Serum and urine pharmacokinetics of tigecycline in obese class III and normal weight adults

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Objectives: To compare the serum and urine pharmacokinetics (PK) of intravenous tigecycline in obese class III (obese-C3) adults with those in normal weight (NW) adults.

Patients and methods: Obese-C3 (n = 8) and NW (n = 4) healthy adult volunteers received a single intravenous dose of 100 mg of tigecycline for 30 min. Serum (0–96 h) and urine (0–48 h) tigecycline concentrations were assayed by liquid chromatography with tandem mass spectrometry. Parametric population PK systems analyses were used to model the data and assess the effects of total body weight (TBW) on PK parameters. The area under the concentration–time curve extrapolated to infinity (AUC0–\text{\infty}) was simulated to estimate the probability of AUC0–\text{\infty}:MIC target attainment and cumulative fraction of response (CFR) based on wild-type MIC distributions of select pathogens. Clinicaltrials.gov: NCT01560143.

Results: The median (range) age, TBW and initial body mass index were 42 (20–50) years, 121 (61–160) kg and 43.8 (20.8–53.8) kg/m², respectively. The serum concentration–time profiles and exposures were similar in the obese-C3 and NW adults, with a mean urine recovery of 15.8% and 13.4%, respectively. The median (range) AUC0–\text{\infty} was 8.19 (6.12, 11.2) and 7.50 (6.78, 9.13) mg·h/L in the obese-C3 and NW groups, respectively. The clearance of tigecycline was not related to TBW. The CFR was calculated to be <90% against Acinetobacter baumannii, Enterobacter cloacae and Klebsiella pneumoniae for an AUC0–\text{\infty}:MIC target \geq 6.96.

Conclusions: The serum and urine PK of tigecycline is similar in obese-C3 and NW healthy adults. A lower CFR is predicted against certain Gram-negative pathogens with the current standard tigecycline dosing regimen, irrespective of TBW.

Keywords: obesity, pharmacodynamics, minocycline, pharmacology, glycylcyclines

Introduction

Tigecycline (Tygacil®) is a marketed intravenous (iv) antimicrobial drug that is used at a fixed dose without regard to weight for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections and community-acquired bacterial pneumonia. Recent meta-analyses have suggested a higher risk of mortality with tigecycline monotherapy relative to comparators, especially when used in patients with ventilator-associated pneumonia (non-regulatory approved). Low systemic exposure, as evaluated by the AUC, of tigecycline has been postulated as one explanation for this inferior response with the current dosing. This association is plausible because the tigecycline AUC:MIC ratio is the pharmacokinetic (PK)/pharmacodynamic (PD) index that has been correlated to clinical response. Furthermore, population PK (POP-PK) studies have linked body size as a covariate of systemic tigecycline clearance (CL). As a result, the potential for low tigecycline exposures in larger individuals (obese adults) with fixed dosing could in part contribute to poor clinical response. 

This potential for low tigecycline exposures in obese patients is problematic because 26% and 36% of adults currently have a body mass index (BMI) ≥ 30 kg/m² in England and the USA, respectively. Obesity contributes to physiological changes such as glomerular hyperfiltration that can in theory enhance the clearance of drugs like tigecycline. Tigecycline and its metabolites are primarily (59%) eliminated through the faeces relative to urine (32%). Previous POP-PK studies have identified measures of kidney function, such as creatinine clearance (CLCR), to be predictive of tigecycline CL. However, most equations used to estimate CLCR include body weight as a parameter and so confound the independent assessment of tigecycline CL to body weight and CLCR. As a consequence, the effects of obesity on the serum and urine concentration–time profiles of tigecycline are not well known. The increasing isolation of multidrug-resistant bacterial pathogens such as the carbapenemase-producing Enterobacteriaceae demands that we continue to optimize the dosing of tigecycline. These multidrug-resistant pathogens can be common in patients with urinary tract infections for which tigecycline is not clinically indicated.
the primary objective of the current study was to use a POP-PK approach to compare serum and urine tigecycline PK among obese class III (obese-C3; ≥40 kg/m²) and normal weight (NW; 18.50–24.99 kg/m²) adult volunteers. The secondary objective of this study was to characterize the probability of target exposure attainment with the current fixed-dose regimen of tigecycline against key pathogens using the developed POP-PK model.

