatively easier to understand than complex PK equations generated as part of the PK modelling process (Roberts *et al*., 2011). In our study, by utilizing this PK/PD simulation, we evaluated the clinical performance of tigecycline at different doses against MDR-Ab caused nosocomial pneumonia and tried optimizing its clinical dosage.

MATERIALS AND METHODS

Microbiology

135 non-duplicate clinical isolates of MDR-Ab which showed resistance to more than three antimicrobial classes were collected from nosocomial pneumonia

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patients of a tertiary hospital in 2007~2012.The values of MIC of tigecycline were determined by agar dilution method based on the Clinical and Laboratory Standards Institute (CLSI) guidelines. *Escherichia coli* ATCC25922 was used as quality control in each batch of tests.

Pharmacokinetic /pharmacodynamic model and Monte-Carlo simulation

A previously described population pharmacokinetic model, derived from patients with community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) enrolled in phase 3 clinical trials, was used as the basis for the simulation of tigecycline exposure. The primary structural parameters of this pharmacokinetic model have been described in detail in past published literature (Rubino *et al*., 2010).

Given the preclinical research of tigecycline have proved that the ratio of the area under the concentration-time curve (AUC) to the MIC is the most suitable PK-PD index to predict its clinical efficacy (Nightingale, *et al*., 2007), a 10000 -patient Monte-Carlo simulation (Crystal Ball2000) was performed to calculate stead-state $fAUC_{0-24h}$/MIC exposures. The equation: $fAUC_{0-24h}$= (fu*dose/ CLt) was used to calculate the steady-state $fAUC_{0-24h}$. The fu which represents the fraction of free drug in the plasma was assumed to be 0.20 (Wyeth Pharmaceuticals Inc, 2011). Then the value of $fAUC_{0-24h}$ was divided by each MIC value to obtain the $fAUC_{0-24h}$/MIC.

The simulated dose was given as follows: 100 mg loading followed by 50 mg q12h; 150mg loading followed by 75mg q12h; 200mg loading followed by 100 mg q12h; 250mg loading followed by 125 mg q12h; 300 mg loading followed by 150 mg q12h.

On the basis of data mentioned above, probability of pharmacodynamic target attainment (PTA) of tigecycline against MDR-Ab at each MIC was calculated. The target goal was set according to a PK/PD model analysis of individuals with nosocomial pneumonia enrolled in a phase 3 clinical trial (Freire *et al*., 2010). In this PK/PD model, the probability of clinical success was mainly affected by the $fAUC_{0-24h}$/MIC ratio and albumin (Bhavnani *et al*., 2012). To simplify the model for facilitating the calculation and reduce confounding factors, we didn't take the influence of albumin into consideration and just assumed homogeneity among simulation patients. Since the value of $fAUC_{0-24}$ /MIC >0.9 means the odds of clinical success was 8.42 times higher for patients in comparison to the value <0.9, we took $fAUC_{0-24h}$/MIC >0.90 as the target for calculating the PTA. Cumulative fraction of response (CFR) was calculated by weighting the PTA at each MIC by the percentage of MDR-Ab with that MIC, as previously described by Drusano *et al* (Drusano *et al*., 2001).

RESULTS

Sensitivity to the drug

Since no universally accepted interpretative MIC breakpoints of tigecycline for *A. baumannii* is available at present, using the breakpoints for *Enterobacteriaceae* (susceptibility at ≦2μg/ml, intermediate at 4μg/ml and resistance at≥8μg/ml), issued by the United States Food and Drug Administration, 97% isolates displayed susceptibility and 3% were intermediate to tigecycline and the values of MIC ranged from 0.125 to 4μg/ml. The MIC_{50}/MIC_{90} values were 1μg/ml; 2μg/ml, respectively.

Probability of target attainment and Cumulative fraction of response by pathogen

The PTA of each dosage regimen calculated through the Monte Carlo simulation, is showed in fig. 1. Tigecycline can achieve >99% target attainment up to MICs of 0.5μg/ml at current dosage. The target attainments began to decline above this MIC and plummeted to 10.97% at the MIC =2μg/ml. With the dosage increasing, the PTA of each MIC dilution displayed corresponding augment. The CFR of each dosage is listed in table 1. If a CFR ≥90% was considered the threshold of achieving a level of microbiologic efficacy that could be confidently relied on in therapy (Jones *et al*., 2005), current drug dosage (50mg q12h) is below target and dosage increased to ≥100mg q12h in this simulation can approach or exceed the threshold.

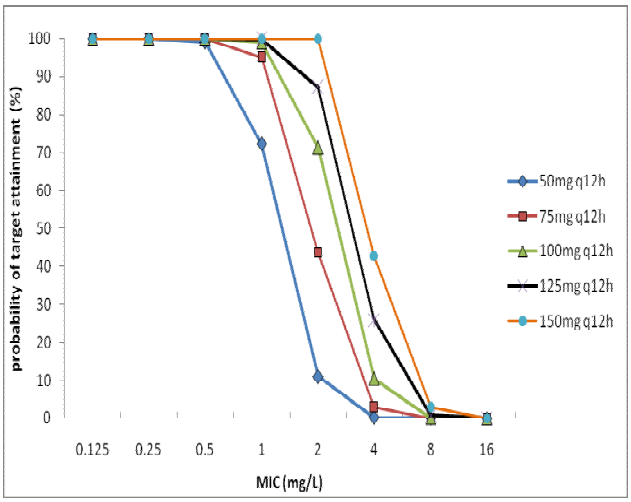

Fig. 1: Probability of target attainment of 10,000 simulated patients given tigecycline at different dosages. The chosen target was $fAUC_{0-24h}$/MIC > 0.90.

