Effect of pharmacokinetic/pharmacodynamic ratio on tigecycline clinical response and toxicity in critically ill patients with multidrug-resistant Gram-negative infections

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Abstract

Introduction: The information about the pharmacokinetics and optimal dose of tigecycline in critically ill patients with severe underlying diseases is limited and controversial. In this study, we evaluate the pharmacokinetic parameters of tigecycline in critically ill patients with multidrug-resistant Gram-negative infection and explore the association between the pharmacokinetic/pharmacodynamic ratio and treatment response.

Methods: A prospective study was designed including critically ill patients treated with tigecycline for multidrug-resistant Gram-negative infections. Blood samples were collected at day 3–5 of treatment, and pharmacokinetics parameters were evaluated using NONMEM® software. Relationship between area under the free concentration–time curve and minimum inhibitory concentration ratio (fAUC/MIC) and treatment failure was evaluated. Association between tigecycline fAUC and hepatobiliary toxicity was also investigated.

Results: Twenty-five critically ill patients were included in the study. In the pharmacokinetic model, weight and total bilirubin level were found to be significant predictors of tigecycline clearance. Fifteen (60.0%) patients achieved an fAUC/MIC ratio >4.5, seven (28.0%) an fAUC/MIC > 6.96 and only three (12.0%) an fAUC/MIC > 17.9. No differences in fAUC/MIC ratio were obtained between those patients with and without clinical failure (5.28 (IC95%: 2.57–7.94) vs 8.71 (3.57–13.84)). fAUC values were higher in those patients who suffered hepatobiliary disorders (7.63 (3.93–11.34) vs 17.63 (7.85–26.28) mg/L/h).

Conclusion: An important percentage of critically ill patients with multidrug-resistant Gram-negative infection treated with tigecycline do not achieve an appropriate pharmacokinetic/pharmacodynamic value. Tigecycline fAUC seems to be associated with hepatobiliary disorders in this study population. The effect of fAUC/MIC ratio on clinical response remains unclear.

Keywords

Antibiotics, critical care, pharmacokinetics

Introduction

The emergence of multidrug-resistant (MDR) bacteria has created a challenge in the treatment of nosocomial infections. The crisis of antibiotics resistance is especially relevant in intensive care units (ICUs), where the highest rates of MDR bacteria are found. Although during the last years new antibiotics have been approved to treat MDR Gram-negative pathogens, severe infections due MDR *Acinetobacter baumannii* or metalloenzyme-producing strains continue without effective alternatives.[1]

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Tigecycline, the first representative of glycylcyclines, has a broad-spectrum activity, effective against MDR strains including Gram-positive and Gram-negative bacteria. Tigecycline has shown to be effective in the treatment of complicated skin and soft tissue infections (cSSTI), complicated intra-abdominal infections (cIAI) and community-acquired pneumonia.[2–4] During the last decade, several studies have shown that tigecycline can be used as an effective alternative for the treatment of serious infections caused by MDR pathogens.[5,6]

However, the experience with tigecycline in critically ill patients with severe underlying diseases is limited and controversial. Several studies have shown that the standard doses of tigecycline are insufficient for the treatment of patients with bacteremia or hospital-acquired pneumonia (HAP).[7–9] On the other hand, tigecycline pharmacokinetics may be different in more critically ill patients.[10]

Therefore, the association between a pharmacokinetic and pharmacodynamic (PK/PD) parameters and the efficacy of tigecycline in critically ill patients need to be evaluated. Tigecycline efficacy has been predicted successfully by the relationship between the area under the free concentration–time curve and the minimum inhibitory concentration (fAUC/MIC).[11] An fAUC/MIC ratio of 17.9 in cSSTI, 6.96 in cIAI and 4.5 in HAP has been associated with a satisfactory response.[12–14] However, the relationship between tigecycline PK/PD ratio and clinical response in critically ill patients is not clear. On the other hand, different studies have reported hepatobiliary disorders associated with tigecycline use,[15,16] although association between tigecycline concentrations and these adverse events have yet to be established.

