ORIGINAL RESEARCH ARTICLES

Single- and Multiple-Dose Pharmacokinetics and Absolute Bioavailability of Tedizolid

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OBJECTIVES Tedizolid phosphate is a novel antibacterial under investigation for the treatment of gram-positive infections. This study was conducted to assess the pharmacokinetics, safety, and tolerability of intravenous tedizolid phosphate as well as the oral bioavailability of tedizolid phosphate.

DESIGN Double-blind, single-ascending dose, multiple-dose pharmacokinetics study, as well as tolerability and open-label crossover studies.

SETTING Single center in the United States (Covance Clinical Research Unit, Madison, WI) between September 2009 and January 2010.

PARTICIPANTS Ninety healthy volunteers.

INTERVENTION Single intravenous (IV) doses of tedizolid phosphate 50 mg (lead-in) and 100–400 mg. Single oral and IV dose of tedizolid phosphate 200 mg in crossover fashion. Multiple IV doses of tedizolid phosphate 200 and 300 mg for up to 7 days.

MEASUREMENTS AND MAIN RESULTS A dose-dependent increase was observed in the maximum plasma concentration (1.2–5.1 μg/ml) and the area under the concentration-time curve (17.4–58.7 μg × hr/ml) of tedizolid (the microbiologically active moiety of tedizolid phosphate) after single IV doses of tedizolid phosphate 100–400 mg. Administration of IV tedizolid phosphate 200 mg once/day for 7 days resulted in minimal (28%) tedizolid accumulation. The absolute oral bioavailability of tedizolid after a single 200-mg dose of tedizolid phosphate was 91%; pharmacokinetic parameters of tedizolid were similar with oral and IV administration. Treatment-related adverse events occurred in 41% of subjects. Most adverse events were related to infusion site and became more frequent with multiple dosing. In an additional 3-day tolerability study, IV tedizolid phosphate 200 mg and placebo were similarly tolerated, based on visual infusion phlebitis scores.

CONCLUSION These results from a population of healthy volunteers support once/day dosing of tedizolid phosphate 200 mg with both the oral and IV formulations, without the need for dose adjustment when switching administration routes.

KEY WORDS tedizolid phosphate, intravenous, pharmacokinetics.

Skin and skin structure infections are some of the most common types of infections treated in clinical practice.[1, 2] Acute bacterial skin and skin structure infections (ABSSSIs) include cellulitis/erysipelas, major cutaneous abscess, and wound infections.[3] More than half of ABSSSIs

are caused by *Staphylococcus aureus*.[1, 4, 5] The emergence of hospital-acquired and community-associated methicillin-resistant *S. aureus* (MRSA) strains has led to an increase in infections due to this pathogen.[4–6]

Vancomycin is a parenteral antibiotic commonly used to treat serious MRSA infections, although the emergence of strains with reduced sensitivity to vancomycin has compromised its clinical use.[7] Linezolid is currently the only antimicrobial approved for the treatment of MRSA infections that can be administered both intravenously and orally.

Tedizolid phosphate is a novel oxazolidinone prodrug being investigated for the treatment of gram-positive infections including those caused by MRSA.[8] Tedizolid phosphate is rapidly converted by endogenous phosphatases to tedizolid, the microbiologically active moiety.[9, 10] Tedizolid has minimal and predictable accumulation at steady state and an elimination half-life that supports once/day administration.[10] In two recent phase III trials in patients with ABSSSIs, tedizolid phosphate (200 mg once/day for 6 days) was noninferior to linezolid (600 mg twice/day for 10 days).[2, 11]

In patients with comorbidities or signs of extensive or systemic disease, initial treatment with intravenous (IV) antimicrobials is common. The ability to easily switch an antimicrobial agent from IV to oral administration once patients are clinically stable, ideally without dose adjustments, can reduce the duration of catheterization and hospitalization as well as the associated costs.[12–14] To determine whether dose modifications are necessary when switching between IV and oral administration of tedizolid phosphate, this study assessed the pharmacokinetics (PK), safety, and tolerability of single and multiple doses of IV tedizolid phosphate. In addition, the absolute oral bioavailability of tedizolid was determined, and the tolerability of IV tedizolid phosphate was compared with placebo.

Methods

This study was conducted at a single center in the United States (Covance Clinical Research Unit, Madison, WI) between September 2009 and January 2010. Written informed consent was obtained from all subjects before undergoing any study-related procedures. The study was conducted in accordance with the International Conference on Harmonization and U.S. Food and Drug Administration guidelines, Good Clinical Practice, and the Declaration of Helsinki. The Covance Clinical Research Unit institutional review board approved the protocol, amendments, and informed consent documents prior to study initiation. The study was registered at ClinicalTrials.gov (identifier NCT00983255).

Study Design

The study was conducted in four sequential phases: two studies that assessed the PK of IV tedizolid phosphate at doses ranging from 100–400 mg/day (i.e., a single-ascending dose study followed by a multiple-dose study), an absolute bioavailability study, and a venous tolerability study (Figure 1).

The study also included an open-label pilot phase with IV tedizolid phosphate (50 mg in 250 ml saline over a 180-min infusion) to establish a baseline reference level of venous tolerability; the subjects enrolled in the pilot phase were included in the overall safety population, but PK data were not collected. In the double-blind, single-ascending dose, *first* phase of the study, IV tedizolid phosphate at a dose of 100, 200 or 400 mg once/day or placebo was administered in three different regimens: a 500-ml 120-minute infusion, a 250-ml 120-minute infusion, or a 250-ml 60-minute infusion.

