Role of Drug Efflux Transporters on Atazanavir Tissue Distribution at Sanctuary Sites of HIV-1 Infection

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Introduction: The blood-testis barrier (BTB) and the blood-brain barrier (BBB) are responsible for protecting male genital tract and CNS from xenobiotic exposure. Clinical studies in HIV-treated patients have reported low concentrations of antiretroviral drugs (ARVs) in cerebrospinal fluid and seminal fluid. One mechanism that may contribute to reduced ARVs concentrations in tissues is the functional expression of ATP-binding cassette (ABC) membrane-associated drug efflux transporters such as, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Recently, our laboratory has demonstrated, in vitro, that these transporters can significantly restrict the accumulation of ARVs in rodent and human Sertoli cells of the BTB. The objectives of this study were to investigate in vivo, the tissue distribution of PI atazanavir in wild type (WT) and P-gp/Bcrp knockout (abcb1a/1b-/-, abcg2-/-) (TKO) mice.

Methods: Atazanavir (10 mg/kg) was administered I.V. to 9-12 week old WT and TKO mice. Animals were sacrificed at various time points (up to 24 h) by cardiac puncture. Blood, brain and testes were collected for analysis. Tissue and plasma atazanavir concentrations were quantified using liquid chromatography and tandem mass spectrometry with a lower limit of detection of 5 ng/ml. Atazanavir plasma concentrations were fitted to a two-compartment I.V. bolus pharmacokinetic model using curve-fitting software Scientist 3.0.

Results: Atazanavir volume of distribution, elimination half-life and clearance were found similar in WT and TKO mice. In TKO mice, we observed a significant increase (p<0.05) in k12, rate constant by which a drug distributes into the tissue compartment from plasma (2.92 ± 1.80 h⁻¹) when compared to WT mice (0.21 ± 0.06 h⁻¹). We did not find any significant changes in the other rate constants k21 or k10. In the absence of P-gp and Bcrp (TKO model), we observed a significant increase in atazanavir brain: plasma ratios (5.3-fold) and atazanavir testes: plasma (4.6-fold) ratios when compared to age-matched WT mice group (p<0.05).

Conclusion: These results demonstrate that ABC drug efflux transporters are involved in limiting the tissue concentrations of atazanavir in rodent brain and genital tract. Since these transport proteins are also known to be expressed in humans, they could contribute to the low CSF and seminal fluid ARVs concentrations observed clinically. (Supported by the Ontario HIV Treatment Network).
Biography

Kevin Robillard completed Honours Bachelor of Medical Sciences degree in Pharmacology and Toxicology and Masters of Sciences in Pharmacology and Toxicology at the University of Western Ontario. His master’s thesis was focused on equilibrative nucleoside transporters and the role in endothelial cell function under the supervision of Dr. James Hammond. Kevin then began his Ph.D. studies under the supervision of Dr. Reina Bendayan. Kevin was a recipient Ontario HIV Treatment Network Studentship from 2007-2011, and was a recipient of a Queen Elizabeth II graduate scholarship in science and technology. Kevin’s research is focused on the drug efflux transporters at the blood-tissue barriers and their role in antiretroviral drug distribution in the context of HIV therapy.