Abstract

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Oral administration of drugs is currently the most common and most convenient method of drug administration. Most drugs administered in this way are subsequently absorbed in the intestine and enter the systemic circulation. The absorption of drugs in the intestine can be influenced by a number of factors. Factors influencing drug absorption include, for example, efflux transporters or biotransformation enzymes. Currently, the most studied intestinal transporter is P-glycoprotein (P-gg), which is able to transport various substances back into the lumen of the intestine. Another factor affecting the absorption of drugs is intestinal metabolism, which in the first phase often takes place through enzymes from the cytochrome P450 family, while most drugs are metabolized through CYP3A4, which is also widely represented in the intestine.

The activity of efflux transporters and biotransformation enzymes can be reduced (inhibition) or, conversely, increased (induction) by some drugs. This can subsequently lead to a whole range of drug interactions. The possible pharmacokinetic consequences of enzyme or transporter induction depend on the specific location. It is believed that the induction of intestinal P-gp can significantly reduce the bioavailability of drugs. The induction of biotransformation enzymes localized in the intestine then offers faster pre-systemic elimination of drugs. In both cases, this induction leads to a reduced bioavailability of the administered drugs, which may result in a reduction or loss of effect.

A combination therapy of two or three antiretrovirals is currently used in the therapy of HIV-positive patients. Antiretrovirals are often substrates, inducers, or inhibitors of CYP3A4 or P-gp, increasing the potential for drug interaction. Due to the effectiveness of treatment and the aging of the HIV-positive population, patients often have additional comorbidities, leading to polypharmacotherapy, which increases the risk of these drug interactions. As part of my thesis, I set out to study the induction potential of two antiretrovirals, darunavir and atazanavir, on the expression of *ABCB1*, *CYP3A4*

and selected intracellular receptors in the intestinal barrier. The study was performed on an *ex vivo* model of precision-cut intestinal slices prepared from human jejunum. These slices were incubated for 12, 24 and 48 hours. In addition to expression, we assessed the effect of drugs on the viability of intestinal slices and also verified the function of ABCB1 using the model substrate rhodamine123 (RHD123).

According to the measured ATP levels, we found that the studied substances had no effect on the lifetime of the tissue. Significantly increased gene expression for both *CYP3A4* and *ABCB1* was confirmed for both drugs. We did not observe a change in the expression of intracellular receptors. The study did not confirm an effect on the increased function of ABCB1 using the model substrate RHD123.