

PHARMACOKINETIC/PHARMACODYNAMIC MODEL FOR THE TOLERABILITY OF TIGECYCLINE IN HEALTHY VOLUNTEERS

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ABSTRACT

Objectives:

Tigecycline, a first-in-class glycylicycline, is an antimicrobial agent with demonstrated *in vitro* activity against susceptible and multiple-drug resistant gram-positive and gram-negative bacteria. Similar to tetracyclines, nausea and vomiting are frequently reported adverse events. Exposure-response relationships and subject covariates predictive of the first occurrence of nausea and vomiting in healthy volunteers were evaluated.

Methods:

Subjects with PK data from 3 single-dose (12.5, 25, 50, 75, 100, 200, and 300 mg) phase 1 studies were pooled for analysis. Nausea and vomiting (definitely, possibly, or probably related to tigecycline) reported from the start of infusion until 24hrs post dose were included. Subjects administered ondansetron or with severe or end-stage renal disease were excluded. Individual tigecycline exposure measures [AUC_{0-∞} (AUC) and C_{max}] were obtained from previously conducted noncompartmental analyses. Covariates included age, weight, gender, and geographic location. Logistic regression and Kaplan-Meier methods were used to evaluate the first occurrence of nausea and vomiting.

Results:

The dataset included 136 subjects. Mean (SD) age and weight were 38 (20) years and 74 (12) kg. Approximately 87% were Caucasian, 84% were male, 38% were enrolled in USA, and 62% in Europe. Single nausea occurrences were reported in 51 (38%) and vomiting in 25 (18%) subjects. Two nausea or vomiting events were reported in 4 subjects. Nausea (vomiting) was reported in 12% (4%) of placebo subjects, 17% (0%) on tigecycline 25 mg, and 33% (0%) on tigecycline 50 mg. Females had a higher occurrence of nausea and vomiting (45% and 19%) versus males (36% and 14%). France and USA had similar nausea rates (39% versus 35%); France had a much higher vomiting rate (24% versus 10%). Most nausea (vomiting) events occurred ≤ 4 hours (≤ 6 hours) after tigecycline infusion for all doses. For doses ≤ 100 mg, median duration of nausea and vomiting was < 1 hour and increased dramatically for 200 and 300 mg dose groups (≤ 3 hours). Most nausea (vomiting) occurrences were mild [49% (20%)] and 27% (44%) were moderate. 111 subjects had PK. Final statistical model concluded AUC and C_{max} as significant predictors of nausea (p ≤ 0.0001, p = 0.0022) and vomiting (p ≤ 0.0001, p = 0.0006). Increased exposures resulted in increased events. At the median AUC (C_{max}) of 2.6 μg-hr/mL (0.39 μg/mL) for the 50-mg dose group, nausea probability was 0.26 (0.29) and vomiting probability was 0.07 (0.11).

Conclusion:

Tigecycline exposure (AUC > C_{max}) was a significant predictor of the probability of nausea and vomiting events in phase 1 subjects. Model predicted rates of nausea and vomiting were comparable with those seen with the tetracycline class of antibiotics, with tolerable rates predicted at the targeted tigecycline dose of 50 mg every 12 hours.

BACKGROUND

- Tigecycline, a first-in-class glycylicycline, is an antimicrobial agent with demonstrated *in vitro* activity against susceptible and multiple-drug resistant gram-positive and gram-negative bacteria.
- Tigecycline appears to be generally well tolerated, with the most frequently reported treatment-emergent adverse events related to GI tolerability, specifically nausea, vomiting, and diarrhea.
- In clinical trials, nausea and vomiting have been categorized as mild to moderate in severity.
- GI tolerability appears to be improved if tigecycline is administered following a meal and the drug also appears to be better tolerated in older subjects.
- Exposure-response analyses were performed to explore the relationship between tigecycline exposure measures and the first occurrence of nausea and vomiting in healthy subjects.
- A statistical model was developed to describe the first occurrence of nausea and vomiting, including the potential impact of selected subject demographic characteristics and exposure measurements.

