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Title of diploma thesis: IN VITRO STUDY OF DRUG-DRUG INTERACTIONS OF HIV PROTEASE INHIBITOR DARUNAVIR ON EFFLUX ABC TRANSPORTERS

Abstract:

Darunavir is a drug used in the therapy of HIV belonging to the group of protease inhibitors. These protease inhibitors are used as a part of the combination antiretroviral therapy. For the increase of bioavailability, darunavir is always used in combination with ritonavir or cobicistat. As the CYP3A4 and ABCB1 (P-glycoprotein) transporter substrate, darunavir is a drug with a high potential to drug interactions. Considering the amount of adverse effects that can be caused by darunavir, it is necessary to know these drug interactions for the safety of therapy. Inhibition of the intestinal ABCB1 by the co-administrated drugs could also lead to the increased bioavailability of darunavir and to reduction of frequency of administration leading to a cheaper therapy.

This thesis studies the drug-drug interactions of darunavir with *in vitro* methods using two cell lines – MDCKII and Caco-2 cells. The results from the transport of darunavir across the MDCKII cell monolayer indicates that darunavir is a ABCB1 substrate, not a ABCG2 and ABCC2 substrate. The results of the drug-drug interactions with the model inhibitor GF120918 and studied antivirals on MDCKII were significantly contaminated by the activity of endogenous transporters. We concluded that MDCKII cell line is not an appropriate model for the study of the drug-drug interactions of darunavir on human ABCB1 transporter. The results from the Caco-2 cell line suggested that darunavir is the substrate of ABCB1 and to a lesser extent the substrate of ABCG2. Its efflux was inhibited by all of the studied antivirals (lopinavir, ritonavir and asunaprevir). By testing the transporters saturation we found that the efflux inhibition will probably not have a significant influence on the intestinal absorption of darunavir, however can be of importance in other biological barriers such as hepatocytes.