In the double-blind, multiple-dose, *second* phase of the study, IV tedizolid phosphate 200 mg once/day or 300 mg once/day or placebo was administered as a 250-ml 60-minute infusion for 7 days.

The open-label, crossover, *third* phase of the study compared the absolute bioavailability of tedizolid after oral (single 200-mg tablet) or IV (200 mg administered as a single 250-ml 60-min infusion) tedizolid phosphate, separated by at least a 7-day washout period between doses.

The *fourth* phase of the study compared the venous tolerability of IV tedizolid phosphate 200 mg every day (administered as a 250-ml 60-min infusion) or placebo using a crossover design, with each treatment administered for 3 days. In the venous tolerability phase, each treatment was administered on one side of the body (hand or wrist) for 3 days, followed by the alternate treatment in a separate catheter placed on the opposite side of the body (hand or wrist) for 3 days. Every effort was made to administer all three doses of the given treatment regimen using the same catheter placement; catheters were removed approximately 2–4 hours after the third dose of each treatment.
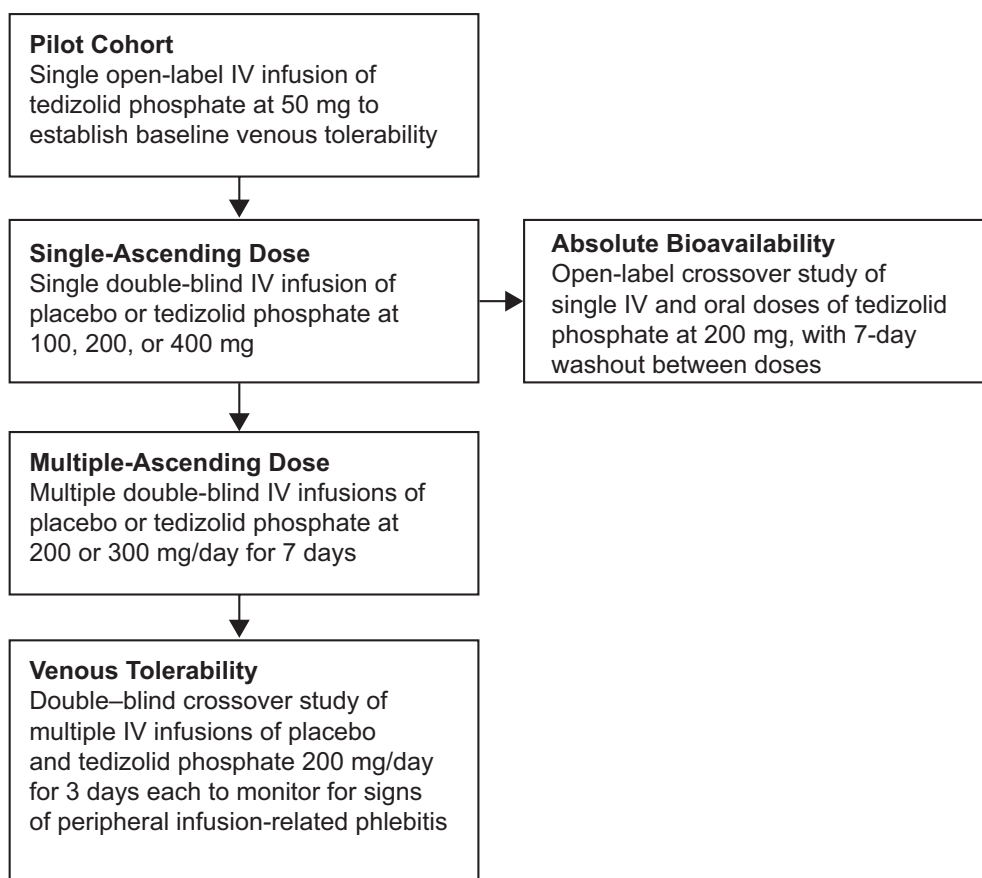
Pilot Cohort
Single open-label IV infusion of
tedizolid phosphate at 50 mg to
establish baseline venous tolerability

Single-Ascending Dose
Single double-blind IV infusion of
placebo or tedizolid phosphate at
100, 200, or 400 mg

Absolute Bioavailability
Open-label crossover study of
single IV and oral doses of tedizolid
phosphate at 200 mg, with 7-day
washout between doses

Multiple-Ascending Dose
Multiple double-blind IV infusions of
placebo or tedizolid phosphate at
200 or 300 mg/day for 7 days

Venous Tolerability
Double–blind crossover study of
multiple IV infusions of placebo
and tedizolid phosphate 200 mg/day
for 3 days each to monitor for signs
of peripheral infusion-related phlebitis

Figure 1. Study design. IV = intravenous.

After completion of each phase, the decision
to proceed with the next phase of the study was
made by the clinical research unit and the spon-
sor medical monitor, based on an assessment of
the available blinded safety data from at least six
subjects (or three of four subjects in the pilot
study) and all available PK data.

Participants

In all four phases of the study, subjects
eligible for enrollment were in good health
based on medical history, physical examina-
tion, electrocardiography (ECG) results,
vital signs, and laboratory test results; tested
negative for drugs of abuse and for preg-
nancy; and were able to provide written
informed consent.

