

Stability of Crushed Tedizolid Phosphate Tablets for Nasogastric Tube Administration

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Abstract Tedizolid phosphate is approved for the treatment of acute bacterial skin and skin structure infections. To determine whether the expected dose of tedizolid phosphate can be delivered via nasogastric tube in patients who have difficulty swallowing and in whom venous access is not suitable, this in vitro study evaluated the recovery of tedizolid phosphate 200-mg tablets after crushing, dispersion in water, and passage through a nasogastric tube. To analyze the chemical stability of the crushed tablet dispersed in water, the aqueous preparation was assayed initially after dispersion and again after 4 h at room temperature. Recovery of tedizolid phosphate after the crushed tablets were dispersed in water and passed through nasogastric tubes ranged from 92.5 to 97.1 %, which is within the specified acceptance criteria of 90 to 110 %. There was no significant change in recovery values after 4 h of storage at room temperature (93.9 % initially and 94.7 % after 4 h). The stability and recovery findings support the feasibility of administering an aqueous dispersion of crushed tedizolid phosphate tablets through a

nasogastric tube in patients who have difficulty swallowing and in whom intravenous administration is not possible.

Key Points

Crushed tedizolid phosphate 200-mg tablets are stable for at least 4 h after being dispersed in water.

The ability to administer aqueous dispersions of crushed tedizolid phosphate tablets through a nasogastric tube with acceptable recovery was demonstrated.

The administration of crushed tedizolid phosphate 200-mg tablets, compared with whole tablets, is unlikely to alter the pharmacokinetics of tedizolid.

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1 Introduction

Acute bacterial skin and skin structure infections (ABSSSIs), which include cellulitis/erysipelas, wound infections, and major cutaneous abscesses, are an increasing cause of hospitalization and are an indication for antibacterial therapy globally [1–4]. Tedizolid phosphate, the prodrug of the active moiety tedizolid, is an oxazolidinone antibacterial approved for the treatment of ABSSSI in adults [5, 6]. The approved regimen for both intravenous and oral administration is 200 mg once daily for 6 days [5]. Tedizolid exerts its antibacterial activity by binding to the 23s ribosomal RNA (rRNA) component of the large subunit (50S) of the bacterial ribosome, resulting in inhibition of protein synthesis [7]. It has potent in vitro activity against a

wide range of Gram-positive pathogens, including resistant strains such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci (VRE) [8–10]. Two phase III trials, ESTABLISH-1 and ESTABLISH-2, demonstrated the noninferior efficacy of tedizolid (200 mg once daily for 6 days) to linezolid (600 mg twice daily for 10 days), and that tedizolid was generally well tolerated in patients with ABSSSI [11–13].

Tedizolid phosphate is rapidly converted to tedizolid in the body by nonspecific endogenous phosphatases [14, 15] and freely distributes into tissues [16]. After oral administration at the standard therapeutic dose of 200 mg, the absolute bioavailability of tedizolid is 91 %, allowing intravenous and oral forms to be interchanged at the same dose [17]. The pharmacokinetics of tedizolid are not affected by patient age, sex, weight, body mass index, renal/hepatic impairment, or administration with or without food [14, 18, 19]. The solubility of the drug is highest when fully deprotonated at a high pH and lowest when fully protonated at a low pH, with a steep increase in solubility between pH 4.0 and 6.0 [20].

It is common practice to crush solid oral formulations, such as tablets, and disperse them in various solutions or food/beverages to facilitate administration to patients who have difficulty swallowing [21]. In patients who may have difficulty swallowing, insertion of a nasogastric tube facilitates feeding and drug delivery. Results of a previous study [14] showed that the clinical pharmacokinetics of tedizolid was similar for orally administered tedizolid phosphate powder in a capsule and tedizolid phosphate tablets, suggesting that crushing the tablets would not alter the pharmacokinetics of tedizolid, provided no drug was lost during administration. Delivering an accurate dose of crushed tedizolid phosphate via nasogastric tube would be a valuable alternative to oral tablets or intravenous administration for patients who have difficulty swallowing and are not suitable to receive venous access (e.g., geriatric or other patients in whom insertion and maintenance of an intravenous line is not feasible). To determine the feasibility of administering tedizolid phosphate via nasogastric tube, this *in vitro* study evaluated the stability and recovery of tedizolid phosphate 200-mg tablets after crushing, dispersal in water, and passage through a nasogastric tube.

