ABSTRACT

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Title of diploma thesis: Study of interactions of betrixaban with antiretrovirals in an intestinal barrier model

Oral administration of drugs is a practical and simple choice for the patient, which ensures high adherence to the treatment, and thanks to that, it is the most frequently used dosage form. The vast majority of these drugs penetrate intestinal barrier after oral administration, and many clinically significant drug interactions can occur right in this place. Several determinants, including membrane transport systems, have an impact on whether or not the effect is manifested. The most observed and studied transporter from the superfamily of ABC transporters in the small intestine is undoubtedly P-glycoprotein (P-gp). It functions as an efflux pump preventing the transfer of xenobiotics, including drugs, into the systemic circulation, thereby protecting the organism and thus creating a barrier against the possible toxic effect of substances. The direct-acting anticoagulant betrixaban is a substrate of P-gp in the intestinal barrier, and therefore simultaneous administration with drugs inhibiting or inducing this transporter can change its exposure in the bloodstream and the resulting clinical effect. Such interactions may also occur in HIV patients who use lifelong antiretroviral therapy concomitantly with thromboprophylactic anticoagulants due to the high risk of developing venous thrombosis.

This diploma thesis deals with the study of interactions of anticoagulant betrixaban with antiretroviral drug darunavir (inhibitor and inducer of P-gp) from the group of protease inhibitors on the intestinal barrier model, specifically using human precision-cut intestinal slices prepared from the *jejunum*. Interactions between darunavir and betrixaban were studied both at the level of inhibition and induction. The results from the inhibition study (two-hour incubation of slices) show that darunavir (100 μM) significantly inhibits the transport of betrixaban (10 μM) across the intestinal barrier in tissue slices via efflux transporters. The increase in betrixaban accumulation compared to the non-inhibited control was on average

almost twofold higher (208%). The recorded inhibitory effect of darunavir was even higher compared to using the model inhibitor CP-100356 (2 μM), where we observed an increase to 162% on average in accumulation compared to the control. In contrast, the results from the induction study (24- and 48-hour exposure of slices to darunavir (50 μM)) did not bring a significant observable effect in the form of increased efflux and reduced concentration of betrixaban in the intestinal slices. During long-term exposure to the drug darunavir, which occurs during chronic use of drugs in HIV patients, we could not confirm the induction potential of darunavir on the expression of P gp in the model of human intestinal tissue slices.