The aims of this study were to estimate the tigecycline pharmacokinetics and probability of achieving adequate fAUC/MIC ratio values against Gram-negative bacteria in a critically ill population, to explore the association between fAUC/MIC and treatment success, and the relationship between serum concentrations and the development of hepatobiliary disorders.

Material and methods

We designed a prospective pharmacokinetic/pharmacodynamic study. Patients older than 18 years admitted in a medical critical care unit in treatment with tigecycline for MDR Gram-negative infections from January 2017 till December 2017 were included.

Blood samples

Blood samples were collected over one dosing interval in each patient between day 3 and 5 of treatment at 0 (pre-dose), 1 h (post-dose), 2, 6 and 12 h after the start of infusion. Plasma samples were obtained after centrifugation (1000 r/min × 10 min) and stored at −80°C until assayed. Tigecycline serum concentrations were measured by liquid chromatography tandem-mass spectrometry method. The method consisted of protein precipitation of the serum samples by addition of acetonitrile, separation of tigecycline on a Supelco LC-18 DB column and subsequent UV detection of tigecycline at 350 nm. The extraction efficiency was higher than 75%, and the lower limit of quantitation was 25 ng/mL. The lower limit of quantitation was 0.08 ng/mL, and the upper limit of quantitation was 20 mcg/mL. Quality control (QC) samples of tigecycline prepared in human serum at concentrations of 20, 10, 5, 2.5, 1.25, 0.63, 0.31 and 0.16 mcg/mL, were analyzed, along with the subject samples. The overall precision and accuracy for the standards and the QC samples were in the range of 1%–10% and 91%–110%, respectively.

Pharmacokinetic model

Population pharmacokinetics analyses were performed using the computer program NONMEM® (v.5), implementing a first-order conditional estimation method with interaction.[17] A two-compartment model with zero-order input and first-order elimination (ADVAN 3, TRANS 3) was used to describe the serum tigecycline concentration–time data during a 12-h dosing interval at steady state. Goodness-of-fit was assessed graphically by evaluation of the agreement between observed and predicted tigecycline concentrations, reductions in the range of weighted residuals, and uniformity of the distribution of weighted residuals about zero across the range of both the predicted concentrations and time since last dose.

Covariate analyses were conducted using a stepwise forward selection procedure. Variables evaluated included age, sex, weight, serum creatinine, creatinine clearance according to Cockcroft–Gault formula, fluid balance, diuresis, hemofiltration, total bilirubin and liver enzymes aspartate aminotransferase/alanine aminotransferase (AST/ALT). Age, body weight, sex, AST and ALT values were evaluated as predictors of total clearance. Plots of the individual deviations for each parameter versus each of the patient covariates were examined for observable trends and were used to assess the functional form of the relationship between the PK parameter and the covariate. In each step of forward selection, a univariate analysis of each patient covariate with an observable trend was performed, and the most significant covariate was added to the model. Covariates contributing at least a 3.84 reduction in the minimum value of the objective function (MVOF) ($\alpha = 0.05$, 1 degree of freedom) when added to the model were considered significant. fAUC was calculated based on the following formula: fAUC: dose/Cl, where dose is equal to the total daily dose of tigecycline and Cl is the clearance value generated from a previously conducted population PK analysis.[13,14]

To estimate the fAUC/MIC ratio, MIC testing was performed and pharmacokinetic parameters were calculated. The MIC of tigecycline for the first isolate in each patient was determined by E-test according to the Clinical and Laboratory Standards Institute.[18]

Treatment failure and adverse events

Relationship between fAUC/MIC ≥4.5, ≥6.96 and ≥17.9 achievement and treatment failure and 30-day mortality was evaluated. Treatment failure was defined as withdrawal of the treatment due to a poor response (persistent fever or non-decreased leukocyte count or reactive C-protein (RCP) value during treatment) or death associated with the infection. Microbiological response at the end of treatment was considered positive if the responsible organism was eradicated from biological samples.

