Abstract

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Title of diploma thesis: Study of interactions antiretroviral drug maraviroc with drug transporters ABCB1 and ABCG2.

Maraviroc is inhibitor of CCR5 HIV virus entry into the cells representing one of the important components of antiretroviral therapy. To optimize the treatment strategies and minimize the therapeutic risks of maraviroc-containing combination antiretroviral therapy, it is important to know the interactions of this drug with other antiretrovirals. In particular, interaction on membrane transporters may affect pharmacokinetics and thereby the tissue concentrations of administered drugs, leading to insufficient efficacy of the therapy or increased toxicity.

The aim of this study was to experimentally evaluate interaction of maraviroc with the two most important active drug transporters of the ABC transporter superfamily, ABCB1 (P-glycoprotein) and ABCG2 (BCRP). Using *in vitro* methods employing cell lines we aimed to fulfil two main goals: (1) to evaluate the inhibitory effect of maraviroc on ABCB1 and ABCG2 transporters and (2) to study if any of these transporters could transfer maraviroc as their substrate.

The data obtained in this study clearly indicate that maraviroc does not inhibit efflux of Hoechst 33342 from the ABCB1- and ABCG2- expressing cells *in vitro* and therefore cannot be considered as inhibitor of any of these two ABC transporters. Transport studies employing monolayers of ABCB1- and ABCG2-expressing MDCKII cells revealed that maraviroc is not substrate of human

ABCG2. Interestingly, the antiretroviral drug is not transported by human ABCB1, but it is the substrate of endogenous canine Abcb1 in MDCKII cells, indicating interspecies differences in the substrate affinity of the transporter to maraviroc.

When considering the optimization of safety and efficacy during combined antiretroviral therapy in HIV patients and the study on drug-drug interactions among antiretrovirals, we can conclude that there is only negligible risk of pharmacokinetic ABCB1- or ABCG2-mediated drug-drug interactions of maraviroc with other antiretrovirals.