Ivermectin as an Antiparasitic Agent in Cattle

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This paper summarizes the efficacy and safety evaluation of ivermectin given as a single subcutaneous injection for the control of a wide range of nematode and arthropod parasites of cattle. The avermectins are a complex of chemically related agents that exhibit extraordinarily potent anthelmintic and ectoparasitic activity. They are produced by fermentation from a novel species of actinomycete which was isolated at the Kitasato Institute from a soil sample collected at Kawana, Ito City, Shizuoka Prefecture, Japan. The actinomycete was named *Streptomyces avermitilis.* The naturally occurring avermectins have been identified as a series of macrocyclic lactone derivatives, which in contrast to the macrolide or polyene antibiotics, lack significant antibacterial or antifungal activity.[9]

Four closely related major components and their homologous minor components were separated from the avermectin complex. For example, a mixture of avermectin B_1a and its homologue, avermectin B_1b, can also be described by omission of the subscript letters simply as avermectin B_1[34]. A chemical modification of avermectin B_1 was selected as the candidate for commerical development and the balance of this presentation will address itself to the clinical efficacy and safety evaluation of this product now known by the generic name, ivermectin. Ivermectin is 22, 23-dihydroavermectin B_1 and is a mixture of two closely related homologues differing only by a methylene (CH_2) group. Ivermectin is defined as not less than 80% of 22,23-dihydroavermectin B_1a and not more than 20% 22,23-dihydroavermectin B_1b.

Mode of Action

Ivermectin paralyzes and ultimately kills parasitic nematodes, arachnids and insects. Its action on the nematodes is by inhibiting the transmission of nerve impulses from the ventral cord interneurons to the excitatory motor neurons. It acts by stimulating the release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) from presynaptic nerve terminals as well as by potentiating GABA binding to the postsynaptic receptors. The ivermectin treated nematodes lose central command to move while maintaining normal muscle contractibility. Ivermectin acts on the arthropods by inhibiting nerve impulse transmission at the neuromuscular junctions via the same mechanism of amplifying GABA action. The treated arthropods become paralyzed and die.

Ivermectin is apparently not effective against fluke and tapeworms, in which GABA is not found as a neurotransmitter. At therapeutic doses, ivermectin has no effect on mammals since their GABA systems involved in neurotransmission are confined within the central nervous system into which ivermectin does not penetrate readily. This is the apparent reason for the wide safety margin in the host animals.

Ivermectin is unrelated structurally to any of the presently available parasiticides. Studies to date have indicated that because of this and its unique mode of action not shared by any other antiparasitic agents, cross resistance has not occurred.

The avermectins do not block cholinergic nerve transmission, nor do they inhibit the acetylcholinesterase needed for deactivation of choline, as in the case of the organophosphates. They do not paralyze by depolarizing the muscle cell membrane, as pyrantel and morantel do, nor do they paralyze by hyperpolarizing the muscle cell membrane, as piperazine does. They do not paralyze in the manner of levamisole, which is believed to stimulate the nerve ganglion directly. The benzimidazole anthelmintics have no paralytic action and have been shown to inhibit the polymerization of tubulin thereby blocking the formation of microtubules in the worm.

The reader may wish to inquire further about the discovery of the avermectins and the commercial development of ivermectin in particular. An excellent review article[11] has recently been published in *Science* that condenses an extensive bibliography covering the microbiology, isolation, chemistry, metabolic disposition, mode of action, safety and general antiparasitic efficacy of ivermectin.

Efficacy Studies

Ivermectin for the treatment and control of parasites in cattle was evaluated in 56 efficacy studies and 181 field trials prior to market introduction. A total of 8,205 cattle were involved, of which 5,094 received ivermectin at 200 mcg/kg or more, the remainder serving as contemporary controls.

All the trials involving efficacy determination against nematodes and arthropod parasites were conducted as controlled studies.

The cattle were either experimentally or naturally infected with one or more species of parasites. Each claim for a

species was supported by at least two adequate and well controlled studies. A number of papers have been published on the activity of ivermectin against nematode parasites of cattle [1 5 8 9 10 12 15 20 22 24 25 27 30 39 42-46]. Ivermectin also demonstrated efficacy against a wide range of arthropod parasites of cattle.

Many of these published results and some data as yet unpublished[a] have provided the data in support of the registration in the U.S.A. of ivermectin for cattle.

