The Pharmacokinetic and Pharmacodynamic Profile of Tigecycline

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Tigecycline, a first-in-class expanded-spectrum antimicrobial agent, has demonstrated efficacy in the treatment of complicated intra-abdominal and skin and skin-structure infections. This new antibiotic is available as an intravenous formulation and exhibits linear pharmacokinetics. It is rapidly distributed and has a large volume of distribution, indicating extensive tissue penetration. After a 100-milligram loading dose, followed by 50 milligrams every 12 h, the steady-state maximum concentration in serum after a 1-h infusion is ∼0.6 mg/mL, the 24-h steady-state area under the concentration–time curve is ∼5–6 mg·h/mL, and the terminal elimination half-life is ∼40 h. The major route of elimination of tigecycline is through the feces, primarily as unchanged drug. The pharmacokinetic profile is not affected by severe or end-stage renal disease, nor is it significantly altered by hemodialysis. The pharmacokinetics of tigecycline are also not affected by food, although tolerability is increased if the drug is administered following a meal.

Glycylcyclines are a novel class of antimicrobial agents, and tigecycline (figure 1) is the first of the glycyclcines to reach the final stage of clinical development. Tigecycline inhibits translation of bacterial proteins through its action on the 30S ribosomal subunit and circumvents resistance mechanisms, primarily ribosomal protection and efflux of the antibiotic, thus retaining activity against both tetracycline- and minocycline-resistant bacterial strains [1–3]. This new antimicrobial agent has demonstrated broad-spectrum in vitro and in vivo activity against a wide spectrum of aerobic and anaerobic gram-positive and gram-negative bacteria, including resistant strains. The activity of tigecycline against methicillin-resistant Staphylococcus aureus, penicillin-resistant Streptococcus pneumoniae, and vancomycin-resistant enterococci is impressive, and the susceptibility of most genera of Enterobacteriaceae, including extended-spectrum β-lactamase-producing and –nonproducing strains, and most strains of Bacteroides fragilis is notable [1–9]. Encouraging results have been observed with tigecycline in the treatment of hospitalized patients with severe complicated skin and skin-structure infections and complicated intra-abdominal infections [10–13]. Tigecycline has the potential to be an option for monotherapy in treating patients with these serious infectious diseases.

The importance of the pharmacokinetics of antimicrobial agents is well established and serves as the foundation for the identification of critical pharmacokinetic and pharmacodynamic exposure response relationships in in vitro, animal, and human systems. Here, we review the initial pharmacokinetic profile of tigecycline, with an emphasis on pharmacokinetics established in healthy subjects, as well as relevant in vitro and animal pharmacokinetic and pharmacodynamic studies.

PHARMACOKINETICS IN EXPERIMENTAL ANIMALS AND IN VITRO MODELS

The pharmacokinetic properties of tigecycline have been studied in several animal species. Overall, the pharmacokinetics in animals is characterized by a low
total clearance (CL_t), a large apparent volume of distribution at steady state (Vss), and a long elimination half-life (t1/2). In all studies, tigecycline was administered as an intravenous infusion because of low bioavailability following oral administration.

A tissue distribution study with [14C]tigecycline and tissue dissection in rats revealed peak radioactivity concentrations at the end of a 30-min infusion [14]. Radioactivity was well distributed to most tissues, with the highest overall exposure observed in bone, liver, spleen, and kidney. In these tissues, the ratio of the area under the concentration-time curve (AUC) in tissue to the AUC in plasma was >8, with the AUC value in bone ~250-fold higher than that in plasma. Tissue exposure in the lung, as measured by the AUC value, was ~4 times higher than the exposure in plasma. All tissues had detectable radioactivity 1 week after dosing, and long-term radioactivity was observed in bone, with an estimated t1/2 >200 h. Chelation to calcium and adherence to bone is well documented for members of the tetracycline class of antibiotics [15], and so it is anticipated to be true for members of the glycyccycline class.

In vitro binding of tigecycline was evaluated in human plasma by both ultrafiltration and ultracentrifugation [16]. Increased protein binding was observed with increasing tigecycline concentrations. The mechanism for the concentration-dependent binding is unknown to date but may be attributable to the formation of metal ion complexes, as has been documented with tetracycline [17–19]. At tigecycline concentrations of 0.1 and 1.0 μg/mL, protein binding was 71% and 87%, respectively, as determined by use of an ultrafiltration technique, and was 73% and 79%, respectively, as determined by use of ultracentrifugation. As a point of reference, the mean (+ SD) maximum steady-state serum concentration of tigecycline from a phase 3 trial of hospitalized patients with complicated skin and skin-structure infections was 0.63 ± 0.28 μg/mL [20].

