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Poster Session VI
PK/PD of antibiotics against Gram-positives

Pharmacokinetics of 7-day multiple-dose tedizolid phosphate in healthy Japanese subjects in a phase I placebo-controlled study

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Objectives

Tedizolid phosphate (TZDP) is a novel oxazolidinone antibiotic prodrug for infections caused by Gram-positive bacteria, including MRSA. TZDP is rapidly converted into tedizolid, its active moiety, by phosphatases *in vivo*. The objective of this Phase I study was to assess the pharmacokinetic (PK) properties of tedizolid in Japanese subjects after 7-day administration of TZDP.

Methods

This was a placebo-controlled, double-blind Phase I study. Healthy male subjects were randomised to receive TZDP or placebo for 7 days once daily between Day 0 and Day 6. In cohort 1, subjects received TZDP 200 mg intravenously (IV, n=8) or saline infusion (n=4) over 60 minutes. In cohort 2, subjects received oral (PO) TZDP 200 mg tablets (n=8) or placebo tablets (n=4). Plasma samples were collected at baseline prior to drug administration and at subsequent time points up to 72 hours after administration of the last dose of the study drug. The plasma and urine concentrations of TZDP and tedizolid were measured by validated LC-MS/MS assay. PK parameters were calculated and compared between Day 0 and Day 6. Data are expressed as geometric mean (% coefficient of variance). Drug accumulation ratio (R_A) was calculated as $AUC_{0\text{-}24md}$ / $AUC_{0\text{-}24}$ and linearity factor (R_{Lin}) of pharmacokinetics was calculated after repeated administration of identical doses as $AUC_{0\text{-}24md}$ / AUC.

Results

All subjects completed the 7-day treatment and had a cumulative dose of 1400 mg TZDP. After IV administration of TZDP, the plasma concentration of tedizolid on Day 0 reached a C_{max} of 3.54 (9.16) µg/mL ≈ at the end of the 1 hour infusion (T_{max}=1.03 hours). The $AUC_{0\text{-}\infty}$ was 34.0 (19.5) µg•h/mL and $AUC_{0\text{-}24h}$ was 28.1 (15.9) µg•h/mL. After PO administration of TZDP, tedizolid plasma concentration on Day 0 reached a C_{max} of 2.08 (24.6) µg/mL within ≈3 hours. The $AUC_{0\text{-}\infty}$ was 25.0 (24.1) µg•h/mL and $AUC_{0\text{-}24h}$ was 20.8 (21.6) µg•h/mL. PK data on Day 6 were comparable to those on Day 0 in both cohorts. Accumulation of tedizolid was minimal with R_A values of 1.22 (5.53) for IV and 1.28 (6.31) for PO routes, and it was predicted by the single dose kinetics R_{Lin} values of 1.02 (5.05) for IV and 1.06 (5.90) for PO routes. Urinary excretion of tedizolid was negligible (IV: 1.2% and PO: 0.8%, arithmetic mean) in a 24-hour period.

The plasma concentration of TZDP after IV administration declined rapidly to below LLOQ (5 µg/L) within 3 hours after start of infusion. TZDP was not detected after PO administration in plasma and in urine.

Conclusion

Tedizolid plasma concentration reached steady state within 3 days of TZDP 200 mg once-daily administration, regardless of the route of administration. Pharmacokinetics of tedizolid showed minimal accumulation following 7-day repeated-dose TZDP administration.