A Review of the Pharmacology and Clinical Uses of Ivermectin

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Abstract

The avermectins were introduced in 1981 and constitute a potent new class of anthelmintic agents. They are naturally-derived products of microbial action displaying an exceptionally wide range of antiparasitic efficacy against internal and external parasites of domestic animals. This paper reviews their isolation and chemistry, mechanism of action, chemical efficacy and safety in cattle, sheep, swine, horses and dogs.

Key words: Ivermectin, anthelmintics, cattle, sheep, swine, horses, dogs, efficacy, safety.

Résumé

Une revue de la pharmacologie et des usages cliniques de l'ivermectin

L'avènement des avermectins remonte à 1981 et ils constituent une nouvelle classe d'anthelminthiques puissants. Ils représentent des dérivés naturels d'une activité microbienne qui affiche une efficacité contre une variété exceptionnellement grande de parasites internes et externes des animaux domestiques. L'auteur rapelle l'isolement de ces substances, leur composition chimique, leur mode d'action, ainsi que leur efficacité et leur innocuité, chez les bovins, les moutons, les porcs, les chevaux et les chiens.

Mots clés: ivermectin, anthelminthiques, bovins, moutons, porcs, chevaux, chiens, efficacité, innocuité.

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Introduction

The avermectins constitute a new chemical class of anthelmintic agents which display a novel mode of action against a broad spectrum of nematode and arthropod parasites of animals. They are also active against plant parasites and free-living nematodes and arthropods. Avermectins are naturally-occurring fermentation products elaborated by the morphologically distinct soil organism *Streptomyces avermitilis* (1, 2). Early studies on the broth culture from this mold indicated the presence of a substance of unparalleled anthelmintic potency (3). Furthermore this new substance displayed very high potency and high safety in the crude form as it occurred in nature and without chemical modification. Early chromatographic studies yielded four separate entities, and on thin layer chromatography these were seen to represent compounds with varying degrees of anthelmintic efficacy (4). The complex was seen to contain four components designated A_1, A_2, B_1, B_2 in varying proportions. These major components existed as two varients designated a and b. The *b* series was the lower homologue of the corresponding major *a* component (i.e. A_{1a} more potent than A_{1b}). Component B_{1a} was outstanding, being active against nematodes in sheep at a dosage rate of 0.025 mg/kg. The basic chemical structure of the avermectins is that of a macrocyclic lactone with two sugars attached (3). Removal of the sugar fraction from the molecule results in a marked diminution in potency and in the anthelmintic activity. Analogues have been developed chemically and such derivatives can be compared to the parent compound in relation to activity and safety. The derivative of most interest in this context is 22,23-dihydroavermectin B_1, or ivermectin. This compound displayed good characteristics of efficacy and safety in the early laboratory and *in vivo* studies, and was therefore selected for further study and development (5, 6, 7). Ivermectin comprises at least 80% 22,23-dihydroavermectin B_{1a} and more than 20% of the B_{1b} homologue.

Mechanism of Action

Gamma-amino-butyric acid (GABA) is the neurotransmitter substance mediating transmission of inhibitory signals from the interneurons to the motor neurons in the ventral nerve cord of parasites. It is now established that ivermectin acts as a GABA agonist (8, 9, 10, 11). The function of this GABA transmitter is to open the chloride channels on the postsynaptic junction, allowing inflow of Cl^- ions and the induction of the resting potential. Ivermectin potentiates this effect by stimulating the presynaptic release of GABA and by increasing its binding to the postsynaptic receptors (1, 11). In the presence of ivermectin, the chloride channels are open when they should be closed, the net effect being that signals and impulses are not received by the recipient cell. Although the motor neuron and muscle cells are both capable of individual excitation, passage of the electrical impulse across the synapse is blocked.

Arthropods utilize GABA as a neurotransmitter but tend to utilize it not between two sets of nerve cells, as in nematodes, but between nerve and muscle cells (7). Prolonged stimulation of GABA release renders the effects of ivermectin sustained and irreversible (6). For most parasites this results in neuromuscular blockade, paralysis, and death.

The overall GABA-mediated chloride ion conductance effect may be due to (a) ivermectin acting as a GABA agonist either at the GABA binding site or elsewhere on the protein, (b) stimulation of presynaptic GABA release, or (c) potentiation of GABA binding to its receptors (1). In experimental work it was further observed that washing neurons with picrotoxin (an antagonist of GABA) abolished this ivermectin-induced paralysis (1, 11, 12).

