ABSTRACT

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Title of Doctoral Thesis

METABOLISM AND EFFECTS OF NEW ANTHELMINTIC DRUG IN HELMINTHS AND ITS HOSTS

Diseases caused by helminths, called helminthoses, are one of the most serious problems in veterinary and human medicine. These diseases are treated by anthelmintics but their effectiveness is often not sufficient due to resistance of helminths against common anthelmintics. The global anthelmintic resistance encouraged the developing of new drugs with a different mode of action. Monepantel (MOP) belongs to a new class of anthelmintic drugs known as amino-acetonitrile derivatives (AADs) that act on the nicotinic acetylcholine receptors. In 2011, MOP was approved for the treatment of gastrointestinal diseases caused by nematodes in the veterinary practice in the Czech Republic. It is produced commercially under the trade name Zolvix® (Novartis AG).

The aim of this doctoral thesis was to study metabolism and effects of MOP and other AADs in order to contribute to the global research in this field. For this purpose, adults nematodes *Haemonchus contortus* (the sensitive strain ISE and the resistant strain WR) and its hosts *Ovis* spp. were used. In this study, metabolites of MOP formed *in vitro* (in ovine hepatocytes), *in vivo* (in urine and faeces from sheep) and *ex vivo* (in living nematodes) were identified. Furthermore, metabolism of the other AADs were also studied *in vitro* in ovine hepatocytes. Metabolic pathways of the MOP and its derivatives were compared with each other and in different model systems. In the second part of the doctoral thesis, the modulatory effect of MOP on the activity and expression of cytochromes P450 (CYP), main biotransformation enzymes, was studied in target species- sheep. Significant inducing effect of MOP on

the CYP3A24 was detected. Last but not least, the efficacy of MOP and its derivatives against lower developmental stages of *H. contortus* was tested. Current information about MOP, available from literary sources and obtained also from our experiments, were processed to the review article.

The obtained results of this doctoral thesis extend the knowledge about AADs, new class of anthelmintic drugs. The information about metabolic pathways, CYP induction and efficacy of MOP and its derivatives is very important for the safety of therapy and evaluation of risks of drug-resistance development in helminths. It may lead to improvement and streamlining of helminthosis treatment.