Patients and methods

Regulatory review

The current study met the requirement for a waiver of Investigation New Drug application (IND Exempt #113517). The study was approved by the Albany College of Pharmacy and Health Sciences Institutional Review Board and through IntegReview (Austin, TX, USA). This clinical trial was registered through clinicaltrials.gov; the registry number is NCT01560143.

Subjects

Subjects fulfilling the following criteria were eligible: (i) males and females, 18–50 years of age; (ii) non-smoking or light-smoking (five or fewer cigarettes per day) volunteers; (iii) BMI 18.50–24.99 kg/m² (NW) or ≥40 kg/m² (obese-C3); and (iv) female subjects of childbearing potential (self-reported) either surgically sterilized, using an effective method of contraception (diaphragm, cervical cap or condom) or agreeing to abstain from sex from the time of pre-study screening, during the entire study period and for 1 month following the study period. All volunteers underwent a physical examination, review of their medical history and clinical laboratory evaluation. Volunteers were excluded if they: (i) had a history of significant hypersensitivity reaction to any components of tigecycline; (ii) had a history of significant clinical illness requiring pharmacological management; (iii) had a history of blood donation in the past 8 weeks; (iv) had an abnormal serum electrolyte or complete blood count requiring further clinical work-up; (v) had an abnormal bilirubin or transaminases (aspartate aminotransferase or alanine aminotransferase) >2.5x upper limit of normal; (vi) had stage 4 or 5 chronic kidney disease; (vii) had a positive pregnancy test (if female); (viii) had an abnormal electrocardiogram as judged by the study physician; (ix) were unable to tolerate venepuncture and multiple blood draws; (x) had a clinically significant abnormal physical examination defined as a physical finding requiring further clinical work-up; and (xi) were unable to independently provide a written informed consent. A total of 12 subjects (8 obese-C3 and 4 NW subjects) were recruited for this study.

Study design

This was a prospective, open-label, single-dose PK study that included a 96 h blood sample collection period, given the long mean half-life of tigecycline (38 h). The subjects consumed a standardized medium-fat (20%–30%) breakfast 15–45 min prior to the infusion of tigecycline in order to reduce the potential for nausea. The tigecycline (Tygaci1, New York City, NY, USA) doses used in this study were provided by the manufacturer from a single lot. The single iv dose of 100 mg of tigecycline (100 mL of normal saline) was administered over 30 min. Assessment of vital signs and laboratory assays were performed for each volunteer prior to the start of the study. Study personnel monitored and questioned each subject for any adverse event during the in-house collection sample collection period and at every visit. Adverse events were graded by study personnel according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

Blood and urine sample collection

Blood samples (5 mL) were collected via direct venepuncture or midline indwelling catheter into glass serum collection tubes (BD, Franklin Lakes, NJ, USA). Serial blood samples were collected as follows: 0 (just prior to the dose), 0.5 (end of infusion), 1.5, 3, 6, 9, 12, 24, 48, 72 and 96 h after the dose. All blood samples were allowed to clot for ≥30 min and then centrifuged at 1200 g for 10 min at 4°C within 60 min of collection. The serum was separated from the cells and stored at −20°C for the initial 12 h collection period and then at −70°C until assay. Urine samples were collected over five periods from each subject, including (i) pre-dose and (ii) 0–6 h, (iii) 6–12 h, (iv) 12–24 h, and (v) 24–48 h after the dose. Urine was stored at 2–8°C during the collection period, the volume measured at the end of the collection period and aliquots stored at −70°C until assay.

Tigecycline stability in urine

A portion of the pre-dose urine collected from each of the initial group of research subjects was pooled into a single batch. Tigecycline (Tygaci1) was reconstituted per the product label and subsequently diluted with this pooled urine to four nominal concentrations of 100, 10, 0.1 mg/L and incubated at 4°C (2–8°C excursions permitted). The nominal concentrations were based on the average expectation of 15% recovery of 1°C tigecycline in urine from mass balance studies over 48 h.12 Aliquots were sampled from each nominal concentration tube at 0 (baseline), 6, 12, 24 and 48 h of incubation and stored at −70°C until assay. This procedure was performed to mimic the urine collection and sample storage schema prior to assay.

