Ivermectin, An Antiparasitic Agent

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I. INTRODUCTION

Ivermectin has been in commercial use as an antiparasitic agent for ten years, and a vast amount of information has been accumulated concerning its basic scientific properties and field performance. It has been used most widely in the control of parasites in domestic animals, having become the dominant chemotherapeutic agent in combatting diseases that cause losses of hundreds of millions of dollars annually. Its use in human medicine, while limited in scope, has received considerable attention because of the special circumstances surrounding its use in controlling the ravages of a single tropical disease.

In the present review ivermectin is considered broadly, and summary information is given on basic and developmental aspects of the drug, and on its

Medicinal Research Reviews, Vol. 13, No. 1, 61–79 (1993)

CCC 0198-6325/93/010061-19

use in domestic animals and in humans. For additional detail the reader is referred to a recent monograph.[1]

II. DISCOVERY

Ivermectin is one of the avermectin family of compounds. These compounds were discovered in an empirical screening operation conducted at the Merck Sharp & Dohme Research Laboratories (MSDRL) in Rahway, NJ, and the discovery was made possible by an agreement with the Kitasato Institute in Tokyo, Japan. Under this agreement, isolates of soil microorganisms would be selected for distinctive appearance or cultural characteristics and sent to MSDRL for use in screening programs. The focus of the anthelmintic screen at MSDRL had recently been switched from synthetic chemicals to natural products, and the Kitasato Institute cultures were included in the input for that assay.

The assay, which had been developed by Dr. J. R. Egerton, Mr. J. DiNetta, and colleagues, specifically for use with fermentation broths, entailed the incorporation of broths into the diet of mice infected with the nematode parasite *Heligmosomoides polygyrus* (*Nematospiroides dubius*). Examination of mouse feces (for the presence of worm eggs) and intestine (for the presence of worms) served as an indicator of drug efficacy. In 1975 a batch of Kitasato Institute microbial cultures was re-grown in Rahway and tested in this assay. The fermentation broth of one organism, which had been isolated from soil by Dr. Ruiko Oiwa under the direction of Dr. Satoshi Omura, proved active against the parasite.[2] The broth was therefore subjected to isolation studies; the efficacy of crude concentrates was confirmed in a variety of tests; and the identity of the active principle was determined.[3–6] The story of the discovery has been told in detail elsewhere.[7,8]

III. CHEMISTRY

Isolation studies using thin-layer chromatography showed that the newly discovered substance consisted of four major and four minor components.[3] They were named avermectins because of their activity against worms and ectoparasitic arthropods. By means of mass spectrometry and nuclear magnetic resonance spectroscopy, the avermectins were shown to be 16-membered macrocyclic lactones with a disaccharide substituent at the carbon-13 position.[5] Subsequent crystallization of the major components permitted confirmation of structures by x-ray crystallography. The structure of the avermectins are shown in Fig. 1. They are quite different from the antibacterial

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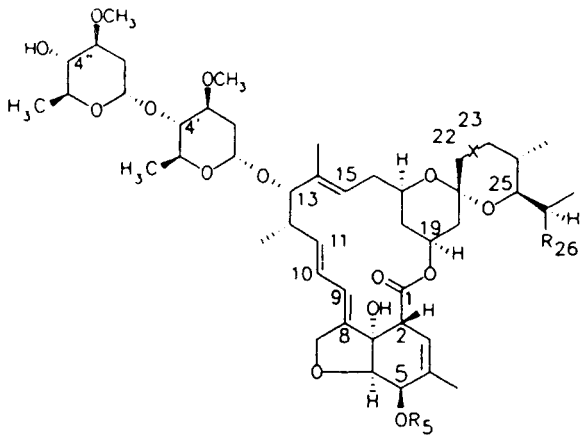
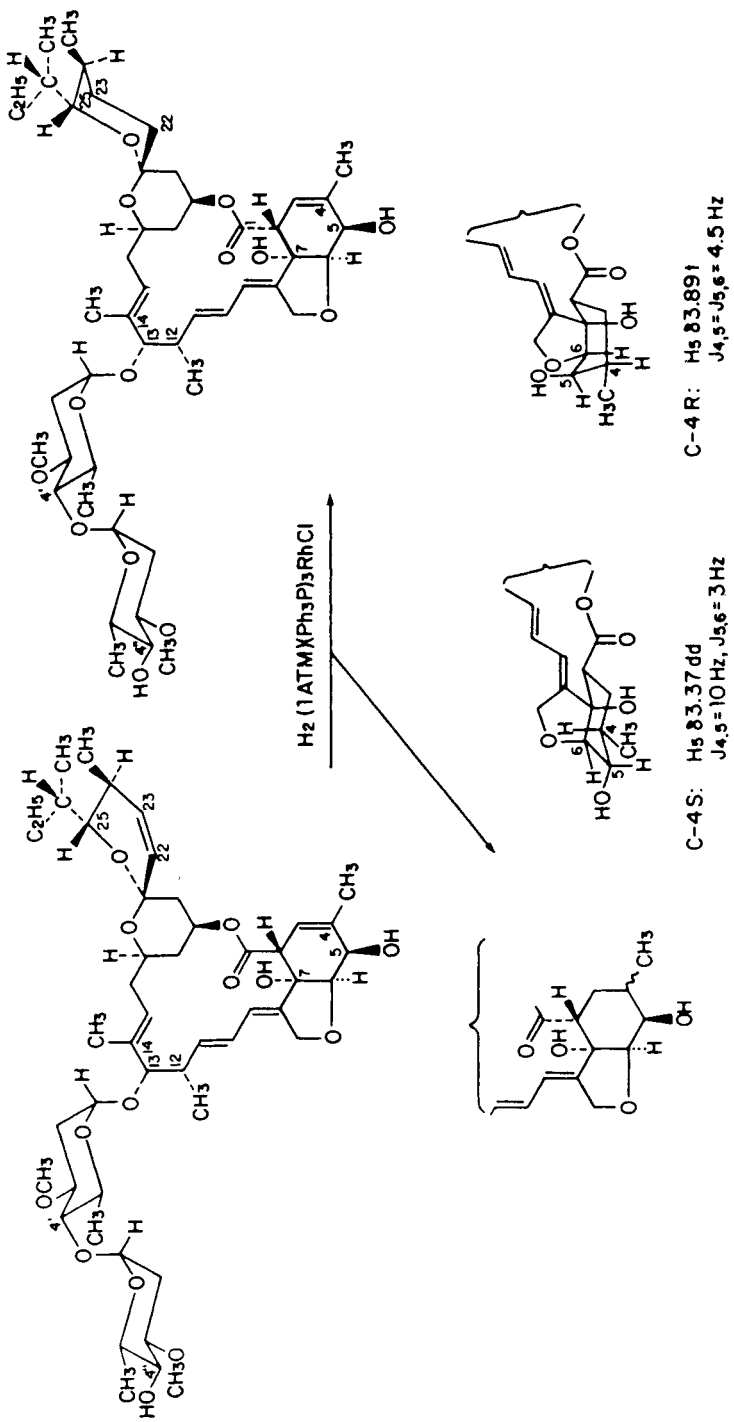