Association between the tigecycline fAUC serum levels and the appearance of hepatobiliary toxicity was also investigated. Hepatobiliary disorder was defined as the elevation of total bilirubin, AST/ALT, alkaline phosphatase (AP) and/or gamma-glutamyl transpeptidase (GGT). The appearance of adverse events and their relationship with tigecycline was classified in accordance with the Common Terminology Criteria for Adverse Events v4.0 (CTCAE),[19] considering as an adverse event an elevation on one or more degrees in the CTCAE scale of any of the analytical parameters mentioned.

Statistical analysis

The statistical analysis was performed using the Stata® v.13.0 software. Univariable and multivariable analysis were conducted to identify factors associated with clinical failure, 30-day mortality and hepatobiliary disorders. The independent variables included in the univariable analysis were age, immunosuppression, serum albumin concentration, APACHE II score, mechanical ventilation support, neutropenia, renal replacement therapy, concomitant antimicrobial therapy, focus of infection and carbapenemases-producing strains, including previous hepatobiliary alterations in the hepatobiliary disorders analysis. Each of the fAUC/MIC values (>4.5, 6.96 and 17.9) was included separately in the model. Univariable predictors with a p-value < 0.2 were entered into a multivariable logistic regression model, conducted using forward inclusion of independent variables. Interactions among resulting independent variables retained in the final model were evaluated. A p-value < 0.05 was considered statistically significant.

The study had the approval of the Biomedical Research Ethics Committee of the Hospital La Fe (Nº 2015/0368). In compliance with the Helsinki Declaration, the participants or their relatives received oral and written information about the study and were included after providing their written consent.

Results

In total, 25 critically ill patients were included in the study, 16 (64.0%) of them were affected by pneumonia, 5 (20.0%) by central venous catheter–related infection and 4 (16.0%) by abdominal infection. Ten (40.0%) patients received standard dose (50 mg/12 h) and 15 (60.0%) received high dose (100 mg/12 h) of tigecycline, according to the criteria of the

Table 1. Clinical and demographic characteristics of patients treated with tigecycline.

	Total (n = 25)
Age (mean, SD)	47.7 (12.8)
Male (%)	18 (72.0)
Body mass index (kg/m²) (median, range)	23.8 (19.5–40.1)
Obese (>30 kg/m²) (%)	4 (16.0)
APACHE II score (median, range)	19 (12–38)
SOFA score >7 (%)	15 (60.0)
Length of ICU stay (days) before treatment (mean; SD)	22.5 (16.5)
Mechanical ventilation (%)	19 (76.0)
Renal replacement therapy (%)	3 (12.0)
Vasoactive drugs during treatment (%)	12 (48.0)
Comorbidities	
Neutropenia (%)	7 (28.0)
Diabetes mellitus Insulin use	3 (12.0)
Liver cirrhosis	2 (8.0)
Immunosuppression	11 (44.0)
Source of infection (%)	
Lung	16 (64.0)
Venous catheter–related abdominal infection	5 (20.0)
Abdominal infection	4 (16.0)
Combination therapy (%)	
No concomitant treatment	3 (12.0)
Carbapenem	13 (52.0)
Aminoglycosides	16 (64.0)
Colistin	5 (20.0)

SD: standard deviation.

doctor responsible for each patient. Demographics and clinical characteristics of patients included are reflected in Table 1. Most often MDR Gram-negative bacteria were *Klebsiella pneumoniae* (n = 17, 64.0%) followed by *Enterobacter cloacae* (n = 4, 16.0%). Carbapenemases enzymes were detected in 20 (80.0%) isolates and extended-spectrum beta-lactamases (ESBLs) in 5 (20.0%). Tigecycline MIC value was 0.5 μg/mL in 2 (8.0%), 1 μg/mL in 10 (40.0%), 2 μg/mL in 12 (48.0%) and 4 μg/mL in 1 (4.0%) isolated.