Tigecycline assay

Blood and urine samples were quantified for tigecycline using a validated high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay. Briefly, [1-butyl-d9]-tigecycline served as the internal standard and deproteinization (serum) was achieved using a combination of trifluoroacetic acid and ammonium trifluoroacetate solution. Separation was performed using a Phenomenex® Synergi Hydro RP column (Torrance, CA, USA), 2.0 × 100 mm (4 μm particle size), with an isocratic flow of trifluoroacetic acid and 4 mM ammonium trifluoroacetate solution in 89:11 (v:v) deionized water:acetonitrile (mobile phase A) mixed post-column with 2.5 mM ammonium trifluoroacetate solution in 95.5:4.5 (v:v) methanol:deionized water (mobile phase B). Detection of the analyte (tigecycline) and the internal standard was achieved using a Scieix API 4000 triple quadrupole LC-MS/MS system (Framingham, MA, USA) equipped with a TurboIonSpray® ionization source that was operated in the positive ion mode with multiple reaction monitoring. The mass-to-charge (m/z) transitions were (i) tigecycline m/z 586.5 → m/z 513.2 and (ii) [1-butyl-d9]-tigecycline m/z 595.5 → m/z 514.2, with a retention time of 1.6–2.6 min. The calibration curves ranged from 10 to 2000 ng/mL and included six independent quality control (QC) samples for each concentration at 25, 200 and 1500 ng/mL. The mean accuracy (%bias) and precision (%coefficient of variation (%CV)) for the serum QC samples was ±4.9% and ±6.0%, respectively. The limit of quantification for tigecycline was 10 ng/mL. Similar procedures were performed for the urine samples but included independent QC samples at 0.5, 7.0 and 70 ng/mL. The mean accuracy and precision for the urine QC samples was ±8.7% and ±4.6%, respectively.

POP-PK model development

Parametric POP-PK systems analysis was performed using ADAPT 5, developed by David D’Argenio, Alan Schumitzky and Xiaoning Wang at the Biomedical Simulations Resource, University of Southern California.15 The maximum likelihood expectation maximization algorithm that was used includes two steps. The first step (E-step) estimates system parameters.
using the latest predicted parameter values and the observed data. In the second step (M-step), the parameter values are changed to maximize the log-likelihood function of the first step. These new values are then reused for the subsequent iteration. To prevent linearization approximation and a biased estimate of the integral, an importance sampling procedure was used. This procedure included selection of 1000–3000 samples (2000 samples were used) to approximate the integrals in the E-step. The initial exploratory approach included stepwise modelling of the serum concentration–time profile of tigecycline using a one-, two- and three-compartment model, with zero-order input and first-order output and transfer between compartments. After this initial approach, the serum and urine concentrations were modelled using a linear three-compartment \((X_1, X_2, X_3)\) system with two additional compartments \((X_4, X_5)\) to define the urine concentrations, as illustrated in Figure 1. The model included \(R_1(t)\) to represent the rate of tigecycline infusion; \(V_1\) as the volume of the central compartment; \(V_2\) and \(V_3\) as the volume terms of the respective peripheral compartments; \(CL_1\) and \(CL_3\) as the intercompartment distribution clearance between the respective central and peripheral compartments; \(CL_1\) as the clearance from the central compartment; and \(CL_R\) as renal clearance from the central to the urine compartment. The urine compartment was used to define the amount of drug in the urine \((X_4)\) during collection with urine volume \([R_5(t)]\) during each collection period \((X_5)\). The initial condition of the compartments labelled \(X_2\) and \(X_3\) were set to 0.0 at the end of each urine collection period. Discrimination between the initial and alternate models was accomplished by the rule of parsimony based on Akaike's information criterion (AIC). An additive and proportional error variance model was used to estimate the relationship between measured serum and urine concentrations and variance. The additive component was fixed (SD intercept) and the proportional component (SD slope) was fitted for the population. Covariates of system parameters were evaluated post hoc through a review of scatterplots followed by linear and power-function regression analysis. Significant covariates were introduced into the structural model as linear or power functions and final model selection was based on AIC.

**POP-PK model evaluation**

Evaluation of the final POP-PK model was performed using diagnostic plots. The diagnostic plots included population and individual predicted versus observed plots, weighted residuals versus model-predicted concentration, and normalized prediction distribution error (NPDE) versus time. The predictive check of the final POP-PK model was performed via Monte Carlo simulation of 5000 subjects to compare concentration–time and area under the serum concentration–time curve integrated to: 12 h \((AUC_{0-12})\); 24 h \((AUC_{0-24})\); 48 h \((AUC_{0-48})\); 72 h \((AUC_{0-72})\); 96 h \((AUC_{0-96})\); and infinity \((AUC_{0-\infty})\). A visual predictive check was also performed by overlaying the model-simulated median, 5th percentile and 95th percentile predicted concentrations over the observed concentrations. Eta shrinkage was also evaluated to ensure that the model was appropriate for inclusion of covariates into the model and for dosing simulations. The POP-PK model estimates of \(AUC_{0-\infty}\) were compared with those derived by non-compartmental analysis using STATA/SE version 11 (Stata Corp., College Station, TX, USA) by the linear-trapezoidal method with extrapolation to infinity. The simulation was based on a single dose of 100 mg of tigecycline infused over 30 min.

