Pharmacokinetics (PK) of Tigecycline (TG) in Healthy Adult Volunteers and in Subjects with Renal Impairment

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ABSTRACT

Background:

TG is a novel glycylcycline antibiotic with an expanded spectrum of activity, which includes gram-positive, gram-negative, atypical, and anaerobic pathogens. TG has also shown activity against pathogens resistant to other antibiotics. The goal of this analysis is to summarize the PK of intravenous TG in healthy volunteers and subjects with renal impairment.

Methods:

PK data have been collected and analyzed using noncompartmental methods for 174 subjects in 5 Phase I studies: 3 single intravenous dose (SD) and 2 multiple intravenous dose (MD) studies. This included 6 subjects with severe renal impairment (CrCl<30mL/min) and 8 subjects with end stage renal disease (ESRD) receiving hemodialysis (HD). Doses ranged from 12.5 mg to 300 mg in SD and 25 mg to 100 mg q12h in the MD studies. TG was given under both fasting and fed conditions. Plasma and urine samples were collected and analyzed using validated HPLC or LC/MS/MS methods. PK parameters, including maximum plasma concentration (Cmax), half-life ($t_{1/2}$), area under the concentration-time curve (AUC), total clearance (CLt), and volume of distribution at steady state (Vss), were calculated.

Results:

The plasma concentration-time profile was characterized by a steep decline in the distribution phase during the first 2 hours, followed by a slower terminal phase. Steady state was reached in ~3 days. Healthy volunteer PK values are listed in Table 1. With multiple doses, both Cmax and AUC increased roughly in proportion with dose. CLr accounted for ~20% of CLt and less than 13% of TG was excreted unchanged in urine. CLt was reported to be reduced by ~20% in subjects with severe renal impairment or ESRD. TG was not removed by HD. Results of an SD age and gender study concluded Cmax was lowest in young men and highest in elderly women (26% difference) and AUC was higher in young women than in young men (21% difference), with only a 4% difference between elderly women and men. At the target clinical dose of 100 mg load infused over 30-60 min followed by 50 mg q12h, Cmax and AUC_{ss} (mean ± stdev) were 621±93 ng/mL and 3069±381 ng·h/mL, respectively.

Conclusions:

TG exhibited approximate linear PK across all dose ranges evaluated in multiple-dose studies. TG has a long $t_{1/2}$ with a high Vss, indicating extensive tissue distribution. PK parameters were not significantly affected by food, age, or gender. TG is currently being developed for the treatment of complicated skin/soft tissue and intra-abdominal infections.

INTRO & PURPOSE

- Widespread resistance within the tetracycline class of antibiotics has limited the clinical utility of these agents (1)
- Tigecycline, an analog of minocycline, is the first in a novel class of glycylcycline antibiotics to reach clinical trials
- Bacteria that carry any of the classical tetracycline resistance genes conferring either ribosomal protection or a tetracycline efflux pump remain susceptible to tigecycline (2)
- Tigecycline has an expanded spectrum of activity, which includes gram-positive, gram-negative, atypical, and anaerobic pathogens
- Tigecycline has demonstrated impressive activity against multiple-drug resistant gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococcal species (VRE)
- As an agent that could restore therapeutic utility to the tetracycline class of antibiotics, tigecycline provides activity against emerging multidrug-resistant pathogens
- The safety, tolerability, and pharmacokinetics of intravenous tigecycline, given under both fasting and fed conditions, have been assessed in single-dose and multiple-dose Phase I clinical studies
- This analysis provides a comprehensive summary of PK results in healthy subjects from five completed Phase I studies
- This analysis also explores the influence of subject covariates, including age, gender, race, and renal dysfunction, upon the PK of tigecycline
- The results of this analysis will be used as the foundation for development of a robust population PK model, which will be used to characterize exposure-response relationships for patients in Phases II and III of clinical development