Subjects were assigned to treatment using
computer-generated block randomization. For
each dose in the single- and multiple- ascending
dose portion of the study, subjects were
randomized to active drug or placebo with
ratios of 3:1, or 8:2, respectively. In the IV

tolerability portion of the study, subjects were
randomly assigned to a treatment sequence
(active to placebo or placebo to active) using
block randomization.

The investigator and clinical staff remained
blinded during the study and until completion
of the clinical database. Randomization informa-
tion was available to the investigator in the
event of an emergency or medical event.

Procedures

Tedizolid phosphate (lyophilized powder for
injection or 200-mg oral tablet) and placebo
(USP sterile saline) were supplied by Cubist
(San Diego, CA, USA). Intravenous tedizolid
phosphate was administered in USP 0.9% sterile
saline, and each dose of oral tedizolid phos-
phate 200 mg was administered with 240 ml
water. For all IV infusions, the vein used for
the infusion was recorded, and infusion-site
pain and vein tolerance were monitored.
Indwelling catheters were used for the multiple-
dose and venous tolerability phases.

Pharmacokinetics

Plasma and urine tedizolid phosphate and tedizolid concentrations were determined by Covance Bioanalytical Laboratory Services using validated tandem mass spectrometry methods with a lower limit of quantification (LLOQ) of 5 ng/ml. Urine was collected on days 1 and 7: −2 to 0 (predose; day 1 only), 0–4, 4–8, 8–12, and 12–24 hours after the start of infusion. Plasma samples were collected prior to the start of infusion (0 hr); 0.25 and 0.5 hours after the start of infusion; every 0.5 hour during infusion (as needed); immediately prior to the end of infusion; and 0.08, 0.17, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postinfusion (relative to the end of infusion) for the single-dose portion and on day 7 of the multiple-dose portion. Samples were collected at these time points through the first 12 hours only for day 1 of the multiple-dose portion followed by predose sampling on days 2–6. For analysis, plasma samples were extracted with acetonitrile and precipitated with hydrochloric acid, followed by low-speed $(3800 \times g)$ centrifugation at room temperature for 5 minutes. Supernatants were evaporated to dryness and reconstituted in methanol/water (3:7, v/v). Tedizolid and tedizolid phosphate were separated by high-power liquid chromatography (1200 series; Agilent Technologies, Santa Clara, CA, USA) with a Hypersil GOLD aQ column (50 × 3 mm, 5-micron particle size; Thermo Fisher Scientific, Waltham, MA, USA). Samples were eluted using a gradient from 80% 20 mM ammonium phosphate (pH 9.0)/20% methanol to 80% methanol over 4.5 minutes at a flow rate of 0.5 ml/minute. The column eluent was directed to an API 4000 triple quadrupole mass spectrometer (AB SCIEX, Framingham, MA, USA) for compound quantification. Data were processed using the Analyst v.1.4.1 software package (AB SCIEX) and the Watson LIMS laboratory information management system (Thermo Fisher Scientific). The intra- and interassay precision relative standard deviations (SDs) were 3.3% or less (4.5% or less for LLOQ) and 2.2% or less (4.2% or less for LLOQ), respectively, for this method for tedizolid quantitation. The intra- and interassay mean accuracy ranged from 95.0–103.3% and 98.2–102.7%, respectively. Urine samples were diluted (in a 20-mM ammonium formate buffer, pH ~9.0) and centrifuged to remove solids prior to sample analysis, which followed similar bioanalytic procedures as previously described.

Noncompartmental PK calculations were performed using WinNonlin (v.5.2; Pharsight Corporation, Cary, NC, USA) according to the model independent approach, using the observed plasma concentrations of tedizolid phosphate and tedizolid. Tedizolid parameters included area under the concentration-time curve (AUC, from $t = 0$ to the last quantifiable concentration [t], extrapolated to time infinity [$_\infty$], or over the dosing interval [$_{24}$], using the linear trapezoidal rule); maximum observed plasma concentrations over a single dosing interval (C_{max}), time to C_{max} over a single dosing interval (T_{max}), apparent terminal phase half-life ($t_{1/2}$), oral clearance (CL/F, calculated as dose/$AUC_{0-\infty}$ for the open-label crossover third phase only), volume of distribution during the terminal phase (V_z/F), linearity ratio ($AUC_{0-24,\ day\ 7}/AUC_{0-\infty,\ day\ 1}$), observed accumulation ratio ($AUC_{0-24,\ day\ 7}/AUC_{0-24,\ day\ 1}$), and predicted accumulation ratio ($AUC_{0-\infty,\ day\ 1}/AUC_{0-24,\ day\ 1}$).

Safety and Tolerability

The safety population comprised all randomly assigned subjects who received the study drug. Safety procedures included adverse event (AE) assessments, 12-lead ECGs, vital signs, physical examinations, and laboratory assessments. Venous tolerance at each infusion site and associated vein was assessed daily by monitoring for signs of peripheral infusion site–related phlebitis using modified visual infusion phlebitis (VIP) scoring criteria,[15] that is, a rating scale of 0 (*IV site appeared healthy; no signs of phlebitis*) to 5 (*all signs of thrombophlebitis evident and extensive*). The VIP scores were recorded before, during, immediately after, and 6 hours after the end of the infusion or at the start of any infusion site–related AE. Catheters were removed at the first sign of early-stage phlebitis (VIP score 2 or higher). In all study phases, infusion-site pain was assessed on a scale of 0 (no pain) through 10 (worst possible pain).