**Probability of target attainment (PTA)**

Previous PK/PD analyses defined PTA for tigecycline based on the ratio of the steady-state \(AUC_{0-24}/\text{MIC}\) or alternatively as \(AUC_{0-\infty}/\text{MIC}\). Target values of \(AUC_{0-24}/\text{MIC} \geq 6.96\) and 12.5 or \(AUC_{0-\infty}/\text{MIC} \geq 3.10\) have been reported to be predictive of clinical response. As a consequence, \(AUC_{0-24}\) was simulated \((n=5000)\) after the end of a standard 14 day dosing schema of 100 mg iv dose (loading \(x1\) dose) followed by 50 mg every 12 h (maintenance \(x2\) doses), as 30 min infusions. The tigecycline serum \(AUC_{0-24}\) values were compared with \(AUC_{0-\infty}\) values that were derived from the single 100 mg iv dose (30 min infusion) simulation. The PTA for achievement of the three aforementioned targets was determined for a log2 MIC range of 0.03125–16 mg/L. Finally, given publication of the wild-type MIC distributions for *Acinetobacter baumannii* \((n=190)\), *Enterobacter cloacae* \((n=242)\), *Escherichia coli* \((n=1871)\), *Klebsiella pneumoniae* \((n=894)\) and *Staphylococcus aureus* \((n=1363)\) by EUCAST, the cumulative fraction of response (CFR) was calculated as:

\[
\sum_{i=1}^{n} PTA_i \times F_i
\]

where \(i\) is the MIC category ranked from the lowest to the highest MIC value of a population of microorganisms, \(PTAi\) is the PTA for the \(i\)th MIC category, and \(Fi\) is the fraction of the population of microorganisms for the \(i\)th MIC category.

**Statistical analyses**

Individual POP-PK parameter and \(AUC_{0-\infty}\) estimates (including non-compartmental) were compared using the Wilcoxon signed rank test. Computation of NPDE was performed based on the approach developed by Comets et al. using R version 2.15.3 (The R Foundation for Statistical Computing). Scatterplots, linear and non-linear (power, polynomial etc.) regression models and graphs were created using STATA/SE version 11 (Stata Corp.).

**Results**

**Subjects and tolerability**

Twelve (8 obese-C3 and 4 NW) adults with a mean (SD) age of 37.5 (10.5) years completed the study. The mean (SD) height was similar in the obese-C3 \((168.8 (13.3)\) cm) and NW \((172.6 (6.04)\) cm) groups. The mean (SD) weight was 135 (4.7) and 65.3 (4.98) kg in these two groups, respectively, with an overall median (range) weight of 121 (61–160) kg for the population. The majority of subjects were female \((n=8)\) and white \((n=7)\). The median (range) serum creatinine was 73.4 (49.5, 95.5) mmol/L. The median (range) estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation was 99 (81.3, 109) ml/min/1.73 m² in the NW group and 103 (97.0, 126) ml/min/1.73 m² in the
obese-C₃ group. Gastrointestinal adverse events were reported by three subjects (25%) and were graded as mild nausea in two obese-C₃ subjects and moderate nausea in one NW subject. This NW subject also experienced an episode of emesis. These adverse events began 3–4 h after the tigecycline was infused and resolved without any medical interventions.

