Abstract

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Title of diploma thesis: Effect of anthelmintics on the transport of drugs in the intestine

Several classes of drugs are currently available for the treatment of helminthiasis in humans and animals, the so-called anthelmintics. Most of these drugs are administered by the oral route, where absorption into the systemic circulation occurs through the intestinal barrier. However, the course and extent of this absorption may be limited by biotransforming enzymes and transport proteins, in particular the family of so-called ATP-binding cassette transporters. These transporters are capable of returning many xenobiotics, including many drugs, back into the lumen of the gut and are the first line of defence against the entry of these substances into the body. An important representative of this group of transporters is P-glycoprotein, which is known for its broad substrate specificity. On this transporter, drugs can act as substrates but also as inhibitors and/or inducers, which may lead to the risk of drug-drug interactions.

There is relatively little information about the effect of anthelmintics on P-glycoprotein inhibition. The most studied anthelmintic in the context of P-glycoprotein is ivermectin, from the group of macrocyclic lactones, which has been considered for many years as a proven inhibitor of this efflux transporter.

The aim of this thesis was to investigate whether and to what extent other anthelmintics inhibit P-glycoprotein function in the intestinal barrier. For this purpose, we used the *ex vivo* method of precision-cut intestinal slices prepared from the rat ileum. Rhodamine 123 was used as a model substrate and CP-100356 as a specific inhibitor. We tested anthelmintics from different classes at concentrations of 1 and/or 10 μM and their ability to increase rhodamine 123 accumulation in intestinal tissue. In addition, concentration-dependence tests on rhodamine 123 accumulation were performed for three selected drugs (ivermectin, closantel and niclosamide).

A number of agents showed statistically significant increases in relative rhodamine 123 accumulation, namely ivermectin, moxidectin, oxyclosanide, rafoxanide, niclosamide, monepantel and praziquantel, all at a concentration of 10 μM. Doramectin then showed a significant increase in accumulation at both 1 and 10 μM. No inhibitory effect was observed with benzimidazole anthelmintics at a concentration of 10 μM.