

ANIMAL HEALTH APPLICATIONS OF IVERMECTIN^{1/ 2/}

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ABSTRACT

Development of ivermectin represents an important advance in anti-parasitic therapy. The compound, which is a derivative of a natural fermentation product, has a broad range of efficacy against the developing and adult stages of most nematode parasites of economic importance affecting domesticated animals. Several arthropod parasites are also affected. Ivermectin given according to label instructions possesses a wide margin of safety.

INTRODUCTION

Ivermectin is a member of the avermectin class of compounds. The avermectins are a group of fermentation products derived from the actinomycete, Streptomyces avermitilis. Discovery of the antiparasitic activity occurred after the organism was cultured in the laboratory and the broth medium was fed to infected animals (Burg et al. 1979).

The basic chemical structure of the avermectins is a macrocyclic lactone with two sugars attached. There are four major components (A₁, A₂, B₁ and B₂) of the avermectin class, and each exists as two variants (designated a and b). Thus, the avermectins are composed of eight compounds (Miller et al. 1979). Ivermectin is a chemical derivative composed of at least 80% 22,23-dihydroavermectin B_{1a} and not more than 20% 22,23-dihydroavermectin B_{1b}.

The purpose of this review is to describe the animal health applications of ivermectin. Special consideration is directed at the important clinical aspects of products marketed and those nearing development completion. Applications within the United States are emphasized.

MODE OF ACTION

Ivermectin affects neural transmission mediated by gamma aminobutyric acid, or GABA (Kass et al. 1980) and thereby causes death of certain parasitic nematodes and arthropods.

In nematodes, ivermectin stimulates the release of GABA from nerve endings and enhances the binding of GABA to special receptors at nerve junctions. This action interrupts nerve impulses, thereby paralyzing and killing the parasites.

The enhancement of the GABA effect in arthropods, such as mites and lice, resembles that in nematodes except that nerve impulses are interrupted between the nerve ending and the muscle cell. Again, this leads to paralysis and death.

¹)Product of Merck & Co., Inc., Rahway, NJ

²)IVOMEC and EQVALAN are registered trademarks of Merck & Co., Inc., Rahway, NJ for ivermectin. Zimecterin is a registered trademark of Farnam Companies, Inc., Omaha, NE for ivermectin paste for horses.

Ivermectin has no measurable effect against flukes or tapeworms, presumably because they do not have GABA as a nerve impulse transmitter. Protozoa also are not affected.

Recommended therapeutic doses of ivermectin have a wide safety margin in domesticated animals (Campbell and Benz 1984). The principal peripheral neurotransmitter in mammals, acetylcholine, is unaffected by ivermectin. Ivermectin does not readily penetrate the central nervous system of mammals where GABA functions as a neurotransmitter.

ADMINISTRATION

Cattle should be injected with ivermectin subcutaneously. A sterile solution of 1% ivermectin in organic solvents (IVOME^R Injection for Cattle) is commercially available in the United States as well as in many countries internationally. The dose of 1 ml/50 kg of body weight is equivalent to 200 ug ivermectin/kg.

Sheep are given ivermectin orally in a solution (IVOME^R Liquid for Sheep). This formulation contains 0.08% ivermectin dissolved in a micellar solution. The dose is 2.5 ml/10 kg of body weight, or 200 ug ivermectin/kg.

Horses should be given an oral paste formulation of ivermectin (EQVALAN^R or Zimecterin^R Oral Paste for Horses) at 200 ug/kg. This formulation is available in the United States and in certain countries internationally. A micellar formulation intended for intramuscular injection at the same dose formerly was available worldwide but has been withdrawn from marketing.

Swine are given ivermectin subcutaneously at 300 µg/kg. IVOME^R Injection for Swine is only available internationally at the present time.

Additional formulations of ivermectin intended for use in dogs are under development, but no commercial formulations are currently available.

EFFICACY

Nematodes. Ivermectin has a broad range of activity against nematodes, including adults and developmental stages. Published data have been extensively reviewed (Campbell 1981; Campbell et al. 1983; Campbell and Benz 1984) and this review is limited to the clinically important aspects and recently published data.

