Abstract

Flubendazole, a benzimidazole-like drug with strong effect on Nematoda and Cestoda (endoparasites), is routinely used in therapy of monogastric animals. Lately, it has been considered to use flubendazole also in treatment of ruminants. Hence, it is essential to obtain information about flubendazole metabolism in these species.

The main aims of study presented here were to identify an enzyme participating in flubendazole metabolism (in sheep) (with use of specific enzyme inhibitors) and to examine whether male or female sex has a significant influence on rate of flubendazole metabolism in domestic sheep. Consequently, the contribution of phase I and mainly phase II enzymes (conjugation with glucuronic acid) to metabolism of flubendazole in rats was thoroughly studied.

In the inhibition experiment, many specific enzyme inhibitors (menadione, naloxone, ketoprofen, coumarine, pyrazole, phenobarbital, quercitrin, α-methylcinnamic acid and estrone) were used to reveal a particular enzyme responsible for flubendazole biotransformation (reduction). Only menadion (specific inhibitor of cytosolic carbonyl reductase) was found to have strong inhibition effect on flubendazole reduction. Based on this result, cytosolic carbonyl reductase is assumed to be the main enzyme participating in flubendazole metabolism in domestic sheep.

In second step of the study, the differences in kinetics of flubendazole reduction in liver and intestinal cytosolic fraction between sheep and rams were substantially examined. The results have showed that strong reduction of flubendazole ocurred not only in liver but also in intestine. The Km and Vmax values in females were higher than in males but without great significance. This fact excluded considerable influence of sex-difference on flubendazole metabolism.

In *in vivo* study of flubendazole metabolism, flubendazole was perorally administered to rats. After 48 hours faeces and urine samples were taken and subjected to HPLC analysis. HPLC analysis did not detected any phase II metabolites of flubendazole in urine or faceces. Moreover, flubendazole was not conjugated with glucuronic acid *in vitro.*