IN VITRO EVALUATION OF ANTI-HIV AND ANTI-HCV DRUGS EFFECTS ON DIGOXIN INTESTINAL ABSORPTION

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The intestinal barrier plays a significant role in drug absorption of orally administered drugs. Efflux transporter P-glycoprotein (ABCB1) is known to limit intestinal absorption of its substrates and represents site of drug-drug interactions (DDIs). Inhibition of intestinal ABCB1 is hypothesized to be the crucial moment responsible for increased digoxin bioavailability and thus elevated risk of toxicity. Using *in vitro* bi-directional transport studies across Caco-2 cells and *ex vivo* method of accumulation in rat- and human-derived precision cut intestinal slices (PCIS) we showed in previous study that numerous anti-HIV and anti-HCV drugs reveal capability to increase absorption of model ABCB1 substrate, rhodamine123 (RHD123). In this follow-up project we aimed to investigate the potency of anti-HIV and anti-HCV drugs to decrease intestinal ABCB1-controlled efflux of digoxin and thus to bring direct evidence about molecular mechanism of interactions between antivirals and digoxin in the intestinal barrier. In the initial phase, we found that lopinavir (5 μM, 50 μM), ritonavir (100 μM), atazanavir (50 μM), darunavir (50 μM, 100 μM), rilpivirine (20 μM) daclatasvir (20 μM), grazoprevir (20 μM, 50 μM), asunaprevir (20 μM, 50 μM) and ledipasvir (50 μM) inhibit the efflux of digoxin in Caco-2 cells, while abacavir(100 μM), dolutegravir (10 μM), elbasvir (5 μM), velpatasvir (5 μM) and sofosbuvir (100 μM) revealed no inhibition of intestinal ABCB1 in tested concentrations. In conclusion, we have demonstrated that antivirals have potency for DDIs on intestinal ABCB1 and our data contributes to explaining the molecular mechanism of reported increased bioavailability of digoxin, when administered together with antivirals. The study will continue by testing the interactions between digoxin and antivirals using the *ex vivo* model of human-derived PCIS.

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