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Pharmacokinetics of Tedizolid in Subjects with Renal or Hepatic Impairment

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Two open-label, single-dose, parallel-group studies were conducted to characterize the pharmacokinetics of the novel antibacterial tedizolid and the safety of tedizolid phosphate, its prodrug, in renally or hepatically impaired subjects. Tedizolid pharmacokinetics in subjects with severe renal impairment without dialysis support was compared with that of matched control subjects with normal renal function. Effects of hemodialysis on tedizolid pharmacokinetics were determined in a separate cohort of subjects undergoing long-term hemodialysis. Effects of hepatic impairment on tedizolid pharmacokinetics were determined in subjects with moderate or severe hepatic impairment and compared with those of matched control subjects with normal hepatic function. Each participant received a single oral (hepatic impairment) or intravenous (renal impairment) dose of tedizolid phosphate at 200 mg; hemodialysis subjects received two doses (separated by 7 days), before and after dialysis, in a crossover fashion. The pharmacokinetics of tedizolid was similar in subjects with severe renal impairment and controls (~8% lower area under the concentration-time curve [AUC], with a nearly identical peak concentration) and in subjects undergoing hemodialysis before and after tedizolid phosphate administration (~9% lower AUC, with a 15% higher peak concentration); <10% of the dose was removed during 4 h of hemodialysis. Tedizolid pharmacokinetics was only minimally altered in subjects with moderate or severe hepatic impairment; the AUC was increased approximately 22% and 34%, respectively, compared with that of subjects in the control group. Tedizolid phosphate was generally well tolerated in all participants. These results suggest that tedizolid phosphate dose adjustments are not necessary in patients with any degree of renal or hepatic impairment. (This study has been registered at ClinicalTrials.gov under registration numbers NCT01452828 [renal study] and NCT01431833 [hepatic study].)

Management of infections resulting from Gram-positive pathogens, including strains resistant to older antibacterials, continues to pose challenges (1–3). Tedizolid phosphate is the prodrug of the active moiety tedizolid, a novel oxazolidinone antibacterial under investigation for use in the treatment of Gram-positive infections, including those caused by multidrug-resistant strains (4, 5). Tedizolid recently demonstrated noninferior efficacy to linezolid for the treatment of acute bacterial skin and skin structure infections (6–8). Tedizolid phosphate is administered once daily (200 mg) either orally or by intravenous infusion (9).

Many antibacterials necessitate adjustments to dose size, dose frequency, or both when patients with impaired renal or hepatic function are treated (10, 11) because chronic kidney disease and serious liver disease cause complex changes to the metabolism and elimination of many antibacterials (10, 11). These disorders are also associated with increased risk of serious infections, including those due to drug-resistant Gram-positive pathogens (10, 12, 13), and clinically significant adverse effects caused by antibacterial treatment itself (10, 14, 15). Because of aging populations, the prevalences of chronic kidney disease (16) and chronic liver disease (17) are increasing. Therefore, to achieve safe and successful treatment outcomes, it is necessary to understand the potential need for antibacterial dose adjustments in these special patient populations (10, 18, 19).

To elucidate this important point as it relates to the clinical use of tedizolid, two open-label, single-dose, parallel-group studies were undertaken to assess the pharmacokinetic properties of tedizolid and the safety of the prodrug tedizolid phosphate in subjects with moderately to severely impaired hepatic function or severely impaired renal function, including those requiring hemodialysis. These clinical trials are registered at www.ClinicalTrials.gov as NCT01452828 (renal study) and NCT01431833 (hepatic study).

MATERIALS AND METHODS

Study subjects. Individuals with impaired renal or hepatic function and matched controls were enrolled in two open-label phase 1 trials to assess tedizolid pharmacokinetics. Subjects 18 to 75 years of age (renal study) and 18 to 70 years (hepatic study) with a body mass index (BMI) between 18.0 and 40.0 kg/m^2 were eligible. Screening included assessing organ dysfunction by estimated glomerular filtration rate (renal study) and Child-Pugh classification (hepatic study). The presence of stable disease and the absence of confounding factors were determined by assessing patient medical history, physical examination results, laboratory findings, and electrocardiography results.

