

Abstract

Charles University in Prague, Faculty of Pharmacy in Hradec Králové

Department of Pharmacology and Toxicology

Candidate: Mgr. Zuzana Ptáčková

Supervisor: prof. PharmDr. František Štaud, Ph.D.

Consultant: PharmDr. Lukáš Červený, Ph.D.

Title of doctoral thesis: Interactions of antiretrovirals with drug efflux transporters and their role in the transplacental pharmacokinetics

The combination antiretroviral therapy that should be administered during the whole pregnancy is the backbone of prevention of mother-to-child transmission of HIV infection. One of the prophylactic mechanisms of such treatment is the presence of antiretrovirals in the fetal circulation. However this can be associated with the potentially harmful effects of drugs on the developing fetus. To select optimal therapy while minimizing risks it is inevitable to have detailed knowledge of all the factors affecting transplacental transport of drugs.

The aim of this study was to detect whether drug efflux transporters are able to protect fetus against xenobiotics can affect the transplacental pharmacokinetics of the selected antiretroviral drugs. Employing variety of *in vitro*, *in vivo*, *in situ* and *ex vivo* methods we determined the role of the drug efflux transporters in the distribution of drugs between mother and fetus.

We suggested that antiretrovirals zidovudine, abacavir and tenofovir disoproxil fumarate to be the substrates of placental ABCB1 and ABCG2 transporters. However, passive diffusion and/or other transporters enabled the penetration of abacavir and zidovudine into the fetus. Conversely, the transplacental transport of lamivudine and parent drug tenofovir was not affected by the activity of ABC efflux transporters. Further we detected that long-term administration of tenofovir and emtricitabine to pregnant rats altered expression of the main drug efflux transporters in the selected organs of neither fetus nor mother.

The presented results contribute to the complex knowledge regarding transplacental pharmacokinetics of antiretroviral drugs. These findings should be taken into account when antiretroviral therapy of HIV positive pregnant women is selected and the risk factors and prophylactic efficacy of the particular regimens are assessed. Moreover our results indicate the potential of drug-drug interactions of antiretrovirals tested.