Editorial

Ivermectin was the first macrocyclic lactone introduced in the veterinary market by Merck Sharp & Dohme in 1981, quickly becoming one of the most commonly used antiparasitic agents across animal species worldwide. Since then, several other macrocyclic lactone compounds have been developed and used for the treatment of internal and external parasites.

Readers interested in this class of drugs are referred to those 2 following books:

- *Ivermectin and abamectin*. Campbell, W.C., Ed.; Springer-Verlag: New York, 1989.
- *Macrocyclic lactones in antiparasitic therapy*. Vercruysse, J., Rew, R.S., Ed.; CAB International: UK, 2002.

It's been nearly one decade since the publication of *Macrocyclic lactones in antiparasitic therapy,* and with this special issue of *Current Pharmaceutical Biotechnology* we would like to update information of the current knowledge of these drugs. For this purpose, this especial issue includes 18 review papers covering several different aspects, with update information on history, pharmacology, toxicity and safety, including safety for the consumer and the environment, status of resistance, analytical methods for determination of macrocyclic lactones, and the clinical uses in cattle, equids, pets and exotic animals, fish and humans.

The first review in this special issue, written by ***Dr. Campbell***, provides additional detail, and offers a personal perspective on the ***history*** of ivermectin and related avermectins. Brief notes are included on the subsequent development of other macrocyclic lactones. The chapter is focused on discovery, development and early clinical trials.

Dr. Geary and Dr. Moreno summarize recent progress in understanding the ***mechanism of action*** of this class of drugs in the context of the spectrum of their clinical utility. The authors also highlight gaps in their understanding of the receptor-level pharmacology of the macrocyclic lactones. The spectrum of action can now be understood based on the phylogenetic distribution of glutamate-gated chloride channels, the primary target for the macrocyclic lactone class of endectocides. The ability of these drugs to remove gastrointestinal nematodes from a host is due to their effects on somatic and pharyngeal muscles, paralyzing and starving the nematodes. Actions on filarial nematodes may be due instead to inhibition of the secretion by these parasites of immunomodulatory molecules. How macrocyclic lactones kill insects has not been as fully elucidated, and the complexity of receptors for these drugs in arthropods requires further investigation.

Dr. Wolstenholme and Dr. Kaplan briefly survey some recent reports on the current state of ***resistance*** in livestock parasites and mention the current situation in companion animal and human parasites. The authors also examine some of the current thinking surrounding the mechanisms and genetics of macrocyclic lactones resistance and discuss both current and future methods for its detection. The implications of resistance for the continued use of these compounds are also discussed.

In the next paper, ***Dr. McKellar and Dr. Gokbulut*** provide a comprehensive review of the ***pharmacokinetics*** of macrocyclic lactones and interpret where that information may prove clinically useful. The authors have divided the manuscript in different sections related to the factors that could affect the kinetics properties of these compounds.

An update on the available information concerning drug-drug ***interactions*** involving the macrocyclic lactones is presented by ***Dr. Lifschitz and colleagues***. Concomitant administration of multiple drugs may drastically induce changes to the disposition kinetics and pharmacological activity of macrocyclic lactones. Therefore, the understanding of the pharmacology-based interactions involving the macrocyclic lactones may provide relevant information to optimize their therapeutic use.

In ***non-traditional domesticated wild ruminants*** veterinarians need to use this drug in an ***extra-label*** manner, extrapolating data from one species to another. A review of the main aspects regarding the pharmacokinetic behaviour of ivermectin in these species, and also some basic information about its spectrum of activity, is ***our contribution*** to this special issue.

The manuscript of ***Dr. Danaher and colleagues*** is focused on recent developments in food ***analysis*** of macrocyclic lactones in the last five years. A more extensive report is carried out on environmental analytical determinations because this has not been reviewed before.

The ***toxicity*** of this class of drugs in ***laboratory animals and target species*** is reviewed by ***Dr. Woodward***. Although the macrocyclic lactones have a long history of safe use in animals, signs of neurotoxicity have been noted in laboratory species, albeit at higher doses, and in animals rendered susceptible to the neurotoxic effects by virtue of specific mutations which allow penetration of these drugs into the central nervous system. In target animals, toxicity is also seen when the normal therapeutic dose is exceeded and in dogs in particular, in susceptible individuals predisposed through mutations.