AVERMECTIN	R_5	R_{26}	$C_{22}-X-C_{23}$
A_{1a}	CH_3	C_2H_5	$-CH=CH-$
A_{1b}	CH_3	CH_3	$-CH=CH-$
B_{1a}	H	C_2H_5	$-CH=CH-$
B_{1b}	H	CH_3	$-CH=CH-$
A_{2a}	CH_3	C_2H_5	$-CH_2-\overset{OH}{\overset{\vert}{C}}H-$
A_{2b}	CH_3	CH_3	$-CH_2-\overset{OH}{\overset{\vert}{C}}H-$
B_{2a}	H	C_2H_5	$-CH_2-\overset{OH}{\overset{\vert}{C}}H-$
B_{2b}	H	CH_3	$-CH_2-\overset{OH}{\overset{\vert}{C}}H-$
IVERMECTIN	H	>80% C_2H_5 <20% CH_3	$-CH_2-CH_2-$

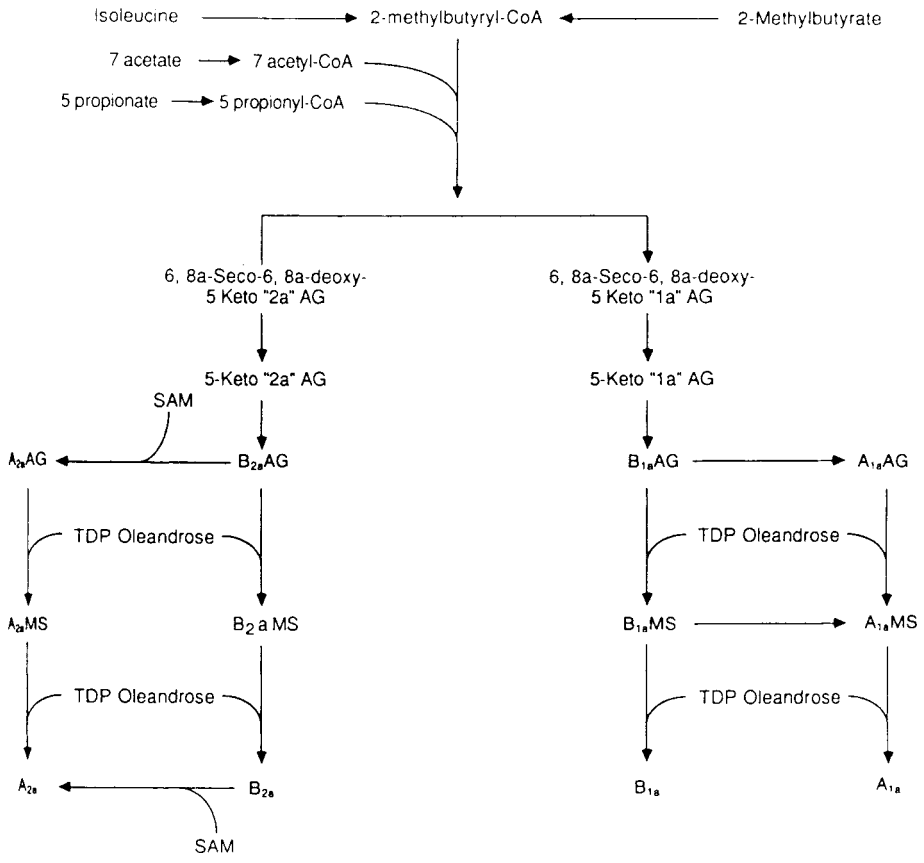
Figure 1. Avermectin structures.[9]

macrolides or the antifungal polyenes, although they share some structural features with them.[9] They are more closely related to the acaricidal-nematocidal milbemycins, but the latter lack the disaccharide group at carbon-13.