Paralysis is the most evident effect of ivermectin in parasites but suppression of reproductive function has also been observed in ticks (1, 2, 6). Ivermectin displays no activity against cestodes or trematodes as these parasites do not utilize GABA as a neurotransmitter (1). This is consistent with the hypothesis regarding mode of action.

Tissue Disposition of Ivermectin

Ivermectin is well absorbed when administered orally or parenterally. The route of administration and the formulation employed affect its disposition profile. Concentrations of ivermectin are maintained in body fluids for prolonged periods of time (13). In cattle dosed subcutaneously with ivermectin at 0.3 mg/kg, a half-life of 70 hours per total radioactive residue in plasma was reported (14). Following intravenous delivery of 0.2 mg/kg ivermectin in sheep a terminal half-life of 178 hours was detected (15). This relatively long half-life is related to the very high potency of the compound, as studies with other anthelmintics have indicated that efficacy is profoundly affected by the kinetic profile (16). In sheep, low bioavailability was reported when ivermectin was administered into the rumen (12). Some degradation in the rumen may account for this reduced bioavailability. The monosaccharide and aglycone derivatives (two possible metabolites or rumenal degradation) are less potent than the parent drug (5). The lower efficacy and shorter duration of action of orally-administered ivermectin (compared with parenteral dosing) may explain the less potent effect against certain ticks (*Boophilus* spp.) in cattle (17), and body lice in sheep (18).

Most of the administered dose of ivermectin is excreted in the feces, the remainder in the urine (1). Minimal residues are present in the muscle and kidneys, highest concentrations being detected in the liver and fat tissues (1). Residues in all tissues are extractable in nature with little or no macromolecularly bound drug or metabolites present. The major single component in the edible tissues of cattle, sheep and pigs is the unaltered parent drug (1).

Although mammals utilize gamma-aminobutyric acid as a central neurotransmitter they are generally not adversely affected by ivermectin. This is because being a macrolide of large molecular weight ivermectin does not readily cross the blood-brain barrier of the mammal to affect the GABA within the central nervous system (19).

In tests of brain concentration of the drug in cattle, radioactive residue assays revealed only minute traces of ivermectin. This was the lowest concentration of all tissues analyzed (1). There have been a number of cases of central nervous system depression in purebred and crossbred long-haired Collies (20). The reason for this breed susceptibility is not known. It has been postulated that the blood-brain barrier in the Collie may be more permeable to ivermectin than in other species, allowing ivermectin to enter the central nervous system (2, 21, 22).

Clinical Use

Cattle

Ivermectin is effective against all of the gastrointestinal nematodes that are of pathogenic or economic importance in cattle (23, 24, 25, 26).

At a dosage of 0.2 mg/kg, ivermectin has been shown to be highly effective against at least seven species of gastrointestinal nematodes including the adult and larval stages of *Ostertagia* spp. (27, 28) *Trichostrongylus* spp. (27, 28), *Oesophagostomum* spp. (28), *Haemonchus* spp. (27, 28), as well as the lungworm *Dictyocaulus viviparus* (25, 27). Immature larvae, hypobiotic fourth stage larvae, and strains with established resistance to other anthelmintics are also susceptible (2). The drug is equally effective against nematodes when administered orally or parenterally. A dosage rate of 0.2 mg/kg by subcutaneous injection is used commercially for field conditions.

A feature of many anthelmintics is poor or variable activity against early hypobiotic fourth stage *Ostertagia* spp. larvae. At the recommended dosage rate, ivermectin is effective against these parasites by either the oral or parenteral route (24, 30).

A useful feature of parenteral treatment in cattle is the persistent efficacy against the immature stages of certain nematodes (31). This period of protection depends on the susceptibility of the nematode species to ivermectin, but it can be up to 21 days. Such longevity of efficacy is consistent with the plasma and tissue kinetics of the drug. Trials have indicated that the protection period against *Dictyocaulus viviparus* is of longer duration than for gastrointestinal nematodes (31, 32).

Ivermectin also displays activity against a number of economically important arthropod parasites of cattle (33, 34). Lice (2, 30, 35), mange mites (36, 37, 38, 39, 40), ticks (6, 40), and warble grubs (2, 30, 42) are susceptible to ivermectin. As a systemic acaricide ivermectin is fairly slow in attaining maximum efficacy, and attempts have been made to simulate controlled release systems to optimize therapy (43, 44).