Subjects were excluded if they had received monoamine oxidase inhibitors or serotonergic agents within 14 days or sympathomimetic agents within 48 h of the first tedizolid phosphate dose. Lifestyle restrictions included avoidance of high-tyramine diets, alcohol, and strenuous exercise from the 48 h preceding tedizolid phosphate administration to the follow-up visit.

In the renal study, subjects with severely impaired renal function and

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TABLE 1 Mean tedizolid pharmacokinetics in the renal-impairment study[a]

Study group	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-t} (μg · h/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2}$ (h)
Control ($n = 8$)	3.11 (0.75)	1.00 (1.00–2.50)	32.02 (9.32)	32.43 (9.53)	12.25 (2.04)
Severe renal impairment ($n = 8$)	3.12 (0.85)	1.26 (1.00–2.00)	29.69 (8.93)	29.99 (8.97)	12.85 (2.28)
Predialysis infusion ($n = 7$)	2.53 (0.95)	1.00 (0.50–1.50)	22.97 (8.02)	23.15 (8.10)	11.41 (1.78)
Postdialysis infusion ($n = 8$)	2.86 (1.01)	1.50 (1.00–1.50)	20.81 (4.65)	21.01 (4.71)	11.73 (2.33)

[a] AUC_{0-t}, integrated area under the curve based on samples from time zero to the time of the last collected sample; $AUC_{0-\infty}$, area under the curve based on the terminal rate constant; C_{max}, maximum concentration observed with a 200-mg dose; $t_{1/2}$, tedizolid half-life; T_{max}, time to reach the maximum concentration. Pharmacokinetic parameters are presented as means (standard deviations), except for T_{max} values, which are presented as medians (ranges).

not undergoing hemodialysis had an estimated glomerular filtration rate of <30 ml/min/1.73 m^2 using the four-variable modification of the diet in renal disease formula (20), had stable hemoglobin and hematocrit values for the preceding 3 months, and had stable medication doses for the prior month. Subjects with end-stage renal disease necessitating long-term hemodialysis had a 3-month history of stable urea clearance during dialysis (≥1.2 times the total body water).

Additional exclusion criteria for the hepatic study included an alanine transaminase level ≥5 times the upper limit of normal for moderate disease and ≥8 times the upper limit of normal for severe disease, a hemoglobin concentration of <10 mg/dl for moderate disease and <9 mg/dl for severe disease, and a total bilirubin level of >5 mg/dl for moderate disease, with no limit for severe disease. Acute hepatic function deterioration within 8 weeks of screening, creatinine clearance of <50 ml/min, and electrocardiography abnormalities (including a corrected QT interval [a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle] of >500 ms) were additional exclusion criteria.

Overall study design. Screening visits were conducted within the 21 days (renal study) or 28 days (hepatic study) before the first tedizolid phosphate dose. Subjects entered the study center 1 day before the first dose. They remained at the center for routine blood and urine sample collection for 72 h (renal study) or 5 days (hepatic study) after the last dose. Additional details of sample collection are provided in the supplemental material. A final safety follow-up visit took place 7 days (±1 day) after the last dose.

In the renal study, the pharmacokinetic properties of a single 200-mg intravenous dose of tedizolid phosphate (in 250 ml saline infused over 1 h) were compared among healthy matched control subjects, subjects with severe renal impairment, and subjects with end-stage renal disease requiring long-term hemodialysis. In the hepatic study, controls and subjects with hepatic impairment were matched to compare the pharmacokinetic properties of a single oral 200-mg tedizolid phosphate dose. Serial plasma samples were collected from predose through 72 h postdose in the renal study and from predose through 96 h postdose in the hepatic study. In both studies, subjects were matched by sex, age (±10%), and BMI (±15%). Additional design elements for the individual studies are described in the supplemental material.

Ethical considerations. Studies were conducted in accordance with current U.S. Food and Drug Administration regulations, International Conference on Harmonization Good Clinical Practice guidelines, and the Basic Principles of the Declaration of Helsinki.