Pharmacokinetic model
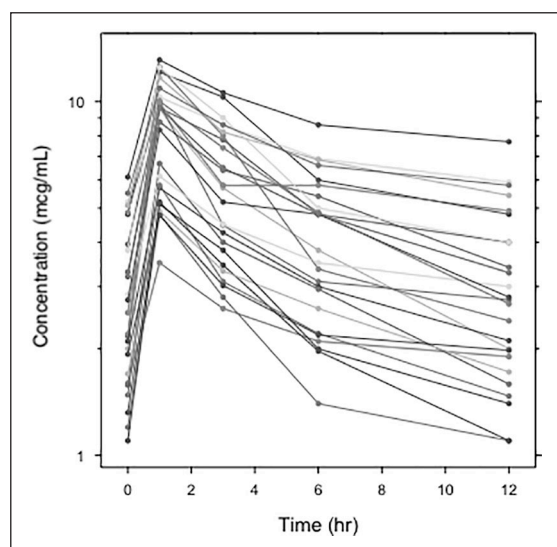
Results from the mean observed concentration–time profile of tigecycline from patients included in the study are shown in Figure 1. Mean ± standard deviation (SD) population pharmacokinetic parameters estimated are shown in Table 2. A two-compartment model with zero-order input and first-order elimination, utilizing a proportional residual variability (RV) model, adequately described the steady state of tigecycline concentration–time data. The covariates weight (linear relationship; p = 0.012) and total bilirubin level (inverse relationship; p = 0.028) were found to be significant predictors of plasma clearance, resulting in a significant improvement in the log-likelihood value. All parameters were estimated with

acceptable precision, and the goodness-of-fit plots indicated a reasonably unbiased fit to the data. The diagnostic plot confirming the appropriateness of the model is shown in Figure 2.

Fifteen (60.0%) patients achieved an fAUC/MIC ratio >4.5. Of these 15 patients, 7 reached an fAUC/MIC > 6.96 and only 3 of them an fAUC/MIC > 17.9. The probability of target attainment was higher for those patients who received high dose of tigecycline, (fAUC/MIC > 4.5: 9/15 (60%) vs 4/10 (40%); fAUC/MIC > 6.96: 5/15 (33%) vs 2/10 (20%); fAUC/MIC > 17.9: 2/15 (13%) vs 1/10 (10%)).

Treatment failure

Among the patients that received tigecycline, 14 (58.3%) had treatment failure, being in 9 (36.0%) cases due to lack of response and 5 (20.0%) due to toxicity. Those patients with failure associated with a lack of response to the treatment had a mean fAUC/MIC ratio lower than those patients that responded to treatment, although no significant differences were achieved (5.28 (IC95%: 2.57–7.94) vs 8.71

Figure 1. Tigecycline free serum concentrations observed.

(3.57–13.84) mg/h/L; p = 0.317). Fifteen (60.0%) patients presented microbiologic response to tigecycline treatment, and nine (36.0%) patients died at day 30. No differences were found in fAUC/MIC values between those patients with and without microbiological response (7.36 (2.74–12.00) vs 7.63 (1.89–13.38) mg/h/L).

Regression analysis

Independent factors associated with patient's clinical failure and 30-day mortality are reflected in Table 3. In the univariate analysis, meropenem concomitant therapy, high dose of tigecycline and an fAUC/MIC ratio <4.5 were associated with lower clinical failure. Neutropenia, high dose of tigecycline, combined therapy with meropenem and an fAUC/MIC ratio <4.5 were associated with a higher 30-day mortality.

In the multivariable analysis (Table 3), combined therapy with meropenem was associated with significant lower clinical failure (odds ratio (OR): 0.05 (0.01–0.66)). An fAUC/MIC < 4.5 showed a tendency to a higher clinical failure (OR: 5.89 (0.48–21.59)), although no significant differences were achieved. The presence of neutropenia was the only significantly factor associated with higher 30-day mortality.

Adverse events

Eight patients (32.0%) presented adverse events related to tigecycline administration. In five (20.0%) patients, elevation in bilirubin and liver enzymes were observed, finding elevation only in bilirubin value in the other three (12.0%). Hepatobiliary disorders severity were classified as grade 2 in three and grade 3 in five patients. fAUC values were significant higher in those patients who suffered hepatobiliary disorders (7.63 (3.93–11.34) vs 17.63 (7.85–26.28) mg/L/h). In the univariate analysis, high tigecycline dose and an fAUC/MIC > 17.9 were associated with hepatobiliary disorders, although no significant results were obtained in the multivariable analysis.

