[ volume 41 | supplement 1 | june 2018 ]

JOURNAL OF

# Veterinary Pharmacology and Therapeutics

## Including veterinary toxicology

**14th International Congress of the European Association for Veterinary Pharmacology and Toxicology held in Wroclaw, Poland, June 24–27, 2018**

Guest edited by Błażej Poźniak, Marcin Świtała and Johanna Fink-Gremmels

ISSN 0140-7783 (paper)
ISSN 1365-2885 (online)

Available online at wileyonlinelibrary.com/journal/jvp

WILEY

JOURNAL OF

# Veterinary Pharmacology and Therapeutics

## Including veterinary toxicology

[ volume 41 | supplement 1 | june 2018 ]

## 14th International Congress of the European Association for Veterinary Pharmacology and Toxicology held in Wroclaw, Poland, June 24–27, 2018

Guest edited by Błażej Poźniak, Marcin Świtała and Johanna Fink-Gremmels

DOI: 10.1111/jvp.12641

WILEY JOURNAL OF Veterinary Pharmacology and Therapeutics

# ABSTRACTS

## PLENARY LECTURES, KEYNOTES AND ORAL COMMUNICATIONS – WEDNESDAY

## SESSION 22: ANTIPARASITICS

### O22.1 | KN Worm War: developing a better understanding of the pharmacology of anthelmintics

R. J. Martin

*Department of Biomedical Sciences, Iowa State University, IA, USA*

**Introduction**: Helminth parasites produce grinding diseases in humans and affect all animal species; they degrade human productivity, education of children, agricultural production and animal welfare. In the absence of effective vaccination and proper sanitation, treatment with anthelmintic drugs is required for treatment and prophylaxis. The limited number of anthelmintic drugs and their continuous use in animals has been associated with the development of resistance; the regular use of mass drug administration in humans has also given rise to concerns about resistance. There is an urgent need for novel 'resistance-busting' anthelmintics. With this in mind we have studied the pharmacology of anthelmintics to determine how they work and how resistance may arise. By this means we can contribute to development of more sustainable and effective therapies.
**Materials and Methods**: A number of anthelmintic drugs act on membrane ion-channels. We use molecular, electrophysiological, and expression techniques to examine their effects on G.I. worms, like *Ascaris suum*, *Oesophagostomum dentatum*, and filaria, like *Brugia malayi*. We have studied effects of the cholinergic agonist levamisole, pyrantel, and tribendimidine, as well as the antagonist derquantel. In addition we have studied the effects of the macrocyclic lactones ivermectin and abamectin, the cyclodepsipeptide emodepside, the GABA agonist piperazine and non-GABA agonist diethylcarbamazine.
**Results and Conclusions**: We have found that each anthelmintic is different, even within the same class. For example the individual nicotinic anthelmintics act selectively on different heterogeneous of muscle nicotinic receptors so that resistance to levamisole does not necessarily give rise to resistance of pyrantel. We have also seen significant unexpected effects: ivermectin and abamectin activate GluCl ion-channels in the pharynx of worms but in addition also inhibit the opening of nicotinic acetylcholine channels. This latter effect contributes to a synergism of derquantel and abamectin. Emodepside has a different mode of action, opening SLO-1 K channels, but on worms, the effect depends on the spice-variant of the channel, being more potent in male than the female worms. Piperazine inhibits muscle and behaves like a simple GABA agonist, opening Cl channels, but diethylcarbamazine does not, and produces muscle contraction. During our observations we have seen that there is greater complexity that we had first thought and in transcriptomic studies found that levamisole resistance was polygenic. It is likely that molecular tests for anthelmintic resistance, apart from resistance to benzimidazole drugs will not be simple and that phenotypic tests will endure. To conclude with a positive note: we have seen that there are many suitable drug targets in the worm and we now have more information for developing combination therapies that limit the advance of resistance. We look forward to that development.
**Acknowledgements**: Supported by NIH R01AI047194.