Statistical analysis. Standard noncompartmental analysis was conducted using the WinNonlin Professional edition (version 5.2; Pharsight Corporation, St. Louis, MO, USA). The following pharmacokinetic parameters were calculated for tedizolid and tedizolid phosphate when applicable: the peak plasma concentration (C_{max}; μg/ml), the time to the peak plasma concentration (T_{max}; hours), the area under the concentration-time curve from time zero to the time of the last collected sample (AUC_{0-t}; μg · h/ml), the AUC from time zero to infinity ($AUC_{0-\infty}$; μg · h/ml), and the apparent terminal half-life (h). The geometric mean ratios for tedizolid C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and corresponding 90% confidence intervals (CIs) were determined for each study group and their corresponding controls using analysis of variance models. AUC ratios and associated 90% CIs within a range of 0.5 to 2.0—boundaries that represent no clinically meaningful change for tedizolid plasma exposure—were prespecified, and studies were powered accordingly. For each comparison, the log-transformed pharmacokinetic parameter was the response variable, the group was the fixed factor, and the subject was the random effect. Plasma concentration-time profiles were generated for individuals receiving tedizolid phosphate, and median or mean plasma concentration-time profiles (linear and semilogarithmic scales) were generated for each treatment group.

RESULTS

Whether administered intravenously (to subjects with renal insufficiency) or orally (to subjects with hepatic insufficiency), tedizolid phosphate was rapidly and extensively converted to tedizolid. Therefore, presentation of study results focuses on tedizolid plasma kinetics.

Renal impairment study. (i) Pharmacokinetics. Twenty-four subjects were enrolled in the renal impairment study, and 23 completed the study. One subject in the dialysis group completed only one dose of study drug and was later withdrawn for reasons other than an adverse event before completing the crossover dose administration. Groups were balanced in terms of age, sex, and BMI (see Table S1 in the supplemental material).

Tedizolid pharmacokinetics remained essentially unchanged in subjects with severe renal impairment, compared with healthy controls (Table 1; Fig. 1). Comparing the geometric mean pharmacokinetic exposure parameters between the severe renal impairment and control groups revealed no meaningful difference in C_{max} or AUC (C_{max} geometric mean ratio, 0.994; 90% CIs, 0.777 to 1.273; $AUC_{0-\infty}$, 0.925; 90% CIs, 0.698 to 1.227). When tedizolid pharmacokinetics was compared between infusions administered before and after hemodialysis, both C_{max} and AUC were lower than observed in the control or severe renal impairment group (Table 1). However, there were no meaningful differences in the geometric mean values for C_{max} or AUC when postdialysis and predialysis infusion data were compared (C_{max} geometric mean ratio, 1.148; 90% CIs, 1.053 to 1.252; $AUC_{0-\infty}$ geometric mean ratio, 0.913; 90% CIs, 0.827 to 1.007). When samples were collected during high-flux hemodialysis from subjects who received infusion before dialysis, <10% of the administered tedizolid dose was removed by 4 h of hemodialysis (data not shown). Mean levels of tedizolid protein binding were similar (73.2% to 76.8%) across all groups.

(ii) Tolerability and safety. Tedizolid phosphate was generally well tolerated in subjects with severe renal impairment. Less than half the treated subjects experienced at least one treatment-emergent adverse event. This included three subjects in the control group, five in the nondialysis group, and three in the dialysis group. Headache was the only adverse event experienced by more than one subject per group. The severity of most treatment-emer-