METHODS

- Data from subjects with pharmacokinetic (PK) information were collected from three single-dose phase 1 studies for the exposure-response analyses of safety.
 - In an ascending single-dose study in healthy, predominately Caucasian, males, tigecycline was administered by IV infusion in doses ranging from 12.5 to 300 mg under both fasting and fed conditions, with most doses infused over 1 hour. The 200 and 300 mg doses were also administered as 4-hour infusions and the 200 mg dose was administered to fasting subjects who received pre-treatment with ondansetron.
 - Age and gender effects were evaluated in a single-dose study of tigecycline 100 mg infused over 1 hour in healthy young (18 to 50 years), young-elderly (65-75 years), and elderly (>75 years) men and women.
 - Tigecycline was administered as a single 100-mg IV dose infused over 60 minutes to evaluate the effect of severe renal impairment and end stage renal disease versus age-matched subjects.
- Subjects administered ondansetron and those with severe or end-stage renal disease were excluded from all safety analyses.
- Analyses of the first occurrence of nausea and vomiting were conducted separately.
- The occurrence of the adverse events of nausea and vomiting included any reported instance occurring from the start of the first infusion until 24 hours after the last infusion.
- Only adverse events classified as definitely, possibly, or probably related to tigecycline were considered.
- Individual PK exposure measures were obtained from previously conducted noncompartmental analyses: area under the concentration-time curve from time zero to infinity (AUC) and the observed maximum serum concentration (C_{max}).
- The following subject demographics were evaluated as potential predictors of nausea and vomiting: age, weight, gender, and geographic location.
- All data processing, data clean-up, database creation activities, and statistical analyses were performed using SAS[®] software, Version 8.2.
- Logistic regression analyses or other nonlinear analyses were used to determine whether exposure measures and covariates were statistically significant predictors of the first occurrences of nausea and vomiting.
- A backward elimination procedure was utilized with a level of significance of 0.05 to identify predictor variables with a statistically significant influence on safety.
- Goodness-of-fit of the logistic regression model was assessed using the Hosmer-Lemeshow goodness-of-fit test.
- Predictive ability of the model was assessed using the area under the receiver operating characteristic (ROC) curve.
- Survival analysis using the non-parametric Kaplan-Meier method was used to determine whether exposure measures and covariates were statistically significant predictors of the time to the first occurrences of nausea and vomiting.

RESULTS

Subject Population

- There were 136 subjects in the final dataset. Subject demographics are displayed in **Table 1**.
 - 111 subjects had tigecycline exposure measures. For subjects administered the 50-mg dose, the mean (SD) AUC and C_{max} was 2.56 (0.53) μg-hr/mL and 0.38 (0.064) μg/mL, respectively.
 - Region of origin could not be assessed in the logistic regression analysis since all subjects from France were less than 50 years of age, resulting in confounding of country and age.

RESULTS *cont'd.*

Table 1. Phase 1 Subject Demographics (n=136)

| Demographic Characteristics | Summary Statistics |
|-----------------------------|--------------------|
| Age (years) [mean (SD)] | 38.4 (19.7) |
| Weight (kg) [mean (SD)] | 73.7 (12.2) |
| Gender, n (%) | |
| Male | 114 (84) |
| Female | 22 (16) |
| Ethnicity, n (%) | |
| Caucasian | 118 (87) |
| Black | 15 (11) |
| Hispanic | 2 (1) |
| Other | 1 (1) |
| Geographic Location, n (%) | |
| Europe | 84 (62) |
| North America | 52 (38) |