METHODS

- Intravenous TG was administered to and PK samples were collected in 174 subjects in 3 single-dose (SD) and 2 multiple-dose (MD) studies:
  - Single doses ranged from 12.5 to 300 mg, given under both fasting and fed conditions
  - Multiple doses ranged from 25 to 100 mg given twice daily for 10 days
  - Infusion durations ranged from 0.5 to 4 hours
- Subjects enrolled included young, healthy male and female subjects, elderly male and female subjects, subjects with severe renal impairment (CrCl<30mL/min), and subjects with end stage renal disease (ESRD) receiving hemodialysis (HD).
- Plasma and urine samples were collected following intensive sampling strategies and analyzed using validated HPLC or LC/MS/MS methods (LLQ = 25 ng/mL)
- PK data were analyzed using noncompartmental methods (3)
- PK parameters included maximum plasma concentration (Cmax); half-life ($t_{1/2}$); area under the concentration-time curve (AUC); total clearance (CLt); and volume of distribution at steady state (Vss)
- Graphical displays of PK parameters and patient descriptors were evaluated for trends and relationships
- Nonparametric tests (Kruskal-Wallis, alpha = 0.01) were used to explore the relationships between the PK parameters and patient descriptors stratified by dose levels, duration of infusion, and treatment day
- If significant differences in PK parameters were identified across dose arms, the select parameter was normalized to the 100 mg dose group for all subsequent analyses
- For PK parameters displaying a strong relationship to total body weight:
  - If the intercept value of the regression was not found to be significantly different from zero, the PK parameter was proportionally adjusted for total body weight;
  - If the intercept value of the regression line was significantly different than zero, simply dividing the parameter by weight would not remove this relationship and exploration of the parameter was performed comparing populations with similar weight ranges
- All statistical analyses were done using SAS® Version 8.2

RESULTS

Figure 1: CLt (L/h/kg) versus race for normal healthy young subjects on Day 1

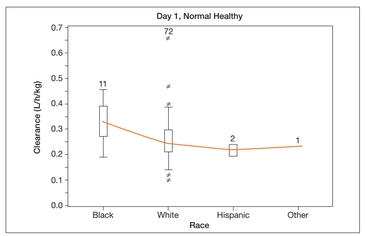
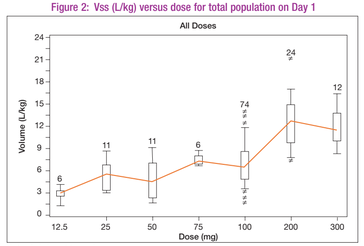
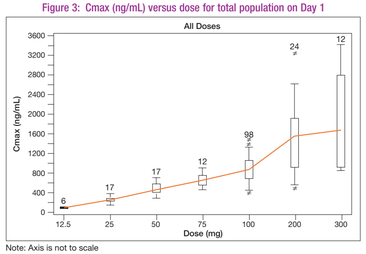


Figure 2: Vss (L/kg) versus dose for total population on Day 1



Note: Axis is not to scale

Figure 3: Cmax (ng/mL) versus dose for total population on Day 1



Note: Axis is not to scale

Figure 4: Dose Normalized Cmax (ng/mL) versus age category for healthy subjects on Day 1 following a 1-hour infusion

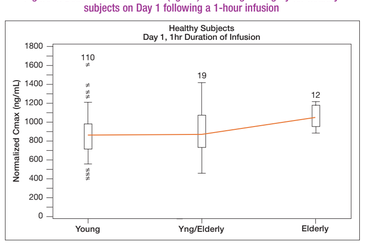
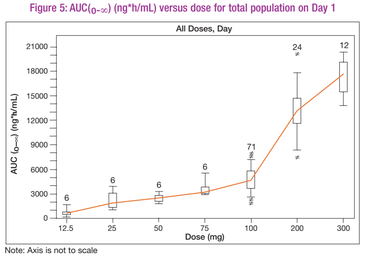
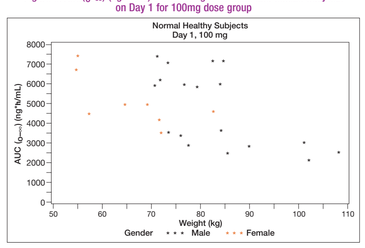