Data Analysis

The sample size chosen for this study was based on precedent set by other PK studies of a similar nature and was not based on power calculations. There were no formal sample-size determinations for tolerability comparisons.

Descriptive statistics were calculated for PK parameters of tedizolid phosphate and tedizolid.

Table 1. Subject Demographics

	Pilot phase	Single-ascending dose	Multiple-ascending dose	Absolute bioavailability	Venous tolerability
No. of subjects	4	47	21	8	10
Age, yrs	34 (9.9)	29 (9.4)	29 (8.4)	30 (5.4)	33 (8.3)
Weight, kg	80.7 (8.1)	78.2 (11.8)	74.7 (13.8)	73.2 (9.5)	77.6 (12.2)
BMI, kg/m^2	25.4 (3.6)	25.6 (3.0)	25.0 (2.9)	24.7 (1.3)	24.8 (2.0)
Male, %	100	72	76	75	80
Race, %, white/black/other	100/0/0	87/13/0	76/14/10	88/13/0	90/10/0
Ethnicity, % Latino	0	4	24	13	0

BMI = body mass index.
Data are mean (standard deviation) or percentage of subjects. Percentages may not add up to 100 due to rounding.

An analysis of variance (ANOVA) was performed to determine the absolute bioavailability between the oral formulation and IV formulation of tedizolid phosphate. The ANOVA model included log-transformed AUC as the dependent variable; study period, route of administration, and sequence as fixed factors; and a random subject effect. The 90% confidence intervals (CIs) of the oral formulation group PK parameter means relative to the IV formulation group PK parameter means were obtained by taking the antilog of the corresponding 90% CIs for the differences between the means on the natural log scale.

Safety data were summarized by study phase and treatment route. Venous tolerability was assessed by regular monitoring of the subject's infusion site and checked for evidence of phlebitis before the start of each dose administration, during infusion (30 min into infusion), at the end of infusion, and 6 hours after end of infusion (or at the start of an IV-related AE). The VIP scores were analyzed based on the worst (highest) VIP score for each day; the difference between the worst VIP score while receiving tedizolid phosphate and while receiving placebo was calculated for each subject for each day, and the distribution of resulting scores was summarized by day and over all study days. The time to the worst score was determined using Kaplan-Meier curves created for tedizolid and placebo.

Results

A total of 78 of 90 enrolled subjects completed the study including all four subjects enrolled in the pilot phase. In the single-ascending dose phase, 46 of 47 enrolled subjects completed the study; one subject discontinued because of an AE (influenza). In the multiple-dose phase, 10 of 21 subjects completed the study; seven subjects discontinued because of an AE (one subject each from the placebo and the

200-mg tedizolid phosphate treatment groups, and five from the 300-mg tedizolid phosphate treatment group). In addition, four subjects in the 300-mg tedizolid phosphate treatment group were discontinued after a decision to end treatment in that dose group. All 8 enrolled subjects completed the absolute bioavailability phase and all 10 enrolled subjects completed the venous tolerability phase. Baseline characteristics were similar across studies (Table 1). Subjects ranged in age from 18–48 years and were primarily white men. Body mass index ranged from 19.8 to 31.5 kg/m^2.

Tedizolid Phosphate Pharmacokinetics

Following IV administration of tedizolid phosphate 200 mg, plasma tedizolid phosphate concentrations reached a plateau by the first time point (15 min postdose), decreased rapidly at the end of the infusion, and generally fell below
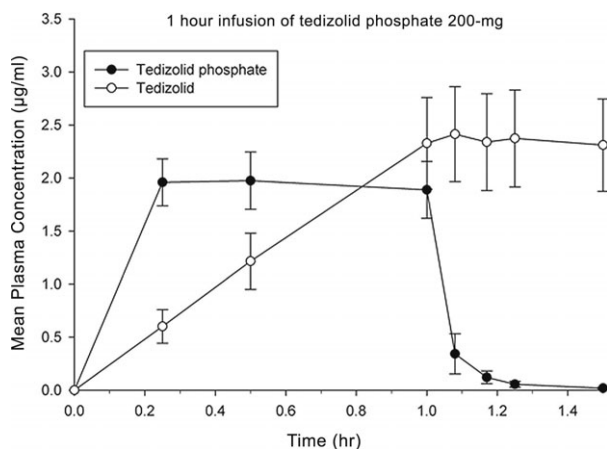
Figure 2. Mean plasma tedizolid phosphate or tedizolid concentrations during a 1-hour intravenous (IV) infusion of tedizolid phosphate 200 mg (n=8). These data are from the IV portion of the crossover bioavailability phase of the study. Error bars denote standard deviations.

the LLOQ by 2 hours after the start of the infusion (Figure 2). The mean (SD) C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ of tedizolid phosphate following IV administration of 200 mg over 1 hour were 2.1 (0.3) µg/ml, 1.8 (0.2) µg × hour/ml, and 11.8 (3.0) minute, respectively. After oral administration of tedizolid phosphate 200 mg, all tedizolid phosphate plasma measurements were below the LLOQ. Urine levels of tedizolid phosphate were generally below the LLOQ and, in the few subjects with detectable concentrations, accounted for less than 0.005% of the total administered dose. Because of the very low tedizolid phosphate exposure, analyses focused on the PK of the active moiety tedizolid.