The avermectins designated B (those with a hydroxy group at C-5) have greater anthelmintic efficacy than the A series (those with a 5-methoxy group). The B compound with an olefin linkage at C22-23 (designated B_1) is



Scheme I. Synthesis of ivermectin by selective hydrogenation of avermectin B_1.[9]



Scheme II. Proposed pathway for biosynthesis of the avermectins in *S. avermitilis*.[10]

similar in efficacy to the one with a hydrated linkage and hydroxyl group at C23 (B_2), but the latter has a weakness against the adult stage of an important nematode species (*Haemonchus contortus*). Because of this, and because the milbemycins were known to have a saturated linkage at C22-23, without substitution, avermectin B_1 was modified by selective hydrogenation of the double bond at C22-23. This was accomplished by the use of Wilkinson's homogeneous catalyst (Scheme I). The resultant compound, 22-23-dihydro avermectin B_1, had the chair-shaped stereochemistry of B_2, as opposed to the rather flat ring of B_1, and did not have a substituent at C23. It was active against the full spectrum of target parasites, including *H. contortus*. It was given the nonpropietary name ivermectin, and selected for commercial development. Ivermectin is not more potent than avermectin B_1, but its safety profile in toxicological tests was judged slightly preferable to that of B_1. Avermectin B_1, named abamectin, was subsequently developed for commercial use in various animal health and agricultural markets.

Within the avermectin series of compounds are major homologs, with an *iso*-propyl substituent at C25, and minor homologs, with a *sec*-butyl group in that position. They appear to be biologically equivalent and are not separated in the commercial production of B_1 for conversion to ivermectin. They occur

in a ratio of approximately 4:1. Ivermectin, by definition, contains at least 80% of the major homolog and not more than 20% of the minor homolog.

Based on a variety of experimental approaches, a pathway for the biosynthesis of avermectin has been proposed[10] and is summarized in Scheme II.

Ivermectin is an off-white powder with very low solubility in water and high solubility in organic solvents. The molecular weight of the B_1a component is 874, and of the B_1b component is 860. The compound is highly lipophilic. When in aqueous solution, it binds readily to the wall of glass or plastic vessels.

IV. FERMENTATION

To support the expanding research effort and to make commercialization feasible, a vast program of fermentation development was needed. The microorganism that produced the first detected avermectins proved to be a new species of actinomycete bacterium, *Streptomyces avermitilis*.[2,11] The original isolate of the organism produced only small quantities of avermectins, and so spores were irradiated with ultraviolet light for various periods in order to produce mutants that might yield larger amounts. Spores were also exposed to chemical mutagens for various periods for the same purpose. At the same time, improvements were continually being made in the culture medium in which the organism was grown, and in the physical and chemical conditions under which the fermentation took place. The objective was not only to enhance avermectin production, but to do so without loss of the B_1 component that was essential for conversion into ivermectin. By these means fermentation methods were developed that yielded much more avermectin product than the original methods (per unit of volume) and with much higher content of avermectin B_1.[12]

As the promise of ivermectin became more evident, it became necessary to scale up the avermectin fermentation process from a laboratory scale (20 ml of culture medium in a 250-ml flask) to a production scale (50,000 liters of medium in a commercial fermentor). An intermediate step in the 2.5-million-fold increase was the development of a pilot-plant process using a tank with 500 ml of medium.[12]

V. MODE OF ACTION

The mode of action of ivermectin has been reviewed elsewhere.[13,14] Early studies on the mode of action of avermectins were conducted on nerve preparations from lobsters or the large nematode *Ascaris lumbricoides*, or from rat brain synaptosomes. The data suggested that ivermectin (and other avermectins) causes paralysis in arthropods and nematodes by interfering with the transmission of nerve signals, and that this is the result of increased cell membrane permeability to chloride ions, which in turn is due to the effect of the drug on the neurotransmitter γ-amino-butyric acid (GABA). At the concentrations used, the drug caused not only an agonist action on the GABA receptor but also a potentiation of presynaptic release and postsynaptic binding of the neurotransmitter. It subsequently was found that ivermectin (at even lower concentrations) can cause an influx of chloride ions at sites that lack GABA binding sites. Specific avermectin binding sites have been identi-

fied in rat brain and in the free-living nematode *Caenorhabditis elegans*, with the affinity of the former being about a hundred times less than the affinity of the latter.[15,16] There are technical difficulties, however, in working with the very small nematode, and recent studies have employed oocytes of the toad *Xenopus laevis* that have been injected with mRNA of *C. elegans*.[17] These large cells, when thus injected, express an ivermectin-dependent chloride current. The unusual electrophysiological and biochemical properties of the ivermectin-dependent current raise the possibility that ivermectin may be acting on a kind of chloride ion channel that has not previously been identified.

It was reported that avermectins block fungal growth by inhibiting chitin synthesis, but this was apparently the result of using an impure avermectin preparation.

VI. TOXICOLOGY

A. Acute Toxicity

The acute toxicity of ivermectin in mammals is manifested in CNS effects, and this may be related to its effect on GABA in the mammalian brain and spinal cord. Common signs of acute toxicity include ataxia, tremors, and in severe cases, coma and death.[18] The LD_{50} of ivermectin in various animal species was found to be as shown in Table I.

Mice are especially sensitive to ivermectin toxicity. Of special concern, idiosyncratic toxicity has been reported in mice, with severe reactions and death occurring at dosages as low as 0.2 mg/kg—the dosage that is used therapeutically in several target species. Adverse effects were not seen in rhesus monkeys at this dosage, and the same dosage has been used in human onchocerciasis patients without toxicity attributable to the drug itself—even though the plasma concentrations of the drug in monkeys and man are similar to those in mice. Idiosyncratic toxicity has also been observed in dogs, especially of the Collie breed.

