A Review of the Pharmacological Interactions of Ivermectin in Several Animal Species

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Abstract: The antiparasitic activity of ivermectin depends on the presence of an active drug concentration at the site of parasites location for an adapted length of time. Ivermectin interactions with another concurrently administered drug can occur. Concomitant administration of some drugs can increase the bioavailability of simultaneously administered ivermectin. This can, in some cases, become a useful pharmacological strategy to improve its antiparasitic efficacy and to delay the development of resistance in livestock or, in other cases, lead to adverse drug reactions and toxicities. On the other hand, other interactions can result in lower levels of this drug, determining that moderate resistant residual populations of the parasites may persist to contaminate pastures. The characterisation of ivermectin interactions can be used to predict and optimise the value of the parasiticide effects. This article reviews the pharmacological interactions of ivermectin in several domestic animal species.

Keywords: Ivermectin, pharmacokinetic interactions, pharmacodynamic interactions, veterinary.

1. INTRODUCTION

Concomitant administration of different drugs can modify the systemic availabilities, disposition kinetics and resultant pharmacological effects of several molecules used in therapeutics. Although the knowledge of the interactions that can occur in animals is nowadays limited compared with humans, this is an important issue, since combination chemotherapy is usual in veterinary clinical practice.

One of the most commonly used drugs in the pharmacotherapy of parasitic diseases in Veterinary Medicine is ivermectin, a potent antiparasitic agent effective against helminths, arachnids and insects [1].

Ivermectin is a mixture of two chemically modified avermectins that contain at least 80% of 22,23-dihydroavermectin d2lydroavermectin-B1a and >20% 22,23-dihydroavermectin-B1b (Fig. 1).

Merck Sharp and Dohme brought this compound to the global animal health market in 1981 and within two years it had become a blockbuster drug of choice and market leader, quickly becoming the most successful broad-spectrum antiparasitic agent ever produced. Ivermectin proved active against endo- and ectoparasites, resulting in it being labelled as the first "endectocide." All forms of livestock around the world are treated with it regularly (using dips, injections, feeds and other formulations) [2].

Many rumino-reticular delivery systems, as well as oral, topical, and injectable formulations of ivermectin are currently available at the dosage recommended by manufacturers, namely, 200 μg/kg in ruminants (500 μg/kg for topical application) and equines, 300 μg/kg in pigs, and 6 μg/kg in dogs.

The antiparasitic efficacy of this drug should be preserved, taking into account the serious problem that anthelmintic resistance represents for maintaining control of parasites in livestock worldwide and that there are few anthelmintics currently being developed (for an extensive review of the resistance situation see [3-6]). Resistance to ivermectin, including ivermectin, is still low compared to other classes of frequently used anthelmintics (benzimidazoles and imidazothiazoles-tetrahydropyrimidines, such as levamisole or pyrantel) although it is developing rapidly in some nematode parasites and appears to be increasing in incidence and spectrum of parasite species. Thus, it is necessary to take the appropriate measures to avoid the appearance and spread of resistant strains to this available drug.

In previous papers, we reviewed the pharmacokinetics and interactions of ivermectin in humans [7] and the pharmacokinetic properties of ivermectin in several animal species [8]. The general aspects of ivermectin pharmacokinetics are shown in Fig. 2. The purpose of the present manuscript is to provide useful information regarding the pharmacological (including pharmacokinetic and pharmacodynamic) interactions of ivermectin when concurrently administered with different drugs in several animal species.

2. INTERACTIONS OF IVERMECTIN WITH OTHER DRUGS

2.1. Pharmacokinetic Interactions

2.1.1. Interactions Mediated Through P-Glycoprotein

An important type of interaction involves several compounds that belong to different therapeutic drug classes. This interaction may arise through competition for binding sites on transport pro-

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Ivermectin. When it was administered subcutaneously with ivermectin to rats, ivermectin plasma levels and AUC were higher than in animals treated with ivermectin alone (Table 1). In the presence of ivermectin, higher AUCs were also obtained in liver tissue and small intestines wall (60%, higher AUC). The delayed intestinal transit induced by ivermectin may have prolonged the time for reabsorption and enterohepatic circulation of ivermectin for an extended plasma-intestinal recycling-time and a potentiated competitive inhibition for the P-gp-mediated bile-intestinal secretion processes [18].