**Tigecycline concentration–time profiles**

The concentrations observed in NW were similar to those observed in the obese-C₃ subjects at each timepoint. As illustrative examples, the median concentrations (at 0.5, 3 and 12 h) in NW subjects (1617, 270.7 and 119.2 ng/mL, respectively) were comparable to those observed in obese-C₃ subjects (1603, 237.5 and 105.4 ng/mL, respectively). The maximum concentration in serum was observed at the end of infusion (0.5 h) and declined in a triphasic manner over the 96 h period. Similarly, the tigecycline concentration observed in urine was comparable in NW and obese-C₃ subjects and was markedly variable during the 0–6 h collection period (Figure 2a). The mean (SD) urine concentrations (mg/L) for the 0–6, 6–12, 12–24 and 24–48 periods were 22.45 (11.41), 5.931 (2.703), 4.025 (2.539) and 2.325 (1.003), respectively. The mean

![Figure 2](https://academic.oup.com/jac/article-abstract/69/1/190/848358)
(SD) cumulative percentage recovery of tigecycline in urine was 13.4% (3.20) and 15.8% (4.83) in the NW and obese-C3 groups, respectively. As shown in Figure 2(b), two obese female patients demonstrated a higher cumulative percentage recovery (>25%) than the average tendency. This deviation from average tendency could not be explained by any covariates of kidney function. No significant \((P > 0.2)\) change in tigecycline concentrations were observed between 0 and 48 h measurements of the urine stability experiment for any of the four nominal concentrations. The geometric mean (90%) CI ratio of the observed to the nominal urine concentration was 98.76% (97.29%, 100.3%) for the tigecycline urine stability experiment.

**POP-PK**

A stepwise summary of the models evaluated and parameter estimates is provided in Table 1. As shown, the model fit improved significantly with the use of a three-compartment system and was further improved by comodelling serum and urine concentrations (Model 4, final) as illustrated in Figure 1. The population and individual model-predicted concentrations to observed concentrations, weighted residuals to predicted concentrations and NPDE versus time are all provided in Figure 3. A visual predictive check of the population predicted serum concentrations and exposures mimicked those observed and estimated by non-compartmental analysis (Table 2). Although not statistically significant, the median (minimum, maximum) AUC\(_{\text{0-24h}}\) by non-compartmental analysis was 8.19 (6.12, 11.2) and 7.50 (6.78, 9.13) mg·h/L in the obese-C3 and NW groups, respectively.

**PTA**

As indicated in the methods, the PTA of tigecycline has been defined in the literature based on AUC\(_{0-\text{MIC}}\) and AUC\(_{0-24h}\). As a consequence, AUC\(_{0-24h}\) was calculated by simulation of the current standard tigecycline regimen over 14 days. The mean (SD) AUC\(_{0-24h}\) was 7.61 (1.26) mg·h/L, which was virtually identical to the estimated AUC\(_{0-\text{MIC}}\), with a single infusion of 100 mg of tigecycline reported above. Given this close result, the specified PTA was based on achievement of the AUC\(_{0-\text{MIC}}\) targets of \(\geq 3.10, \geq 6.96\) and \(\geq 12.5\) against the specific bacterial pathogens. Table 3 summarizes the CFR and the MIC values where \(\geq 90\%\) PTA was expected by target value and pathogen with the current dosing. The individual pathogen-specific wild-type MIC distribution and PTA information are provided in Tables S1 to S5 (available as Supplementary data at JAC Online). As shown in Table 3, the CFR was \(\geq 90\%\) if the AUC\(_{0-\text{MIC}}\) target of \(\geq 3.10\) is considered to be the optimal breakpoint for all pathogens. When considering *E. coli* and *S. aureus* as pathogens, a CFR \(\geq 90\%\) is predicted irrespective of the AUC\(_{0-\text{MIC}}\). In contrast, CFRs of \(\leq 71.2\%\), \(\leq 56.9\%\) and \(\leq 82.0\%\) are expected with *A. baumannii*, *E. cloacae* and *K. pneumoniae* if the AUC\(_{0-\text{MIC}}\) target of \(\geq 6.96\) is considered optimal. Overall, the MIC (mg/L) breakpoints of \(\leq 1.0, \leq 0.5, \leq 0.25\) where PTA \(\geq 90\%\) was identical across pathogen by targets. This finding was expected, given that the AUC\(_{0-\text{MIC}}\) follows a log\(_2\) scale.