B. Subchronic Toxicity in Primates

Ivermectin was given orally to immature rhesus monkeys at dosages up to 1.2 mg/kg for 2 weeks, and no adverse effects were seen.[18] Similarly, no adverse effects were seen when the drug was given orally to neonatal rhesus

TABLE I
LD_{50} of Ivermectin in Various Animal Species

Species	Route of Administration	LD_{50} (mg/kg)
Mouse	Oral	25
Mouse	Intraperitoneal	30
Rat	Oral	50
Rat	Intraperitoneal	55
Rat (infant)	Oral	2–3
Rat	Dermal	>600
Rabbit	Dermal	406
Dog	Oral	~80
Rhesus monkey	Oral	>24

monkeys for 2 weeks at dosages up to 0.1 mg/kg. This suggests that the neonatal exposure of humans would not be likely to cause toxic effects at dosages up to 0.1 mg/kg. In lactating women, low levels were found in milk assayed one day after treatment (see Sec. VII) with the conventional dosage.

C. Developmental Toxicity

When ivermectin was given daily to pregnant mice, dosages of 0.2 mg/kg/day, or higher, were toxic to the mice; and dosages of 0.4 mg/kg/day were toxic to both the mice and the developing fetus (producing cleft palate in the latter). In rats, a dosage of 5 mg/kg/day was not toxic to either the mother or the fetus, while 10 mg/kg/day was toxic to the mother and caused cleft palate in the fetus. In rabbits, a dosage of 1.5 mg/kg/day was not toxic to mother or fetus; a dosage of 3.0 mg/kg/day caused cleft palate and clubbed forefeet in the fetus; and a dosage of 6.0 mg/kg/day was toxic to the mother. It was concluded that ivermectin causes abnormal fetal development only at or near maternotoxic dosages.[18]

D. Other Animal Studies

The general assessment of ivermectin safety included a three-month toxicity study in rats (with *in utero* exposure); a three-month toxicity study in dogs; and a multigenerational toxicity study in rats, with observations on mating, fertility, pregnancy, and length of gestation. The studies have been comprehensively reviewed.[18] In preparation for commercial use, ivermectin was also evaluated for safety in horses, cattle, sheep, goats, swine, and dogs. These studies included safety in breeding animals. The findings, which have been summarized,[19] indicate that ivermectin has a wide margin of safety. Environmental aspects of the use of ivermectin in farm animals have been studied.[20] Concern has been expressed about the environmental consequences of excreted drug on dung-breeding fauna, and this needs further evaluation.[21,22]

E. Safety in Humans

Evidence of the safety of ivermectin in humans has been derived from the clinical efficacy trials,[23] supported by the basic toxicology data reviewed above. Adverse reactions during the clinical trials have included fever, pruritus, dizziness, edema, and ocular inflammation (in patients with parasitic invasion of the eye). These reactions were generally mild and transient. Occasionally severe reactions have been recorded, the most prominent being postural hypotension. Such hypotensive episodes have also been reported in occasional patients treated with diethylcarbamazine (DEC), and their cause and significance are unclear. The adverse reactions observed after ivermectin treatment, like those seen after DEC treatment, are believed to represent host reaction to the destruction of parasites. For reasons that are not understood, but which may relate to the precise mode of destruction, the reactions that follow ivermectin are both less frequent and less severe than those that follow DEC. Ivermectin has been well tolerated even when the standard treatment was repeated every two weeks for a total of six treatments.

Reports of possible linkage between ivermectin treatment and epileptic seizures, asthma, and prolongation of prothrombin time have not been substantiated. The severity of the other observed reactions appears to be related to the density of parasites in the skin, and may also be related to the degree of previous exposure to infection. Although pregnant women are excluded from current treatment programs, several hundred women were treated in the early stages of pregnancy without detectable adverse effect on their progeny.

On the basis of early trials, ivermectin was judged safe enough for large-scale treatment programs for the control of onchocerciasis. More than 100,000 people have been treated in community-based programs and the drug has been well tolerated.

VII. PHARMACOLOGY

Ivermectin is absorbed rapidly into the blood stream following oral or parenteral administration. Practically all of it (at least 90%) is excreted as intact drug in the feces of the treated animal. The remainder is excreted in urine. The plasma profile of the absorbed drug depends on the species of animal and the formulation of the drug.

A. Domestic Animals

The commercial injectable formulation for cattle contains 1% ivermectin in a vehicle consisting of propylene glycol (60%) and glycerol formal (40%), and is injected subcutaneously at 200 μg/kg. This results in a plasma peak of 44 ng/ml within 2 days, and a biological half-life of 8.3 days. In contrast, intravenous injection of a similar preparation gives a plasma half-life of only 2.8 days. The longer half-life associated with the subcutaneous injection is attributed to the slow absorption of nonaqueous formulations from parenteral sites. Absorption can be speeded up by putting the drug in an aqueous medium. This can be done by using a surfactant to prepare a micellar solution. When such a micellar formulation of ivermectin is injected subcutaneously the plasma peak is reached faster than with the conventional solvent solution (1 day, instead of 2), and the peak plasma concentration is higher (84 ng/kg instead of 44). In animal health use, the prolonged plasma life associated with nonaqueous vehicle gives the more desirable efficacy profile.

In sheep, pharmacological findings were similar to those in cattle (plasma half-life = 2.7 days), but the volume of distribution was larger. In dogs, ivermectin is eliminated faster than in sheep or cattle, with the plasma half-life after intravenous injection being 1.8 days. When the drug is given to dogs in tablet form (as for heartworm prevention) it is rapidly absorbed, reaching a peak in plasma at 2–4 hours and then decaying exponentially. In horses, the liquid oral formulation gives a plasma peak in 4–5 hours, whereas the paste oral formulation takes 15 hours to reach a peak. In swine, an oral solution of ivermectin gave a plasma peak in about 12 hours. As in cattle, parenteral administration of a solution resulted in slower absorption, perhaps because of precipitation of drug at the injection site. The peak plasma concentration following subcutaneous injection occurred at 2 days, but the proportion of the dose that was absorbed was greater than in the case of oral treatment.