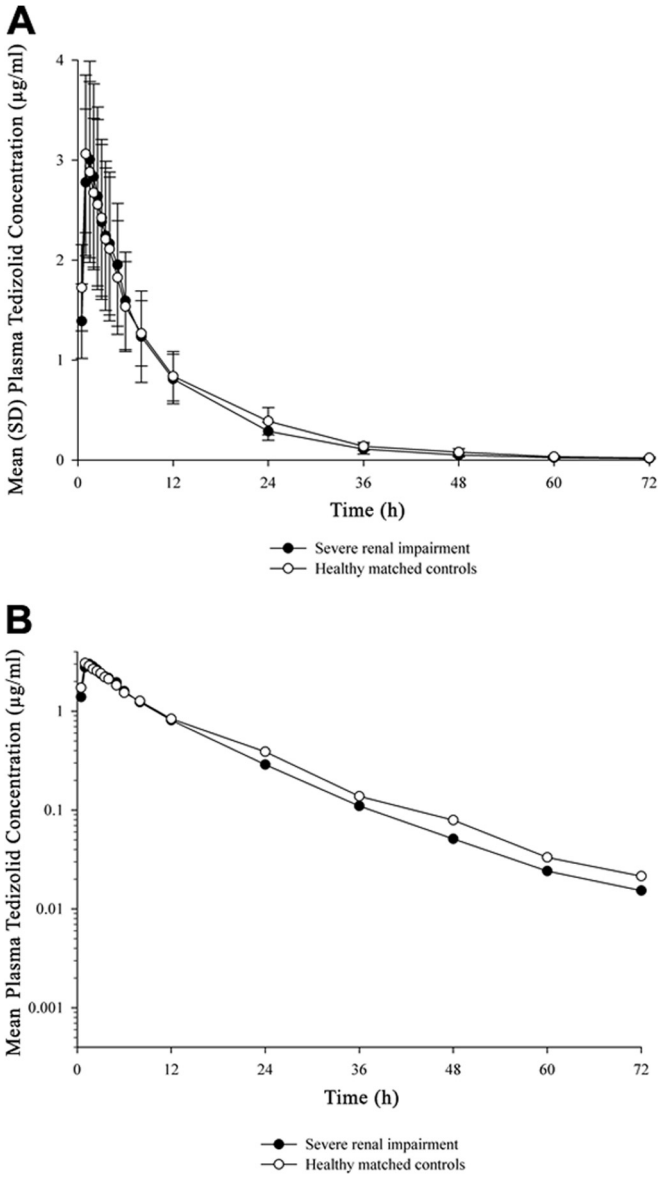

FIG 1 Plasma tedizolid concentrations over time in subjects with severe renal impairment and matched controls, shown on a linear scale (A) and on a semilogarithmic scale (B).

gent adverse events was mild or moderate; two severe treatment-emergent adverse events (nausea and vomiting) were reported for one subject with severe renal impairment. No serious adverse events were reported.

Clinically significant abnormal electrocardiography results were not observed in any participant. Five subjects in the end-stage renal disease group and four in the severe renal impairment group had abnormal electrocardiography results that were not clinically significant. None had a Bazett-corrected QT interval (QTcB) increase of ≥30 ms from predose. One subject in the end-stage renal disease group (underwent dialysis after infusion) had a postdose absolute QTcB interval of >500 ms, which was unchanged from baseline.

There were no substantial abnormalities in hematologic parameters beyond the diminished red blood cell levels associated with renal impairment and no significant coagulation panel changes. The majority of subjects in the renal-impairment groups had abnormal results for multiple chemistry laboratory tests at baseline and during follow-up, but these were deemed typical of this population. Creatinine and electrolyte level imbalances were particularly common.

Hepatic-impairment study. (i) Pharmacokinetics. Thirty-two subjects were enrolled in the hepatic impairment group and completed the study. Groups were balanced in terms of age, sex, and BMI (see Table S2 in the supplemental material).

Overall, tedizolid pharmacokinetics (Table 2) and plasma concentration-time profiles (Fig. 2) after administration of 200-mg oral tedizolid phosphate were minimally different between subjects with moderate/severe hepatic impairment and matched controls. The largest pharmacokinetic differences between subjects with hepatic impairment and controls were seen in $AUC_{0-\infty}$, which were approximately 34% higher among those with severe impairment than in controls (geometric mean ratio, 1.341; 90% CIs, 0.927 to 1.939) and 22% higher among those with moderate impairment than in controls (geometric mean ratio, 1.216; 90% CIs, 0.862 to 1.716). C_{max} values were relatively unchanged in patients with moderate or severe hepatic impairment compared with those in the control groups (moderate impairment geometric mean ratio, 1.093; 90% CIs, 0.849 to 1.408; severe impairment geometric mean ratio, 0.992; 90% CIs, 0.703 to 1.400).