Sucking lice tend to be more consistently susceptible than biting lice, presumably reflecting the more superficial or intermittent feeding habits of the latter (45). *Sarcoptes* spp. are usually affected within seven days and *Psoroptes* spp., a more superficial parasite, is eliminated after 14 days (46). Death of ticks normally occurs two-to-three days following treatment (46). Numerous studies have demonstrated exceptional activity against parasitic larvae (grubs) of warble flies. A single dose of ivermectin (0.2 mg/kg subcutaneously) is 100% effective against first, second, and third stage larvae of *Hypoderma bovis* (47, 48).

Sheep

As an oral drench in sheep, ivermectin displays 93-100% efficacy against immature and adult stages of commonly occurring endoparasites including *Haemonchus contortus* (49, 50, 51), *Ostertagia* spp. (49, 50, 51), *Trichostrongylus* spp. (50, 51), *Cooperia* spp. (51), *Nematodirus* spp. (49, 50), *Chabertia ovina* (50), *Trichuris* spp. (49, 50), and *Strongyloides papillosus* (49). Efficacy is maintained against benzimidazole-resistant strains of *Haemonchus* spp. and *Trichostrongylus* spp. (52). Some metabolism to less potent products occurs in the rumen and this may explain the relatively lower efficacy of oral ivermectin, when compared to subcutaneous injection, against body lice in sheep (53). High potency against larvae of *Lucilia* spp. has been reported, but activity against *Mallophagus ovinus*, the sheep ked, is variable (2). All three larval stages of the nasal bot fly *Oestrus ovis* are

completely removed at the standard dose rate (54).

Swine

For routine use in swine, ivermectin is presented as a one percent injection for subcutaneous administration at a dosage of 0.3 mg/kg. In this species the spectrum of action includes the adult and larval stages of *Ascaris suum* (55, 56), *Hyostrongylus rubidus* (5, 7), *Oesophagostomum* spp. (3, 57), *Trichuris* spp. (55, 56, 57), and the lungworm *Metastrongylus apri* (56). The treatment of pregnant sows can block the transcolostral transmission of *Strongyloides ransomi* to the piglets (58).

Ivermectin is highly efficacious against the porcine mange mite *Sarcoptes scabiei* and also the sucking louse *Haematopinus suis* (54, 60, 61, 62).

Horses

As an oral paste, ivermectin displays an efficacy in the equine species of greater than 98% against *Gastrophilus* spp., *Trichostrongylus axei, Parascaris equorum, Osyuris equi, Strongylus vulgaris, Strongylus edentatus, Habronema muscae, Draschia megastoma, Strongyloides westeri, Dictyocaulus arnfieldi*, and *Onchocerca* spp. (63, 64, 65, 66, 67, 68). In the case of *Habronema, Draschia* and *Onchocerca* spp., ivermectin exerts a larvicidal acton (67, 68).

Initially, studies indicated that ivermectin was active at dosages as low as 0.02 mg/kg (69), but, as in the case of many other host species, a dosage of 0.2 mg/kg was shown to provide broad spectrum efficacy and was selected for commercial usage. Although an intramuscular formulation was originally employed for the equine species (70, 71, 72), the oral paste formulation containing 1.87% of the active ingredient is now the only preparation approved for use in the horse. The oral route is claimed to be marginally more effective than the parenteral route in respect of efficacy against *Oxyuris equi* (73).

Other reports indicate that the parenteral route extends for approximately two weeks the efficacy of ivermectin in reducing strongyle egg production and in reducing subsequent pasture contamination (74).

Arterial larval stages of *Strongylus vulgaris* tend to be refractory to most equine anthelmintic agents. Intensive therapy with certain members of the benzimidazole class has been reportedly useful against these migratory pathogenic strongyle stages (75). Many studies have indicated 100% efficacy against arterial larvae using a single dose of ivermectin at the recommended dosage rate. Such treatment has prevented vascular damage following experimental infection, reduced the size of cranial mesenteric aneurysms, and increased circulation to arteries distal to the aneurysm (76, 77, 78). Resolution of arteritis and thrombosis and a return of the smooth contour of the arteries has been reported following such treatments (79). The ubiquitous but less pathogenic "small strongyles" are equally susceptible to ivermectin therapy (80). All stages of bot fly larvae are removed also (73). Ivermectin efficacy against adult *Parascaris equorum* has been confirmed (81), and while the drug is ineffective against migratory *Parascaris* larvae, ascarids which return to the bowel are susceptible to treatment (2, 82).