Ivermectin is used in animals that provide food for people, and therefore it was necessary to develop methods for determining the nature and amount of drug residues in edible tissues at various intervals after treatment. The residues of ivermectin found in the tissues of animals after treatment are essentially free rather than tissue-bound and can be extracted almost quantitatively by organic solvents (assessed by radio labeling of drug). In cattle, 25 edible and inedible tissues (including body fluids) were examined. Brain had the lowest level of drug residue (4ppb) at 7 days after treatment. Liver (782ppb), bile (273 ppb), and fat (270 ppb) had by far the highest residue levels at the same interval.

Although most of the residue found in cattle liver consists of the parent drug, some is metabolized. The major metabolite is 24-hydroxymethyl ivermectin. This is also the major liver metabolite in sheep and rats, while in swine the major liver metabolite is 3″-O-desmethyl-ivermectin.

The development of an assay to measure the amount of drug residue in animal tissues proved a formidable task. Because of the extremely low dosage administered (200 μg/kg in cattle) the tissue residues are found in the order of parts per billion (above). Based on toxicological studies in mice, the "negligible residue" was defined as 10–20 ppb for many tissues. In order to provide reliable data at this level, an assay was sought that would have a limit of detection of about 1 ppb (1 ng/g). Such an assay, using a fluorescent derivative of the residual drug, was developed and has been used to assay ivermectin residues in many tissues from many animal species. A confirmatory assay was also developed.

References to the literature on the pharmacokinetics and metabolism of ivermectin in cattle, sheep, swine, horses, dogs, and rats may be found in more extensive reviews.[24,25] The analytical methods for assay tissue residues have also been reviewed.[26]

B. Humans

Little is known of the pharmacokinetics of ivermectin in human beings because the studies done to date have been limited to those relating to the drug's very restricted use in humans.

Following oral administration of tritium-labeled drug to healthy volunteers, the ivermectin concentration in blood peaked at about 4 hours and then decreased slowly (Fig. 2). Metabolites peaked at about 7 hours. The plasma half-life is estimated as approximately 12 hours for the parent drug and about 3 days for the metabolites. Almost all of the drug (parent and metabolites) is eliminated in the bile and feces, with less than one percent detected in urine and, in lactating women, small amounts in milk (maximum 23 ng/ml one day after oral dose of 150–200 μg/kg). Metabolites in urine and feces have been identified as the 3″-O-desmethyl and monosaccharide derivatives of ivermectin, respectively. Plasma metabolites have not been positively identified.

The bioavailability of ivermectin in solution is greater than in solid formulations (AUC for an aqueous alcohol solution in human was 1.73–1.96 times greater than for capsules or tablets). However, administration of the drug in tablets, capsules, and solutions resulted in a plasma peak at about 4 hours in each instance, suggesting that absorption is limited by dissolution rate. Other

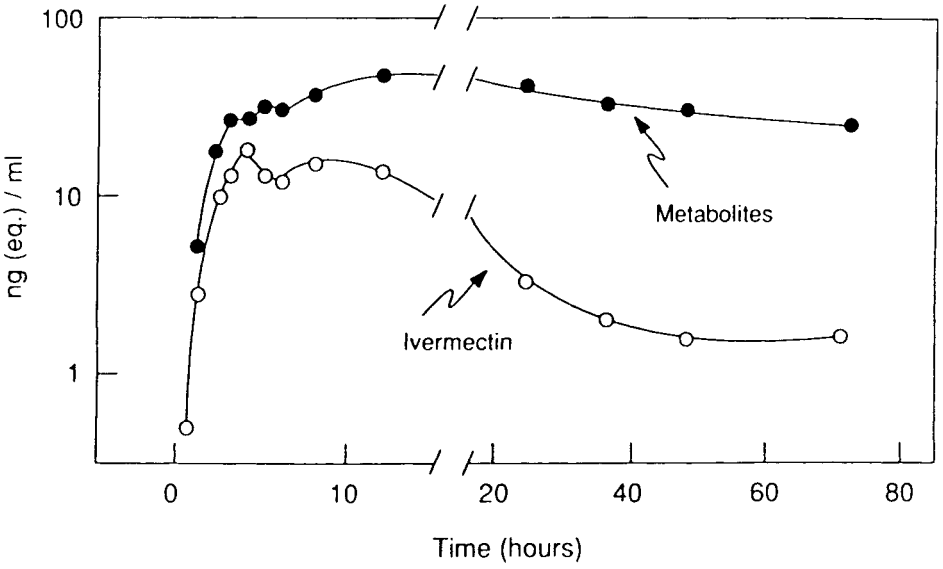


Figure 2. Mean concentrations of ivermectin and metabolites in human plasma after administration of a 14-mg dose of ^{3}H-labeled drug (average from four subjects).[24]

studies in humans revealed no detectable effect of dosage on the time taken to reach peak plasma concentration.

These human pharmacokinetic studies have been reviewed elsewhere.[24]

VIII. ANTIPARASITIC ACTIVITY

A. General

Laboratory studies showed that ivermectin is active against a wide range of nematode and arthropod parasites, and this information, together with basic data on chemistry, fermentation, pharmacology, and toxicology, resulted in its selection as a candidate for commercial development.[6] Under the direction of Dr. W. H. D. Leaning and Dr. I. Sutherland, efficacy, safety, and pharmacological studies were expanded to cover many target animal species, a wide spectrum of parasites, and a variety of formulations, routes of administration, and geographical regions. Because of the large number of susceptible organisms involved, readers are referred to several reviews of the topic,[27,28] including one that lists all known susceptible nematode species.[29]

It was found that the drug is active when given orally, intramuscularly, subcutaneously, or even cutaneously. In general, efficacy against ectoparasitic arthropods (e.g., mites) is better when treatment is given parenterally rather than orally. Efficacy may be profoundly affected by formulation of the drug in ways that affect plasma profile. In general, ivermectin is active against both immature and mature stages of susceptible species, but there are notable exceptions to this (e.g., *Dirofilaria immitis*). The antiparasitic potency of the drug was found to be quite unprecedented, with the pre-adult stage of heartworm (*D. immitis*) in dogs being affected at dosages as low as 2 μg/kg (0.002

mg/kg)[30] and cattle grub (larvae of *Hypoderma* sp.) being affected when the host cattle are given dosages as low as 0.2 μg/kg (0.0002 mg/kg).[31]

Despite some incidental data that suggested activity against certain tapeworms, ivermectin is not believed to be active against trematodes (flukes) or cestodes (tapeworms).