The range of efficacy in cattle (Table 1) and in sheep (Table 2) encompasses essentially all of the adult and fourth larval stages of gastrointestinal nematodes. Included in the spectrum are inhibited fourth-stage Ostertagia ostertagi (Stiles) in cattle as well as O. circumcincta (Stadelmann) and Haemonchus contortus (Rudolphi) in sheep. The adult and fourth-stage of the common lungworms, Dictyocaulus viviparus (Bloch) and D. filaria (Rudolphi), in cattle and sheep also are effectively removed. Internationally, claims are registered for adult Strongyloides papillosus (Wedl) and Bunostomum phlebotomum (Railliet). Efficacy has been demonstrated (Swan et al. 1983) for adult Parafilaria bovicola (de Jesus). Ivermectin effectively controls infections with Ostertagia spp. and Cooperia spp. acquired up to at least 7 days after treatment (Barth 1983; Bremner and Berrie 1983; Swan and Harvey 1984).

Horses also have essentially all the clinically important nematodes removed following a single oral administration of ivermectin (Table 3). Of particular importance, the arterial larval stages of Strongylus vulgaris (Looss) are removed (Slocombe et al. 1982) as well as thiabendazole-resistant small strongyles (Baker et al. 1984). Clinical regression occurs in the dermal lesions associated with Habronema spp. and Draschia spp. (Herd and Donham 1981) as well as Onchocerca sp. (Herd and Donham 1983).

TABLE 1. Cattle Nematode Efficacy Claims Registered in the United States and Internationally for Ivermectin Given Once Subcutaneously at 200 µg/kg.

Nematodes	Developmental stage ^{a/}
<u>Haemonchus placei</u> ^{b/}	A, L ₄
<u>Ostertagia ostertagi</u> ^{b/}	A, L ₄ , IL ₄
<u>O. lyrata</u> ^{b/}	A, L ₄
<u>Trichostrongylus axei</u> ^{b/}	A, L ₄
<u>I. colubriformis</u> ^{b/}	A, L ₄
<u>Cooperia oncophora</u> ^{b/}	A, L ₄
<u>C. punctata</u> ^{b/}	A, L ₄
<u>C. pectinata</u> ^{b/}	A, L ₄
<u>Bunostomum phlebotomum</u>	A
<u>Strongyloides papillosus</u>	A
<u>Oesophagostomum radiatum</u> ^{b/}	A, L ₄
<u>Nematodirus helvetianus</u> ^{b/}	A
<u>N. spathiger</u> ^{b/}	A
<u>Dictyocaulus viviparus</u> ^{b/}	A, L ₄
<u>Parafilaria bovicola</u>	A
<u>Thelazia spp.</u>	A

^{a/}A=adults; L₄ = fourth-stage larvae; IL₄ = inhibited fourth-stage larvae.
^{b/}Claims registered in United States.

TABLE 2. Sheep Nematode Efficacy Claims Registered Internationally for Ivermectin Given Once Orally at 200 µg/kg.

Nematodes	Developmental stage ^{a/}
<u>Haemonchus contortus</u>	A, L ₄ , IL ₄
<u>H. placei</u>	A
<u>Ostertagia circumcincta</u>	A, L ₄ , IL ₄
<u>Trichostrongylus axei</u>	A
<u>I. colubriformis</u>	A, L ₄
<u>Cooperia curticei</u>	A, L ₄
<u>C. oncophora</u>	A
<u>Gaigeria pachyscelis</u>	A, L ₄
<u>Oesophagostomum columbianum</u>	A, L ₄
<u>O. venulosum</u>	A
<u>Nematodirus battus</u>	A, L ₄
<u>N. spathiger</u>	A, L ₄
<u>Strongyloides papillosus</u>	A, L ₄
<u>Chabertia ovina</u>	A, L ₄
<u>Trichuris ovis</u>	A
<u>Dictyocaulus filaria</u>	A, L ₄

^{a/}A = adults; L₄ = fourth-stage larvae; IL₄ = inhibited fourth-stage larvae.

Ivermectin efficacy in swine when given subcutaneously at 300 µg/kg (Barth et al. 1980) includes adult and fourth-stage larvae of Ascaris suum (Goeze), Hyostromylylus rubidus (Hassall and Stiles), and Oesophagostomum spp. as well as adult Strongyloides ransomi (Schwartz and Alicata) and Metastrongylus spp., Table 4. Stephanurus dentatus (Diesing) is also killed (Stewart et al. 1981). The swine injectable formulation is still in registration review in the United States but has been registered internationally.

