P1428

Abstract (poster session)

TP-834, an isoindoline-containing pentacycline antibiotic, is orally bioavailable, metabolically stable and has low potential for drug-drug interactions

T. Grossman*, M. Ronn, N. Dunwoody, J. Sutcliffe (Watertown, US)

Objective: The goal of these studies was to evaluate the pharmacokinetics (PK) and metabolic stability of TP-834, a novel pentacycline antibiotic with activity against MDR community respiratory and problematic Gram-positive pathogens. Methods: PK: Groups of 3 male Sprague Dawley rats were given TP-834 1 mg/kg IV or 10 mg/kg PO. Three non-naïve cynomolgus monkeys were administered TP-834 1 mg/kg IV or 10 mg/kg PO. Plasma was sampled over 24 hrs, TP-834 levels were quantified by LC/MS/MS, and PK parameters were calculated using WinNonLin. Metabolic Stability: TP-834 (1 uM) was incubated with cryopreserved pooled human hepatocytes for 1 hour at 37°C. The disappearance of TP-834 over time was monitored by LC/MS/MS. Cytochrome P450 (CYP) enzyme inhibition and induction: Inhibition or induction of CYP enzymes was determined using CYP-selective substrates and LC/MS/MS detection. MDR1 efflux: The apparent passive permeability (Papp A>B) and potential transport (Papp B>A) of 1 uM TP-834 in MDCK cell cultures over-expressing Multi-Drug Resistance 1 gene (MDR1) was measured by adding TP-834 to apical (A) or basolateral (B) sides of the cultures. TP-834 at 1 and 2 hrs was quantified by LC/MS/MS. Results: PK: TP-834 given IV and PO in rats produced areas under the curve inf (AUC(inf)) of 3746+/-500 and 18079+/-11693 ng•h/ml, respectively. Oral bioavailability was 48.3%. In monkeys, the IV and PO AUC(inf) values were 9310+/-2201 and 35433+/-19111 ng•h/ml, respectively. The oral bioavailability was 33.7%. Metabolic Stability: The T1/2 of TP-834 was >145 min, with a CL(int) of <4.78 µL/min/10^6 cells. CYP enzyme inhibition/induction: TP-834 inhibited CYP2C8 with an IC50 value of 46 uM and CYP3A4/5 with an IC50 ranging from 140 ->200 uM. IC50 values were >200 uM for CYP1A2, CYP2B6, CYP2C9, CYP2C19,and CYP2D6. There was no evidence of either time- or metabolism-dependent inhibition of any CYP enzyme. TP-834 up to 20 uM, did not induce CYP1A2, CYP2B6, and CYP3A4/5. MDR1 efflux: TP-834 was classified as having a low brain penetration potential, with a mean Papp A>B of 1.69 x 10^-6 cm/sec. The mean efflux Papp B>A was 8.63 x 10^-6 cm/sec. Conclusions: The oral bioavailability, metabolic stability, lack of CYP inhibition and induction support further studies to advance TP-834 into clinical development as an IV/oral drug with low potential for drug-drug interactions.