B. Domestic Animals

Ivermectin is used commercially for the broad-spectrum control of nematode and arthropod parasites in domestic animals. Because of its activity against both endoparasitic and ectoparasitic organisms, it has become known as the first "endectocide." Essentially all important nematode species are susceptible. Resistant populations of particular species can be selected by drug pressure in the laboratory,[32] and have recently been reported in the field.[33–36] Among the arthropods, mites and parasitic dipteran larvae are especially sensitive (see *Hypoderma* in preceding section). Ivermectin also has systemic activity against other arthropods, such as ticks and biting flies, but the degree, duration, and regulatory status of the effect depends upon the species and circumstances involved.

Details of the animal-health formulations and their efficacy against various parasites may be found elsewhere,[37–39] but a brief account is given below for the major farm animals and companion species. Ivermectin is also registered for use in reindeer, camel, and bison, and has been tested to a greater or lesser extent in various wild or exotic animal species.[40]

1. Cattle

Ivermectin (Ivomec®) was introduced as a solution for subcutaneous injection in cattle, and was later supplemented by formulations designed for oral or cutaneous use. The injectable formulation is given at a dosage of 200 μg/kg, and provides at least 95% efficacy against the following nematode species: *Haemonchus placei, Mecistocirrus digitatus, Ostertagia ostertagi, O. lyrata, Trichostrongylus axei, T. colubriformis, Cooperia* spp., *C. oncophora, C. punctata, C. pectinata, Nematodirus spathiger, Strongyloides papillosus, Toxocara vitulorum, Bunostomum phlebotomum, Oesophagostomum radiatum, Dictyocaulus viviparus, Thelazia* spp. It is moderately effective against *N. helvetianus*. It has not been tested against the immature (fourth-stage) forms of all of the above species, but is at least 95% efficacious against those that have been subjected to trial, namely: *H. placei, O. ostertagi, T. axei, T. colubriformis, C. oncophora, C. punctata, B. phlebotomum, O. radiatum, D. viviparus.*

It will be noted that the susceptible adults and immatures include the lungworms as well as the gastrointestinal nematodes. It should also be pointed out that ivermectin is effective against the notoriously refractory hypobiotic stages of susceptible species and is effective against benzimidazole-resistant strains.

In addition to its activity against nematode parasites, the standard injectable dosage of ivermectin is also active against several important ectoparasites of cattle, especially grubs (*Hypoderma* spp., *Dermatobia* sp.), screwworms (*Chrysomya* sp.), sucking lice (*Haematopinus* sp.; *Linognathus* sp., *Solenopotes* sp.), and mange mites (*Sarcoptes* sp., *Psoroptes* sp.). It is only moderately effec-

tive against biting lice (*Damalinia* sp.) and surface-dwelling mange mites (*Chorioptes* sp.). The standard treatment suppresses engorgment and oviposition in ticks (*Boophilus* spp., *Ornithodorus* sp.) but the practical value of these effects in controlling tick infestation depends on the species and epidemiological circumstances.

The oral formulation is a paste that is delivered by an automatic dosing gun, giving a dosage of 200 μg/kg. Its efficacy is basically similar to that of the injectable formulation; but systemic absorption of the drug is somewhat less complete and less persistent, and probably for that reason, efficacy against mange mites is considerably reduced. The cutaneous ("topical") formulation is a solution that is poured along the back (topline) of cattle to penetrate the skin and give systemic drug delivery. In order to achieve systemic concentrations sufficient to control gastrointestinal worms and lungworms, the dosage (500 μg/kg) is higher than that of the other formulations. Efficacy against one kind of mange mite, *Psoroptes* sp., is not satisfactory, but the cutaneous formulation has an approved claim for the control of horn-fly, *Haematobia* sp., for a period of five weeks after application. As with the injectable formulation, it persists in the animal body long enough to provide a measure of prophylaxis against incoming nematode larvae. Intraruminal devices have been developed for the purpose of releasing ivermectin over prolonged periods.[41] They have not yet been marketed, but prototypes have been successfully tested.

2. *Sheep and Goats*

The injectable solution used for cattle is also approved for use in sheep, but an oral "drench" solution has also been developed for this species. Both formulations are used at 200 μg/kg for broad-spectrum activity, but the oral formulation lacks potency against some species of mange mite. In goats, the same oral formulation is approved for use against endoparasitic nematodes but not for ectoparasitic arthropods.

3. *Swine*

In swine, ivermectin is given as a subcutaneous injection at a dosage of 300 μg/kg. Treatment is at least 95% effective against the adult forms of the following nematode species, which include kidney worms and lungworms as well as gastrointestinal worms: *Ascaris suum, Hyostrongylus rubidus, Oesophagostomum* spp., *Strongloides ransomi, Trichuris suis.* It is at least 95% effective against the fourth-stage larvae of *A. suum, H. rubidus, Oesophagostomum* spp., and *S. dentatus.* The swine formulation is also effective against lice (*Haematopinus* sp.) and mange mites (*Sarcoptes* sp.).