**Discussion**

The selection of an optimal drug dose in an individual patient is of paramount importance when using an antimicrobial agent to treat an infection. PK/PD systems analyses have been applied to support this objective through identification of covariates that influence drug disposition. A major covariate that is most often taken into account is body size.
consideration is the body size of an individual that is measured by their TBW. The TBWs of adults that are often studied in early Phase 1 clinical trials tend to be narrow in distribution.6 This limitation can lead to the selection of a dosing paradigm that may not be appropriate across a larger TBW spectrum. This larger TBW distribution is now common in the clinical setting, as evidenced by a marked increase in the prevalence of obesity in England and the USA.7,8 Obesity is associated with physiological changes that have the potential to alter the clearance and distribution of drugs.27 Glomerular hyperfiltration has been observed in obese adults as one potential mechanism for enhanced drug clearance.9 Similarly, lipophilic drugs may, in theory, partition into adipose tissue, which is anatomically larger in obese adults.25 Tigecycline is a lipophilic antimicrobial agent that is currently dosed without regard to TBW and has a PK/PD profile that suggests that the systemic exposure of this agent is predictive of clinical efficacy.1 However, a study dedicated to the detailed characterization of tigecycline PK in obese individuals has not been published to date. As a consequence, the current study characterized the serum and urine concentration profiles of tigecycline in obese-C3 and NW healthy adults.

This study included adults across a 2.62-fold TBW range of 61–160 kg. The serum and urine concentration–time profiles were remarkably similar after the administration of a single 100 mg dose. The average maximal concentration of 1.60 mg/L was consistent with the product label, which reports a mean (%CV) value of 1.45 mg/L (22%) with administration of a single 100 mg dose over 30 min.12 Muralidharan et al.11 have previously summarized the single and multiple dose (12.5–300 mg) non-compartmental PK of tigecycline in healthy subjects. These authors included healthy adults (18–44 years of age) with a TBW range of 51–95 kg.11 They reported a mean (%CV) AUC0–9 of 6.40 (10) mg .h/L with a single 100 mg dose, which very closely matches the 6.78 (14) mg .h/L reported in this study. Muralidharan et al.11 also reported a mean CL and CLR of 0.20 L/h/kg (14.6 L/h in a 73 kg individual) and 2.6 L/h, respectively. Although these previous estimates were derived by non-compartmental analysis, they closely match those estimated in the current study. Similarly, the recovery of

Figure 3. Diagnostic plots for the final tigecycline model. (a) Population model-predicted concentrations versus observed concentrations. (b) Individual model-predicted concentrations versus observed serum concentrations. (c) Weighted residuals versus predicted concentrations. (d) NPDE versus time. RMSE, root mean square error.
tigecycline over 48 h in urine was 13.4%–15.8% in this study, compared with 16.1% in a recent study of healthy adults. Hence, the serum and urine tigecycline concentrations noted in this study matched previous data even with inclusion of a heavier population with a wider weight distribution.

The POP-PK system parameter estimates derived in this study are similar to those reported in previous studies. Two of these previous studies included data from infected adults and defined the final model as a two-compartment system. In contrast, the third population model included only healthy volunteer subject data and defined the final model as a three-compartment system. This difference in model selection may have been a function of the number of individual concentration–time data points from healthy volunteers (typically information rich) as opposed to infected patients (typically information sparse). Although these previous models did not include an integrated comodel of both serum and urine concentrations, the estimates of $CL_1$ and $V_1$ are strikingly similar. For example, the mean tigecycline $CL_1$ and $V_1$ of 16.3 L/h and 23.9 L from previous health volunteer data were comparable to ‘Model 3’ (serum only) mean estimates of 14.2 L/h and 28.5 L in this healthy volunteer study. While a similarity in system parameter estimates was observed with this comparison of healthy subjects, models developed using infected patients identified a relationship between CL and body size. Van Wart et al. constructed a tigecycline POP-PK model utilizing Phase 2 and 3 clinical trial data from 325 individuals across a wide weight distribution of 47–227 kg. This model identified TBW, $CL_{CR}$ and male sex as covariates of tigecycline CL. Similarly, Rubino et al. constructed a tigecycline POP-PK model using data from 410 patients with community- and hospital-acquired pneumonia with a median (minimum, maximum) weight of 74.0 (33.8, 140) kg. This group identified body surface area and $CL_{CR}$ as covariates of CL. Given this association between CL and body size, lower systemic exposures would be predicted in larger compared with smaller individuals. The empirical observations (Figure 5) in the current study did not conform to these former predictions. However, this comparison is confounded by the fact that the relationship between CL and body size may be different in infected compared with healthy individuals.