DISCUSSION

Considering that tigecycline may result in increased mortality risk compared with other antibiotics, the FDA has disapproved it in treatment of nosocomial pneumonia. However, tigecycline should not be abandoned

incautiously without a comprehensive evaluation, since no antibiotics, except for polymyxins, has reliable in vitro activity against MDR-Ab at present (Moon *et al*., 2012). In the 135 MDR-Ab isolates from HAP patients of our hospital, 99.7% was sensitive to tigecycline and merely 3% showed immediate resistance.

Table 1: Cumulative fraction of response (CFR) of different dosage regimens against MDR-Ab isolated from nosocomial pneumonia patients (n=10000).

Antibiotic Regimen*	CFR, %
Tigecycline 50 mg q12h	61.62
Tigecycline 75 mg q12h	81.00
Tigecycline 100 mg q12h	89.86
Tigecycline 125 mg q12h	94.57
Tigecycline 150 mg q12h	96.77

*The first administration is a loading dose which is two times of the antibiotic regimen

Nevertheless, regardless of the good susceptibility, many studies have revealed that the clinical efficacy of tigecycline were not optimal. A systematic review found an overall response rate of 76% to tigecycline for a wide range of MDR-Ab infections (Karageorgopoulos *et al*., 2008). Several studies on the treatment of MDR gram-negative pathogens have reported that the proportion of clinical success is 60.3-73% with or without concomitant antibiotic therapy (Freire *et al*., 2010; Curcio *et al*., 2009; Guner *et al*., 2011; Ye *et al*., 2011; Shin *et al.*, 2012).In our simulation, success rate was 61.62% at current dosage (50mg q12h), which is substantially the same as published clinical results. It is apparent that correlation between clinical outcome and the susceptibility in vitro was significantly poor.

One explanation about this poor correlation is the value of MIC. Falagas, *et al* had suggested that there is an association between MICs and outcomes for patients with Gram-negative infections (Falagas *et al*., 2012). The treatment failure and mortality rate for patients infected with Gram-negative nonfermentative bacilli with high MICs, despite within the susceptible range, was higher than for those with low MICs. The outcome of this simulation is also based on the distribution of MICs. Tigecycline can achieve >99% target attainment if the MICs below 1μg/ml. However, the target drastically declined to below 11% at MIC≥2μg/ml. The MIC_{50} and MIC_{90} of 135 MDR-Ab isolates were 1μg/ml and 2μg/ml, respectively and 28.15% isolates had MIC values ≥ 2μg/ml. Therefore, although 99.7% isolates exhibited susceptibility to tigecycline, a higher proportion of high MICs lead to a disappointed result.

In addition, the penetration and distribution of the drug also has great influence on its effects (Mouton *et al*., 2007). When dealing with lower respiratory tract infections, the drug's concentration in lung tissues can be best parameters to predict clinical response. After a loading dose of 100mg followed by 50mg twice daily, pharmacokinetic measurements in health volunteers indicated that the mean C_{max} and the $AUC_{0\text{-}12h}$ of the drug in serum and ELF were not optimal (Conte *et al*., 2005). In a clinical research evaluating the PK parameters of tigecycline in individuals with ventilator acquired pneumonia (VAP), the similar result has been obtained (Burkhardt *et al.*, 2009). Considering the pathogenicity of MDR-Ab, the ELF and serum concentration of tigecycline was obviously insufficient for microbiological eradication.

Since the AUC/MIC ratios were the best PK/PD index to predict the clinical efficacy of tigecycline (Nightingale, *et al.*, 2007), a higher AUC/MIC ratio for better response can be achieved by increasing the dose. So several studies have pointed that tigecycline may not be suitable for bacteremia and lung infection at current recommended dosage (Burkhardt *et al*., 2009; Falagas and Burkhardt., 2009) Through the PK/PD simulation, CFR values could achieve 81%, when the dosage 75mg q12h was used. And a favorable CFR value can be obtained by increasing the dosage up to 100mg q12h. Results of pharmacokinetic analysis of tigecycline in healthy subjects indicated the $AUC_{0\text{-}12h}$ in serum was 4.98μg *h/ml after multiple doses of 100mg and the $AUC_{0\text{-}12h}$ in serum were 13.2 and 17.3μg*h/ml after receiving 200mg and 300mg in a single-dose study (Meagher *et al*., 2005). However, we can't be too careful to weigh the pros and cons when using an increased dosage because more adverse events may occur.

Some limitations that exist in this study deserve deeper consideration. First, the PK/PD simulation is just based on a number of assumptions and many potential confounding factors can influence the result (Canut *et al*., 2012). Except for the $fAUC_{0\text{-}24h}$/MIC ratio, other factors such as albumin, VAP status, mental status, *et al* may also influence the outcome of patients with nosocomial pneumonia (Bhavnani *et al*., 2012). Second, we used a fixed value (0.20) for the free drugs in serum, which is likely to be errant in critically ill patients where a range of alterations in protein binding may occur between patients (Roberts *et al*., 2011). Additionally, MIC distribution may vary widely in different locations and the values of MIC in this simulation were obtained from a single-center.

CONCLUSIONS

On the basis of PK/PD model, we evaluated the clinical efficacy of different dose regimens of tigecycline to treat patients suffering from nosocomial peumonia caused by MDR-Ab in our hospital. Despite MDR-Ab isolates presented higher susceptibility, the CFR obtained was not

optimal at current dosage. A higher CFR indicating a better clinical efficacy can be gained by increasing the dosage. In the future, multicenter controlled clinical studies for tigecycline of higher doses should be conducted to clarify its efficacy and safety in MDR and XDR gram-negatives infections.

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