Human pharmacokinetics of XBD173 and etifoxine distinguish their potential for pharmacodynamic effects mediated by TSPO

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Abstract

Background The 18kDa Translocator Protein (TSPO) has been proposed as a novel anti-inflammatory drug target. XBD173 and etifoxine are TSPO ligands that modulate inflammatory responses in preclinical models. Limited pharmacokinetic data is available publicly for either molecule. Purpose To derive pharmacokinetic data for orally administered etifoxine and XBD173 in humans and determine the binding affinity of etifoxine for TSPO. Experimental Approach We measured plasma concentrations serially after dosing 4 healthy volunteers with XBD173 90mg once a day (OD) for 7 days or etifoxine 50mg three times a day (TDS) for 7 days. We separately performed competition assays between etifoxine and [3H]PK11195 in human brain tissue to determine its TSPO binding affinity. Key Results The average XBD173 Cmax was 129 ng/mL with free fraction was 0.34%, predicting a maximal free concentration of 1.1 nM. For etifoxine, the average plasma Cmax was 32 ng/mL with a free fraction of 0.29%, predicting a maximal free etifoxine concentration of 0.31 nM. The Ki for etifoxine in human brain was 7.8uM (95% CI 4.5-14.6uM) Conclusion Oral XBD173 dosing at 90mg OD will achieve pharmacologically relevant TSPO occupancy. However, the occupancy is too low for TSPO mediated effects after oral dosing of etifoxine at 50mg TDS. Implications Our pharmacokinetic and brain affinity data suggest that physiological effects of oral XBD173 could be mediated by TSPO, but that any physiological effects of oral etifoxine cannot be a consequence of direct interaction with this target.

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