Figure 5: $AUC_{(0-\infty)}$ (ng*h/mL) versus dose for total population on Day 1



Note: Axis is not to scale

Figure 6: $AUC_{(0-\infty)}$ (ng*h/mL) versus weight for male and female Subjects on Day 1 for 100mg dose group



RESULTS

- **Area under the concentration-time curve (AUC, ng·h/mL)**
  - All Day 1 evaluations were performed using $AUC_{0-\infty}$ and all Day 10 evaluations utilized AUC_{ss}
  - Median AUC values on Day 1 ranged from 665 to 17,711 ng·h/mL for doses ranging from 12.5 to 300 mg, respectively
  - Boxplots of Day 1 AUC values revealed a less than proportional increase in AUC values across some dosage groups (Figure 5)
  - A large degree of inter-individual variability in the kinetics of tigecycline was displayed and comparable AUC values on Day 1 and Day 10 were not available in the same subjects. Therefore, no direct comparison of AUC from Day 1 to Day 10 could be made
  - Dose normalization did not remove the significant differences in AUC values across doses and thus, exploration of AUC was performed using the 100 mg dose group on Day 1, comparing subjects in similar weight ranges (n=26)
    - Within a similar weight range, median AUC values were 5942 and 4781 ng·h/mL for male and female subjects, respectively (Figure 6)
    - Although there was a slight trend for AUC to decrease in black versus non-black subjects, the difference was not significant (p=0.09)
    - The elderly population (76+ years) experienced a slightly higher AUC (approximately 10% greater) than the young healthy population with no discernable difference noted between the young and the young elderly subjects (p=0.11)
    - The AUC in ESRD subjects (n=8) was ~23% lower than the healthy population within the same weight range
    - Subjects with severe renal impairment (n=6), however, experienced similar AUC values compared to healthy subjects within the same weight range

RESULTS

- **Study population description**
  - PK data were collected from 174 subjects
  - One MD study contributed only Day 1 Cmax values (n=19)
  - Ages ranged from 19 to 84 years of age [mean (sd), 40.1 (17.5)]
  - Mean (sd) weight (kg) was 75.8 (12.5) kg with a range from 49.6 to 112.1 kg
  - Creatinine clearance, as calculated using Cockroft and Gault, ranged from 4.9 to 186 mL/min (4)
  - Approximately 14% of the population was female (n=25) and the population was 69.5% white (n=121), 26.4% black (n=46), and 4% other (n=7)
- **Healthy volunteer PK values (mean ± sd) are listed in Table 1**
  - The plasma concentration-time profile was characterized by a steep decline in the distribution phase during the first 2 hours, followed by a slower terminal phase
  - Steady state concentrations were reached in ~3 days

Table 1: Pharmacokinetic parameters for tigecycline (mean ± sd)