(ii) Tolerability and safety. Eight subjects with hepatic impairment experienced a total of five treatment-emergent adverse events related to tedizolid phosphate: diarrhea ($n = 2$), flatulence, transient flushing, and fine downy hair growth on the scalp. No serious or severe adverse events or deaths related to the drug were reported during the study, and most events were mild. There were no serious electrocardiography changes. After tedizolid phosphate administration, no subject experienced a QTcB increase of >30 ms, compared with predose values, or an absolute QTcB interval of >500 ms.

Four subjects in the severe impairment group, three in the moderate impairment group, and none in the control group had substantially abnormal postbaseline values for hematologic pa-

TABLE 2 Mean tedizolid pharmacokinetic parameters of the hepatic-impairment group[a]

Study group	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-t} (μg · h/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2}$ (h)
Moderate impairment ($n = 8$)	2.08 (0.74)	1.75 (0.50–3.00)	29.89 (16.76)	30.47 (17.50)	14.94 (3.49)
Matched controls ($n = 8$)	1.85 (0.49)	2.00 (1.00–4.00)	22.80 (5.63)	23.00 (5.70)	13.42 (3.93)
Severe impairment ($n = 8$)	2.20 (1.07)	2.00 (0.50–3.00)	34.80 (20.72)	35.23 (21.13)	14.19 (2.92)
Matched controls ($n = 8$)	2.12 (0.80)	3.00 (1.00–8.00)	24.37 (8.03)	24.56 (8.05)	13.68 (3.71)

[a] AUC_{0-t}, integrated area under the curve based on samples from time zero to the time of the last collected sample; $AUC_{0-\infty}$, area under the curve based on the terminal rate constant; C_{max}, maximum concentration observed with a 200-mg dose; $t_{1/2}$, tedizolid half-life; T_{max}, time to reach the maximum concentration. Pharmacokinetic parameters are presented as means (standard deviations), except for T_{max} values, which are presented as medians (ranges).