4. *Horses*

For a brief period ivermectin was used in horses in the form of an aqueous micellar solution for intramuscular injection. Because of adverse reactions associated with improper injection, clostridial contamination of the injection site, or hypersensitivity to an excipient, this formulation was withdrawn.

Currently, ivermectin (Equalan®) is used orally in horses, either as a paste for delivery by syringe into the horse's mouth, or as a clear solution that

veterinarians administer as an oral drench or by nasogastric intubation. In either case the recommended dosage of 200 μg/kg gives activity against stomach bots as well as a broad spectrum of nematode worms. The susceptible stages and species are listed in Table II.

5. Dogs

In dogs, ivermectin (Heartgard®) is used for a very specific purpose—the prevention of heartworm disease (dirofilariasis). The dosage is 6 μg/kg and the drug is given in the form of small swallow-tablets or chewable tablets (beef-flavored "treats"). Its main advantage over the previously conventional treatment is that it is given monthly instead of daily. The dosage is well tolerated even in ivermectin-sensitive Collies. Broad-spectrum activity could be obtained at higher dosage, but because of possible idiosyncratic reactions, ivermectin is used in dogs as a single entity for heartworm prevention. Canadian authorities recently approved a combination of ivermectin and pyrantel pamoate for control of ascarids and hookworms as well as heartworm.

TABLE II
Horse Parasites for which Ivermectin Oral Paste Has Been Approved at a Dosage of 200 μg/kg[a]

Large Strongyles
Strongylus vulgaris, adult and arterial larval stage
S. edentatus, adult and tissue stage
S. equinus, adult
Triodontophorus spp., adult
Small Strongyles
Cyathostomum spp., adult and L_4 stage
Cylicocyclus spp., adult and L_4 stage
Cylicostephanus spp., adult and L_4 stage
Cylicodontophorus spp., adult and L_4 stage
Gyalocephalus sp., adult and immature[b]
Other Nematodes
Parascaris equorum, adult, L_3 and L_4 stage
Oxyuris equi, adult and L_4 stage
Trichostongylus axei, adult
Habronema muscae, adult and cutaneous L_3 stage
Draschia spp., cutaneous L_3 stage[b]
Onchocerca sp., microfilaria
Dictyocaulus arnfieldi, adult and L_4 stage
Bots
Gastrophilus spp., oral and gastric stages

[a]Unless otherwise specified, approval refers to the Food and Drug Administration of the United States of America.

[b]Approved in country or countries other than United States.

C. Humans

1. Onchocerciasis

Ivermectin has become the drug of choice in the treatment of onchocerciasis (River Blindness) but it is important to understand what it will do in this disease, and what it will not do.

The skin-dwelling larvae or microfilariae (mf.) of *Onchocerca volvulus* are the primary pathogen in this infection, causing progressive skin lesions that are often severe, and in many individuals causing ocular lesions and eventual blindness. Numerous clinical studies have established that ivermectin at 100–200 μg/kg will greatly reduce the numbers of mf. in skin and eye tissues and will thereby halt the disease process. If instituted before lesions become significant, treatment will thus prevent the onset of clinical disease or blindness. Administration of an annual or semiannual dose of the drug, at 150 μg/kg, is now being used to provide protection indefinitely (or until transmission has been broken). The fact that the drug is given as a single oral dose, and is well tolerated, has given it a practicability of vital importance in countries where public-health resources are extremely limited.

The proprietary name of the human formulation of ivermectin is Mectizan. Supplies of Mectizan tablets, donated by Merck & Co., Inc., are shipped to health authorities upon approval by a Mectizan Expert Committee set up jointly by the manufacturer and the World Health Organization.[42,43] Treatments are approved both for community-based programs and for hospitals or clinics with specific needs. As of this writing, approval has been granted for almost four million treatments, and well over one million have already been administered. Community-based treatment programs have begun, or are scheduled to begin, in 23 of the 27 African countries in which onchocerciasis is known to be endemic, and in all five of the Central or South American countries. Most of the treatments administered so far have been carried out by the Onchocerciasis Control Programme under the direction of Dr. Ebrahim Samba. In the summer of 1991 the Mectizan Expert Committee decided to accelerate its treatment program, and now hopes to have six million people under sustainable treatment programs by 1993, the sixth year of the program.[44]

Ivermectin does not kill the adult *O. volvulus* worms, but it does effect them in such a way that the female worms cease shedding mf. for a period of months. Thus, although this infection is not eradicated, the microfilaricidal action of the drug is supplemented by a reduction in mf. production.

Ivermectin does not, as far as one can deduce from a study in chimpanzees, kill the pre-adult stages of *O. volvulus* as they migrate through the subcutaneous tissues. Thus there seems to be no prospect of employing ivermectin for prophylaxis in the way that it is employed in the prevention of canine heartworm disease.

Community-based ivermectin treatment reduces the prevalence of infective *O. volvulus* larvae in vector flies by reducing the population of mf. in human skin and by diminishing the developmental capability of those mf. that are picked up from the skin. Thus community-based treatment may reduce transmission of the disease, but the epidemiological significance of this will depend on many regional factors and remains uncertain.

The use of ivermectin in human onchocerciasis has been reviewed in detail elsewhere.[45–49]

2. Lymphatic Filariasis

Ivermectin is active against the parasites that cause bancroftian or lymphatic filariasis (which results, in some patients, in the disturbing condition known as elephantiasis) and the closely related brugian filariasis.[50,51] The situation, however, is quite different from that in onchocerciasis. The mf. are highly sensitive to treatment with ivermectin (being destroyed, in some clinical trials, by dosages as low as 25 μg/kg); but they live in blood, not skin, and are not considered to be important pathogens. Thus it is not clear that their elimination will benefit a treated patient. The adult worms, as in onchocerciasis, are apparently not killed by treatment; but because they are the primary pathogens in lymphatic filariasis, failure to remove them is more serious, and means that treatment may not be beneficial in reversing the clinical condition or even in halting its progress.