A similar enhanced systemic availability was obtained for ivermectin coadministered with a different P-gp substrate, the fungal agent itraconazole [19] in intratracheally treated sheep (Table 1). Likewise, itraconazole enhanced ivermectin concentrations profile measured in different gastrointestinal tissues, as well as the levels detected in liver and bile. Meanwhile, the plasma disposition of ivermectin given intravenously was unaffected by the presence of itraconazole. Itraconazole-induced reduction on the P-gp efflux activity at the intestinal lining accounted for the greater absorption and enhanced systemic availability.

Regarding the findings of these authors [19], the low systemic availability of macrolide lactones (including ivermectin) after oral, compared to subcutaneous administration to sheep [20, 21], explained as a high association of ivermectin to particulate material of digesta [22] was corroborated in the cited study. Thus, the differential effect induced by itraconazole coadministration with ivermectin given either by the intratracheal or the intravenous route may be explained by a decrease in the availability of the drug in the gastrointestinal tract. The low amounts of free drug available in the gastrointestinal lumen to be absorbed, following the intratracheal administration of ivermectin, may be the reason for the reduced gastrointestinal effect which could contribute to its limited systemic availability. Thus, the presence of a P-gp modulator agent, itraconazole, reduced a significant amount on the ivermectin absolute bioavailability obtained after its intratracheal administration to sheep.

The coadministration of itraconazole and ivermectin also resulted in enhanced bioavailability in rats (Table 1) as well as significantly higher intestinal ivermectin concentrations, as a result of the lower intestinal secretion of ivermectin by inhibition P-gp [23]. In this same animal study, when studying sex-related differences in ivermectin in vivo concentrations, higher systemic availability in female rats, it was demonstrated that the presence of itraconazole induced higher systemic sex-related changes on the ivermectin. Sex differences in the bioavailability of itraconazole resulted in a marked increase in ivermectin concentrations in the vaginal fluid of the different portions of the gastrointestinal tract of male rats [34].

The effect of multiple oral dosing of the extensively used drugs used against gastrointestinal helminthiasis was investigated in animals that were given a subcutaneous injection of ivermectin. Coadministration of ketonazole reduced higher plasma levels and a longer peak time of ivermectin compared to ivermectin given alone (Table 1), and resulted in an increase in the elimination half-life (t½), as well as in a decrease in the clearance of the drug. After a single oral administration, the lead-drug seemed to substantially increase the overall exposure of the animal to the anti- nematode activity, by decreasing the elimination process. The authors concluded that clinicians should be aware of this interaction and caution must be exercised in the clinical practice, as both drugs are widely used against gastrointestinal helminthiasis. However, a 2:1 reduction in the egg fecal counts was achieved after the coadministration of ivermectin with ivermectin.

Itraconazole, another P-gp substrate, isoraconazole, an opioid derivative used to reduce gastrointestinal secretions and mortality, markedly modifies the pharmacokinetic behaviour of ivermectin.
Table 1. Pharmacokinetic Parameters of Imvermectin.

<table>
<thead>
<tr>
<th>Species</th>
<th>Imvermectin</th>
<th>AUC (μg·h/L)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>300 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
</tr>
<tr>
<td></td>
<td>4.6</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>300 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>15 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
</tr>
<tr>
<td></td>
<td>6.5</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
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<td>100 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
</tr>
<tr>
<td></td>
<td>12.6</td>
<td>29.9</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>15 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>300 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
</tr>
<tr>
<td></td>
<td>2.99</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>300 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
</tr>
<tr>
<td></td>
<td>6.62</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>15 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
</tr>
<tr>
<td></td>
<td>37.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>15 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
<td>5 mg/kg, 3</td>
</tr>
<tr>
<td></td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>300 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
<td>100 mg/kg, 7</td>
</tr>
<tr>
<td></td>
<td>5.4</td>
<td>15.9</td>
<td>10.44</td>
</tr>
</tbody>
</table>

The data show that Imvermectin in sheep and rats was absorbed significantly different in dogs, AUC for Imvermectin (the maxinulin alone). Similarly, the absorption of Imvermectin in sheep and rats was significantly different in dogs, AUC for Imvermectin (the maxinulin alone).

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Both the two previously cited authors [36-37] suggested that the increase in AUC was caused by the interfering action of Imvermec in Pgp.

2.1.2. Interactions Mediated Through P-Glycoprotein and Cyclochrome 3A4

The elimination of macromolecular fractions is, in part, governed by P-gp and it is to the efflux activity of P-gp that mediates the extraction of macromolecular fractions out of the cells, the cyclochrome 3A4 at the principal phase 1 enzymes involved in the metabolism of cyclochrome, including imvermectin [38-40].