PK parameter	Dose (mg), with MD given q12h						
	12.5	25	50	75	100	200	300
SD CLt (L/hr/kg)	0.29±0.20 (n=6)	0.20±0.10 (n=6)	0.28±0.04 (n=6)	0.29±0.04 (n=6)	0.30±0.08 (n=57)	0.23±0.04 (n=24)	0.25±0.03 (n=12)
MD CLt (L/hr/kg)	---	0.20±0.04 (n=5)	0.20±0.02 (n=5)	---	0.24±0.045 (n=3)	---	---
SD AUC_{∞} (ng·h/mL)	753±515 (n=6)	2255±1023 (n=6)	2558±534 (n=6)	3658±1003 (n=6)	4872±1405 (n=57)	13211±2796 (n=24)	17294±2176 (n=12)
MD AUC_{ss} (ng·h/mL)	---	1482±259 (n=5)	3069±381 (n=5)	---	4980±925 (n=3)	---	---
SD $t_{1/2}$(h)	11±10 (n=6)	32±20 (n=6)	18±3.6 (n=6)	22±5.3 (n=6)	22±10 (n=57)	52±12 (n=24)	44±7.8 (n=12)
MD $t_{1/2}$(h)	---	49±35 (n=5)	37±12 (n=5)	---	66±23 (n=3)	---	---
SD Vss (L/kg)	2.8±0.95 (n=6)	6.4±1.3 (n=6)	6.5±2.0 (n=6)	7.5±0.77 (n=6)	6.8±2.5 (n=57)	13±3.3 (n=24)	12±2.4 (n=12)
MD Vss (L/kg)	---	4.0±1.2 (n=5)	2.4±0.66 (n=5)	---	2.9±1.4 (n=3)	---	---
SD Cmax after 1hr infusion (ng/mL)	109±11 (n=6)	252±63 (n=6)	383±64 (n=6)	566±78 (n=6)	927±224 (n=57)	1787±525 (n=18)	2817±479 (n=12)
MD $Cmax_{ss}$ after 1hr infusion (ng/mL)	---	324±54 (n=5)	621±93 (n=5)	---	1173±176 (n=3)	---	---

