ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology & Toxicology

Student: Zdeněk Záboj

Supervisor: PharmDr. Lukáš Červený, Ph.D.

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

Sofosbuvir is an antiviral agent widely used in the treatment of chronic hepatitis C. This orally administered prodrug is a designed substrate of ATP-binding (ABC) efflux transporters, P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2). ABCB1 and ABCG2 are important determinants of intestinal absorption and are the site of significant pharmacokinetic drug interactions, leading to changes in drug exposure. Pharmacokinetic drug interactions may be undesirable (increasing the toxicity of the treatment) or desirable (allowing dose reduction). Because sofosbuvir is often administered in combination regimens with other anti(retro)virotics, the aim of this thesis was to study the ability to enhance intestinal absorption of sofosbuvir. To study the pharmacokinetic drug interactions on ABCB1 and ABCG2, a widely established *in vitro* bi-directional transport method through a polarized monolayer formed by the Caco-2 cell line derived from colorectal cancer has been used. We analyzed the drug interactions of sofosbuvir on these efflux transporters with selected anti(retro)virotics. Specific Ko134 inhibitors for ABCG2, zosuquidar for ABCB1 and elacridar as both ABCB1 and ABCG2 inhibitors were used as positive transport inhibition controls. The results showed us only the inhibition of ABCB1 in the 5 µM concentration of sofosbuvir. From the used anti-virotics, atazanavir, daclatasvir, ledipasvir, lopinavir, simeprevir and ritonavir, as ABCB1 inhibitors, demonstrated significant inhibitory potential and thus the potential to increase the intestinal absorption of sofosbuvir *in vivo*. Analyzing the data of several research concentrations of inhibitor lopinavir demonstrated a concentration-dependent inhibition of lopinavir. In this thesis, we demonstrated the possibility of using drug interactions on intestinal efflux transporters as a possible aspect leading to dose reduction and thus an overall reduction in the cost of pharmacotherapy.