Endoparasite Dose Titration Trials

In view of the excellent activity shown by the natural avermectins when given by subcutaneous injection, a proposed commercial formulation of ivermectin was evaluated in a series of 13 dose titration studies in Australia, Germany, South Africa, the United Kingdom, and the U.S.A. These studies provided the efficacy data from which the optimal dose for the control of a wide range of nematode parasites was chosen. For both adult and immature nematodes, doses as low as 50 mcg/kg body weight were adequate for several species. However, adult *Cooperia oncophora, C. punctata* and *Cooperia* spp., *Trichostrongylus colubriformis* and *Nematodirus helvetianus* were not adequately controlled by 100 mcg/kg or less. Against L_4 immature stages, 200 mcg/kg was needed for good control of *Haemonchus placei, Cooperia oncophora, Nematodirus helvetianus* and *T. colubriformis.*

Endoparasite Dose Confirmation

Having selected 200 mcg/kg as the optimal dose, a further series of 18 dose confirmation studies using both induced and natural nematode infections was carried out in Australia, Germany, New Zealand, South Africa, the United Kingdom, and the U.S.A. A total of 31 trials provided data useful for evaluating the efficacy of the selected dose (200 mcg/kg) against a wide range of endoparasites. As with the dose titration studies, independent investigators, as well as Merck Sharp & Dohme Laboratory personnel, were involved. The efficacy profile of the 1% w/v ivermectin commercial formulation at the recommended use level of 200 mcg/kg is presented in Tables 1 and 2 for gastrointestinal and pulmonary nematodes. With the exception of adult *Nematodirus helvetianus* and adult *Trichostrongylus colubriformis,* efficacy is 95% or better against adult and immature gastrointestinal and pulmonary nematodes. Of particular note is the extraordinary activity against *Ostertagia ostertagi* where practically complete elimination of all stages of the parasite, including the inhibited early L_4, is possible.

Ectoparasite Efficacy Trials

The dose rate confirmed as optimal against a wide range of nematode parasites also proved very effective against certain economically important ectoparasites (lice and mites) in 18 studies carried out in Australia, Germany, South Africa, the United Kingdom, and the U.S.A.

In most of the trials, the degree of louse or mite infestation was assessed by counting the parasites in several designated areas on the animal's body surface. In two early mite trials, the infestations were simply scored as present or absent.

In ten trials, the long nosed sucking louse, *Linognathus vituli,* was identified. In nine of the ten trials, no living lice were found on the treated animals 7 days after treatment, nor had they reappeared up to 21 days after subcutaneous injection of ivermectin. In the one remaining trial, the numbers of *Linognathus* were reduced by 97.4% at 6 days.

In five trials, the sucking louse, *Haematopinus eurysternus,* was identified. In all five trials, this louse was eliminated from the cattle by seven days and where subsequent examinations were carried on, live lice did not reappear for the duration of the studies. In twelve trials, the biting louse, *Damalinia bovis,* was identified and the effect, although variable, could be considered as an aid in the control of this infestation. Efficacy apparently increased over time probably due to the intermittent feeding habits of this ectoparasite.

In four trials, *Psoroptes ovis* infestations were evaluated

TABLE 1. Efficacy of Invermectin at 200 MCG/KG S/C

Against Adult Endoparasites of Cattle		
Parasite	**No. of Trials**	**% Reduction**
Haemonchus placei	8	98
Ostertagia ostertagi	23	>99
Ostertagia lyrata	3	99
Trichostrongylus axei	17	>99
Cooperia oncophora	15	95
Cooperia punctata	6	98
Cooperia pectinata	2	99
Cooperia spp.	9	97
Nematodirus helvetianus	6	84
Nematodirus spathiger	2	>99
Trichostrongylus colubriformis	8	93
Oesophagostomum radiatum	12	98
Dictyocaulus viviparus	5	100

TABLE 2. Efficacy of Ivermectin at 200 MCG/KG S/C

Against L Endoparasites of Cattle		
Parasite	**No. of Trials**	**% Reduction**
Haemonchus placei	4	96
Ostertagia ostertagi	14	98
Ostertagia ostertagi, Inhibited L	8	>99
Ostertagia spp.	2	>99
Trichostrongylus axei	9	98
Cooperia oncophora	6	99
Cooperia punctata	2	95
Cooperia spp.	9	97
Trichostrongylus colubriformis	4	97
Oesophagostomum radiatum	4	>99
Dictyocaulus viviparus	3	>99

[a]*Data on file Merck Sharp & Dohme Research Laboratories, Rahway, NJ 07065*

and no living mites were found on the treated animals 14 days after a single subcutaneous injection of 200 mcg/kg of ivermectin. Treated animals remained free of mites throughout the 56-day duration of the trials and showed clinical recovery as manifested by hair regrowth and return to a supple skin.