Table 2. Estimated tigecycline pharmacokinetics parameters.

Parameter	Total (n = 24)		100 mg/12 h (n = 15)		50 mg/12 h (n = 10)	
	Mean (SD)	Coefficient of variation (%)	Mean (SD)	Coefficient of variation (%)	Mean (SD)	Coefficient of variation (%)
Clearance (L/h/kg)	0.18 (0.13)	72.2	0.16 (0.13)	79.7	0.21 (0.13)	74.5
Vss (L/kg)[a]	3.16 (0.50)	23.3	3.13 (0.55)	25.9	3.20 (0.44)	20.1
fAUC (mg/L/h)[b]	10.4 (9.2)	89.3	13.0 (9.4)	72.7	6.4 (7.9)	122.9
fCmax (mg/L)[c]	8.45 (2.94)	34.7	10.61 (1.47)	13.9	5.26 (0.88)	16.8

SD: standard deviation.
[a]Vss: total volume of distribution.
[b]fAUC: free area under curve.
[c]fCmax: maximum free serum concentration (post-dose).

Discussion

The results of our study show that an important percentage of patients treated with tigecycline do not achieve an appropriate fAUC/MIC value and that the blood concentrations are associated with the development of hepatobiliary disorders in critically ill patients with MDR Gram-negative infections. However, significant association between fAUC/MIC ratio and clinical failure could not be properly evaluated.

The emergence of MDR bacteria in critical care units has made tigecycline an alternative therapeutic option and off-label indications, such as nosocomial pneumonia or bacteremia, are currently increasing.[20] However, serious concern has risen regarding a possible tigecycline underdosing with the standard tigecycline regimen in critically patients.[21] Different meta-analyses have shown an increased overall mortality of tigecycline in severe infections.[22,23] It has been proposed that the excess on mortality rates might be associated to low tigecycline concentrations particularly in patients with pneumonia and bacteremia.[24–26] An important finding in this study is that only 60.0% of the patients achieved an fAUC/MIC > 4.5 value after the first 96h of treatment. Low serum concentrations caused by the large volume of distribution could be the main cause of therapeutic failure observed with tigecycline when this drug is used in monotherapy. These findings suggest that concomitant use with other antibiotics in patients with
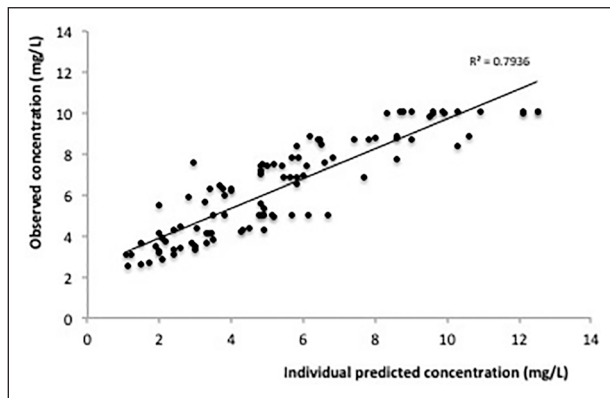
Figure 2. Observed versus individual-predicted tigecycline free concentrations.

Gram-negative bacteremia is needed. In fact, the multivariable analysis has identified concomitant use of meropenem as a protective factor for clinical failure. Several authors have proposed that tigecycline should be used associated with other antibiotics for the treatment of infections caused bay MDR strains, as better outcomes have been reported with combined therapy.[27] Although tigecycline has been shown to have an adequate lung pentration,[28] high dose of tigecycline has also been suggested as an alternative to improve patient's outcomes in patients with HAP. Actually, high-dose regimen has been associated with better outcomes than conventional dosing regimen for the treatment of Gram-negative MDR bacteria.[5] The results obtained in this study have not found association between high dose and clinical failure in the set of infections evaluated, although the low number of patients included prevents us from obtaining clear conclusions.

