

Abstract

Charles University in Prague
Faculty of Pharmacy in Hradec Králové
Department of Biochemical Sciences

Title, Name, Surname of candidate: Martina Štěpničková

Title, Name, Surname of tutor: Doc. Ing. Barbora Szotáková, Ph.D.

Title of a diploma work: Modulation of biotransformation enzymes by repeated administration of flubendazole in domestic sheep.

Flubendazole is benzimidazole anthelmintic widely used in veterinary medicine for treatment and prevention of helminthosis in domestic and wild animals. Currently the effectiveness of available anthelmintics is being diminished by the worms newly formed resistance mechanisms. This work was designed to test the influence of flubendazole on cytochrome P450 isoforms, flavine monooxygenases, some carbonyl reducing enzymes, glutathion S-transferase and UDP-glucuronosyl transferase in domestic sheep. Activities of these enzymes were observed in subcellular fractions which were prepared from the liver and small intestine of the following groups of tested subjects: control sheeps, flubendazole treated sheeps and *Haemonchus contortus* infected sheeps that were subsequently treated by flubendazole. Flubendazole was administered to each sheep three times in a dose of 15mg/kg. The results indicated that flubendazole does not influence the activity of CYP 2B, CYP 3A, and glutathion-S-transferases. After the flubendazole therapy was observed the inhibition in activities of CYP 2E. Activities of CYP 1A, CYP 2B, CYP 2C9, flavinmonooxygenases and UDP-glucuronosyl transferases were depended on animal gender and helminthosis. The largest influence of flubendazole on reduction enzymes was appeared in activities of 11 β -HSD and carbonylreductase. Especially the induction of oxidation, reduction and conjugation enzymes has a profound negative effect on the efficacy and pharmacokinetics of flubendazole itself and any other simultaneously or consecutively administered drugs. Induction of these enzymes results in a faster metabolism and elimination of flubendazol which cuts down its therapeutic levels. Under these conditions, worms are able to survive flubendazole administration and activate their resistance mechanisms.