Tedizolid Pharmacokinetics

Single-Ascending Dose Study

Tolerability and PK of tedizolid were similar for the three infusion regimens, reaching similar peak concentrations when infused in 250 or 500 ml over 2 hours or in 250 ml over 1 hour (data not shown), leading to the selection of the 250-ml 1-hour infusion for the multiple-dose and bioavailability portions of the study. Unlike levels of the prodrug, plasma tedizolid concentrations increased during the infusion and then reached a plateau (250-ml 1-hr infusion is shown in Figure 2). Single doses of IV tedizolid phosphate produced dose-dependent increases in tedizolid (Figure 3A, B). Mean tedizolid exposure parameters (AUC and C_{max}) increased with ascending doses of tedizolid phosphate (Figure 4). Median T_{max} values for tedizolid were determined primarily by the length of infusion and ranged from 1.2–2.2 hours (Table 2). Mean tedizolid $t_{1/2}$ values ranged from 9.3–13.4 hours for all doses of tedizolid phosphate. There was a dose-dependent increase in the tedizolid C_{max} (range 1.2–5.1 µg/ml) for increasing doses of tedizolid phosphate. Similar results were observed for mean AUC_{0-t} and $AUC_{0-\infty}$. Mean apparent volume of distribution at steady state (Vd_{ss}) values ranged from 61.2–74.5 L across groups and were dose independent. Clearance values were generally similar, ranging from 4.8–5.8 L/hour, and also indicated dose independence.

Multiple-Dose Study

Extensively sampled plasma tedizolid concentrations on days 1 and 7, and trough measurements, which were similar from days 2–6, for IV tedizolid phosphate 200 mg every day are shown in Figures 3C, D. Tedizolid exposure was slightly greater on day 7 than on day 1. The mean (SD) tedizolid C_{max} was also slightly greater on day 7 (3.0 [0.7] µg/ml) than on day 1 (2.3 [0.6] µg/ml), as was the mean AUC_{0-24} (29.2 [6.2] µg × hr/ml and 22.3 [4.2] µg × hr/ml, respectively). Clearance rates were similar on day 1 (6.4 [1.2] L/hr) and day 7 (5.9 [1.4] L/hr), as was the volume of distribution (77.6 [15.9] and 80.1 [21.0] L, respectively). The mean 24-hour recovery of tedizolid in urine was approximately 1% on days 1 and 7. The mean estimated accumulation ratio of tedizolid on day 7 was 1.28 (0.08); the predicted accumulation ratio was 1.19, and the linearity ratio was 1.08 (0.10). Tedizolid exposure (AUC and C_{max}) was similar with single and multiple doses of IV tedizolid phosphate (Figure 4).

The second treatment group (IV tedizolid phosphate 300 mg every day) for the multiple-dose study was initiated but was discontinued after six subjects (five tedizolid phosphate, one placebo) experienced infusion site–related AEs such as pain, tenderness, or swelling. Single-dose PK data from this group are included with other single-dose results from the first study phase.

