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Poster Session VI
New quinolones, oxazolidones, and a chimera of both

Changes in intestinal flora during 7-day tedizolid phosphate administration in a phase I study in healthy Japanese subjects

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Objectives

Antibiotic treatment might lead to changes in the bacterial flora of the intestine resulting in colitis. *Clostridium difficile*-colitis is the most prevalent form of nosocomial diarrhoea due to antibiotic treatment. For new antibiotics under development, potential effects on intestinal flora need to be evaluated. Tedizolid phosphate (TZDP) is a novel oxazolidinone antibiotic prodrug under clinical development against infections caused by Gram-positive bacteria, including MRSA. TZDP is rapidly converted to its active moiety tedizolid after intravenous or oral administration. Tedizolid is approximately 4-32 fold more potent *in vitro* than linezolid. To comply with Japanese guidelines for clinical assessment of antibacterial drugs, impact on intestinal flora was investigated after administration of TZDP.

Methods

Twenty four healthy male Japanese subjects were randomised to receive TZDP 200 mg or placebo once daily for 7 days intravenously (IV) in cohort 1 (TZDP: n=8; placebo: n=4) and orally (PO) in cohort 2 (TZDP: n=8; placebo: n=4). Bacterial flora was assessed by bacteria identification and quantification from faeces samples collected three times per subject: prior to drug administration, 4–6 days after administration of the first dose, and 14–21 days after administration of the last dose. All collected samples were kept under anaerobic condition at 4°C and then transferred to the laboratory to isolate and identify bacteria. Presence of *C. difficile*-toxin was checked in all samples by enzyme immunoassay. In addition, tedizolid concentration in faeces samples was determined by validated LC-MS/MS method with LLOQ: 0.200 µg/g.

Results

Administration of TZDP for 7 days (either IV or PO) transiently reduced mainly the number of Gram-positive bacteria in the intestine compared with placebo during administration (Figure 1). Levels of Gram-positive bacteria were restored to nearly pre-administration amounts by the follow-up visit for all subjects, with the total number of bacteria not affected. There was one subject in the TZDP PO cohort in whom *C. difficile* was detected at the follow-up visit. However, a *C. difficile* toxin test was negative and the subject did not show any subjective or objective symptoms. In another subject in the TZDP IV cohort, *C. difficile*-toxin was detected in the post-dose sample without obvious signs and symptoms; the toxin was no longer detected at 16 days after the last examination.

In all subjects receiving TZDP, tedizolid was detected in faeces samples only during administration (concentration ranged: 9.95-52.3 µg/g faeces) but not in post-dose samples.

Conclusion

The impact of multiple-dose TDZP on the intestinal flora was shown to be limited and reversible in the present study. There were no signs of microbiological substitution after 7-day administration of TZDP 200 mg once daily in healthy Japanese subjects following both IV and PO administration.

Figure 1. Changes in intestinal flora after 7-day tedizolid phosphate administration