Development of ivermectin in dogs is still in progress, but several reports of efficacy have been published. The prepatent and adult stages of Ancylostoma caninum (Ercolani), Toxocara canis (Werner), Toxascaris leonina (v. Linston), and Trichuris vulpis (Frohlich) are eliminated (Yazwinski et al. 1982). The microfilariae and precordial stages of the dog heartworm, Dirofilaria immitis (Leidy), are very sensitive to ivermectin but the adults are apparently refractory (Blair and Campbell 1980).

TABLE 3. Horse Nematode Efficacy Claims Registered in the United States and Internationally for Ivermectin Given Once Orally at 200 µg/kg.

Nematodes	Developmental stage ^{a/}
<u>Habronema muscae</u>	A
<u>Trichostrongylus axei</u>	A
<u>Parascaris equorum</u>	A
<u>Strongyloides westeri</u>	
<u>Oxyuris equi</u>	A, L
<u>Strongylus vulgaris</u>	A, AL
<u>S. edentatus</u>	A, TL
<u>S. equinus</u>	A
<u>Tridontophorus</u> spp.	A
<u>Cyathostomum</u> spp.	A, L
<u>Cylicocyclus</u> spp.	A, L
<u>Cylicodontophorus</u> spp.	A, L
<u>Cylicostephanus</u> spp.	A, L
<u>Gyalocephalus</u> sp.	A, L
<u>Onchocerca</u> sp.	MF
<u>Dictyocaulus arnfieldi</u>	A, L

^{a/}A = adults; L = larvae; AL = arterial larvae; TL = tissue larvae; MF = microfilariae.

TABLE 4. Swine Nematode Efficacy Claim Registered Internationally for Ivermectin Given Once Subcutaneously at 200 µg/kg.

Nematodes	Developmental stage ^{a/}
<u>Ascaris suum</u>	A, L ₄
<u>Hyostromylylus rubidus</u>	A, L ₄
<u>Oesophagostomum</u> spp.	A, L ₄
<u>Strongyloides ransomi</u>	A
<u>Metastrongylus</u> spp.	A

^{a/}A = adults; L₄ = fourth-stage larvae.

Arthropods. Efficacy of ivermectin extends to a variety of arthropods. Effectiveness against several which are economically important in animal health have been investigated, and research is continuing.

Cattle have several arthropods which are effectively removed (Table 5). The mange mites, Sarcoptes scabiei (DeGeer) and Psoroptes ovis (Hering), are effectively killed by 7 and 14 days after treatment, respectively (Barth and Sutherland 1984). Sucking lice, Linognathus vituli (L.) and Haematopinus eurysternus (Nitzsch), are killed within 7 days after treatment (Barth and Sutherland 1980). A claim for Solenopotes capillatus (Enderlein) is registered internationally. An "aid in the control" of Damalinia bovis (Linne) is also registered internationally.

Ivermectin is highly effective in cattle (Roncalli et al. 1981) against all 3 larval stages of the heel (warble) flies, Hypoderma bovis (L.) and H. lineatum (Villiers). However, proper timing of treatment is important. For most effective results, cattle should be treated as soon as possible after the end of the heel fly season. While not peculiar to ivermectin, destruction of Hypoderma larvae at the period when these grubs are in vital areas may cause sporadic, undesirable host-parasite reactions. Killing H. lineatum when present in the esophageal tissues may cause potentially fatal bloat; killing H. bovis when present in the vertebral canal may cause staggering or paralysis. Cattle should be treated either before or after these stages of grub development. Dermatobia hominis (L.) larvae in cattle also are very sensitive to ivermectin (Roncalli and Benitez-Usher 1982).

Cattle ticks are affected in varying degrees by ivermectin. The sand tampan, Ornithodoros savignyi (Audouin), an important argasid tick in South Africa, is controlled for up to three days after treatment (Soll 1984). An "aid in the control" of Boophilus microplus (Canestrini) and B. decoloratus (Koch) is registered internationally. Amblyomma americanum (L.) is one of the more sensitive of the multi-host ticks and while repletion is interfered with (Lancaster et al. 1982), the effect of ivermectin given once lasts only a few days and this is not sufficient for a label claim. Repeated treatments have been shown to be useful but the withdrawal period (35 days in the United States and 21 to 45 days internationally) as well as practicality and cost preclude such a regimen. Sustained-release formulations theoretically may be useful but have not yet been successfully developed.