Nausea

- 38% of subjects (51/136) had at least one occurrence of nausea and 2 subjects had two occurrences of nausea following a single dose of tigecycline.
- Approximately 12%, 17%, and 33% of subjects administered placebo, tigecycline 25 mg, and tigecycline 50 mg had at least one nausea occurrence, respectively. Higher percentages of nausea were reported for larger doses: 50%, 36%, 67%, and 75% of subjects administered tigecycline 75 mg, 100 mg, 200 mg, and 300 mg experienced nausea, respectively.
- Female subjects (45%) had a higher occurrence of nausea as compared to male subjects (36%).
- France and the US had similar incidences of reported nausea (39% versus 35%, respectively).
- The majority of first nausea events occurred within 4 hours of the start of tigecycline treatment.
- As dose increased from placebo to 300 mg, the median time since first dose for the first nausea occurrence remained in the range of 3 to 4 hours. However, the median duration of first nausea occurrence dramatically increased for the 200 and 300 mg dose groups as compared to the placebo and lower dose groups (**Figure 1**).
- Approximately 49% of first nausea occurrences were mild in nature and 27% were moderate.
- The first occurrence of nausea appeared to be directly related to AUC in this sub-population (**Figure 2**). As exposure to tigecycline increased, the incidence of first nausea increased.
- The univariate logistic regression models revealed that AUC, C_{max}, and age were statistically significant predictors of the probability of first nausea occurrence (p < 0.0001, p = 0.0022, and p = 0.0157, respectively).
- After multivariable modeling, the final logistic regression models included only exposure measures, AUC and C_{max}, as significant predictors of the probability of first nausea occurrence (p < 0.0001 and = 0.0022, respectively).

Figure 1. Median Time Since First Dose and Median Duration for First Nausea Occurrence

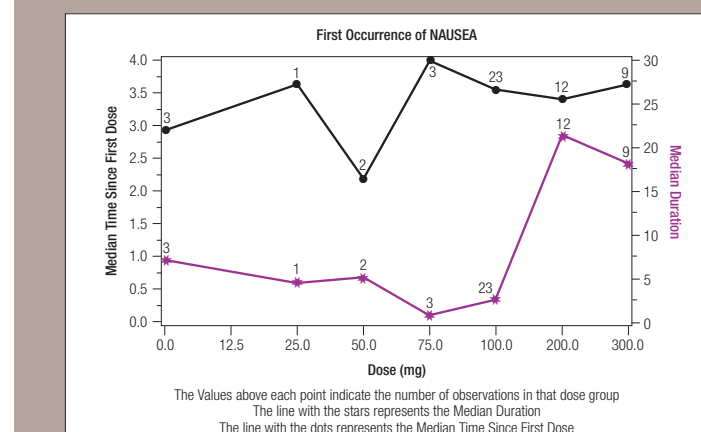
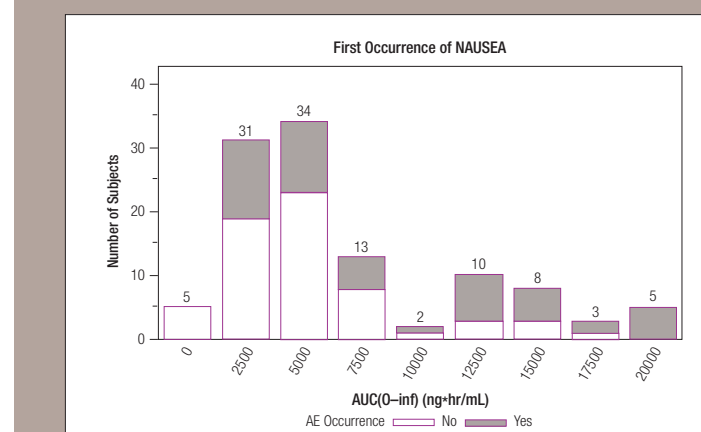


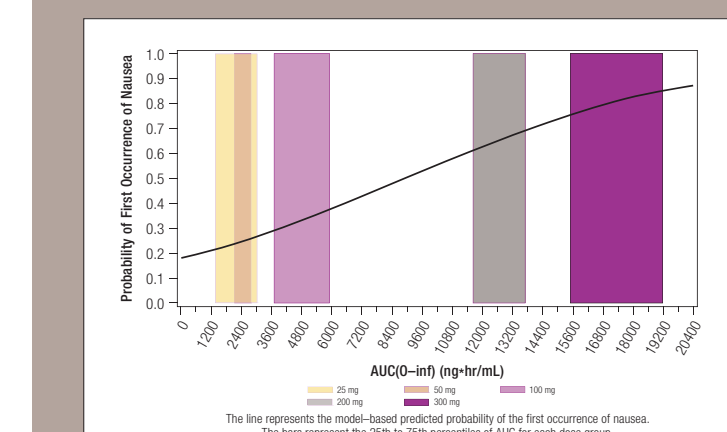
Figure 2. Frequency Distribution of AUC_{0-∞} Values Stratified by Nausea Occurrence