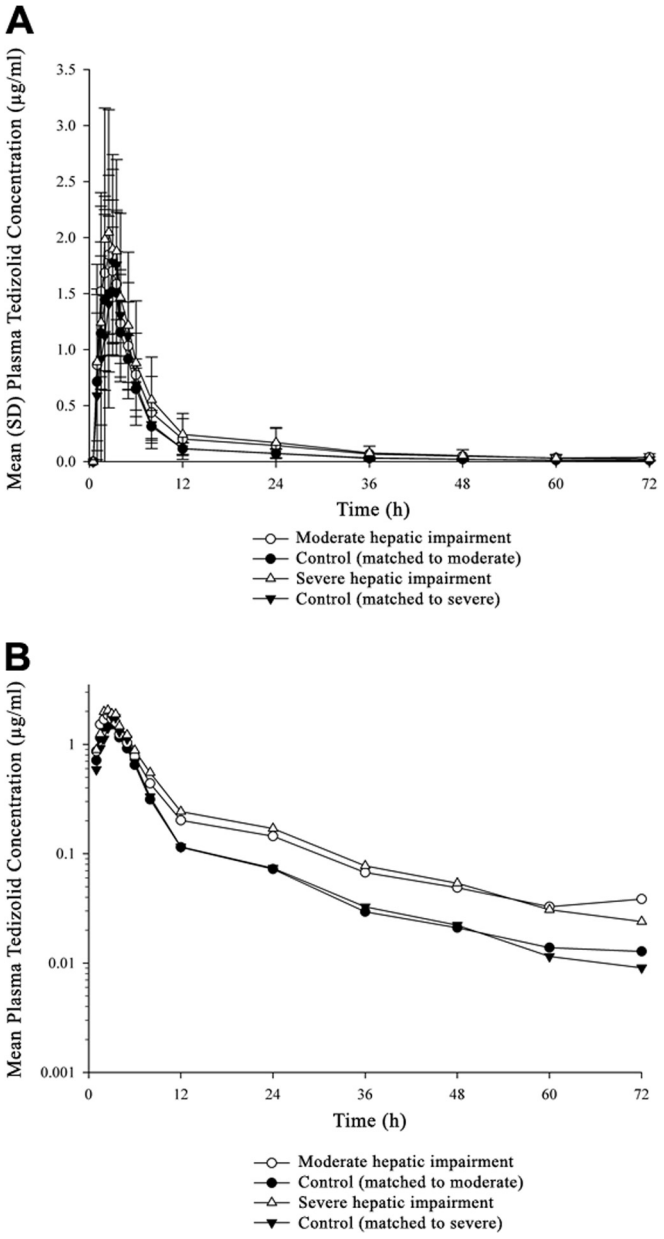

FIG 2 Plasma tedizolid concentrations over time in subjects with impaired hepatic function and matched controls, shown on a linear scale (A) and on a semilogarithmic scale (B).

rameters (seven had abnormal platelet values, and one had an abnormal absolute neutrophil count). All values were abnormal at baseline and did not worsen with tedizolid phosphate administration. The majority of subjects with moderate and severe impairment had baseline abnormalities for multiple chemistry laboratory test results, but no parameters worsened after tedizolid phosphate administration. The hematologic and chemistry laboratory abnormalities in the subjects with hepatic impairment were considered typical of such individuals. No subject had a clinically significant abnormal coagulation panel or urinalysis result.

DISCUSSION

Tedizolid elimination is primarily nonrenal; only ~18% of the administered dose is eliminated in urine (~1% as unchanged tedizolid, the remainder as metabolites) (21). However, because renal impairment can also affect nonrenal drug clearance (22), an empirical study was necessary to assess whether tedizolid dose adjustments are needed in patients with renal impairment. For instance, uremia can alter several aspects of nonrenal drug clearance (including membrane transport functions, but not first-pass effects) (19, 23, 24). For this reason, tedizolid phosphate was administered intravenously in the current study to permit better assessment of tedizolid metabolism and excretion. Under these sensitive assessment conditions, tedizolid pharmacokinetic parameters were comparable between controls and subjects with severe renal impairment.

By comparison, approximately 80% of the administered dose of linezolid is eliminated renally (including 30% as linezolid, 40% as the metabolite PNU-142586, and 10% as the metabolite PNU-142300) (25). Linezolid-associated thrombocytopenia rates are higher in patients with severe renal impairment than in subjects with normal renal function (26–28) and might be related to drug or metabolite accumulation, because renal insufficiency is also associated with significant increases in linezolid plasma metabolite levels (29–31). Some authors have suggested therapeutic trough monitoring during linezolid use to improve efficacy and safety outcomes in patients with renal insufficiency (32). However, dose adjustments and drug monitoring further complicate the treatment of critically ill patients, and antibacterial agents that can be safely and conveniently administered without dose adjustments are therefore preferable in this population.

Because of the fast clearance of small-molecular-weight compounds during dialysis, additional dosing considerations come into play when hemodialysis support is necessary (11, 18). Tedizolid exhibits high protein binding (~80%) compared with the low (~30%) protein binding of linezolid (33). Because dialysis clearance is associated with the free-drug fraction (18, 19), it is no surprise that tedizolid clearance during hemodialysis (i.e., ~10% of the administered dose) is less than the ~30% clearance for linezolid during dialysis (33). While linezolid should be administered only after dialysis (33), tedizolid phosphate may allow for more-flexible timing of dose administration in hemodialysis patients.

In the current study, mean AUC values in end-stage renal disease subjects were ~25% lower than in subjects with severe renal impairment not undergoing dialysis or their matched controls. However, these differences (which were well within the prespecified no-effect boundaries) were not in the direction of change generally associated with impaired function of a clearance organ (19, 34) and therefore likely reflect minor variability between small groups of subjects rather than a physiological effect. Other available data suggest that even if the observed lower tedizolid AUC in subjects requiring hemodialysis had represented a true pharmacokinetic difference, a decrease this small in magnitude would have minimal impact on efficacy. Based on a target attainment study reported in the companion paper to this article, pharmacokinetic/pharmacodynamic changes that are analogous to an AUC decrease of one-third would still result in more than 95% of patients achieving the tedizolid pharmacokinetic/pharmacodynamic target for clinical efficacy, compared with 98% at the reference AUC; decreases in AUC of about 50% were required before probability fell below 90% (35).

