Presented at the
16th ECCMID
European Congress of
Clinical Microbiology and Infectious Diseases
Nice, France
April 1 - 4, 2006

Pharmacokinetic/Pharmacodynamic (PK/PD) Model for the Safety of Tigecycline (T) in Patients with Complicated Intra-Abdominal Infections (cIAI)

AK Meagher,[1] K Liolios,[1] JA Passarell,[1] BB Cirincione,[1] SA Van Wart,[1] J Fiedler-Kelly,[1] T Babinchak,[2] and EJ Ellis-Grosse[2]
[1]Cognigen Corporation, Buffalo, NY and [2]Wyeth Research, Collegeville, PA

For more information, please contact:
Julie A. Passarell
Assistant Director, Statistics
Cognigen Corporation
395 Youngs Road
Buffalo, NY 14221
(716) 633-3463, ext. 266
Julie.Passarell@cognigencorp.com

ABSTRACT

Purpose. Nausea (N) and vomiting (V) have been reported with tigecycline, a new glycylcycline with expanded broad spectrum activity. 140 exposure-response relationships and patient covariates predictive of the first N and V occurrence were evaluated in patients with complicated intra-abdominal infections (cIAI).

Methods. Data from three cIAI studies (one Phase 2 and two Phase 3), receiving 100mg loading dose and 50mg every 12 hours, were pooled for analysis. N and V (classified as definitely, possibly, or probably related) reported from the start of infusion until 24 hours after the last dose were included. Individual exposure measures [$AUC_{SS(0-12)}$ and C_{max}] were calculated using a previously developed population PK model. Logistic regression was used to evaluate predictors of first N and V occurrence. Covariates included age, weight, sex, region of treatment, and baseline N and V.

Results. The dataset included 928 patients (218 with PK). Mean (SD) age and weight were 46 (18) years and 73 (16) kg. 64% of patients were men and 24%, 37%, and 18% were enrolled in North America, Europe, and Latin America, respectively. Baseline nausea or vomiting was reported in 47% and 35%. Overall, N and V occurred in 18% and 13% of patients receiving tigecycline, however most (62%; 67%) of first N and V events were mild in nature. Women had more N and V (23%; 17%) than men (15%; 11%). N and V were lower in Europe (10%; 6%) than in other regions. $AUC_{SS(0-12)}$ and C_{max} were not predictive. The final nausea model included weight, sex, region, baseline nausea, and the interaction of weight/region as predictors of the first nausea occurrence (p=0.671, 0.0006, 0.205, 0.033, & 0.023, respectively). The final vomiting model included weight, sex, region, & 4 interactions (weight/sex, weight/region, sex/region, & weight/sex/region) as predictors of the first vomiting occurrence (p=0.054, 0.819, 0.083, 0.815, 0.02, 0.005, & 0.01, respectively).

Conclusions. $AUC_{SS(0-12)}$ and C_{max} were not predictors of nausea and vomiting events for tigecycline. The final nausea model would predict: nausea to be less in men, Europeans, and in the absence of baseline nausea. The final vomiting model would predict: heavier men, from all regions except Latin America, and heavier women have less vomiting.

BACKGROUND

- Tigecycline, a novel first-in-class glycylcycline, is approved for the treatment of complicated skin and skin-structure infections (cSSSI) and complicated intra-abdominal infections (cIAI).
- Tigecycline has expanded broad spectrum of activity against both gram-negative and gram-positive aerobes, anaerobes, and atypical organisms, including multiple-drug resistant strains.
- This antimicrobial agent appears to be generally well tolerated, with nausea and vomiting as the most frequently reported treatment-emergent adverse events.
- The severity of nausea and vomiting reported in clinical trials of tigecycline was predominantly classified as mild to moderate in nature, and generally occurred within the first few days of therapy.
- Few discontinuations of tigecycline occurred due to nausea and vomiting.
- A statistical model was developed to evaluate the potential influence of demographic characteristics and tigecycline exposure measures ($AUC_{SS(0-12)}$ or C_{max}) on the first occurrence of nausea and vomiting in patients with cIAI.

METHODS

- Data were pooled from patients enrolled in one Phase 2 and two Phase 3 studies.
- The occurrence of nausea and vomiting included any instance reported as “on treatment” and only those events classified as definitely, possibly, or probably related to tigecycline. “On treatment” was conservatively defined as those events observed from the start of the first infusion until 24 hours after the last infusion.
- PK samples were collected per protocol (4 samples per patient); all patients received 100mg/50mg dose (infusion duration was 1 hour in Phase 2 and 30 minutes in Phase 3).
- Observed C_{max} values and individual predicted estimates of steady-state 12-hour AUC values obtained using a tigecycline population PK model were used in the exposure-response analyses.
- The following patient covariates were evaluated as potential predictors of nausea and vomiting: age, weight, sex, region of treatment, and presence of baseline nausea and vomiting.
- All data processing and statistical analyses were performed using SAS® software, Version 8.2.
- Exploratory analysis was performed to assess the overall adverse event rates, and the relationship between the first occurrence of nausea and vomiting and tigecycline exposure measurements/patient demographic characteristics.
- Logistic regression analyses assessed whether exposure measures and covariates were statistically significant predictors of the first occurrence of nausea and vomiting.
- Backward elimination was performed with a level of significance of 0.05.
- 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 occurrence of nausea and vomiting.
- Graphical analysis of antiemetic utilization was performed for the Phase 3 studies.