Certain dogs, in particular ***Collies***, are highly sensitive against this class of drugs. Today we know that macrocyclic lactones are transported by the drug efflux carrier P-glycoprotein, encoded by the *multidrug resistance* gene *MDR1*, which is highly expressed at the blood-brain barrier of vertebrates. Here P-glycoprotein highly restricts the entry of these drugs into the CNS and their access to GABA-gated chloride channels, which are confined to the central nervous system in vertebrates. A 4-bp deletion mutation exists in the *MDR1* gene of these sensitive dogs which results in the expression of a completely non-functional P-glycoprotein. In this paper, ***Dr. Geyer and Dr. Janko*** review and discuss the neurotoxicological potential of different macrocyclic lactones as well as their treatment options in *MDR1* mutant dogs.

The potential risks related to the presence of drug ***residues*** in edible tissues, milk, and other derived products of food-producing animals are controlled by the medicines agencies or regulatory organisms of each country by means of the establishment of maximum residue limits. Some basic information about the procedures for the adoption of these maximum residue limits and an overall review of the studies carried out concerning ivermectin residues in animal foodstuffs are presented in the paper of ***Dr. Escribano and colleagues***.

Ivermectin therapy is generally well tolerated in ***humans***, although ***adverse effects*** that are usually transient and mild-to-moderate can occur. Severe adverse effects are rare and can generally be effectively controlled by symptomatic measures. Non-therapeutic exposures to ivermectin and other macrocyclic lactones may also result in toxic effects. ***Dr. Yang*** contributed a manuscript with detailed information on these aspects.

Dr. Lumaret and colleagues critically review the present knowledge about the acute and chronic ***ecotoxicological*** effects of macrocyclic lactones on organisms, mainly invertebrates, in the terrestrial and aquatic environment. Available information is presented on the mode-of-action as well as the ecotoxicity of the most important compounds representing the three groups of macrocyclic lactones.

Those drugs that are currently approved for ***use in cattle*** in the United States are reviewed in the manuscript written by ***Dr. Ballweber and Dr. Baeten***. The general efficacy, tissue distribution and toxicity of each drug formulation are discussed. Also provided is a discussion regarding the current status for nematode anthelmintic resistance in cattle populations within the United States and a summary of ecological effects of macrocyclic lactones residues in manure.

A paper covering the most relevant aspects of the use of these compounds in ***equids*** is presented by ***Dr. Lyons and Dr. Tolliver***. When macrocyclic lactones such as ivermectin were first marketed it seemed that they were the panacea for parasite control in equids because of their broad-spectrum activity. As has occurred with several other classes of parasiticides after a period of usage, efficacy decreased on some nematode species. However, the macrocyclic lactones still are important means of controlling parasites in equids.

The anti-parasitic applications of macrocyclic lactones in ***small companion animal medicine*** are described in the paper written by ***Dr. Nolan and Dr. Lok***. Their main use, among others, is for the prevention of heartworm (given on a monthly basis), although there are indications that resistance may be developing in some populations of *D. immitis*. The extra-label use in ***exotic small mammals and reptiles*** is also reviewed.

Dr. Horsberg described several aspects of the use of avermectins as antiparasitic agents in ***fish***. Ivermectin and emamectin benzoate are predominantly used as in-feed formulations on salmonid fish against copepods in the family Caligidae. The safety margin for ivermectin is narrow, but better for emamectin benzoate. Resistance has developed against these agents in *L. salmonis* in almost all major salmon producing areas. The situation must be viewed as serious and can render these agents completely ineffective for salmon lice control.

A comprehensive overview of ivermectin's uses in human medicine is presented by ***Dr. González and colleagues***. Ivermectin has widely shown its efficacy in onchocerciasis, strongyloidiasis and lymphatic filariasis infestations, and recent trials have shown its potential to treat a broad variety of parasitic infections such as gnathostomiasis, scabies, ascariasis and mansonella. The authors also give some basic information about the parasitic diseases for which it is recommended.

Finally, ***Dr. Hopkins*** has written a review on the ***Mectizan donations***. This was a ground breaking phenomenon in corporate philanthropy, with the donation of "as much as is needed for as long as is needed" and opened the door to the whole neglected tropical diseases programmes. This longstanding donation (over 20 years) has lead to major worldwide public health programmes for onchocerciasis and lymphatic filariasis and two diseases are now being targeted for worldwide eradication as a result, onchocerciasis and lymphatic filariasis.

I would like to thank all the authors that participated in this project, and hope that all the hard work dedicated to this special issue will result in a helpful reading for those interested in topics related to the macrocyclic lactones.

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