Administration to mares at foaling protected offspring against *Strongyloids westeri* infection received through the mare's milk (83, 84). Good clinical response has been documented in the treatment of *Onchocerca* spp. infection (86). Cutaneous habronemiasis responds well to orally-administered ivermectin (87, 88).

Ivermectin displays high clinical potency against a wide range of benzimidazole-resistant parasites (89, 90). This would be anticipated considering its unique structure and mode of action.

Dogs

Hookworkms are particularly susceptible to ivermectin with efficacy of 96-100% being demonstrated against adults and larval stages of *Ancylostoma caninum* and *Uncinaria stenocephala* at dosages of 0.002 mg/kg orally (91). Doses of 0.2 mg/kg are necessary for control of adult *Ascaris, Strongyloides*, and *Trichuris* species (2, 91, 92). Ivermectin is not active against the adult stage of *Dirofilaria immitis* (93) but efficacy has been demonstrated against microfilariae (94) and precardiac stages of the heartworm at dosages of 0.005 mg/kg orally or 0.2 mg/kg subcutaneously. Reports have indicated that greater than 99% of *Trichuris vulpis* infections are expelled at dosages of 0.1 mg/kg or greater, and 0.2 mg/kg will remove 90% of all adult stages and 97% of the intestinal larval stages of *Toxocara canis* (92). High dosages (1-2 mg/kg) are required to produce an effect against tissue dwelling stages of *Toxocara canis* in dogs (2) and in mice (95). Against canine ectoparasites, a single dose of ivermectin at 0.2 mg/kg gave complete cure of natural infection of *Otodectes cynotis* and *Sarcoptes scabiei* (96, 97). In severe cases of sarcotic mange, two treatments at 14 day intervals have been advocated (97).

Target Animal Safety

Cattle

The breeding performance including semen quality of bulls was evaluated before dosing with ivermectin at 0.4 mg/kg (twice the normal dosage level) and for 70 days thereafter. No adverse effects were observed (46). No ill effects during early, mid, or late pregnancy were noted in cows treated at a similar dosage (46). Oral dosages of 2 mg/kg caused no adverse effects (2) but 8 mg/kg administered subcutaneously resulted in listlessness, ataxia, and death in some cases (2). One calf died as a result of bloat during an efficacy trial with ivermectin. An eosinophilic esophagitis apparently had developed in response to death of *Hypoderma* spp. larvae (28). Posterior paresis was recorded in other infected cattle as a result of spinal cord hemorrhages following treatment (46, 47).

Sheep

Sheep given 4.0 mg/kg ivermectin in propylene glycol displayed ataxia and depression, with hemoglobinuria evident in a number of cases. However, the control animals given the vehicle alone displayed similar effects (2). Propylene glycol can give rise to hemoglobinuria in calves (98).

Swine

Clinical signs of toxicosis including lethargy, ataxia, mydriasis, tremors, and lateral recumbency were observed in swine receiving 30 mg/kg ivermectin (2). No adverse effects on breeding performance were noted.

Horses

Adverse reactions in the equine species have been associated exclusively

with intramuscular administration of ivermectin. Such reactions are unrelated to GABA potentiation. The most frequently reported problems have included the development of local abscessation, transient midventral edema associated with death of *Onchocerca* microfilariae, and swelling at the injection site (19, 84, 99). Introduction of clostridial infection at the injection site and anaphylactoid reactions to the vehicle polysorbate 80 have also been observed in a number of cases (74, 84, 100). Impaired vision, ataxia, and depression have been recorded following oral administration of 2 mg/kg ivermectin to horses (2). Rarely, posttreatment drowsiness has been observed (101).

Dogs

The safety of ivermectin in dogs following extra-label usage must not be assumed. Both overdosage and breed susceptibility are involved in canine toxicity states. Collies are adversely affected by ivermectin and this breed idiosyncrasy is manifested by depression, muscle weakness, blindness, coma, and death (21). Many cases of ataxia progress to paralysis and decreased consciousness (21, 22, 102). Relatively higher brain concentrations of ivermectin are found in Collies than in Beagles, mice, cattle, sheep, and pigs (103). Thus, greater penetration across the blood-brain barrier occurs in the Collie (21). Reports have indicated that picrotoxin infusion might be a useful antidote in such cases (104). Anaphylactic reactions attributable to polysorbate 80 in the injectable formulation have been described in the dog (2). Recently a specific oral formulation for prevention of heartworm disease has been licenced in the United States. This product in tablet form is given monthly at a minimum dosage level of 0.006 mg/kg.

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