The metabolic disposition and mass balance of tigecycline has been evaluated in rats and dogs by using radiolabeled tigecycline [21]. The predominant compound recovered from both species was parent drug, followed by an epimer of tigecycline and a metabolite resulting from amide hydrolysis of the t-butyrlaminoacetylamino side chain. Mass balance and excretion studies conducted in rats and dogs revealed that fecal elimination is the primary route of excretion (~50%), which is suggestive of biliary excretion. Approximately 35% of recovered tigecycline was excreted in urine as unchanged drug in these studies.

**ANIMAL PHARMACOKINETIC AND PHARMACODYNAMIC MODELS**

The interrelationship between the pharmacokinetics and pharmacodynamics of antimicrobial agents has become increasingly important. Data from in vitro and in vivo infection models, including dose fractionation studies, can examine the effect of a broad range of drug exposures on bacteria of interest. The information derived from these studies can be integrated with data from human clinical trials to define the pharmacokinetic/pharmacodynamic target and the magnitude of that target associated with optimal microbiological and clinical outcomes. Several studies have successfully demonstrated the concordance among pharmacokinetic/pharmacodynamic targets derived from nonclinical models of infection with those from clinical data [22–26].

In vitro studies have shown that tigecycline exhibits a time-dependent pattern of bactericidal activity against several gram-positive and -negative organisms, including *S. pneumoniae, Haemophilus influenzae*, and *Neisseria gonorrhoeae* [3]. The pharmacokinetic/pharmacodynamic index often associated with drugs that display a time-dependent pattern of killing, such as the β-lactams, is the time above the MIC for the organism. For antimicrobial agents with moderate to prolonged postantibiotic effects, however, the time of exposure is less important, and the ratio of AUC to MIC is the important determinant of efficacy [27]. As a result of the substantial postantibiotic effects associated with the tetracycline antibiotics, for example, the ratio of AUC to MIC is the pharmacokinetic/pharmacodynamic index characteristically associated with this class of drugs. Although there is a relative lack of data with older antibiotics within the tetracycline class, the ratio of AUC to MIC is the pharmacokinetic/pharmacodynamic index that has been documented to best predict the in vivo activity of doxycycline against *S. pneumoniae* [28].

By use of a neutropenic mouse thigh-infection model, van Ogtrop et al. [29] conducted a pharmacodynamic study to identify and characterize the pharmacokinetic/pharmacodynamic indices required for optimal in vivo activity and the efficacy of tigecycline against selected gram-negative and gram-positive organisms. The in vivo antibacterial activity of tigecycline against several isolates of common human pathogens (e.g., *S. pneumoniae, S. aureus, Escherichia coli*, and *Klebsiella pneumoniae*) were determined, and the postantibiotic effect was evaluated. Single-dose pharmacokinetics of tigecycline were characterized in serum obtained from thigh-infected mice after

![Figure 1. Molecular structure of tigecycline (molecular mass, 585 Da)](image-url)
administration of subcutaneous intravenous doses (0.75–192 mg/kg/day), with most doses given on a twice-daily dosing schedule. Pharmacokinetic parameters of tigecycline, including $t_{1/2}$, maximum serum concentration ($C_{max}$), apparent volume of distribution ($V_d$), and AUC, were determined.

The evaluation of the pharmacokinetics of tigecycline over this very broad dosage range in mice revealed nonlinear kinetics and $t_{1/2}$ values ranging from 1.05 h at the lowest dose of 3 mg/kg up to 2.34 h at the highest dose of 48 mg/kg. The AUC from time zero to infinity (AUC$_{0-\infty}$) ranged from 0.68–36.5 $\mu$g·h/mL, and the $C_{max}$ ranged from 0.42–11.1 $\mu$g/mL. Serum protein binding in mice was determined to be 59%.

The in vivo postantibiotic effect of tigecycline against S. pneumoniae ATCC 10813 and E. coli ATCC 25922 was determined following infection and administration of a 3-mg/kg dose. The postantibiotic effect was found to be 8.9 and 4.9 h against S. pneumoniae and E. coli, respectively. Study results indicated that tigecycline exhibited time-dependent in vivo antimicrobial activity. Time above a certain factor (range, 0.5–4) times the MIC for 5 of the 6 organism-drug combinations studied was the predictor of drug efficacy. However, because of the relatively long $t_{1/2}$ and the extended postantibiotic effect of tigecycline, the AUC was also reasonably predictive, with slightly lower $r^2$ values (figure 2).