TABLE 5. Cattle Arthropod Efficacy Claims Registered in the United States and Internationally for Ivermectin Given Once Subcutaneously at 200/ μ g/kg.

<u>Arthropods</u>
<u>Psoroptes ovis</u> ^{a/}
<u>Sarcoptes scabiei</u> ^{a/}
<u>Linognathus vituli</u> ^{a/}
<u>Haematopinus eurysternus</u> ^{a/}
<u>Solenopotes capillatus</u>
<u>Hypoderma bovis</u> ^{a/}
<u>H. lineatum</u> ^{a/}
<u>Dermatobia hominis</u>
<u>Ornithodoros savignyi</u>

^{a/}Claims registered in the United States.

Sheep arthropod efficacy claims are listed in Table 6. All 3 larval stages (instars) of the bot fly, Oestrus ovis (L.), are affected (Roncalli 1983). Control of the mite, Psorergates ovis (Tyrrell), also is registered internationally. A single oral treatment of sheep for Psoroptes ovis is not entirely efficacious, but two injections at 200 μ g/kg given with a 7-day interval have been found to be satisfactory.

Larvae of the horse bot flies, Gastrophilus intestinalis (DeGeer) and G. nasalis (L.), (Table 7) are killed by ivermectin (Bello and Norfleet 1981).

Swine arthropods which have been controlled by ivermectin given once subcutaneously at 300 µg/kg (Barth et al. 1980) include the sucking louse, Haematopinus suis (L.), and the mange mite, Sarcoptes scabiei, Table 8. These claims have been registered internationally.

A single dose of ivermectin in dogs when given subcutaneously at 200 µg/kg has been reported (Yazwinski et al. 1981) to control Sarcoptes scabiei as well as Otodectes cyanotis (Hering).

TABLE 6. Sheep Arthropod Efficacy Claims Registered Internationally for Ivermectin Given Once Orally at 200 µg/kg.

Arthropods

Psorergates ovis

Oestrus ovis

TABLE 7. Horse Arthropod Efficacy Claims Registered in the United States and Internationally for Ivermectin Given Once Intramuscularly at 200 µg/kg.

Arthropods

Gastrophilus nasalis

G. intestinalis

TABLE 8. Swine Arthropod Efficacy Claims Registered Internationally for Ivermectin Given Once Subcutaneously at 300 µg/kg.

Arthropods

Haematopinus suis

Sarcoptes scabiei

SAFETY

Safety of ivermectin has been reviewed recently (Campbell and Benz 1984). Each formulation intended for commercial application has been shown to have a wide margin of safety. No effects on the breeding performance of cattle, sheep, swine, horses or dogs have been observed. The acute toxic syndrome observed in cattle, swine, horses and dogs given ivermectin at elevated doses is characterized by mydriasis, ataxia, and depression; death in the highest treatment groups has occurred within a few days of treatment.

Administration of the oral paste formulation to horses has not resulted in adverse reactions other than occasional minor, subcutaneous edema, apparently a sequela to the death of Onchocerca sp. microfilariae. The equine micellar solution for intramuscular injection formerly available was withdrawn from marketing after the oral paste formulation became available. Use of the oral paste formulation has not resulted in the low death rate caused principally by clostridial myositis at the injection site reported from the use of the equine micellar solution.

Use of ivermectin injection in cattle has not resulted in any discernible pattern of adverse reactions. Of the several millions of doses marketed globally, only a very few deaths have been reported and not all were directly attributable to ivermectin. Some reactions have been associated with injection-site infections, presumably a result of nonaseptic techniques. Sporadic host-parasite reactions from the death of Hypoderma bovis and H. lineatum migrating larvae have been observed, as discussed above. Transient, minor signs of pain at the injection site may be observed for a few moments following administration, and subcutaneous swelling may occur but usually disappears within two to three weeks.

No adverse reactions in sheep following oral administration of ivermectin have been reported other than occasional coughing.

Evaluation of the safety of ivermectin in dogs is not complete. However, problems have been reported from the extra-label use of other formulations. Certain dogs (Collies in particular) seem to be especially sensitive to the toxic effects of ivermectin in that depression and even death may occur soon after treatment. Dogs also may exhibit a hypersensitivity resulting from the death of Dirofilaria immitis microfilariae.

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