- **Evaluation of PK parameters**
  - In order to avoid any potential confounding of results, the following subject populations were evaluated for each parameter:
    - Total Subject Population
    - Normal Healthy Subjects (aged 18-50 years with normal renal function)
    - Elderly Subjects (young elderly aged 51-75 years, n=19; elderly aged >75 years, n=12)
    - Renally Impaired and ESRD Subjects (severe renal impairment, n=6; ESRD, n=8)
- **Total Clearance (CLt, L/h/kg)**
  - Total Subject Population Exploration
    - Initial graphical displays revealed a strong relationship between total body weight and CLt (L/h) of tigecycline, therefore all explorations were performed on CL adjusted proportionally for body weight (L/h/kg)
    - Median CLt ranged from 0.20 to 0.31 L/h/kg
  - Normal Healthy Subject Exploration
    - A wide inter-individual variability in CLt was noted within the normal subject population
    - The exploration of CLt across all doses (p=0.015), days (p=0.014), and duration of infusion (p=0.18) did not reveal any statistically significant differences
    - There was a slight increase (p=0.0048) in CLt for female subjects (n=8) versus males (n=90): median CLt 0.302 and 0.230 L/h/kg for female and male subjects, respectively
    - Comparing CLt on Day 1 for normal healthy young subjects (median CLt=0.240) versus black subjects (median CLt=0.325) revealed a significant difference between groups (p=0.0018), with a 35% increase in median CLt for black subjects (Figure 1)
  - Exploration of the Effect of Advanced Age
    - There were no significant differences in CLt by age (young, young elderly, and elderly, p=0.32)
  - Exploration of the Effect of decreased Renal Function
    - In one single dose study, CLt was reduced by ~20% in subjects with severe renal impairment or ESRD, as specified by the randomization procedure, the comparative normal population (n=8) was older as compared to the other healthy volunteer studies included in this analysis
    - By pooling several Phase I studies, the percentage of normal, healthy, white, young male subjects was increased and therefore, there was a slight trend for CLt to increase with decreasing CrCL (p=0.0168)
      - ➤ However, 10 of the 14 subjects with decreased renal function were black [2 (33%) in the severe renal impairment group and 8 (100%) in the ESRD group] and 4 of the 14 subjects were female (1 with severe renal impairment and 3 with ESRD]. Female and black subjects tended to have higher CLt values compared to male and non-black subjects, respectively. Therefore, the apparent trend for increased CLt with decreasing renal function was most likely due to confounding factors
  - Renal clearance is a minor component of total clearance of tigecycline with <13% excreted in urine as unchanged drug
- **Volume of distribution at steady state (Vss, L/kg)**
  - There was a trend for Vss to increase with increasing dose due to the multi-compartment nature of the drug and the ability to detect drug concentrations above the detection limit of the assay for a longer period of time (Figure 2)
  - Median Vss ranged from 2.95 to 12.7 L/kg across dose levels and treatment days
  - Vss was lower on Day 10 versus Day 1 (p<0.001), possibly due to a saturable binding process. Within the 25, 50, and 100 mg dose arms, median Vss on Day 1 was 6.05, 5.95, and 7.00, respectively, while Vss on Day 10 was 3.30, 2.30, and 2.22. However, there were only 13 evaluable subjects on Day 10 (n=5 at 25mg, n=5 at 50mg, and n=3 at 100mg)
  - There were no significant differences in Vss by age category, gender, or race
  - There was a slight trend for increased Vss with decreasing renal function, with little difference between the subjects classified as severe renal impairment and those with ESRD (p=0.043)
- **Half-life ($t_{1/2}$, h)**
  - Median $t_{1/2}$ for the 50, 75, 100, 200 and 300 mg dose arms on Day 1 were 16.5, 20.0, 22.75, 49.0 and 44.0 hours, respectively (p<0.001)
  - $t_{1/2}$ was longer on Day10 versus Day1 (p=0.273 for 25mg, p=0.0174 for 50mg, and p=0.0081 for 100mg group), however, there were only 13 evaluable subjects on Day10
  - $t_{1/2}$ was slightly decreased in female subjects and black subjects, however, the differences were not significant
  - There was no difference in $t_{1/2}$ based on age or renal function
- **Maximum serum concentration (Cmax, ng/mL)**
  - Cmax increased roughly in proportion to dose, with values ranging from 109 ng/mL at the 12.5 mg dose to 2798 ng/mL at the 300 mg dose on Day1 following a 1 hr infusion (Figure 3)
  - An approximate 30% increase in Cmax was noted on Day 10 for the 13 subjects who contributed Cmax values on both Day1 and Day10
  - In comparing male subjects (n=67) to female subjects (n=8) within the same weight range (54.4-82.8 kg), there was a trend for females to experience a higher dose-normalized Cmax
  - There was no difference in dose-normalized Cmax between black and non-black subjects
  - Despite a similar distribution of weight across all 3 age categories, a statistically significant difference in normalized Cmax versus age category (p<0.001) was found at the 100mg dose on Day 1, with elderly subjects (76+ years) experiencing a higher normalized Cmax (approximately 20% greater) than the young healthy population (Figure 4)
  - The severe renal impairment subjects (n=6) tended to be heavier than the ESRD subjects (n=8) and experienced a lower normalized Cmax as compared to the healthy population within the same weight range
  - The ESRD subjects experienced similar normalized Cmax values compared to the healthy subjects within the same weight range

CONCLUSIONS

- Tigecycline exhibited approximate linear PK across all dose ranges evaluated in multiple-dose studies
- Tigecycline has a long $t_{1/2}$ with a high Vss, indicating extensive tissue distribution
- Slight trends for differences in PK parameters for age, race and gender were identified:
  - Female subjects tended to have higher CLt, lower Vss, shorter $t_{1/2}$, and higher Cmax values versus male subjects
  - Black subjects tended to have higher CLt, lower Vss, and shorter $t_{1/2}$ than non-black subjects
  - Elderly subjects had significantly higher Cmax values versus young subjects
  - Due to the small sample size of these subpopulations, however, the clinical significance of these differences will be further evaluated in a subsequent population analysis
- Within this population, the PK of tigecycline was not affected by severe renal impairment or ESRD, including hemodialysis
- Tigecycline is currently being developed for the treatment of complicated skin and skin structure and intra-abdominal infections

Reference List

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