Several limitations of this study should be considered when translating these data to humans. The analysis was somewhat hampered by the nonlinearity of the pharmacokinetics in mice, which became important for the lower doses, for which pharmacokinetic parameters had to be extrapolated. In contrast, tigecycline has exhibited linear kinetics in humans [16]. Furthermore, tigecycline has a relatively long $t_{1/2}$ in humans (~40 h), compared with a $t_{1/2}$ of ~1-2 h in mice. Other points to consider include the fact that animal infection models such as this do not account for host factors, such as neutrophils. The extensive distribution of tigecycline into tissues suggests that serum concentrations may not be reflective of the drug concentration at the clinical site of infection.

In addition, the methodology for susceptibility testing of tigecycline has been modified since the time this study was done. The approved testing methodology for broth dilution tests with tigecycline now requires the use of fresh Mueller-Hinton broth (media prepared and used within 12 h) for aerobic organisms, to minimize the oxidative degradation of tigecycline and standardize testing conditions. Organisms retested by the approved methodology may have MICs that are 1 dilution lower than previously reported values. Interpretation of pharmacokinetic/pharmacodynamic indices relating MIC values determined by nonreference methods must be viewed with caution. Therefore, the long postantibiotic effect of tigecycline, in combination with the relatively long $t_{1/2}$ of the drug in humans, would suggest that the ratio of AUC to MIC is likely to be predictive of the clinical and microbiological efficacy of tigecycline. Further animal studies, possibly simulating human pharmacokinetics data, and evaluation of human pharmacokinetics in conjunction with results from clinical trials will more fully characterize the optimal pharmacokinetic/pharmacodynamic index.

**HUMAN PHARMACOKINETICS**

The pharmacokinetics of tigecycline, including metabolism and mass balance studies, have been evaluated in healthy subjects and in patients with complicated skin and skin-structure infections in a clinical trials program [16, 20, 21, 30–34]. A robust population pharmacokinetics model that will more fully describe the disposition of tigecycline is in development and will be further applied to characterize exposure-response relationships for patients in the phase 2 and phase 3 clinical development programs.

The metabolism and excretion of [14C]tigecycline in human volunteers has been evaluated following intravenous adminis-

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**Figure 2.** Relationship between 3 pharmacokinetic/pharmacodynamic indices and therapeutic efficacy of tigecycline (free drug) against Streptococcus pneumoniae 1199 in the neutropenic mouse thigh muscle infection model. For this organism, the correlation coefficient ($r^2$) was highest for the relationship between the change in log$_{10}$ maximum concentration ($C_{max}$) in colony-forming units per thigh and the percentage of time above 0.5× the MIC, with a comparable $r^2$ value for log$_{10}$ area under the concentration-time curve (AUC).

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Cmax across all age and sex groups was 0.85 and 1.0. These differences were not statistically significant. The mean of women was higher than that of men and women [32]. The mean AUC value across the 3 groups had a t1/2 of ∼40–60 h in subjects receiving doses of 200 and 300 mg, respectively. The mean AUC value in this group was 40% higher (4.76 μg·h/mL). None of these differences was statistically significant, and the higher exposures did not result in an increase in adverse events. The pharmacokinetic profile of subjects who received tigecycline either prior to or after dialysis did not differ, indicating that tigecycline is not significantly cleared by hemodialysis. These results suggest that tigecycline dosing does not require adjustment for patients with renal impairment, and that patients undergoing hemodialysis can receive tigecycline either before or after a dialysis session.

Results of a pharmacokinetic analysis of tigecycline after single and multiple doses in healthy subjects were recently published [16]. Data from subjects enrolled in 3 phase 1 safety and tolerability studies were explored: an ascending single-dose study, an ascending multiple-dose study, and a study of variable volumes and infusion rates. Subjects in the single-dose study received tigecycline doses ranging from 12.5 to 300 mg, as previously described [31]. In the ascending multiple-dose trial, male subjects received 1-h intravenous infusions of tigecycline in doses of 25, 50, and 100 mg administered every 12 h for 9 days, with a single dose on day 10. The study of infusion time and volume was designed to compare the safety and tolerability of tigecycline administered intravenously in 250 mL of saline over 60 min, in 100 mL of saline over 60 min, or in 100 mL of saline over 30 min, after an initial loading dose of 100 mg followed by 50 mg of tigecycline every 12 h for 5 days. This analysis established that tigecycline exhibits linear kinetics, as indicated by the absence of significant differences in systemic clearance (range, 0.2–0.3 L/h/kg) and t1/2 (range, 37–67 h). A VD of 7–10 L/kg revealed extensive tissue distribution. Tigecycline was found to be safe and well tolerated in the dose ranges examined. In addition, differences in rates of adverse events between 30-min and 60-min infusions were not detected,
suggesting that tigecycline can be safely administered with the briefer infusion.