RESULTS

- 928 patients were included in the PK/PD exposure-response analyses of nausea and vomiting.
- **Table 1** provides summary statistics of the demographic characteristics of the Phase 2 and 3 patients.
  - The mean age was 46 years and ranged from 18 to 91 years.
  - The mean weight was 73 kg, with a range of 39 to 157 kg.
  - Tigecycline exposure measures were available in 218 (23%) patients.
  - Mean (SD) $AUC_{SS(0-12)}$ was 3014 (1114) ng·hr/mL and ranged from 1309 to 11291 ng·hr/mL.
  - Mean (SD) observed C_{max} was 804 (460) ng/mL (range 192 to 2410 ng/mL) after 30 minute infusion; 467 (178) ng/mL (range 171 to 825 ng/mL) after 1 hour infusion.

Nausea

- 18% of patients (167/928 patients) had at least one occurrence of nausea in the Phase 2/3 population.
- Approximately 30% of patients in the Phase 2 trial, 20% of patients in the first Phase 3 trial, and 13% of patients in the second Phase 3 trial experienced at least one occurrence of nausea.
- The majority of first nausea events (69%) occurred within two days of the start of tigecycline treatment.
- The majority of patients who had nausea (61%) had only one occurrence.
- Female patients (23%) had a higher occurrence of nausea compared to male patients (15%).
- A lower incidence of first nausea occurrences was observed in Europe (10%) compared to all other regions: North America (25%), Latin America (27%), and other regions (18%).
- The Kaplan-Meier plot of estimated probability of first nausea occurrence versus study day stratified by dose is provided in **Figure 1**.
- Approximately 62% of first nausea occurrences were mild in nature and 34% were moderate.
- In the subset of patients with PK sampling (n=218), first occurrence of nausea did not appear to be related to $AUC_{SS(0-12)}$ (**Figure 2**).
- Univariate logistic regression models assessing the impact of tigecycline exposure and demographic covariates on the probability of the first occurrence of nausea were evaluated.
  - $AUC_{SS(0-12)}$ and C_{max} were not statistically significant predictors of the probability of first nausea occurrence (p = 0.7641 and 0.4817, respectively) and were eliminated from multivariable modeling.
  - Sex, race, age, region of treatment (grouped as Europe versus all other regions), and baseline nausea were statistically significant predictors of the first nausea occurrence (p = 0.0024, 0.0008, 0.0459, <0.0001, and 0.0116, respectively).
- After multivariable modeling, the final logistic regression model included weight, sex, region of treatment, baseline nausea, and the interaction of weight and region of treatment as significant predictors of the probability of first nausea occurrence (**Table 2**).
  - Patients who experienced baseline nausea tended to have a higher probability of first nausea occurrence than patients who did not experience baseline nausea [odds ratio (OR) 1.461].
  - Female patients tended to have a higher probability of first nausea occurrence than male patients (OR 1.914).
- The Hosmer-Lemeshow goodness-of-fit statistic was 2.85 with 8 degrees of freedom (p = 0.9435).
- The area under the ROC curve was 0.69, indicating an adequate fitting and predictive model.
  - For a male patient at the median weight of 70 kg that did not report baseline nausea, the model-predicted probability of first nausea occurrence was 0.06 and 0.16 for Europe and all other regions, respectively.
  - For a female patient with the same weight and baseline nausea status, the model-predicted probability of first nausea occurrence was 0.11 and 0.27 for Europe and all other regions, respectively.

Vomiting

- A total of 13% of patients (123/928) had at least one occurrence of vomiting.
- The majority of patients who had vomiting had only one occurrence (approximately 65%).
- Approximately 17% of females and 11% of males had at least one occurrence of vomiting.
- A lower incidence of vomiting was observed in European patients (6%) compared to all other regions: North America (15%), Latin America (25%), and other regions (14%).
- As with nausea, the majority of first vomiting events occurred within two days of the start of tigecycline treatment.
- Approximately 67% of first vomiting occurrences were mild and 29% were moderate in nature.
- The Kaplan-Meier plot of estimated probability of vomiting versus study day stratified by dose is provided in **Figure 3**.
- The first occurrence of vomiting did not appear to be related to $AUC_{SS(0-12)}$ (**Figure 4**).
- Using univariate logistic regression, neither $AUC_{SS(0-12)}$ nor C_{max} were statistically significant predictors of the probability of first vomiting occurrence (p = 0.6460 and 0.4845, respectively).
- Sex, race (Black versus all others), age, and region of treatment (grouped as Europe versus North America, Latin America, and Other) were statistically significant predictors of the probability of first vomiting occurrence (p = 0.0249, 0.0178, 0.0116, and < 0.0001, respectively).
- As shown in **Table 2**, the final logistic regression model included weight, sex, region of treatment, the interaction between weight and sex, the interaction between sex and region of treatment, the interaction between weight and region of treatment, and the three-way interaction between weight, sex, and region of treatment as significant predictors of the probability of first vomiting occurrence.
- The Hosmer-Lemeshow goodness-of-fit statistic was 4.39 with 8 degrees of freedom (p = 0.8204).
- The area under the ROC curve was 0.71, indicating an adequate fitting and predictive model.
  - At a median weight of 70 kg, a male patient had a model-predicted probability of first vomiting occurrence of 0.155, 0.146, and 0.036 for Latin America, North America and other regions combined, and Europe, respectively.
  - For a median weight of 70 kg, a female patient had a model-predicted probability of first vomiting occurrence of 0.353, 0.138, and 0.099 for Latin America, North America and other regions combined, and Europe, respectively.

