Evaluation of JZP 110 as a Potential Substrate or Inhibitor of a Panel of Human Drug Transporters

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PURPOSE

To determine if JZP-110 is a substrate or inhibitor of key human transporters including the Organic Anion Transporter (OAT)1, OAT3, Organic Cation Transporter (OCT)1, OCT2, Organic Anion Transporting Polypeptide (OATP)1B1, OATP1B3, Multidrug and Toxin Extrusion (MATE)1, MATE2-K, P-glycoprotein (P-gp), and Breast Cancer Resistance Protein (BCRP).

RESULTS

• All probe substrates demonstrated the expected high uptake or efflux. All known inhibitors showed marked inhibition of the corresponding transporters.
• The uptake of JZP-110 by MATE1 was 2.03-, 2.01-, and 1.79-fold over the vector control at 1, 3 and 10 µM, respectively. The fold uptake of JZP-110 by OCT2 was up to 1.80 over the vector control in the presence of vehicle and reduced to ≤0.440 in the presence of quinidine (256 µM), a selective inhibitor of OCT2. The uptake of JZP-110 by other transporters was <2-fold over the vector control (Table 1).
• JZP-110 showed weak inhibition of OCT2, MATE1, and MATE2-K, but not other uptake transporters (Figures 1 through 4). The IC50 value was 146 µM for OCT2, 211 µM for MATE1, and >800 µM for MATE2-K.
• In Caco-2 cells, the apparent permeability of JZP-110 ranged from 13.2 x 10⁻⁶ to 17.9 x 10⁻⁶ cm/s in the apical to basolateral direction and from 12.3 x 10⁻⁶ to 17.5 x 10⁻⁶ cm/s in the basolateral to apical direction. The efflux ratio ranged from 0.929 to 0.978 (Table 2).
• JZP-110 (7.13 and 71.3 µM) showed no inhibition of P-gp or BCRP (Figures 5 and 6).

CONCLUSION

• Results indicate that JZP-110 was a possible substrate of OCT2 and a likely substrate of MATE1, but not other transporters.
• JZP-110 showed weak inhibition of OCT2, MATE1, and MATE2-K with IC50 values of 146, 211, and >800 µM, respectively.
• Such inhibition is not expected to cause drug-drug interactions as the mean plasma Cmax of JZP-110 was 9.1 µM after the highest anticipated therapeutic dose of 300 mg.

DISCLOSURES

Drs. Eller and Zomorodi are employees of Jazz Pharmaceuticals, who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. Dr. Gang Luo is an employee of LabCorp/Covance, who, in the course of this employment, has received restricted stock awards of ordinary shares of LabCorp (stock symbol: LH).

Support: Jazz Pharmaceuticals