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

JA Passarelli, AK Mengher, K Lioles, TH Gresela, T Babichak, EJ Ellis-Grosse
Cognigen Corporation, Buffalo, New York, *Wyeth Research, Collegeville, Pennsylvania

ABSTRACT

Objectives

The demographic characteristics of healthy volunteers for tigecycline were examined to determine if age, weight, height, sex, and disease status were predictive of the first occurrence of nausea and vomiting. A model was developed to predict the probability of nausea and vomiting associated with tigecycline in healthy volunteers.

Methods

Subjects received single-dose oral tigecycline (12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, and 300 mg) in seven phase 1 studies with up to 111 subjects per group. Nausea and vomiting were classified as definitely, possibly, or probably related to tigecycline. Geographical location and race were recorded. 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 all safety analyses were reviewed. A statistical model was developed to examine the relationship between the probability of nausea and vomiting as a function of age, sex, race, disease status, and dose.

RESULTS

A statistical model was developed to predict the probability of nausea occurrence. The relationship between the probability of nausea occurrence and dose is shown in Figure 1. As dose increased from placebo to 300 mg, the median time since first dose for the first vomiting event increased (Figure 2). The Hosmer-Lemeshow goodness-of-fit statistic was 5.18 with 7 degrees of freedom (p = 0.6385) for the model. Only adverse events classified as definitely, possibly, or probably related to tigecycline were considered.

CONCLUSIONS

The Hosmer-Lemeshow goodness-of-fit statistic was 5.18 with 7 degrees of freedom (p = 0.6385) for the model. As AUC increased, the model-predicted probability of first nausea occurrence increased, with an odds ratio of 3.271. The probability of first vomiting occurrence was slightly less predictive with an odds ratio of 2.581.

Figure 1. Predicted probability of nausea occurrence as a function of dose.

Figure 2. Median time since first dose for the first vomiting event as a function of dose.

Figure 3. ROC curve.