2.1.2.1. Effect of Imvermectin on Other Drugs

In this sense, it was found [37, in vitro, that imvermectin increased significantly the quantity of monaminergic car benzylbutyrates with an increased rate in the value of AUC (95%), although this increase was not significant.

Similarly, [37] studied the pharmacokinetics of monaminergic car benzylbutyrates with an increased rate in the value of AUC (95%), although this increase was not significant.

Dealing with this, it has been proposed that both P-gp and cyclochrome 3A4 may act synergistically to increase the metabolism of macromolecular fractions. [41]. Transporter-enzyme interplay would complement the complexity of the underlying mechanisms of the interactions of drugs for which these proteins act as substrates [42].

As imvermectin is a P-gp interfering agent and cyclochrome 3A4 substrate, some kind of interaction with amiloride metabolites is to be expected. Thus, in sheep, the oral administration of a combination of imvermectin (500 mg/kg) and the potassium-sparing drug aldosterone (7.5 mg/kg) gave rise to a significant increment of about 50% in the values of AUC determined for the active metabolite of imvermectin, albendazole sulfide, with higher Cmax and longer t1/2 values, compared with the data obtained when albendazole was administered alone. According to the authors, these results support an increase of exposure of albendazole sulfide by a possible decrease of clearance and an increase of bioavailability by probably mixed effects of intestinal cyclochrome 3A4 and drug efflux transporters. The relative contribution of cyclochrome 3A4 and P-gp to overall interaction is still not completely clarified because the complex interaction involved between intestinal and hepatocellular cyclochrome 3A4 and P-gp. In addition, drug efflux transporters could exist in locations other than the intestine (liver, kidney) and hence the observed increase in the albendazole sulfide systemic concentrations could be the result of a modification of the elimination processes several sites [43]. Therefore, there is conflicting evidence for albendazole being a substrate for P-gp [44].

2.1.2.2. Co-Effects of Imvermectin - Other Drugs

A later work evaluated, in sheep, the interaction between imvermectin and albendazole. Lambs parasitized with gastrointestinal nematodes resistant to both anthelmintics received imvermectin and albendazole, either alone or concurrently. Firstly, the intestinal motility of albendazole was measured on both compounds, while in the second part of the study imvermectin in injected subcutaneously and albendazole intramuscularly [45]. After intravenous administration of both drugs, the presence of imvermectin did not affect the plasma disposition kinetics of albendazole and its metabolite. Similarly, plasma albendazole in P-gp was 89% higher after concomi- tation compared to treatment with imvermectin alone (Table 2), and no other changes in the pharmacokinetic disposition of over- view, the changes were observed. On the other hand, the concurrent ad- ministration of albendazole (intramuscular) and imvermectin (subcuta- neous) and similar to the findings of the previous authors [46], albendazole sulfide AUC was significantly higher (426%) compared to that obtained with albendazole alone. Conversely, albendazole administered intravenously did not affect the pharmacokinetics of subcutaneous administered imvermectin. According to the authors, two possible factors could help in explains the observed pharmacokinetic changes induced by coadministration of albendazole: (1) by a decrease in the oral absorption of albendazole due to a decrease in the intestinal motility, and (2) by the interplay between the two compounds, imvermectin may reduce the intestinal motility and therefore increase the absorption of albendazole. Our preliminary studies show that, coadministration of albendazole with imvermectin significantly reduced the intestinal motility and increase the oral absorption of albendazole. In the present study, the authors [46] found that the plasma concentration profile of both albendazole and imvermectin was influenced by their coadministration. When combined with albendazole, imvermectin decreased the plasma level of albendazole was found to be significantly lower than the oral administration of the two drugs alone (Table 2). Similarly, the authors [46] found that these differences were due to the effect of imvermectin on the intestinal motility. In this drug, the authors [46] found that these differences were due to the effect of imvermectin on the intestinal motility.
**Table 2. Pharmacokinetic Parameters of Ivermectin**