Absolute Bioavailability

Tedizolid bioavailability was similar for IV and oral tedizolid phosphate 200 mg (Figure 3E, F). After reaching C_{max}, the tedizolid $t_{1/2}$ was also similar for oral and IV administration regimens, as were most other PK parameters (Table 3). The least squares (LS) mean AUC_{0-t} for tedizolid after oral tedizolid phosphate was 25.6 µg × hour/ml, 8.7% lower than with IV tedizolid phosphate (28.1 µg × hr/ml). The LS mean $AUC_{0-\infty}$ was 26.0 and 28.4 µg × hour/ml for oral and IV administration, respectively, and the 90% CIs for the ratio of the (oral $AUC_{0-\infty}$)/(IV $AUC_{0-\infty}$) were within the 80–125% bioequivalence range (86.8–96.4%). The percentage bioavailability of tedizolid was 91.5% after oral administration. The absolute bioavailability of tedizolid phosphate could not be determined because of a lack of quantifiable plasma concentrations of tedizolid phosphate after oral administration. The LS mean C_{max} was 2.4 and 1.9 µg × hour/ml for IV and oral administration, respectively, with the 90% CIs ranging from 70.2–82.7% for comparison of oral to IV routes.
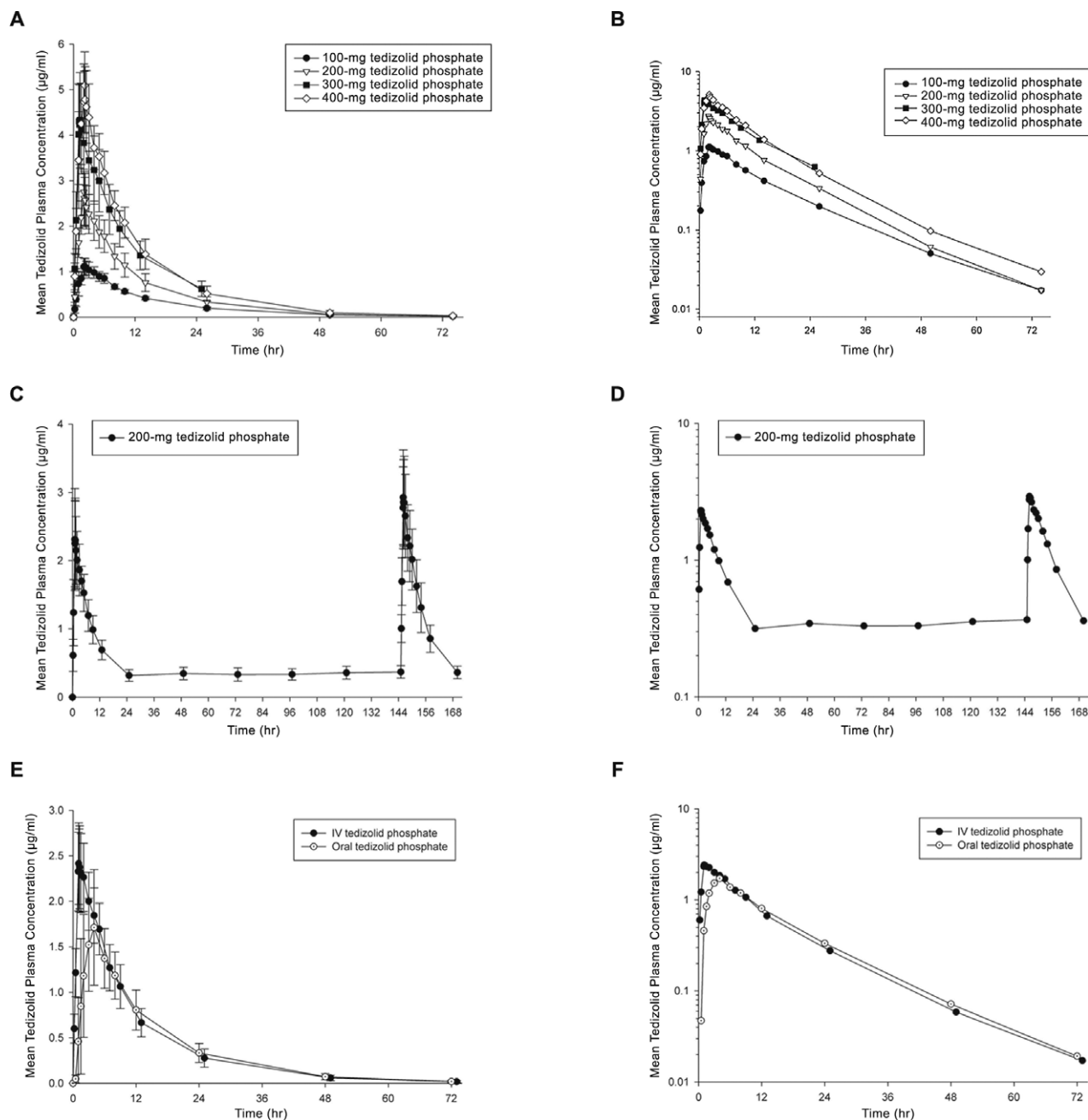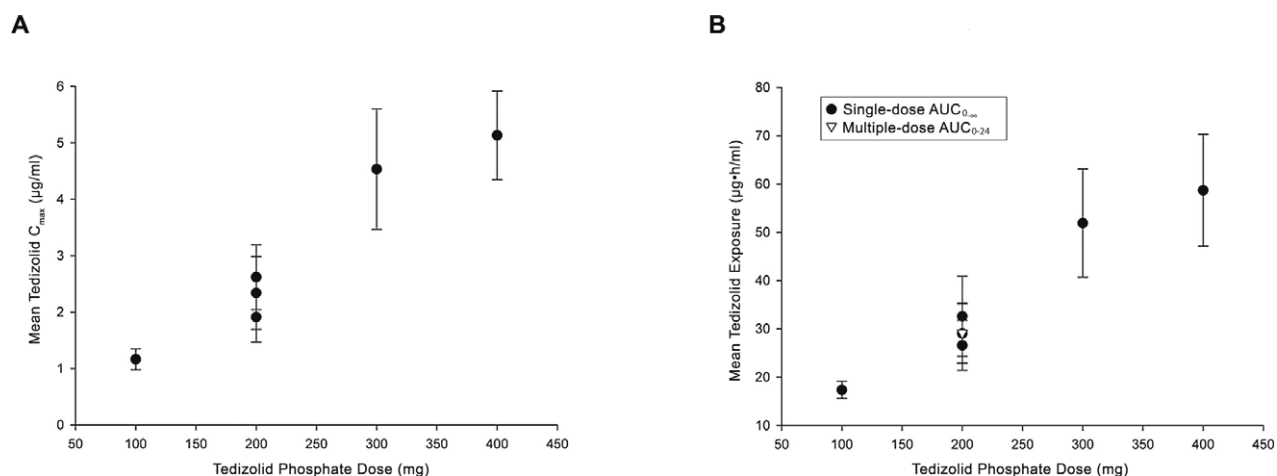
Figure 3. Mean tedizolid plasma concentration after a single dose of intravenous (IV) tedizolid phosphate, plotted on a (A) linear or (B) log time scale (n=9, 9, 8, and 9 for 100-, 200-, 300-, and 400-mg doses, respectively). Postinfusion data from subjects with 1-hour infusions were offset by 1 hour to match postinfusion times of subjects having 2-hour infusions. Mean tedizolid plasma concentration after 7 days of IV tedizolid phosphate 200 mg/day, plotted on a (C) linear or (D) log time scale (n=8). Mean tedizolid plasma concentration after a single dose of IV or oral 200 mg tedizolid phosphate, plotted on a (E) linear or (F) log time scale (n=8). Error bars denote standard deviations.