2 Methods

2.1 Crushing of Tedizolid Phosphate Tablets and Passage through a Nasogastric Tube

Each 200-mg tablet of tedizolid phosphate was crushed to a fine powder using a screw-style tablet crusher (Apex-Carex Health Care, Sioux Falls, SD, USA). The fine powder was

poured from the crusher to a 100-ml glass beaker. Water (30 ml) was added to the beaker and gently swirled to thoroughly wet and disperse the fine powder. Disintegration of the tablet was confirmed by visual inspection. A nasogastric tube was attached to the tip of a 60-ml syringe with the plunger removed. After an initial 30-ml flush with sterile water, the aqueous dispersion of tedizolid phosphate was passed through the syringe and gravity fed through the nasogastric tube by slowly pouring the tablet dispersion into a syringe attached to the nasogastric tube. The administration was followed by up to three 15-ml rinses of the beaker and an additional 30-ml sterile water flush. This is consistent with methodology of nasogastric tube usage in clinical practice [22]. The samples were collected in volumetric flasks. Assays were run in triplicate with two types of commercial nasogastric tubes that varied in dimension and material: type 1, Kangaroo nasogastric feeding tube, 10-French 43" (109 cm) (Covidien Ref 8884-721088); type 2, Salem sump dual-lumen stomach tube, 18-French/CH (6.0 mm) 48" (122 cm) (Covidien Ref 8888264986). The volumetric flasks were brought up to volume with extraction solvent and further diluted for potency analysis.

2.2 Stability of Tedizolid Phosphate/Water Preparation

The stability of tedizolid phosphate was evaluated by preparing two separate samples of a crushed tablet dispersed in water. One preparation was assayed immediately, and the other was assayed after storage at room temperature for 4 h.

2.3 Recovery of Tedizolid Phosphate

The aqueous solutions of crushed tedizolid phosphate were assayed for recovery by high-performance liquid chromatography with ultraviolet detection (HPLC-UV). HPLC separation was performed at 40 °C using gradient elution with 25 mM ammonium acetate buffer (pH 8.5) and a mixture of 90 % acetonitrile and 10 % tetrahydrofuran as the mobile phase. The method used a 4.6- by 150-mm column with US Pharmacopeia L1 packing material. The UV detection was set at 300 nm. The volume of all injections was 5 µl, and the total run time was 37 min. The amount and percentage dose recovery of tedizolid phosphate were measured. The inter-assay accuracy was shown to be within 1.2 % (actual) throughout the analytical run. The inter-assay precision was shown to be within 0.27 % (actual).

2.4 Limits

The prespecified limit for tedizolid phosphate in recovery samples was 90 to 110 % of the dose per 200-mg tablet.

The product specification limit for tedizolid was 1.0 % and 0.2 % for unspecified impurities. The limits were consistent with the shelf-life specification for the drug product.

3 Results

3.1 Recovery of Tedizolid Phosphate

The recovery of tedizolid phosphate after crushing the tedizolid phosphate tablet, dispersing the tablet in water, and passing the dispersed material through a nasogastric tube ranged from 92.5 to 97.1 % of the 200-mg tablet (Table 1). The recovery was 95.8 ± 1.1 % (mean \pm standard deviation) for nasogastric tube type 1 and 93.6 ± 1.7 % for nasogastric tube type 2. The mean and individual replicate recovery values for tedizolid phosphate were within the prespecified limits of 90 to 110 % after passage through both types of nasogastric tubes.

Table 1 Recovery of tedizolid phosphate after passage through nasogastric tube

NG tube	Recovery of 200-mg dose commercial tablet (%)			
	Replicate 1	Replicate 2	Replicate 3	Mean (SD)
Type 1 ^a	95.2	97.1	95.1	95.8 (1.1)
Type 2 ^b	92.5	95.6	92.8	93.6 (1.7)

NG nasogastric, SD standard deviation

^a Type 1, Kangaroo nasogastric feeding tube, 10-French 43" (109 cm) (Covidien Ref 8884-721088)

^b Type 2, Salem sump dual-lumen stomach tube, 18-French/CH (6.0 mm) 48" (122 cm) (Covidien Ref 8888264986)

Levels of specified degradation products (i.e., tedizolid) and unspecified impurities (relative retention time [RRT] 1.37) were also within approved shelf-life specification for the drug product (Table 2). The observed level of the degradation product tedizolid ranged from <0.05 to 0.14 % after the tablet was crushed, dispersed in water, and passed through a nasogastric tube. The level of unspecified impurity (RRT 1.37) was consistently around 0.05 %.