In three trials, the mite, *Sarcoptes bovis,* was studied. In all three cases, the mites were eliminated from the treated animals by seven days after treatment. The controls remained infested throughout the trials.

As a systemic acaricide, ivermectin is rather slow in attaining maximum efficacy. As might be expected from its deeper skin penetration, *Sarcoptes* is usually affected within 7 days and *Psoroptes,* a more superficial parasite, is affected less rapidly, usually within 14 days however. A recent publication[18] has shown that surviving *P. ovis* retained their infectivity for five, but not seven days after treatment. For this reason, treated animals should not be introduced to mange-free herds for at least one week after treatment.

Field experiences in outbreaks of mange confirmed the efficacy of ivermectin. Canadian investigators have reported[23] on the successful control of an outbreak of sarcoptic mange in 12,965 cattle in 65 herds treated once.

In the United States, Wallace and Holste (personal communication) successfully treated 1,404 cattle with psoroptic mange in four different herds.

Hypoderma spp.: Efficacy Trials

Ivermectin at 200 mcg/kg has shown practically complete control of cattle grubs or warbles. Seven controlled efficacy trials were conducted in France, Italy, Spain, and the U.S.A. to evaluate the efficacy of ivermectin given subcutaneously at 200 mcg/kg against the immature stages of both *Hypoderma bovis* and *H. lineatum.*

The animals were dosed at appropriate times in the local seasonal cycle of *Hypoderma* development when the larvae were presumed to be first, second, or third instars. The parasites were allowed to complete their development and appear on the backs of the cattle, at which time they were counted and identified. When *H. bovis* was present alone, or as part of a mixed infection as either first, second, or third instars, no grubs were observed to emerge. The same can be said of *H. lineatum* with the exception of one trial where, of the 8% of grubs that emerged, only 3 became adult flies as compared to 53 in the control group.

Table 3 summarizes the efficacy profile of a single subcutaneous injection of ivermectin at 200 mcg/kg against sucking lice, mange mites, and cattle grubs.

Safety in Hypoderma-Infected Cattle

One calf died during an efficacy trial as a result of bloat. Ivermectin had been administered nine days earlier. No signs of illness were present prior to death. At necropsy, an acutely edematous, eosinophilic esophagitis was present which had apparently developed in response to death of *Hypoderma* (1st-instar) larvae. This host-parasite reaction was considered to be separate from an ivermectin toxic manifestation.

TABLE 3. Reductions of Arthropods on Cattle Given Ivermectin at 200 MCG/KG S/C

Parasite	No. of Trials	Observation Period (Days)	% Reduction
Sucking Lice:			
Linognathus vituli	10	7	>99*
	8	28	>99*
	6	56	>99*
Haematopisus eurysternus	5	7	100
	3	21	100
	2	56	100
Mange Mites:			
Psoroptes ovis	4	56	100
Sarcoptes scabiei var. bovis	3	28	100
	2	56	>99**
Cattle Grub:			
Hypoderma bovis and H. lineatum			
1st Instars	6	***	100
2nd Instars	5	***	>99

* Treated cattle in one trial had low numbers of lice throughout observation period.
** One mite recovered from one treated animal on day 35 after treatment.
*** Observations continued through end of Hypoderma emergency season.

There were 82 trials conducted to further evaluate the safety of ivermectin given to cattle during the season of *Hypoderma* larval migration. Ivermectin was given to 2,088 cattle and 1,005 cattle were vehicle-treated controls. The later observation of warbles in the contemporary controls provided evidence of *Hypoderma* infestations at the time of treatment. A further 44 trials were conducted with 945 ivermectin-treated cattle and 552 vehicle-treated controls which were suspected of having *Hypoderma* infestations at the time of ivermectin administration. Neither ivermectin-related adverse reactions nor adverse host-parasite reactions (i.e., esophagitis related to death of *H. lineatum* larvae or spinal canal hemorrhages related to *H. bovis* larval deaths) were observed during these trials.

Nonetheless, adverse *Hypoderma* host-parasite reactions in yearling cattle have been encountered during marketing of ivermectin injection in France. A few cattle died with acute esophagitis while others developed posterior paresis as a consequence of spinal canal hemorrhages. A label warning was inserted as a result of these experiences.

Field Trials

Several of the field trials, using counts of parasite eggs in the feces of cattle before and after treatment with vehicle alone (controls) or ivermectin, provided confirmatory evidence of activity against gastrointestinal worms under field conditions.

Safety Studies

In the registration documents, a total of 8,560 cattle were used in 246 trials to demonstrate the efficacy and safety of

ivermectin. Of these, 5,094 were treated at the use level of 200 mcg/kg or higher.

