EFFECTIVENESS OF IVERMECTIN FOR CONTROL OF ARTHROPOD PESTS OF LIVESTOCK

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ABSTRACT

This review presents a summary of published data on the effectiveness of ivermectin as an insecticide/acaricide for control of arthropod pests of livestock. In cattle, a single subcutaneous treatment of ivermectin at 200 µg/kg, which is effective against a variety of nematode gastrointestinal parasites, also controls cattle grub larvae, Hypoderma spp., sucking and biting lice, psoroptic and sarcoptic mange mites, the lone star tick, Amblyomma americanum (L.), (for 0-5 days), the southern cattle tick, Boophilus microplus (Canestrini), (for 2-21 days), and manure-dwelling larvae of the horn fly, Haematobia irritans L., (for 28 days) and face fly, Musca autumnalis De Geer, (for 14 days). Single therapeutic treatments also control larvae of the sheep nose bot fly, Oestrus ovis L., in sheep, larvae of horse bot flies, Gasterophilus spp., in horses, and the hog sucking louse, Haematopinus suis L., and scab mites, Sarcoptes scabiei (L.), in swine. Daily administration of 1-5 µg/kg/day of ivermectin orally or subcutaneously controls larvae of the horn fly and face fly in manure of treated cattle. Daily administration of 50-100 µg/kg/day orally or 5-15 µg/kg/day subcutaneously provides control of a variety of 1-host and 3-host ticks. Sustained-release boluses or implants of ivermectin provide extended (7-10 wks) control of fly larvae in manure and of ticks.

Campbell (1981) and Campbell et al. (1983) give an interesting account of the discovery and development of ivermectin (Merck & Co. Inc., MK-933, 22,23-dihydroavermectin B_1--containing at least 80% of 22,23-dihydroavermectin B_{1a} and not more than 20% of 22,23-dihydroavermectin B_{1b}). This material is one of a broad series of avermectins, a group of compounds with the chemical structure of a macrocyclic lactone with two sugars added. Avermectins were isolated from a broth of a fermentation product of Streptomyces avermitilis, a fungus isolated from the soil in Japan. Although originally discovered in the parasitology program at the Merck, Sharp & Dohme Research Laboratories as anthelmintics against the nematode Nematospiroides dubius in mice, the avermectins were soon shown to be highly active against a wide range of parasitic nematodes in a number of hosts. However, the compounds were not active against trematodes or cestodes. Of particular interest in this review is the fact that avermectins were discovered to be highly active as systemic insecticides/acaricides against a variety of insect and acarine parasites of animals. Ivermectin was selected by the company for further development for control of parasites of livestock. The remainder of this review will present a brief summary of published information on the systemic and contact activity of ivermectin against arthropod parasites of animals, especially livestock.

CATTLE

Biting flies. Ivermectin does not appear to be systemically active against the bloodsucking adult stages of important "biting flies" such as the horn fly, Haematobia irritans (L.), and the stable fly, Stomoxys calcitrans (L.). Distlemans et al. (1983), however, showed that adult tsetse flies, Glossina

palpalis palpalis Robineau-Desvoidy, died within 4-8 days after feeding daily on a goat treated subcutaneously once with 10 mg/kg of ivermectin; in guinea pigs they noted some activity at dosages as low as 2 mg/kg.

In contrast, oral and subcutaneous treatments of ivermectin have been reported by Miller et al. (1981b) to be highly effective against horn fly and stable fly larvae that develop in the manure of cattle. A single therapeutic dose of 200 µg/kg of ivermectin given subcutaneously afforded essentially complete control of horn fly larvae for 4 wks in the manure of treated cattle; control of stable fly larvae was never greater than 53% and averaged less than 40% for the first 4 wks posttreatment. Although a single treatment of ivermectin at 200 µg/kg intramuscularly did reduce numbers of a variety of manure-dwelling arthropods, treated manure did not kill all the arthropods (no effect on "gnats" or Staphylinidae), and it appeared to disintegrate at a normal rate (Schmidt 1983).

