Pharmacokinetics, Safety, and Tolerability of Tedizolid Phosphate After Single-dose Administration in Healthy Korean Male Subjects

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ABSTRACT

Purpose: Tedizolid phosphate is a next-generation oxazolidinone prodrug that is transformed into the active moiety tedizolid. Its indication is acute bacterial skin and skin structure infections caused by gram-positive species, including methicillin-resistant *Staphylococcus aureus*. Although tedizolid phosphate has been marketed in Korea, no data on the pharmacokinetic (PK) properties or tolerability of tedizolid phosphate in Korean subjects are available. This study was designed to evaluate the PK properties, oral bioavailability, and tolerability with a single-dose oral and intravenous administration of tedizolid phosphate in healthy Korean male subjects.

Methods: A block-randomized, double-blind, placebo-controlled, single-dose study was conducted in 3 groups (200, 400, and 600 mg; 10 subjects in each group). In the second part of the study, subjects from the 200-mg group received administration orally and intravenously (1-hour infusion) via 2-way crossover for the evaluation of absolute bioavailability. There was a 7-day washout period between treatments in the absolute bioavailability part of the study. Serial blood samples for PK analysis were collected for up to 72 hours. Tolerability was assessed by analysis of adverse events.

Findings: Thirty healthy Korean subjects completed the study and were included in the PK and tolerability analyses. Tedizolid phosphate was rapidly converted into tedizolid. After a single oral dose, the T_{max} of tedizolid was observed to be 1.5 to 2.5 hours, and the plasma concentration–time curve of tedizolid showed a 2-phase elimination pattern, with a half-life of ~11 hours. Dose-dependent increases were observed in the AUC_{last} value (29,441–78,062 μg · h/L) and in the $C_{max\ value}$ (2679–6980 μg/L) with the administration of tedizolid phosphate 200 to 600 mg PO. The absolute bioavailability of tedizolid was 95.2% (90% CI, 92.7%–97.8%) in the 200-mg administration group. There were no serious adverse events or clinically significant changes in the tolerability assessment.

Implications: Tedizolid phosphate at doses of up to 600 mg was well-tolerated in these healthy Korean male subjects. Tedizolid shows dose linearity with oral administration, and no dose adjustment of tedizolid phosphate 200 mg would be needed when switching administration routes. ClinicalTrials.gov identifier: NCT02097043. (*Clin Ther.* 2017;39:1849–1857)

Key words: bioavailability, healthy Korean subjects, oxazolidinone, pharmacokinetics, tedizolid.

INTRODUCTION

A high prevalence of multidrug-resistant pathogens has been reported in many countries, particularly those in Asia.[1–3] Among the multidrug-resistant pathogens, gram-positive organisms have been the

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major reason for the increasing prevalence of serious bacterial infections worldwide, and Korea is no exception.[4,5] Methicillin-resistant *Staphylococcus aureus* (MRSA) infection tends to result in poor clinical outcome, such as bacteremia and septic shock, with prolonged hospitalization. This clinical course is still prevalent in many Asian countries, including Korea.[6,7] Therefore, new antibacterial treatments of multidrug-resistant, gram-positive infections are urgently needed in both the clinical and community settings.[8]

For years, vancomycin has been the primary choice of antibiotic for treating MRSA infections. However, the development of resistance, adverse events, and access only by the intravenous route are major concerns.[9] Oxazolidinones, new synthetic antibiotics with activity against a variety of multidrug-resistant, gram-positive pathogens, exert bacteriostatic activity by inhibiting protein synthesis.[10] Although linezolid, the first antibiotic in the oxazolidinone family to be approved, has been widely used, partially due to the availability of both oral and intravenous formulations,[11] it is subject to the same drawbacks as is vancomycin.[12]

Tedizolid phosphate, a novel prodrug of oxazolidinone, has been approved by the US Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections,[13,14] in which MRSA is the most common bacterial pathogen.[15] Tedizolid phosphate is rapidly converted to microbiologically active tedizolid by endogenous phosphatases.[10,16] After rapid hydrolysis of tedizolid phosphate into tedizolid, the sulfate conjugate of tedizolid is the major metabolite eliminated from the body, primarily in feces, which indicates that cytosolic sulfotransferases are most likely engaged in tedizolid metabolism.[16] The transporters involved in tedizolid transport are not clear, while the inhibitory effect of tedizolid on breast cancer resistance protein was reported through human study.[17] The pharmacokinetic (PK) properties of tedizolid can be summarized as PK linearity, high oral bioavailability, and minimal metabolism.

The PK/pharmacodynamic (PD) relationship is well-known; the efficacy of tedizolid was well-correlated with the free AUC_{0-24}/MIC ratio in animal models.[14,16,18–21] This relationship is supported by various human-simulated studies such as the PD evaluation of human-simulated exposures and target-attainment simulations.[22–24]

Based on these PK characteristics of tedizolid, the extrapolation of clinical data, including PK and PD properties and tolerability data, to the Korean population for the adequate use and clinical development of tedizolid was thought to be possible through a PK bridging study. Therefore, the objective of this study was to assess the PK properties, oral bioavailability, and tolerability of tedizolid with a single oral or intravenous administration of tedizolid phosphate in healthy Korean male subjects.

SUBJECTS AND METHODS

This study was conducted in accordance with the principles set forth in the Korean Good Clinical Practice and the Declaration of Helsinki. The institutional review board of Seoul National University Hospital (Seoul, Republic of Korea) reviewed the study protocol (H-1402-034-556), and the study was registered with ClinicalTrials.gov (NCT02097043). All subjects provided written informed consent before undergoing any study-related procedures.

Subjects

Healthy Korean male subjects aged ≥18 years were eligible for enrollment if they were in good health based on medical history, physical examination, vital sign measurements, laboratory test results, and drugs-of-abuse test results. Subjects were excluded if they had any clinically significant history of gastrointestinal disease or surgery, had serum aspartate aminotransferase or alanine aminotransferase >1.5 times the upper limit of normal, or had taken any prescribed medicine or herbal supplement within 14 days or any nonprescribed medicine or vitamin supplement within 7 days before the first administration of the study product.

Study Drugs

Tedizolid phosphate was provided by the sponsor in an immediate-release formulation for oral administration (200-mg tablet) and in a lyophilized powder for intravenous administration (200-mg vial). Placebo tablets were also supplied by the sponsor; 0.9% sterile saline was used as inactive vehicle for intravenous injection.