Nevertheless, ivermectin may be useful in the control of lymphatic filariasis. Elimination of mf. from peripheral blood will block transmission of the disease by depriving vector mosquitoes of a source of parasites. Community treatment will thus confer community benefit even in the absence of individual benefit. This has long been accomplished by DEC, which is clinically more acceptable in this disease than in onchocerciasis. DEC, however, requires a lengthy series of doses, whereas ivermectin is effective as a single oral dose (100–150 mg/kg in most trials) and would be much easier to employ in mass treatment programs in endemic areas. The critical question is whether ivermectin fully matches DEC in efficacy and safety. Side-by-side comparisons of the two drugs are in progress.

3. Intestinal Nematodes

Ivermectin is not currently approved for use against intestinal roundworms in humans. It has striking activity against some species, but surprising weakness against others.

Studies in Africa, Central America, and South America have shown that single oral doses of 100–200 μg/kg cause expulsion of *Ascaris lumbricoides* and the disappearance of *Ascaris* eggs from the feces. Indeed, the expulsion of worms from people treated for onchocerciasis has been a common and much appreciated "side effect" of ivermectin treatment.

Few controlled trials have been done in patients infected with *Trichuris trichiura, Strongyloides stercoralis,* or *Enterobius vermicularis.* In the treatment of all of these species, ivermectin dosages in the range of 150–200 μg/kg appear to have moderate-to-good efficacy. Additional studies would be needed to define the degree of efficacy, but other anthelmintics are available and the motivation for such trials is limited.

The most surprising information to emerge from studies against intestinal helminths in humans is the low efficacy of the drug against the hookworms *Ancylostoma duodenale* and especially *Necator americanus.* It is surprising because ivermectin is exceptionally potent against the common hookworm species in dogs (*A. caninum, Uncinaria stenocephala*). Studies have shown that the

human *N. americanus*, when put into susceptible laboratory animals, can be removed only by massive doses of ivermectin.

The drugs commonly used for broad-spectrum control of intestinal nematodes in humans are generally effective and well tolerated. While ivermectin may find a place in the treatment of certain infections, e.g., strongyloidiasis, it is unlikely to find utility as a broad-spectrum anthelmintic.

4. Miscellaneous

Laboratory studies suggest that ivermectin would not be useful in the treatment of human trichinellosis. Preliminary clinical trials indicate that it may well be useful in the topical treatment of Cutaneous Larva Migrans (caused by larvae of nonhuman hookworm species). The fact that ivermectin is absorbed through mammalian skin, and that it is highly active against various mites (Acarina) in animals, raises the possibility that this drug may be useful for the topical treatment of human scabies. In some patients scabies responds poorly to current topical treatments. Although ivermectin is generally less effective against ectoparasites when given orally than when given by parenteral injection, it may also be that the drug could become the first effective systemic treatment for otherwise intractable scabies.

IX. NEW DIRECTIONS

The introduction of a successful new drug elicits a search for new and improved structures of the same chemical class. The reasons are both scientific and commercial; and the more successful the drug the more intense the provocation of further research. Avermectin derivatives have been made in large numbers (more than 1000 by one laboratory alone) and untold thousands of microbial isolates have been screened for naturally occurring relatives. It is likely that these pursuits will persist for some years to come, and that the avermectin family will eventually give rise to a "second generation."

There may be a falling off in the search for derivatives when the basic ivermectin patents expire. Equivalent performance in a new compound will not be enough to justify commercial development; superiority will be demanded. As with all such developments in medicinal chemistry, the standards of drug performance have been set at a new high, but improvements are always theoretically possible.

Despite the massive screening of soil microorganisms, new avermectin producers have apparently not been discovered in nature—nor, for that matter, has the original one been isolated from another soil. The naturally occurring precursor of ivermectin, abamectin (Duotin), has been introduced by Merck & Co., Inc. in some markets as an alternative to ivermectin. Scientists at Pfizer Ltd. developed a mutant strain of *S. avermitilis* that cannot produce avermectins with the usual *sec*-butyl or *iso*-propyl substituents at C-25 (unless specific precursors are provided). By feeding the organism on various other precursors (carboxylic acids), they produced avermectins with novel C-25 substituents, and are exploring the commercial potential of such compounds.[52] Milbemycin B-41D, which is structurally equivalent to 13-deoxy-22,23 dihydro avermectin B_1 aglycone, has been used for the control of heartworm in dogs.[53] New compounds of the milbemycin type have been discovered, and

one of them, milbemycin oxime (Interceptor), has been introduced by Ciba-Geigy Animal Health for the control of *Dirofilaria* and *Ancylostoma* infections.[54,55] A new microbial compound of the general milbemycin type, nemadectin, has been shown to have broad-spectrum activity[56] and a derivative, moxidectin, has been introduced by American Cyanamid Company for the control of parasites in cattle. Others will undoubtedly follow. Combination products, such as the ivermectin-pyrantel combination mentioned above, may be used to broaden the efficacy spectrum, but getting regulatory approval of a combination product is a formidable task. As drug resistance develops inexorably from the intensive use of a medication, derivatives of greater potency may for a time be used to control the problem, but compounds with new modes of action are needed if they are to function as cures rather than palliatives for ills of this sort. New antiparasitic drugs that meet the new standard of potency, spectrum, safety, and convenience, and that act by novel biochemical means, will be hard to find or to design. The recent discovery of the antiparasitic activity of paraherquamide[57] encourages the belief that the natural environment still holds chemotherapeutic surprises.

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