Of greater interest in the control of dipterous larvae in the manure of cattle has been the research on the activity of very low dosages of ivermectin administered daily. Miller et al. (1981b) showed that low daily oral or subcutaneous doses of ivermectin were highly effective against horn fly and stable fly larvae (Table 1). The effectiveness of ivermectin at such low daily dosages makes the compound an excellent candidate for inclusion in sustained-release systems (Miller et al. 1981a). Miller et al. (1983) showed that a subcutaneously injected sustained-release implant of about 200 µg/kg provided some 10 wks of control of horn fly larvae in manure, whereas a single injection of a normal formulation provided only 4 wks of control.

Nonbiting flies. As with larvae of biting flies that breed in manure, larvae of two nonbiting flies--the house fly, Musca domestica L., and the face fly, M. autumnalis De Geer--are also controlled in the manure of cattle treated orally or subcutaneously with ivermectin. Meyer et al. (1980) showed that a single injection of 200 µg/kg of ivermectin provided essentially 14 days of 100% control of face fly larvae.

The daily continuous administration of ivermectin both orally and subcutaneously to cattle was also effective against face fly and house fly larvae in manure (Miller et al. 1981b, Meyer et al. 1981); minimum effective dosages are also presented in Table 1. It appears that face fly larvae are about as susceptible to ivermectin as horn fly larvae. The fact that both species also breed in unbroken manure pats and that both are important pests of range cattle makes them ideal targets for sustained-release treatments of cattle. It is conceivable that range cattle could be treated only 1-3 times with a controlled-release bolus or implant of ivermectin that would provide season-long control of horn fly and face fly larvae.

TABLE 1. Minimum Effective Daily Dosages of Ivermectin for Control of Larvae of Manure-Breeding Diptera.[a/]

Species	95-100% control at indicated µg/kg/day	
	Oral	SC
Haematobia irritans	> 1	< 2.5
Musca autumnalis	1-5	2.5-5
Musca domestica	5	--
Stomoxys calcitrans	< 5	> 10

[a/] Data from Miller et al. (1981b) and Meyer et al. (1981).

In other research on the effectiveness of ivermectin for control of larvae of nonbiting flies, James et al. (1980) showed that larvae of Lucilia cuprina (Wiedemann) were very susceptible to topical applications of a crude extract of

avermectins. Chamberlain (1982a) showed that avermectins mixed with larval medium were highly effective against larvae of Cochliomyia macellaria (Fabricius), the secondary screwworm.

Nonfeeding flies. Larvae of both the common cattle grub, Hypoderma lineatum (DeVillers), and the northern cattle grub, H. bovis (L.), were essentially completely controlled by a single subcutaneous injection of 200 µg/kg of ivermectin (Khan 1982, Badiola et al. 1982). In a detailed series of tests, Drummond (1984) treated small numbers of cattle subcutaneously with titrated dosages of ivermectin (Table 2) and found by probit analysis that the LD_{90} for H. lineatum larvae was about 0.1 µg/kg. Thus, a subcutaneous treatment of 200 µg/kg given for control of internal parasites, if administered at the appropriate time of the year, would also be highly effective systemically against cattle grub larvae.

TABLE 2. Effectiveness of Ivermectin as a Subcutaneous Injection for Control of Larvae of the Common Cattle Grub, Hypoderma lineatum.[a/]

Dosage (µg/kg)	% control
200	96
100	100
10	100
1	100
0.2	100
.1	86
.05	59
.02	19

a/ Data from Drummond (1984).

Lice. Barth and Sutherland (1980) reported that two species of sucking lice, Linognathus vituli (L.), the long-nosed cattle louse, and Haematopinis eurysternus (Nitzsch), the short-nosed cattle louse, were both killed by subcutaneous administration of 100, 200, or 400 µg/kg of ivermectin. Lloyd et al. (1981) also found that injection of ivermectin at dosages of 100-400 µg/kg was completely effective systemically against L. vituli and that dosages of 200-400 µg/kg controlled Bovicola bovis L., the cattle biting louse. Meleney (1981a) also reported control of B. bovis in one calf treated at 300 µg/kg subcutaneously. In in vitro tests, Chamberlain (1982b) found that avermectins added to the diet of the Angora goat biting louse, B. limbatus (Gervais), gave 50-80% mortality at 0.1 ppm.