Safety and Tolerability

Treatment-related AEs occurred in 41% (37 of 90) of subjects, and most of these were mild. A greater number of AEs (mostly infusion site–related) occurred in the multiple-dose study,

leading to the discontinuation of the IV 300-mg multiple-dose phase of the study after the IV 200-mg multiple-dose phase had been completed.

Infusion site–related AEs were the most common AEs in the study. In the crossover venous

A

B

Figure 4. (A) Maximum plasma concentration (C_{max}) for tedizolid after single or first multiple dose of intravenous (IV) tedizolid phosphate. (B) Area under the concentration-time curve (AUC) for tedizolid after single ($AUC_{0-\infty}$) and multiple (AUC_{0-24}) doses of IV tedizolid phosphate. There were 9, 26, 8, and 9 individuals in the 100-, 200-, 300-, and 400-mg cohorts, respectively. Error bars denote standard deviations.

Table 2. Plasma Pharmacokinetics of Tedizolid Following Single Doses of IV Tedizolid Phosphate

	100 mg	200 mg	300 mg	400 mg
No. of subjects	9	9	8	9
C_{max}, µg/ml	1.2 (0.2)	2.6 (0.6)	4.5 (1.1)	5.1 (0.8)
T_{max}[a], hr	1.9 (1.1, 2.3)	2.2 (0.9, 2.3)	1.2 (0.9, 1.5)	2.1 (0.9, 2.5)
AUC_{0-t}, µg × hr/ml	17.0 (1.7)	30.0 (10.3)	43.4 (9.1)	58.2 (11.4)
$AUC_{0-\infty}$, µg × hr/ml	17.4 (1.8)	32.6 (8.3)	51.9 (11.2)	58.7 (11.6)
CL, L/hr	4.8 (0.5)	5.4 (1.8)	4.9 (0.9)	5.8 (1.1)
Vd_{ss}, L	74.5 (9.4)	67.1 (15.3)	61.2 (15.2)	67.5 (12.2)
$t_{1/2}$, hr	13.4 (1.1)	11.0 (0.8)	9.3 (1.4)	11.3 (1.2)

AUC = area under the concentration-time curve (over specified time interval); CL = systemic clearance; C_{max} = maximum observed concentration; IV = intravenous; t = last quantifiable time point up to 72 hrs postdose/end of infusion; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time to maximum concentration; Vd_{ss} = apparent volume of distribution at steady state.
Data are mean (standard deviation) except where noted.
[a]T_{max} is median (minimum, maximum).

tolerability study, VIP scores were similar between treatment and placebo. Five of 10 subjects had at least 1 day on which total daily VIP scores indicated that placebo was less well tolerated than tedizolid phosphate, compared with 4 of 10 subjects who had at least 1 day on which tedizolid phosphate was less well tolerated than placebo based on the same measure. In the venous tolerability phase, nine subjects receiving IV tedizolid phosphate 200 mg every day reported infusion site–related AEs, compared with six subjects receiving placebo. In the IV tedizolid phosphate group, these AEs comprised six subjects with pain, six with erythema, three with swelling, two with hematoma, one with anesthesia, one with coldness, and one with paresthesia. Infusion site–related AEs reported with IV placebo were five subjects with erythema, four with pain, and two with swelling.

Overall, 56 of the 90 study subjects reported at least one AE, most of which (seven subjects) were mild or moderate; one severe AE (vomiting) occurred. Infusion site–related AEs were the most frequently reported AEs for all groups including among subjects receiving placebo. The percentage of subjects reporting at least one infusion site–related AE, as well as the number and severity of infusion-site examination findings, increased with multiple dosing/duration of indwelling catheter use.

AEs not related to infusion site reported by more than one subject were observed only in the multiple-dose phase of the study. These AEs occurred in both the 200-mg and the discontinued 300-mg groups, and they comprised vessel puncture-site hematoma (two subjects with multiple-dose tedizolid phosphate 200 mg and four with multiple-dose tedizolid phosphate 300 mg), two with headache (300 mg), and three with abnormal dreams (200 mg). Eight subjects withdrew from the study because of AEs (one with influenza, seven with infusion site–related AEs)

Table 3. Tedizolid Single-Dose Plasma and Urinary Pharmacokinetics in Subjects Receiving Both IV and Oral Tedizolid Phosphate 200 mg, Administered Using a Crossover Design

	IV administration	Oral administration
No. of subjects	8	8
C_{max}, µg/ml	2.5 (0.4)	1.9 (0.4)
T_{max}, hr[a]	1.2 (0.9, 3.0)	3.5 (1.5, 8.0)
AUC_{0-24}, µg × hr/ml	23.5 (4.2)	20.4 (4.0)
AUC_{0-t}, µg × hr/ml	28.7 (6.0)	26.3 (5.9)
$AUC_{0-\infty}$, µg × hr/ml	29.0 (6.1)	26.7 (6.0)
CL, L/hr or CL/F	5.9 (1.5)	6.5 (1.9)
Vd_{ss}, L or V_z/F, L	71.5 (12.7)	100.1 (17.7)
$t_{1/2}$, hr	11.4 (2.0)	11.1 (2.1)