A meta-analysis using data from 174 subjects in five completed phase 1 studies sought to provide a comprehensive description of the pharmacokinetics of tigecycline in healthy volunteers and to explore the relationships between the pharmacokinetic parameters and certain patient descriptors [30]. The 5 studies included an ascending single-dose study [31], an ascending multiple-dose study, an age and sex effects study [32], a renal impairment study [34], and an infusion time and administration volume study [16].

Plasma and urine concentration data were analyzed by non-compartmental methods. Nonparametric tests (Kruskal-Wallis) were used to explore the relationships between pharmacokinetic parameters and patient descriptors stratified by dose levels, duration of infusion, and treatment day. A significance level of 0.01 was used to define statistical significance, as determined with SAS software (version 8.2; SAS).

The mean (± SD) age of the 174 subjects in the study population was 40.1 ± 17.5 years (range, 19–84 years), and the mean weight was 75.8 ± 12.5 kg (range, 49.6–186 kg). Creatinine clearance, as calculated using the method of Cockcroft and Gault [35], ranged from 4.9 to 186 mL/min. Approximately 14% of the population were female (n = 25); 69.5% were white (n = 121), 26.4% were black (n = 46), and 4% were classified as other (n = 7).

Mean pharmacokinetic parameters for single- and multiple-dose studies are listed in table 1. As shown in figure 3, the plasma concentration-time profile was characterized by a steep dose studies are listed in table 1. As shown in figure 3, the plasma concentration-time profile was characterized by a steep dose studies are listed in table 1. As shown in figure 3, the plasma concentration-time profile was characterized by a steep dose studies are listed in table 1. As shown in figure 3, the plasma concentration-time profile was characterized by a steep

### Table 1. Values for pharmacokinetic parameters for subjects in 5 phase 1 trials.

<table>
<thead>
<tr>
<th>Dose regimen, parameter</th>
<th>Tigecycline dose, mg</th>
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<tr>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td>Single dose</td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) mg/mL</td>
<td>0.11 ± 0.01</td>
</tr>
<tr>
<td>( V_{\text{ss}} ) L/kg</td>
<td>2.8 ± 0.95</td>
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<tr>
<td>AUC, mg·h/mL</td>
<td>0.75 ± 0.52</td>
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<tr>
<td>CL, L/h/kg</td>
<td>0.29 ± 0.20</td>
</tr>
<tr>
<td>( t_{1/2} ), h</td>
<td>11 ± 10</td>
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<tr>
<td>Multiple doses</td>
<td></td>
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<tr>
<td>( C_{\text{max}} ) mg/mL</td>
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<tr>
<td>( V_{\text{ss}} ) L/kg</td>
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<td>AUC, mg·h/mL</td>
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<td>( t_{1/2} ), h</td>
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**NOTE.** Data are mean ± SD. AUC, area under the concentration–time curve; CL, total clearance; \( C_{\text{max}} \), maximum concentration; \( t_{1/2} \), elimination half-life; \( V_{\text{ss}} \), apparent volume of distribution at steady state.

- Concentration following a 1-h infusion.
- AUC from time zero to infinity for single dose studies and 12-h AUC at steady state for multiple-dose studies.
- Multiple doses were given every 12 h.
weight, with AUC decreasing with increasing weight. Similar to the assessment of \( C_{\text{max}} \), normalizing the parameter by body weight did not completely explain this association, and the AUC was explored by comparing 26 subjects in similar weight ranges and using only the 100-mg dose group on day 1. Within similar weight ranges, the median AUC values were 5.94 and 4.78 \( \mu \text{g} \cdot \text{h/} \text{mL} \) for male and female subjects, respectively. Significant differences in AUC values across all race and age groups were not detected.