RESULTS *cont'd.*

- The model-based predicted probability of first nausea occurrence versus AUC_{0-∞} is shown in **Figure 3**. As AUC increased, the model-predicted probability of first nausea occurrence increased, with an odds ratio of 1.186.
 - The odds ratio of 1.186 indicated that for a one-unit increase in AUC, a subject was approximately 18.6% more likely to have a first nausea occurrence.
 - The Hosmer-Lemeshow goodness-of-fit statistic was 5.18 with 7 degrees of freedom (p = 0.6385) and the area under the ROC curve was 0.73, indicating an adequate fitting and predictive model.
 - At the median AUC value of 2.60 μg-hr/mL for the 50-mg dose group, the model-predicted probability of first nausea occurrence was 0.26.
 - At the median AUC value of 4.71 μg-hr/mL for the 100-mg loading dose, the probability of first nausea occurrence was 0.33.
- The predicted probability of first nausea occurrence also increased as C_{max} increased (odds ratio = 2.581).
 - The Hosmer-Lemeshow goodness-of-fit statistic was 12.18 with 7 degrees of freedom (p-value = 0.0948) and the area under the ROC curve was 0.65, indicating a model that was slightly less predictive than the AUC model.
 - At the median C_{max} value of 0.39 μg/mL for the 50-mg dose group, the model-predicted probability of first nausea occurrence was 0.2893.
 - At the median C_{max} value of 0.92 μg/mL for the 100-mg loading dose the probability of first nausea occurrence was 0.4027.
- The AUC model was a better fitting, more predictive model as compared to the C_{max} model.

Figure 3. Final Logistic Regression Model for First Nausea Occurrence versus AUC_{0-∞} Values



Vomiting

- 25 (18%) of the 136 subjects had at least one occurrence of vomiting and only two subjects had two occurrences of vomiting.
- 4% of subjects who received placebo experienced vomiting, but none of the subjects administered 12.5, 25, or 50 mg of tigecycline experienced vomiting. As doses increased, the percentage of subjects experiencing vomiting also increased: 17% (n=1) at the 75-mg dose, 12% (n=7) at the 100-mg dose, 50% (n=9) at the 200-mg dose, and 58% (n=7) at the 300-mg dose.
- Female (19%) subjects had a higher occurrence of vomiting as compared to male (14%) subjects.
- A much higher incidence of reported vomiting was observed in France as compared to the US (24% versus 10%, respectively).
- The majority of first vomiting events occurred within 6 hours of the start of tigecycline treatment.
- As dose increased from 75 to 300 mg, the median time since first dose for the first vomiting event remained in the range of 3 to 6 hours. However, the median duration of first vomiting occurrence increased from less than one hour to approximately 3 hours for the 200 and 300 mg dose groups.
- Approximately 20% of first vomiting occurrences were mild in nature and 44% moderate.