In the pharmacokinetic model, the covariates weight and bilirubin were included. These variables have been also considered as predictors of tigecycline blood concentrations by other authors.[12,29,30] In our pharmacokinetic model, other classical variables such a glomerular filtration, diuresis, hemofiltration or fluid balance have not conditioned tigecycline serum concentrations. These results are accorded with the pharmacokinetic profile of tigecycline, due to its high volume of distribution and its low total clearance.[30] The pharmacokinetic data obtained show important differences with those obtained from healthy volunteers,[31] including lower clearance and higher fAUC values. The presence of different degrees of liver dysfunction in the severe patients[32] and high bilirubin values in some of the patients included could explain the differences and reinforce the importance of dose individualization in critically ill patients. The volume of distribution obtained from patients included was also lower than previously reported.[29,30] We could not identify comorbidities that explain this phenomenon. Limited information available on the pharmacokinetics of tigecycline in critically ill patients makes it necessary to continue evaluating the changes in both clearance and volume of distribution of this group of patients.

Certain patients included with standard dose of tigecycline and low weight and high bilirubin levels have achieved high fAUC values. This observation shows the importance of consider these variables in order to select tigecycline dose

Table 3. Results of multivariable analysis.

	Clinical failure	30-day mortality	Hepatobiliary disorders
	OR (95% CI)	OR (95% CI)	OR (95% CI)
High dose of tigecycline	4.09 (0.43–19.92)	3.20 (0.39–22.47)	4.88 (0.56–32.21)
Meropenem combined therapy	0.05 (0.01–0.66)	0.41 (0.03–5.84)	*
fAUC/MIC < 4.5	5.89 (0.48–21.59)	4.95 (0.22–29.99)	*
fAUC/MIC > 17.9	*	*	8.35 (0.44–35.25)
Neutropenia	*	7.66 (1.21–46.38)	*

OR: odds ratio; CI: confidence interval.
*Not included in the multivariable analysis.

and reinforce the importance of therapeutic drug monitoring in severe patients. It should be noticed that only four obese patients were included in our study, so we could not adequately evaluate the risk of underdosing this group of patients. Some authors have suggested that these patients could benefit from a 200-mg dose each 12 h, especially during the treatment of pathogens with high MIC values.[29] Since obesity is an increasingly frequent pathology in critically ill patients, future studies in this group of patients are needed to prevent clinical failures in these patients.

Tigecycline fAUC/MIC has been associated with clinical response in different studies.[12–14] However, the information in severe infections due MDR Gram-negative bacteria with higher MIC to tigecycline is scarce. In this study, we have investigated the effect of the lowest PK/PD value described (fAUC/MIC < 4.5) on treatment failure in order to include all treated infections. On the other hand, as tigecycline presented a high volume of distribution, blood samples may not be representative of the concentration achieved in infections focus, and should be interpreted with caution. However, it should be noticed that in the multivariable analysis those patients with a fAUC/MIC ratio <4.5 showed a tendency to a higher clinical failure, although the study was not powered to do so. Future studies including patients with specific infections are needs to clarify the role of blood concentrations in clinical response in patients treated with tigecycline.

The results of this study show that high tigecycline fAUC is associated with the development of hepatobiliary adverse events. The small sample size has prevented to obtain association between high dose of tigecycline and these types of adverse events. Routsi et al.[33] suggested that high dose could be associated with alterations in coagulation parameters, which could be considered as a biomarker of liver function. As bilirubin and body weight have been associated with tigecycline concentrations, high dose of tigecycline should be used with caution in those patients with high bilirubin levels or low body weight.

The main limitation of this study is the small number of patients included. The lack of sample size calculation and the different sources of infection have prevented identifying a PK/PD ratio associated with clinical response in this group of patients, as statistical analysis could not be properly done for each group of infection. However, despite this limitation, our results show relevant findings that could help to propose alternative dose for the management of infections caused by MDR bacteria in critically ill patients.

Conclusion

Tigecycline fAUC is associated with adverse events in critically ill patients with MDR-Gram negative infection. The effect of fAUC/MIC ratio on clinical response remains unclear. Individualization of tigecycline dose based on patient's bilirubin levels and weight is necessary to minimize toxicity in severe infections.

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