### O22.2 | Modulation of metabolic and transport processes: a valuable tool for improving anthelmintic efficacy?

P. Viviani[1]; G. L. Virkel[1]; S. E. Luque[1]; M. Lloberas[2]; C. E. Lanusse[1]; A. L. Lifschitz[1]

[1]*Laboratorio de Farmacología, Centro de Investigación Veterinaria de Tandil (CIVETAN), CONICET-CICPBA-UNCPBA, Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires (FCV-UNCPBA), Tandil, Argentina;* [2]*Instituto Nacional de Tecnología Agropecuaria (INTA), Estación Experimental Balcarce, Balcarce, Argentina*

**Introduction**: *In vivo* modulation of drug metabolizing enzymes and transporters may delay the elimination and enhance the systemic availability of anthelmintic compounds. Parasite exposure to the active molecules can be enhanced through their combination with transport modulators or other active anthelmintics. However, the practical relevance of such interactions is unknown. This work aims at assessing the occurrence of PK/PD interactions between (a) oxfendazole and triclabendazole; (b) moxidectin and loperamide; and (c) abamectin and ivermectin/itraconazole in lambs.
**Materials and Methods**: Lambs parasitized with nematodes highly resistant to benzimidazole and macrocyclic lactones were used. Experiment 1: Lambs (three groups, $n = 7$ each) were treated with

oxfendazole (5 mg $kg^{-1}$ PO), triclabendazole (12 mg $kg^{-1}$ PO) or their combination. Experiment 2: Lambs (two groups, $n$ = 7 each) were treated with moxidectin (0.2 mg $kg^{-1}$ SC) alone or in combination with loperamide (0.16 mg $kg^{-1}$ PO) and pluronic 123. Experiment 3: Lambs (two groups, $n$ = 10 each) were treated with abamectin (0.2 mg $kg^{-1}$ SC) alone or in combination with ivermectin (0.2 mg $kg^{-1}$ SC) and itraconazole (30 ml PO). Drug/metabolite concentrations in plasma were measured (days 0–15). The faecal egg count reduction test (FECRT) was used as a measure of nematodicidal efficacy.

**Results**: Experiment 1: Coadministration resulted in an increase in both the plasma $AUC_{0\text{-}LOQ}$ and MRT of the metabolite fenbendazole sulfone ($p$ 0.05), whereas all the PK parameters for triclabendazole sulfone were significantly decreased. Efficacy rose from 47.2 and 55.4% (single administration) to 75.7% (coadministration). Experiment 2: No differences in PK parameters were observed upon coadministration. Efficacies were 77.1 and 71.2%, respectively, for the single and combined treatments. Experiment 3: Exposure to ivermectin and itraconazole resulted in an increase in abamectin $C_{max}$ and $AUC_{0\text{-}LOQ}$ (not significant). Efficacies were 0% for both treatments.

**Conclusions**: Combination of active principles with modulators and other active compounds has been advocated as an alternative to enhance anthelmintic efficacy. However, clinical efficacy against resistant nematodes remains elusive in practical terms. In spite of proven *in vitro* pharmacological interactions, translation to clinical settings shows that *in vivo* trials are needed in order to assess the real impact of modulators and combined therapies in parasite control.

## O22.3 | Old drugs for new uses: pharmacokinetic assessment to support oxfendazole repurposing as a flukicidal compound

L. Ceballos[1]; C. Canton[1]; V. Gayo[2]; L. Moreno[1]; P. Dominguez[1]; C. Lanusse[1]; L. Alvarez[1]

[1]*Laboratorio de Farmacología Centro de Investigación Veterinaria de Tandil (CIVETAN), CONICET-CICPBA, Facultad de Ciencias Veterinarias, UNCPBA, Tandil, Argentina;* [2]*Instituto DILAVE, 'Miguel C. Rubino', Montevideo, Uruguay*