RESULTS *cont'd.*

- As is shown in **Figure 4**, the first occurrence of vomiting appeared to be directly related to AUC; as exposure to tigecycline increased, the incidence of first vomiting increased.
- As with the nausea analysis, the final logistic regression models included only exposure measures, AUC and C_{max}, as significant predictors of the probability of first vomiting occurrence (p < 0.0001 and p = 0.0006, respectively) after multivariable modeling.
- As AUC increased, the model-predicted probability of first vomiting occurrence increased (**Figure 5**).
 - The odds ratio of 1.239 for AUC indicated that for a one-unit increase in AUC, a subject was approximately 23.9% more likely to have a first vomiting occurrence.
 - The Hosmer-Lemeshow goodness-of-fit statistic was 3.03 with 7 degrees of freedom (p = 0.8823) and the area under the ROC curve was 0.82, indicating a predictive model.
 - At the median AUC value of 2.6 μg-hr/mL for the 50-mg dose group, the model-predicted probability of first vomiting occurrence was 0.075.
 - At the median AUC value of 4.7 μg-hr/mL for the 100-mg loading dose, the probability of first vomiting occurrence was 0.11.
- As C_{max} increased, the model-predicted probability of first vomiting occurrence increased, with an odds ratio of 3.271.
 - The Hosmer-Lemeshow goodness-of-fit statistic was 7.32 with 7 degrees of freedom (p = 0.3961) and the area under the ROC curve was 0.70, indicating a model that was slightly less predictive than the AUC model.
 - At the median C_{max} value of 0.39 and 0.92 μg/mL for the 50-mg and 100-mg dose groups, the model-predicted probability of first vomiting occurrence was 0.11 and 0.18, respectively.
 - The AUC model was a better fitting, more predictive model as compared to the C_{max} model.

Figure 4. Frequency Distribution of AUC_{0-∞} Values Stratified by First Vomiting Occurrence

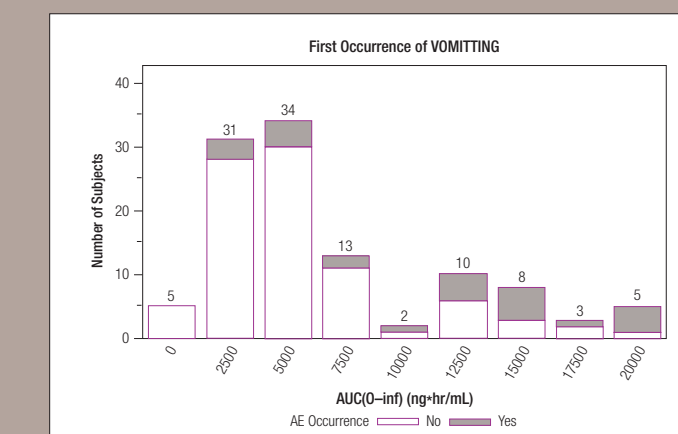
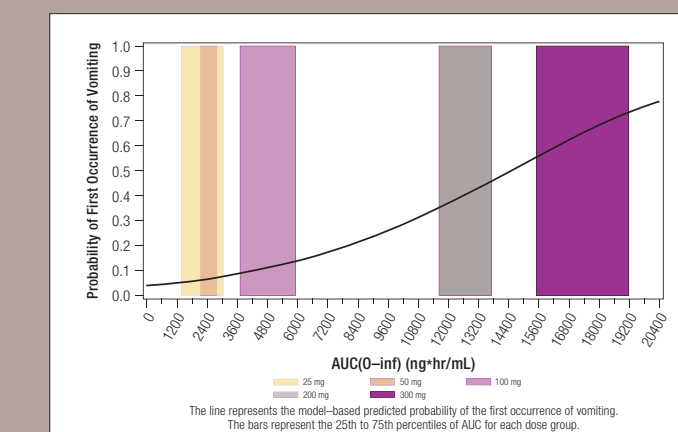


Figure 5. Final Logistic Regression Model for First Vomiting Occurrence versus AUC_{0-∞} Values



CONCLUSIONS

- A statistical model was developed to describe the first occurrence of nausea and vomiting associated with tigecycline exposure in phase 1 subjects, with single doses ranging from 12.5 to 300 mg. This broad range of exposures enabled the identification of a significant exposure-response relationship for tigecycline and these adverse events.
- Both AUC and C_{max} were significant predictors of the probability of first nausea and first vomiting occurrence in this population, with the AUC models slightly more predictive than the C_{max} models.
- These models predict tolerable rates of nausea and vomiting for tigecycline at the targeted dose of 50 mg every 12 hours and are consistent with rates noted in the phase 3 clinical trial programs.