Although further clarification of the potential mechanistic basis for the influence of infection on CL may be needed, the issue at hand is if the current dosing of tigecycline is expected to achieve the desired PK/PD target. Two of the AUC/MIC targets evaluated in this study ($\geq 12.5$ and $\geq 6.96$) were utilized by EUCAST to define the clinical breakpoints of tigecycline. The MICs $\leq 0.25$–0.50 identified in this independent analysis are consistent with breakpoint definitions by EUCAST. However, the CFR with the current tigecycline dosing approach would be $< 90\%$ based on EUCAST wild-type MIC distributions of $A. baumannii$, $E. cloacae$ and $K. pneumoniae$. In contrast, the CFR would be $\geq 95\%$ with the current tigecycline dosing regimen based on wild-type MIC distributions of $E. coli$ and $S. aureus$. The use of a third target value ($\geq 3.10$) in this analysis was derived from a multivariate approach of the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. In that analysis, clinical success was predicted by multivariate logistic regression to be a function of the following: (i) TBW $< 94$ kg; (ii) absence of $Pseudomonas aeruginosa$ in baseline cultures; (iii) APACHE II score $< 13$; (iv) non-Hispanic race; (v) complicated appendicitis or cholecystitis; and (vi) AUC/MIC $\geq 3.10$. Given that intra-abdominal infections are often polymicrobial, these investigators also evaluated the impact of using the highest MIC of the organisms when at least one Enterobacteriaceae was isolated at baseline. When this consideration was taken into account, the AUC/MIC target increased from $\geq 3.10$ to $> 12.0$, which was consistent with former reports. Although this previous model also suggests that patients with a TBW $\geq 94$ kg may be at an increased risk of clinical failure, this association is unlikely to be related to low systemic exposures.
Figure 5. Scatter and linear fit plots of clearance from the central compartment ($CL_1$) versus (a) TBW or LBW and (b) $CL_C$ using the Cockcroft–Gault equation and TBW or LBW for the weight descriptor.

Table 2. Mean (SD) POP-PK model ($n=5000$) compared with observed concentrations or non-compartmental estimates of AUC at specified timepoints after a 0.5 h infusion of a single dose of 100 mg of tigecycline.
Table 3. Percentage CFR across a EUCAST-published MIC distributions and MIC values for each of the selected pathogens for AUC$_{0–\infty}$:MIC PTA $\geq$90%$^{20}$

<table>
<thead>
<tr>
<th>Bacterial pathogen</th>
<th>AUC$_{0–\infty}$:MIC target</th>
<th>≥ 3.10</th>
<th>≥ 6.96</th>
<th>≥ 12.5</th>
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<tbody>
<tr>
<td>Acinetobacter baumannii (n = 190)</td>
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<tr>
<td>CFR</td>
<td></td>
<td>91.9</td>
<td>71.2</td>
<td>58.2</td>
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<td>MIC (mg/L) values where PTA $\geq$90%</td>
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<td>≤ 0.5</td>
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<td>Enterobacter cloacae (n = 242)</td>
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<td>MIC (mg/L) values where PTA $\geq$90%</td>
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<td>≤ 1.0</td>
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<tr>
<td>Escherichia coli (n = 1871)</td>
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<td>CFR</td>
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<td>95.8</td>
</tr>
<tr>
<td>MIC (mg/L) values where PTA $\geq$90%</td>
<td></td>
<td>≤ 1.0</td>
<td>≤ 0.5</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (n = 894)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFR</td>
<td></td>
<td>96.0</td>
<td>82.0</td>
<td>58.3</td>
</tr>
<tr>
<td>MIC (mg/L) values where PTA $\geq$90%</td>
<td></td>
<td>≤ 1.0</td>
<td>≤ 0.5</td>
<td>≤ 0.25</td>
</tr>
<tr>
<td>Staphylococcus aureus (n = 1363)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFR</td>
<td></td>
<td>100</td>
<td>99.9</td>
<td>99.6</td>
</tr>
<tr>
<td>MIC (mg/L) values where PTA $\geq$90%</td>
<td></td>
<td>≤ 1.0</td>
<td>≤ 0.5</td>
<td>≤ 0.25</td>
</tr>
</tbody>
</table>

In summary, the current study demonstrated that the serum and urine concentration–time profiles of tigecycline are similar in healthy obese-C3 compared with NW subjects. The majority (85%) of the elimination of tigecycline occurs through non-renal mechanisms and is not significantly altered in the setting of obesity. Although a reduction in tigecycline systemic exposure was not observed in obese-C3 adults, a lower probability of clinical response is predicted against certain Gram-negative pathogens with the current dosing regimen. Further evaluation of the PK/PD of tigecycline in populations that include obese individuals is necessary to corroborate these predictions.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 to S5 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


