Abstract

The absorption of orally administered drugs takes place especially in the intestine, where it can affect by the activity of drug’s ABC transporters located on the apical membrane of the intestinal epithelium. Study of drug interactions in intestinal ABC transporters is essential to ensure effective and safe pharmacotherapy. Testing of bi-directional transport on Caco-2 cells is generally the preferred method for in vitro evaluation of substrates and inhibitors of ABC transporters. Drawbacks of the Caco-2 model increase the need and necessity to introduce new models. A great potential is the involvement of ex vivo methodologies in the human or rat intestine. The aim of the work was to introduce an in vitro methodology using the Caco-2 cell monolayer and the ex vivo methodology of precision-cut rat intestinal slices. By the bi-directional transport method, we analyzed drug interactions of the model substrate P-gp and BCRP Rhodamine 123 (RHD123) and clinically-used tenofovir disoproxil fumarate (TDF) antiretroviral agents (ARV) with selected P-gp/BCRP inhibitors of the antiretroviral group. Lopinavir, ritonavir and abacavir decreased the efflux ratio of RHD123 and the ex vivo accumulation study with RHD123 demonstrated the concentration-dependent inhibitory effect of lopinavir and ritonavir. In addition, Lopinavir significantly affected transport of TDF through the monolayer of Caco-2 cells. In conclusion, we have been able to introduce in vitro and ex vivo methods for drug interaction analysis on intestinal P-gp and BCRP, and we have confirmed that some ARV (i.e. the protease inhibitor group) can inhibit intestinal P-gp and BCRP and to modify the TDF transmembrane transport.