Toxicity and Tolerance

Thirty-two cattle were used in two trials to examine the effects of doses up to 8 mg/kg of ivermectin. Deaths occurred in three of four animals at this dose rate, but no clinical signs of toxicosis were seen at 6 mg/kg. A further tolerance study in 36 cattle evaluated doses up to 4 mg/kg or 20 times the use level dose rate. One death out of eight cattle occurred at this level.

Teratology

Two trials using 208 heifers were conducted to determine the effect of ivermectin at 400 mcg/kg (twice use level) on the developing bovine embryo and fetus when administered on three occasions during early pregnancy. No abnormalities were detected that could be attributed to ivermectin treatment, and it was concluded that use of ivermectin at 400 mcg/kg in pregnant cows does not induce terata.

Safety in Pregnancy

In a trial with 21 pregnant cows, the effect of monthly dosing with ivermectin at 400 mcg/kg (twice use level) through the second and third trimesters of pregnancy was studied. No adverse effects were observed and normal calves were born indicating that there is no drug-related risk in dosing pregnant cows.

Safety in Bulls

The breeding performance (including semen quality) of ten bulls was studied before dosing with ivermectin at twice the use level and for 70 days thereafter. There were no differences of any kind between the five ivermectin-treated bulls and the five vehicle-treated controls that would indicate impairment of breeding soundness after dosing with ivermectin.

Safety Observations During Efficacy Trials

During 56 trials which were not specifically designed as safety studies, observations were made relative to safety evaluation. In 19 trials, transient behavioral reactions to pain at injection sites after dosing with ivermectin and vehicle were reported. Incidence varied greatly between trials; signs were usually mild and subsided in most cases in less than two minutes. It is concluded that this is a minor side effect of ivermectin injection.

In 26 trials, there were reports of reactions at sites of injection in a variable proportion of cattle. These were usually small, confined to the subcutaneous space, and in many instances, detectable only by palpation. They resolved without treatment (usually before 21 days) and are considered to be of no consequence.

Double-Dose Field Trials

Fifty-three field trials using 2,367 cattle were conducted in Australia, Eire, Italy, New Zealand, and Spain under a variety of farming conditions typical of these countries. Of the 1,207 cattle dosed with ivermectin at 400 mcg/kg (twice use level), 132 exhibited some reaction or health problem. For 1,160 vehicle-treated cattle, there were 117 similar observations. Most of the reactions were interpreted as signs of transient pain at injection sites, and in some countries, swellings at injection sites were observed at inspection seven days after treatment. It is concluded that dosing cattle with ivermectin at twice use level did not result in an increased incidence of health problems compared to similar animals given vehicle.

Environmental Impact

Studies to assess the potential environmental hazard resulting from the presence of ivermectin in fecal residues confirm that the use of the compound would not have a signficant impact on the quality of the environment.[35] This is based on the results which demonstrate that ivermectin is unstable in feces/soil mixtures; aqueous extracts of steer feces contain less than 3 ppb of ivermectin; the compound is strongly bound to soil of all types, precluding entry of the compound into ground or surface water. Experiments suggest moderately slow but extensive degradation of the drug and metabolites. In addition, data support the high probability that ivermectin metabolites and soil degradation products are even less toxic than the parent compound.

Ivermectin is not harmful to soil microorganisms and desireable field animal and insect species at the anticipated soil levels.

Studies on the metabolic disposition of ivermectin in cattle have been reported.[19] Regardless of the route of administration, the major excretion pathway is via the feces. Cattle were slaughtered over a period of from 1 to 28 days for tissue residue studies. Of the edible tissues, the liver and fat contained the highest residues, with very little residue in the muscle and kidney. Residue data show a relatively rapid depletion of both drug and metabolites.

Conclusions

It is concluded from the data that ivermectin is safe for cattle when used under practical husbandry conditions at the recommended use level.

Subsequent to the compiling of the data for registration submission and prior to large scale commercial use of ivermectin injection, a total of 20,838 cattle in 18 countries were successfully involved in the research and development effort.

Ivermectin is an effective, new antiparasitic agent which is not chemically related nor paralleled in its spectrum of activity to any other drug now being marketed. In the proposed form, ivermectin provides the most convenient, ready-to-use method of control without leaving hazardous or potentially dangerous wastes which require careful handling and disposal. Since ivermectin is an injectable product, the environmental concern of disposing of "spent" dips and sprays is obviated.

The unique activity of this product also permits control of external parasites of significance at times of the year when currently available products, such as dips and sprays, cannot be used. Clearly beneficial effects with economic value will result from its use, such as decreased morbidity from parasitism and resultant increases in growth and feed efficiency.

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