Antiemetic Data

- Of the 817 patients in Phase 3 with and without adverse events, 167 reported using at least one antiemetic at some time during the study.
- Further investigation found that 16% of patients required antiemetic use for the entire treatment interval.
  - 48% of patients with reported antiemetic usage received these medications for up to half of the duration of tigecycline treatment.
- For treatment of nausea and/or vomiting, most patients (77%) used prokinetic agents (primarily metoclopramide), 10% used 5-HT3 antagonists, and 7% were administered antihistaminic agents such as dimenhydrinate (**Figure 5**).

Table 1. Patient Demographics

Demographic Characteristics	Summary Statistics
Age (years) [mean (SD)]	46 (18)
Weight (kg) [mean (SD)]	73 (16)
Sex, n (%)	
Male	590 (64)
Female	338 (36)
Ethnicity, n (%)	
Caucasian	554 (60)
Black	59 (6)
Hispanic	132 (14)
Oriental (Asian)	72 (9)
Other	104 (11)
Region of Treatment, n (%)	
Europe	347 (37)
North America	223 (24)
Latin America	165 (18)
Other	193 (21)

Table 2. Final Logistic Regression Models for the First Occurrences of Nausea and Vomiting

Parameter	p-value Nausea	p-value Vomiting
Weight (kg)	0.6709	0.0535
Sex[a]	0.0006[b]	0.8185
Region of Treatment[c]	0.2051	0.0829
Baseline Nausea[d]	0.0331[b]	NA
Weight and Region of Treatment Interaction[c]	0.0227[b]	0.0202[b]
Weight and Gender Interaction	NA	0.8148
Gender and Region of Treatment Interaction[c]	NA	0.0049[b]
Weight, Gender, and Region of Treatment Interaction[c]	NA	0.0104[b]

[a] Males were used as the reference category.
[b] Indicates a statistically significant predictor of first nausea or vomiting occurrence.
[c] Patients from Europe were used as the reference category.
[d] Patients with no baseline nausea were used as the reference category.

Figure 1. Kaplan-Meier Probability of Nausea

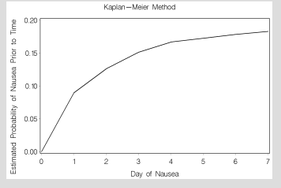


Figure 2. First Occurrence of Nausea

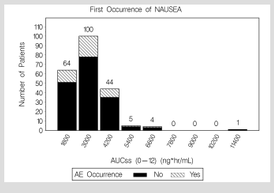


Figure 3. Kaplan-Meier Probability of Vomiting

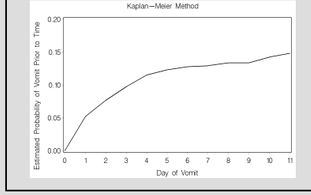


Figure 4. First Occurrence of Vomiting

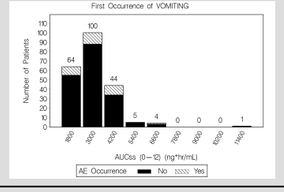
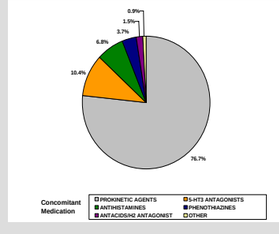


Figure 5. Antiemetic Utilization in Phase 3



CONCLUSIONS

- At least one occurrence of nausea occurred in 18% of patients; 13% of patients experienced at least one occurrence of vomiting.
- Nausea was less likely to occur in men, Europeans, and in the absence of baseline nausea; vomiting was less likely in heavier men from all regions except Latin America, and in heavier women.
- $AUC_{SS(0-12)}$ and C_{max} were not significant predictors of nausea and vomiting in the Phase 2 and 3 patient population.
- The range of AUC values resulting from the 100mg/50mg dose in these Phase 2 and 3 trials, in combination with the small sample size, may not have provided enough power to detect a significant relationship. AUC and C_{max} were previously identified as significant predictors of the probability of the first occurrence of nausea and vomiting (p<0.0001) in analysis of Phase I data (J Passarell, et al. (P894) ECCMID 2004).