Hepatic excretion via bile accounts for the majority of tedizolid elimination; ~80% of the administered dose is eliminated in feces,

primarily as a sulfate conjugate (with ~2% as unchanged tedizolid) (21). Unlike with renal filtration, which correlates reasonably well with creatinine clearance, there is no widely accepted marker for hepatic function to predict the pharmacokinetics or pharmacodynamics of a given drug, and pharmacokinetic studies must be conducted for compounds with significant hepatic elimination (36).

The present study was conducted using oral tedizolid phosphate, because first-pass metabolism can be meaningfully decreased in patients with impaired liver function before significant changes in systemic clearance are evident (37). Given the potential impact of insufficient liver function on tedizolid metabolism, the study was originally designed to evaluate patients with moderate and mild hepatic impairment. When it was found that tedizolid AUC increases were small in moderately impaired subjects relative to those in matched controls, it was assumed that any alterations as a result of mild impairment would also be minimal, and the protocol was amended to study subjects with severe hepatic impairment as the best way to characterize the effects of hepatic insufficiency on tedizolid exposure.

In the hepatic impairment study, the greatest increases in tedizolid AUCs were observed among subjects with severe impairment. However, the overall average AUC increase was only 34%, with CIs remaining well within the preestablished no-effect boundaries. Despite this small increase, tedizolid exposure was well tolerated. This is consistent with results from other single-dose studies (with about 50 subjects, using doses up to 1,200 mg, i.e., 6-fold higher) (9, 38) and from a phase 2 study (with 188 treated patients) that showed no safety differences between the 200-mg dose and a 300- or 400-mg tedizolid dose (7). Therefore, these small relative increases in exposure are unlikely to be clinically relevant. Pharmacokinetic variability was greater in subjects with moderate or severe hepatic dysfunction than in their respective control groups, possibly reflecting the heterogeneity of these populations. No appreciable changes in C_{max} were observed with moderate or severe hepatic impairment.

For patients treated with linezolid, chronic liver disease and impaired liver function are risk factors for thrombocytopenia (26) and for isolated cases of delayed but rapid-onset lactic acidosis (39, 40). Linezolid pharmacokinetic changes have not been formally evaluated in subjects with severe hepatic impairment, but an increase in linezolid AUC of approximately1.3-fold was observed in subjects with mild to moderate hepatic impairment (33). This effect size is similar to the increase seen with tedizolid in subjects with even greater (i.e., severe) hepatic impairment, suggesting that larger increases in linezolid AUC might be expected in subjects with severe hepatic impairment.

Tedizolid is one of the only approved antibacterials active against *S. aureus* (including methicillin-resistant *S. aureus*) that has been studied in subjects with severe hepatic impairment. Furthermore, tedizolid is unique among antibacterials in that it lacks significant renal elimination. The current studies suggest that the pharmacokinetics of tedizolid is not meaningfully altered by impaired renal or hepatic function and that tedizolid was generally well tolerated in patients with such conditions. Therefore, tedizolid dose adjustments or adjustment of dose timing for hemodialysis patients is not necessary for patients with severe renal or hepatic impairment. This might be a practical advantage of tedizolid over other antibacterials that necessitate therapeutic monitoring or dose adjustments or have not been studied in patients with renal or hepatic impairment.

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In collaboration with the authors, employees of the study sponsor were involved in study design, data analysis, interpretation of the results, and review/writing of the manuscript. The studies were conducted and data were collected at Covance (Madison, WI, USA), Orlando Clinical Research Center (Orlando, FL, USA), and DaVita Clinical Research (Minneapolis, MN, USA). All authors had full access to the data. The authors had final responsibility for the decision to submit for publication.

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