

ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Martin Huličiak

Supervisor: PharmDr. Lukáš Červený, Ph.D

Title of diploma thesis: Study of interactions of antiviral drugs with intestinal drug efflux ABC transporters

P-gp, MRP2 and BCRP are efflux transporters, members of the family of ATP binding cassette (ABC) transporters. These transporters are located on the apical membrane of the intestinal epithelium, where they may limit absorption of orally administered drugs. Study of drug interactions with/on intestinal efflux transporters is necessary to provide safe and effective treatment. The Caco-2 cell line is FDA recommended *in vitro* model of intestinal barrier and it is used for bidirectional testing of substrates and inhibitors of ABC transporters in preclinical research. However, this methodology has several shortcomings, so the need of introduction of new experimental models is increasing and the *ex vivo* method based on human or rat intestine is a promising option. Precision-cut intestinal slices (PCIS) represent a mini-model of the organ and contain all types of cells of the tissue. We used both *in vitro* model using Caco-2 cell monolayers for drug transport study and in our lab established *ex vivo* method of PCIS for accumulation study and rhodamine123 (RHD123) as a model substrate of P-gp. We analyzed interactions of selected protease inhibitors (saquinavir, atazanavir) and nucleoside reverse transcriptase inhibitors (zidovudine, tenofovir disoproxil fumarate) on this efflux transporter with subsequent comparison of both methods. Of tested antiretrovirals, saquinavir, and atazanavir caused concentration dependent decrease in the efflux ratio and increase in *ex vivo* accumulation of RHD123 in *in vitro* and *ex vivo* experiments, respectively. In conclusion, we confirmed that saquinavir, and atazanavir might inhibit intestinal P-gp and thus increase the absorption of P-gp substrates. Importantly, we demonstrated that rat PCIS provide comparable results with those obtained using Caco-2 model. Therefore, rat PCIS may represent more physiological alternative to currently preferred *in vitro* method and the establishing of human PCIS would be an additional step closer to real clinical environment.