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

David Owen¹, Alexandra Phillips¹, Desmond O’Connor¹, Gabrielle Grey¹, Lina Aimola¹, Richard Nicholas¹, and Paul Matthews¹

¹Imperial College

March 6, 2022

Abstract

XBD173 and etifoxine are TSPO ligands that modulate inflammatory responses in preclinical models. Limited human pharmacokinetic data is available for either molecule, and the binding affinity of etifoxine for human TSPO is unknown. To allow for design of human challenge experiments, we derived pharmacokinetic data for orally administered etifoxine (50mg TDS) and XBD173 (90mg OD) and determined the binding affinity of etifoxine for TSPO. For XBD173, Cmax and free fraction measurements predicted a maximal free concentration of 1.1 nM, which is similar to XBD173 binding affinity. For etifoxine, Cmax and free fraction measurements predicted a maximal free concentration of 0.31 nM, substantially lower than the Ki for etifoxine in human brain derived here (7.8μM, 95% CI 4.5-14.6μM). We conclude that 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.

Hosted file

Manuscript for submission.doc available at https://authorea.com/users/463818/articles/558844-human-pharmacokinetics-of-xbd173-and-etifoxine-distinguish-their-potential-for-pharmacodynamic-effects-mediated-by-tspo