AUC = area under the concentration-time curve (over specified time interval); C_{max} = maximum observed concentration; CL = systemic clearance; CL/F = oral clearance; IV = intravenous; t = last quantifiable time point up to 72 hrs post dose/end of infusion; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time to maximum concentration; Vd_{ss} = apparent volume of distribution at steady state; V_z/F = volume of distribution during the terminal phase.
Data are mean (standard deviation) except where noted.
[a]T_{max} is median (minimum, maximum).

and four subjects discontinued when the tedizolid phosphate 300-mg multiple-dose study was discontinued. One serious AE of appendicitis occurred in a subject who received seven doses of IV tedizolid phosphate 200 mg; the investigator classified this event as mild in severity and unrelated to study treatment. No clinically significant changes in vital signs, physical examination findings, ECG results, or laboratory findings were observed in any of the subjects enrolled in this study. No deaths occurred during the study.

Discussion

The PK of IV and oral tedizolid phosphate were similar in this group of healthy volunteers. Daily IV administration of tedizolid phosphate 200 mg once/day for 7 days resulted in minimal tedizolid accumulation, and the PK profile of tedizolid was similar after single and multiple (daily) doses. The data presented here suggest linear PK for tedizolid validating previously reported results.[7] The short $t_{1/2}$ with tedizolid phosphate 300 mg was likely because of limitations of the sampling schedule, which was stopped at 24 hours. The absolute bioavailability of tedizolid following oral tedizolid phosphate 200 mg was 91%, indicating similar exposure with IV and oral administration. These results suggest that the efficacy and tolerability of oral and IV tedizolid phosphate 200 mg should be similar, and there is no need for dose adjustments when switching between IV and oral formulations of the drug.

After 7 days of IV tedizolid phosphate 200 mg once/day, there was a minimal and predictable tedizolid accumulation of ~30%, a finding that is consistent with previously reported studies using oral tedizolid phosphate.[10] The clearance and volume of distribution of tedizolid on days 1 and 7 were generally similar, indicating dose independence. Based on the minute amounts of tedizolid detected in the urine, urinary excretion does not appear to be a noteworthy clearance pathway for tedizolid.

Single doses of up to 400 mg of tedizolid phosphate were well tolerated, and venous tolerance in the single-dose phase did not appear to vary with infusion rate or drug concentration. Infusion site–related AEs were the most common AEs and increased with multiple dosing, likely because of the longer residence time of the IV catheter. An apparent reduction in tolerability was also seen at the highest multiple dose tested (300 mg), believed to be the result of some subjects' intolerability to the combination of multiple injections and multiple blood draws, rather than the effect of tedizolid. The placebo-controlled IV tolerability portion of the study was added to assess whether this reduction in tolerability was a true safety finding using a standardized assessment. The crossover venous tolerability phase of the study showed no differences in VIP score between placebo and the 200-mg study drug. These observations are consistent with results from a large phase III study in patients with ABSSSIs, in which IV tedizolid phosphate was generally well tolerated.[16]

Tedizolid phosphate, the inactive and short-lived polar prodrug, is rapidly converted to tedizolid, the biologically active moiety.[9] In this study, 200 mg IV tedizolid phosphate had a short $t_{1/2}$ (~10 min) and was generally only detectable in plasma for less than 1 hour after the end of infusion. The volume of distribution of tedizolid phosphate was ~10 L, a volume slightly smaller than extracellular body fluid, indicating that tedizolid phosphate does not penetrate into tissues. The absolute bioavailability of tedizolid phosphate could not be determined due to the lack of quantifiable tedizolid phosphate plasma concentrations after oral administration. This is consistent with a previous study, in which only one of six subjects in the highest dose group tested (i.e., single dose of 1200 mg) had quantifiable tedizolid phosphate plasma concentrations following oral administration.[10] Comparison with the IV results in this study indicates that the bioavailability of the tedizolid phosphate prodrug is less than 0.25%.

The microbiologically active moiety tedizolid is a lipophilic drug that readily penetrates tissue but has limited absorption when administered orally. Phosphate prodrugs improve solubility and dissolution rates of parent compounds and are thus useful to improve the bioavailability of lipophilic drugs.[17] However, the aqueous solubility of such a prodrug limits the intestinal permeability of the parent compound. Thus, absorption of tedizolid after oral administration of the tedizolid phosphate prodrug likely occurs following dephosphorylation by apical alkaline phosphatase, a nonspecific enzyme that cleaves a wide range of esters and is found on a variety of cell membranes.[18] The finding that tedizolid phosphate was not detected in plasma following oral administration is consistent with this hypothesis.

In summary, this phase I study conducted in healthy volunteers demonstrated that IV and oral tedizolid phosphate had similar PK profiles. Only modest plasma tedizolid accumulation occurred with IV tedizolid phosphate when administered at 200 mg once/day over 7 days. The intravenous tolerability profile of 200-mg IV tedizolid phosphate was generally similar to that of placebo, which suggests that this agent can be safely administered via the IV route. These results support once/day dosing of tedizolid phosphate 200 mg with both the oral and IV formulations in the treatment of gram-positive infections, without the need for dose adjustment when switching administration routes and no requirement for a loading dose.

Acknowledgments

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