Ticks. Single subcutaneous dosages of 100-500 µg/kg of ivermectin have been shown to be systemically effective against a number of species of ticks: Amblyomma variegatum (Fabricius), Rhipicephalus appendiculatus Neumann, and Ornithodoros moubata (Murray), (Centurier and Barth 1980); R. appendiculatus (Schroder et al. 1981); A. americanum (L.) (Wilkins et al. 1981, Lancaster et al. 1982a); Boophilus microplus (Canestrini) (Nolan et al. 1981); and A. americanum, B. decoloratus (Koch), Dermacentor albipictus (Packard), and Hyalomma aegyptium (L.) (Wilkins et al. 1980a). The treatment was apparently not effective against the slow-feeding nymphal stage of Otobius megnini (Duges) in the ears of cattle (Meleney 1981a). The treatment was generally effective against ticks feeding on treatment day and provided control of 3-host species for 3-5 days and of 1-host species for 21 days posttreatment. In general, affected female ticks attached normally and either died while attached or did not feed to repletion. Those small, partially engorged females that detached laid small egg masses that had variable rates of hatch.

In addition to research on long-term control of larvae of manure-breeding flies, there has also been some research on daily or long-term application of low dosages of ivermectin for the control of ticks. Minimum effective daily dosages

for several species of ticks have been determined by Drummond et al. (1981), Lancaster et al. (1982b), and Nolan et al. (1981), and their data are summarized in Table 3. Ivermectin administered as a subcutaneous injection was 5-10 times more effective than when administered orally. In further research on administration of ivermectin in sustained-release systems, Miller et al. (1983) showed that sustained-release implants of ca. 200 µg/kg placed in the ear of cattle afforded >70% control of adult A. cajennense (Fabricius) and >85% control of A. americanum for 7 weeks. In further research, Drummond and Miller (1984) showed that if sustained-release implants provided dosages of over 5 µg/kg/day, control of adult A. americanum could be obtained for 40-80 days depending upon the initial dosage of the implant.

TABLE 3. Minimum Daily Dosages of Ivermectin Systemically Effective Against Ticks.[a/]

Species	95-100% control at indicated µg/kg/day	
	Oral	SC
Amblyomma americanum	50	5
Amblyomma cajennense	> 50	10
Amblyomma maculatum	> 50	10
Boophilus microplus	--	15
Dermacentor albipictus	50	5
Dermacentor andersoni	50	10
Dermacentor variabilis	100	10
Rhipicephalus sanguineus	20	--

[a/] Data from Drummond et al. (1981), Lancaster et al. (1982b), and Nolan et al. (1981).

Mites. Because psoroptic scabies of cattle is a quarantinable disease in the United States, it is important to note that treatments of ivermectin are systemically active against Psoroptes ovis (Hering), the causative agent. Research by Barth and Sutherland (1980), Bailey (1981), Euzeby et al. (1981), Meleney (1981a, 1981b), and Pouplard and Detry (1981) has shown that oral, intramuscular, and subcutaneous treatments of ivermectin were systemically effective against P. ovis in cattle (Table 4).

TABLE 4. Summary of Data on Control of Psoroptes ovis with Ivermectin.[a/]

Method of treatment	Dosage (µg/kg)	% control	Days before no live mites found
Oral	400	100	55
SC	100	high	--
	200	100	10
	300	100	14
	400	100	14
IM	50	100	14
	100	100	14
	200	100	14

[a/] Data from Meleney (1981a) and Barth and Sutherland (1980).

In subsequent research, Meleney et al. (1982) reported that treated calves were protected from reinfestation with P. ovis for as long as 21 days. However, Guillot and Meleney (1982) and Wright and Guillot (1984) reported mites taken from treated calves were still infective after 5 and 9 days posttreatment, respectively. Thus, in order to prevent the spread of this very contagious species, ivermectin-treated cattle should be isolated from untreated cattle for at least 2 wks; however, treated cattle can be returned to mite-contaminated enclosures without risk of reinfestation.

SHEEP

Yazwinski et al. (1983) reported that a single oral treatment of 200 µg/kg of ivermectin, in addition to being highly effective against a variety of gastrointestinal parasites of sheep, was 100% effective against first-instar larvae of Oestrus ovis L., the sheep nose bot fly. Although psoroptic scabies of sheep has been eradicated from the U.S., Psoroptes ovis, the causative agent, was eliminated from a herd of desert bighorn sheep, Ovis canadensis Mexicana, by intramuscular injections of 500 or 1000 µg/kg of ivermectin (Meleney et al. 1980, Kinzer et al. 1983).