3.2 Stability of Tedizolid Phosphate

The crushed tedizolid phosphate tablet dispersed in water was stable for at least 4 h at room temperature (94.7 % dose recovery), which was similar to the stability at initial dispersion (93.9 % dose recovery) (Table 3). The percentage area by HPLC of the degradation products (tedizolid) and the unspecified impurities (RRT 1.37) were approximately 0.05 % and were also within the shelf-life impurity specification of the drug product.

4 Discussion

Before this study, no information was available regarding the stability and recovery of tedizolid phosphate 200-mg tablets when crushed and dispersed in water or on the feasibility of administering tedizolid phosphate through a nasogastric tube. This in vitro study showed that tedizolid phosphate has minimal loss after crushing, dispersal in water, and simulated passage through two types of nasogastric tubes, with measurable levels exceeding 93 %. The crushed suspension of tedizolid phosphate was stable for at least 4 h, with excellent recovery and minimal degradation.

Table 2 Levels of degradation products and impurities

NG tube	Tedizolid (% area by HPLC)			Unspecified RRT 1.37 (% area by HPLC)		
	Replicate 1	Replicate 2	Replicate 3	Replicate 1	Replicate 2	Replicate 3
Type 1 ^a	0.13	0.14	0.05	0.05	0.05	0.05
Type 2 ^b	0.06	0.05	<0.05	0.05	0.06	0.05

HPLC high-performance liquid chromatography, NG nasogastric, RRT relative retention time

^a Type 1, Kangaroo nasogastric feeding tube, 10-French 43" (109 cm) (Covidien Ref 8884-721088)

^b Type 2, Salem sump dual lumen stomach tube, 18-French/CH (6.0 mm) 48" (122 cm) (Covidien Ref 8888264986)

Table 3 Stability of water preparation of tedizolid phosphate and levels of degradation products/impurities after incubation

Time (h)	Recovery of 200-mg dose commercial tablet (%)	Tedizolid (% area by HPLC)	Unspecified RRT 1.37 (% area by HPLC)
0	93.9	<0.05	0.05
4	94.7	0.05	0.06

HPLC high-performance liquid chromatography, RRT relative retention time

These results suggest that the expected dose of tedizolid phosphate 200 mg can be delivered via nasogastric tube after crushing and dispersing in water, therefore accommodating patients who have difficulty swallowing.

Recovery of crushed tedizolid phosphate tablets was excellent using a commercially available tablet crusher and two types of nasogastric tubes. Length, diameter, and composition of the tested tubes differed, suggesting that the type of nasogastric tube is unlikely to influence recovery of tedizolid phosphate from a crushed preparation and would therefore not be a consideration in the decision to administer a crushed tedizolid suspension. Together with previous results showing that the clinical pharmacokinetics for tedizolid phosphate powder in a capsule and tedizolid phosphate tablets were comparable [14], the findings from this study suggest that tablet crushing with or without nasogastric tube administration is unlikely to alter the pharmacokinetics of tedizolid. The dispersed solution of crushed tedizolid phosphate was stable for at least 4 h at room temperature, providing sufficient time to use this alternative means of dosing.

5 Conclusions

This study showed that 200-mg tedizolid phosphate tablets can be crushed, dispersed in water, and delivered through a nasogastric tube, with minimal losses. Therefore, nasogastric tube administration might be a viable alternative to oral tablets or intravenous administration of tedizolid phosphate, particularly for patients who have difficulty swallowing but for whom venous access is not suitable.

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Compliance with Ethical Standards

This study was conducted in accordance with current US FDA regulations and International Conference on Harmonization guidelines.

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Conflict of interest GK, JO, SF, NA, and SB are employees of Merck & Co., Inc., Kenilworth, NJ, USA.

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