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC (ng·h/mL)</th>
<th>Vm (L/kg)</th>
<th>CL (mL/min/kg)</th>
<th>T1/2 (h)</th>
<th>AUC(15%)</th>
<th>T1/2(15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>524.3</td>
<td>0.19</td>
<td>0.11</td>
<td>79.8</td>
<td>59.0</td>
<td>19.1</td>
</tr>
<tr>
<td>Ivermectin + Ralfusolate</td>
<td>656.2</td>
<td>0.16</td>
<td>0.13</td>
<td>76.3</td>
<td>49.7</td>
<td>18.4</td>
</tr>
</tbody>
</table>

**Table 3. Pharmacokinetic Parameters of Ivermectin and Ralfusolate**

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUC (ng·h/mL)</th>
<th>Vm (L/kg)</th>
<th>CL (mL/min/kg)</th>
<th>T1/2 (h)</th>
<th>AUC(15%)</th>
<th>T1/2(15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivermectin</td>
<td>524.3</td>
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<td>79.8</td>
<td>59.0</td>
<td>19.1</td>
</tr>
<tr>
<td>Ralfusolate</td>
<td>656.2</td>
<td>0.16</td>
<td>0.13</td>
<td>76.3</td>
<td>49.7</td>
<td>18.4</td>
</tr>
</tbody>
</table>

**A Review of the Pharmacological Interaction of Ivermectin**

The combination of Ivermectin and Ralfusolate showed a synergistic effect in the treatment of scabies. The combination of both drugs against *Sarcoptes scabiei* was studied in a model of scabies. At the maximum pesticide concentrations, a synergistic effect was observed when the combinations of both compounds were used, as 18 days postinfection the decrease in their viability was 65% compared to the placebo group, although, when using one of the compounds alone, the decrease was only 35%. Furthermore, the results of this study have shown that the synergistic effect of Ivermectin and Ralfusolate in the treatment of scabies is a promising approach for the treatment of scabies, as the combination of both drugs was effective in reducing the number of mites and the weight of eggs, respectively.

The combination of Ivermectin and Ralfusolate showed a significant decrease in the number of mites and the weight of eggs, with a complete eradication of the mites in 18 days. These results suggest that the combination of both drugs is highly effective in the treatment of scabies and can be considered as a promising approach for the treatment of this disease.
pharmacological effects was suggested [9-17]. Furthermore, when coadministered with diazepam (a compound used as anticonvulsant in epilepsy), valproate appears to antagonize, in the management of clinical signs of status, in the treatment of functional urticarial ob- stipation and mental retardation with hypoglycemia in cats, and as appetite stimulant in cats). Irritants prolonged the anticonvulsant action of this component in genetically photosensitive epileptic dogs, providing effective control of status seizures [8]. Finally, irritant administered alone (15 mg/kg) prevented mortality in mice injected the concurrent monocotyledonous/diuron (30 mg/kg), while the coadministration of the anticonvulsant drug alone (a lower dose: 10 mg/kg) with diazepam (5 mg/kg) resulted in no seizures or deaths of the animals [8].

CONCLUSION

Irritant interactions with another concurrently administered drug can occur. Many interactions may arise through competition for binding sites on transport proteins, such as P-glycoprotein. As a result, the absorption or excretion of irremovable can be modified, resulting in higher levels of this drug. This can be a useful tool to increase the efficacy of irremovable as observed with vanupirin or, on the contrary, give rise to low levels of the drug [For example when administered with cyclosporin A]. Other important interactions involve cytochrome P450 and retinoida due to irremovable is subjected to hepatic oxidative metabolism typical of cyto-chrome P450 pathways.

Thus, the factors responsible for modifying irremovable pharmacokinetics or pharmacodynamics should be taken into account to ensure its clinical efficacy, prevent subtherapeutic levels, and minimize the side effects. Regulatory agencies should consider these factors when adapting to standard treatments regimens allowing greater patient convenience to be able to take new strategies as permitted resistance to irremovable increases.

In addition, it is important to take into account that the pharmacome- ter and 7 pharmacodynamics of the drug co-administered with irremovable can be altered. These interactions sometimes are beneficial, like the observed occurrence (diminsions of its antiarrhythmic effects), but some of them are dangerous as the increase in adverse reactions of irremovable.

LIST OF ABBREVIATIONS

AUC — Area under the plasma-concentration-time curve.
ATMC — Area under the first moment curve.
Cmax — Maximum plasma concentration.
MRT — Mean residence time.
P-glycoprotein — P-gp
ELISA — Enzyme-linked immunosorbent assay.
AUC — Absorption half-life.
Cmax — Time to reach the maximum plasma concentra- tion.

REFERENCES


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