SWINE

Ivermectin given orally, intramuscularly, or subcutaneously to swine was systemically effective at various dosages (Table 5) against both Haematopinus suis L., the hog sucking louse, and Sarcoptes scabiei (L.), the common scab mite (Barth and Brokken 1980, Hogg 1981, Lee et al. 1980, and Stewart et al. 1981). Courtney et al. (1983) showed that a single subcutaneous treatment of sows, before farrowing, at 300 µg/kg would provide an effective program for control of S. scabiei.

TABLE 5. Control of Two Swine Ectoparasites with Ivermectin.[a/]

Species	100% control at indicated µg/kg		
	Oral	IM	SC
Sarcoptes scabiei	300-500	300	--
Haematopinus suis	--	--	20-500

a/ Data from Barth and Brokken (1980), Hogg (1981), Lee et al. (1980), and Stewart et al. (1981).

HORSES

A number of authors (Bello 1982, Bello and Norfleet 1981, Craig and Kunde 1981, Dipietro et al. 1982, Egerton et al. 1981, Klei and Torbert 1980, Lyons et al. 1980, Schroder and Swan 1982, Torbert et al. 1982, Yazwinski et al. 1982) have shown that oral (stomach tube or paste) treatments or intramuscular injections of ivermectin were effective against larvae of Gasterophilus nasalis (L.), the throat bot fly, and G. intestinalis (De Geer), the horse bot fly (Table 6). The same treatments listed in Table 6 were also effective against a variety of internal parasites of horses. There appears to be no difference in susceptibility of first-, second- or third-instar horse bot larvae. As with cattle, the treated horses still were infested with immature stages of Otobius megnini, the spinose ear tick (Craig and Kunde 1981).

TABLE 6. Control of Horse Bot Larvae with Ivermectin.[a/]

Gasterophilus species	95-100% control at indicated µg/kg/day	
	Oral	IM
nasalis	50-200	200-300
intestinalis	100-200	200-500

[a/]Data from various authors (see text).

OTHER

DeVaney (College Station, TX, personal communication) has determined that ivermectin was not systemically active against the northern fowl mite, Ornithonyssus sylviarum (Canestrini and Fanzago), feeding on treated birds; however, with high-level topical treatments, ivermectin showed some activity as a contact acaricide. Wilkins et al. (1980b) showed that subcutaneous injections of avermectin analogues at 100 µg/kg were systemically effective against Psoroptes cuniculi (Delafond) in ears of rabbits. In contrast, Wright (1983) did not find complete control of P. cuniculi or P. ovis in rabbits injected subcutaneously or intramuscularly at dosages as high as 400 µg/kg. Yazwinski et al. (1981) observed total cure of natural infestations of Otodectes cynotis (Hering) and Sarcoptes scabiei (De Geer) after treatment of dogs subcutaneously with ivermectin at 200 and 400 µg/kg.

The data presented above show that ivermectin at very low (by current standards of treatment) levels is highly effective against a variety of arthropod parasites of livestock (and other animals). Single therapeutic treatments of cattle (200 µg/kg) for the control of a number of internal parasites will also be effective against cattle grub larvae (critical timing is necessary), horn fly and face fly larvae in manure, sucking lice, ticks, and psoroptic mites. Such similar therapeutic treatments in sheep will control larvae of the sheep nose bot fly, in swine will control sucking lice and mange mites, and in horses will control horse bot larvae. Of considerable interest is the fact that very low dosages given daily are systemically active against ticks and larvae of manure-breeding flies. This activity makes ivermectin an excellent candidate for inclusion in sustained-release devices, such as boluses or implants. Sustained-release treatments could provide for very long-term (weeks or months) control of these important pests.

Generally, it is very encouraging to note the broad-spectrum antiparasitic activity of relatively minute amounts of a naturally occurring product. Such activity should provide a renewed interest in research to determine the activity (not only against parasites but against diseases) of the countless variety of natural products that are yet undiscovered and untested in this world.

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