**Introduction**: Fascioliasis caused by *Fasciola hepatica* can cause considerable financial losses in livestock production. The main strategy for liver fluke control is based on the use of chemical-based treatments. However, the frequent use of effective flukicidal compounds had led to the development of drug resistance, largely to triclabendazole, the most extensively used drug. Oxfendazole (OFZ) is a broad spectrum anthelmintic used as nematodicidal, without flukicidal activity at therapeutic doses (5 mg $kg^{-1}$). However, activity against *F. hepatica* has been reported after a single OFZ dose of 30 mg $kg^{-1}$ in both sheep and pigs. The goals of the current work were (i) to compare the plasma pharmacokinetic (PK) profile of different OFZ doses in non-infected sheep, and (ii) to evaluate the dose-related pattern of *in vivo* accumulation of OFZ/metabolites into adult *F. hepatica*.

**Materials and Methods**: (i)PK trial: sheep were allocated into two groups ($n$ = 6 each) and orally treated with OFZ at a single dose of either 5 ($OFZ_5$) or 30 ($OFZ_{30}$) mg $kg^{-1}$. Blood samples were collected for 96 h post-treatment, and plasma analyzed for OFZ/metabolites by HPLC.

(ii)Drug accumulation trial: Animals (8) were each orally infected with seventy-five (75) metacercariae of *F. hepatica*. Sixteen weeks after infection, animals were randomly allocated into two experimental groups ($n$ = 4) and orally treated with OFZ at either 5 or 30 mg $kg^{-1}$. Animals were killed at different times post-treatment and samples of blood, bile, liver and adult liver flukes were obtained. Samples were analyzed by HPLC.

**Results and Conclusions**: OFZ parent drug was the main analyte detected in plasma from OFZ treated sheep. The $C_{max}$ and $AUC_{0-t}$ values were approx. 4-fold higher in the $OFZ_{30}$ group (2.5 ± 0.6 μg $ml^{-1}$ and 83.7 ± 20.5 μg × h $ml^{-1}$, respectively), compared to that observed after the 5 mg $kg^{-1}$ dose (0.6 ± 0.1 μg $ml^{-1}$ and 18.0 ± 3.7 μg × h $ml^{-1}$, respectively). These differences were also reflected in the pattern of OFZ accumulation into *F. hepatica*, which results 332% higher after the 30 mg $kg^{-1}$ dose (4.28 μg $g^{-1}$) compared to the lower dose (0.99 μg $g^{-1}$). The data shown here demonstrates that the OFZ dose increment is associated with a higher plasma drug exposure and accumulation into the target parasite, which help to explain OFZ efficacy against adult liver flukes at 30 mg $kg^{-1}$ dose. The reported pharmacological data may contribute to assess OFZ repurposing for a new use as a flukicidal compound.

## O22.4 | Efficacy of pyrantel and fenbendazole against *Parascaris univalens* infection in foals in Sweden

E. Tydén; O. Rasmusson; T. Bergström; J. Höglund; F. Martin

*Department of Biomedical Sciences and Veterinary Public, Swedish University of Agricultural Sciences, Uppsala, Sweden*

**Introduction**: *Parascaris univalens* infection in foals is a common problem around the world. Resistance against the anthelmintic ivermectin is well established in the worldwide parascaris population. Also multi-resistance to ivermectin and pyrantel has been reported in North America and Australia. The aim of this study was to investigate the efficacy of pyrantel and fenbendazole on stud farms in Sweden. Previous Swedish studies from 2005 showed resistance to ivermectin on 5 out of 6 investigated farms, but that pyrantel and fenbendazole were still effective.

**Material and Methods**: A Fecal Egg Count Reduction Test (FECRT) was performed on a total of 158 foals on 17 stud farms in Sweden from September 2016 to December 2017. Foals were between 6 and 10 months of age. Individuals with a minimum of 150 eggs per gram feces were included in the study. Faecal samples were collected before treatment with pyrantel or fenbendazole, and 14 days post-treatment. Pyrantel embonat (Banminth® Pharmaxim) was used at a dose of 19 mg $kg^{-1}$ bodyweight (equals 6.6 mg of pyrantel base) or