The median \( V_{\text{ss}} \) for tigecycline ranged from 2.95 to 12.7 L/kg across dose levels and treatment days. Significant differences in \( V_{\text{ss}} \) based on age, sex, or race were not detected. The \( t_{1/2} \) for the 50-, 75-, 100-, 200-, and 300-mg dose arms on day 1 were \( \sim 17, 20, 23, 49, \) and 44 h, respectively (\( P < .001 \)). There were no significant differences in \( t_{1/2} \) on the basis of age, sex, race, or renal function.

Evaluation of CL\( _{T} \) revealed a strong relationship between body weight and clearance of tigecycline, with values ranging from 0.20 to 0.31 L/h/kg in the total population. A wide interindividual variability in CL\( _{T} \) was also noted within the population of healthy subjects. Clearance of tigecycline appeared to increase with decreasing calculated creatinine clearance. Differences in clearance across the dose range tested were not detected, indicative of linear kinetics. CL\( _{T} \) was not significantly affected by age. Evaluation of the potential effect of race on the CL\( _{T} \) of tigecycline, however, revealed a statistically significant difference between healthy young white subjects (median CL\( _{T} \), 0.240 L/h/kg) versus black subjects (median CL\( _{T} \), 0.325 L/h/kg), with a 35% increase in median CL\( _{T} \) for black subjects (\( P = .0018 \)). However, with only 11 black subjects, conclusions regarding racial differences in the clearance of tigecycline will require further evaluation.

From a meta-analysis, the pharmacokinetics of tigecycline were not affected by severe renal impairment or ESRD, including those subjects receiving hemodialysis. However, slight trends for differences in pharmacokinetic parameters for age, race, and sex were identified. Elderly subjects had significantly higher \( C_{\text{max}} \) values than did younger subjects. Female subjects tended to have higher CL\( _{T} \), lower \( V_{\text{ss}} \), shorter \( t_{1/2} \), and higher \( C_{\text{max}} \) values than did male subjects, and black subjects tended to have higher CL\( _{T} \), lower \( V_{\text{ss}} \), and shorter \( t_{1/2} \) than did non-black subjects. However, because of the small sample size of the various subpopulations analyzed, the clinical significance of these differences will require further evaluation in subsequent population pharmacokinetic analyses.

Finally, the preliminary pharmacokinetic profile of tigecycline in a population of patients has been established in a noncompartmental analysis of data from 15 patients with complicated skin and skin-structure infections from a phase 3 randomized trial [20]. After a 100-mg intravenous loading dose of tigecycline and 50 mg infused over 60 min every 12 h for up to 14 days, the mean (\( \pm \text{SD} \)) \( C_{\text{max}} \) and 12-h steady-state AUC were 0.63 \( \pm \) 0.28 \( \mu \text{g/mL} \) and 3.04 \( \pm \) 0.82 \( \mu \text{g} \cdot \text{h/mL} \), respectively. These data supported the previous conclusion that steady-state conditions were reached before administration of the seventh dose.

**CONCLUSIONS**

Tigecycline, a first-in-class glycyclycline antimicrobial agent, has an expanded spectrum of activity against gram-positive, gram-negative, aerobic, anaerobic, and atypical bacteria, including strains that are multidrug resistant. It is active against methicillin-resistant \( S. \text{ aureus} \), penicillin-resistant \( S. \text{ pneumoniae} \), vanco-
mycin-resistant Enterococcus species, and expanded-spectrum β-lactamase–producing E. coli and K. pneumoniae. Tigecycline is available as an intravenous formulation and has displayed a favorable pharmacokinetic profile, with extensive tissue distribution and a long t1/2. Additional data regarding tissue concentrations in humans, such as concentrations in epithelial lining fluid, will help to elucidate the complete profile for tigecycline. Preliminary analyses to identify the pharmacokinetic/pharmacodynamic index associated with efficacy point to the ratio of AUC to MIC as the index most likely to correlate with success. Analysis of clinical data, however, is needed to confirm the pharmacodynamic index and its magnitude required for clinical and microbiological efficacy. Tigecycline has been extensively studied in the treatment of complicated skin and skin-structure infections and complicated intra-abdominal infections and should prove to be a promising, and much needed, addition to our antimicrobial armamentarium.

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References

22. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill pa-
ofloxacin, ciprofloxacin, and ampicillin against Streptococcus pneu-
25. Madaras-Kelly KJ, Ostergaard BE, Hovde LB, Rotschafer JC. Twenty-
four-hour area under the concentration-time curve/MIC ratio as a general predictor of fluoroquinolone antimicrobial effect by using three


