Ivermectin: uses and impact 20 years on

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Purpose of review

Ivermectin was first discovered and used in veterinary medicine over 20 years ago. This review highlights some of the recent published research from 2005 through June 2006 on the use of ivermectin in both helminth and arthropod infection.

Recent findings

In recent years, several published studies have detailed the expanding role for ivermectin in multiple endo and ectoparasitic infections, including scabies, pediculosis, soil transmitted helminths, gnathostomiasis and myiasis. In addition, there is increasing experience with parenteral ivermectin for the treatment of disseminated strongyloidiasis. The success of ivermectin in reducing *Onchocerca volvulus* and *Wuchereria bancrofti* transmission through universal treatment in disease control programs continues to be well documented, but recent epidemiologic data describe suboptimal response to ivermectin by *O. volvulus* in a minority of individuals, the molecular markers for which are currently under investigation.

Summary

Over 20 years of research and clinical use have advanced ivermectin from its beginnings as a veterinary anthelmintic to its significant role in several successful disease control programs. Nevertheless, further research is needed to understand the basis for suboptimal response and to better define optimal drug regimens for varying diseases.

Keywords

ectoparasite, helminth, ivermectin, lymphatic filariasis, onchocerciasis

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Introduction

Since its introduction in 1981 as a veterinary anthelmintic, ivermectin has experienced remarkable success as a broad-spectrum human antiparasitic drug. Approved for human use in 1988, ivermectin plays an essential role in the control and eradication of filarial infection in humans and is presently being used in two global disease elimination programs as part of one of the largest drug donation programs in history [1•]. This review will examine the literature from 2005 through June 2006 that highlights ivermectin's effectiveness in a variety of human nematode and ectoparasite infections as well as its use as a public health tool.

Antiparasitic activity

Ivermectin was discovered in 1979 by Satoshi Omura of the Kitasato Institute in Tokyo, Japan, in partnership with the pharmaceutical company Merck, Sharpe and Dohme [2••]. It is a semisynthetic member of a class of compounds named avermectins, which were isolated from the fermentation broth of *Streptomyces avermectinius*, a species of actinomycete found in soil near a golf course bordering the ocean in Japan [3]. Avermectins are macrocyclic lactone compounds which are structurally similar to macrolide antibiotics, but which lack antibacterial and antifungal activity (Fig. 1). In animals and humans, ivermectin has been shown to have antiparasitic activity against a broad range of nematodes and arthropods including *Dirofilaria immitis*, *Strongyloides stercoralis*, tissue microfilaria of *Onchocerca volvulus*, *Loa loa*, lymphatic filariasis, intestinal nematodes and ectoparasites such as lice, scabies, mites and botflies [4•].

Pharmacology

Ivermectin induces paralysis in arthropods and nematodes by inhibiting glutamate-gated and γ-aminobutyric acid (GABA)-gated chloride ion channels in invertebrate nerve and muscle cells, leading to paralysis of peripheral motor function and parasite death [5•]. In addition, ivermectin has been shown to be transported by a P-glycoprotein transport protein, a plasma-membrane associated drug efflux transporter. In humans, ivermectin has not been proven to cross the intact blood–brain barrier, whereas in collie dogs, central nervous system toxicity and associated sudden death have been described due to a nonfunctional P-glycoprotein transporter on the blood–brain barrier [6•].

Ivermectin is a substrate for cytochrome P450 (CYP) 3A4. Orally administered, it has 50–60% bioavailability,

Figure 1 The structural formula of ivermectin

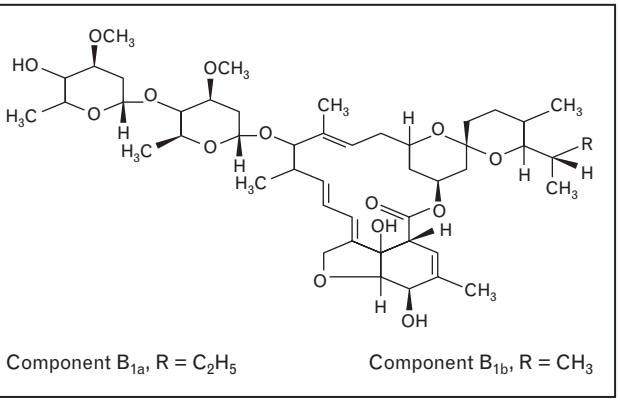

Figure courtesy of Merck & Co., Inc.

reaching peak levels 4–5 h after a single 200 μg/kg dose. It is metabolized in the liver, and metabolites are excreted primarily in the feces (98%) and urine (1%). The half-life of the parent drug is 12–56 h and the half-life of its metabolites is up to 3 days [7••]. In some patients, an enterohepatic cycle produces a secondary plasma peak between 6 and 12 h after dosing.

Adverse effects

Ivermectin has proven to be remarkably safe in humans and millions of doses have been distributed worldwide in mass drug administration programs. Nevertheless, the drug is not recommended for use in children under 5 years of age or weighing less than 15 kg, in pregnancy and lactation, in patients with diseases of the central nervous system or in those hypersensitive to the drug [8]. These restrictions are based on the drug's ability to potentially cross poorly-developed blood–brain barriers leading to possible neurotoxicity, particularly in small children. Recent reports, however, have demonstrated that ivermectin is well tolerated without serious adverse effects in children of less than 5 years of age when treated for scabies [9••]. Most adverse side effects are minor and rare, and include mild gastrointestinal upset, abdominal pain, fatigue, somnolence, dizziness, an urticarial-like or maculopapular eruption and rare biochemical abnormalities such as transaminitis and leucopenia [10]. Presently, there is a need for more data on ivermectin's safety in children. Additionally, although no problems were reported in a study of pregnant women who inadvertently received ivermectin during mass distribution campaigns, data are also needed on ivermectin's safety in pregnant and nursing women [11].

Ivermectin causes a Mazzotti-type reaction when used in the treatment of filariasis due to the death of numerous microfilariae. Encephalopathy has been reported in patients with onchocerciasis who are heavily infected with *Loa loa* microfilariae and are treated with ivermectin [12]. The mechanism for this adverse effect has not yet been determined.

Ivermectin and ectoparasites

Ivermectin has proven efficacious in treating several ectoparasite infections; most data involve the treatment of scabies and lice.

Sarcoptes scabiei

Oral ivermectin has been recommended as a systemic alternative to topical scabicides due to its ease of administration, convenience, safety and favorable side-effect profile. The efficacy and effectiveness of oral ivermectin has been found to be equivalent to or better than that of first-line topical therapy, including 5% permethrin, lindane and benzyl benzoate [13••]. The efficacy of single-dose ivermectin for curing scabies is generally lower than with two-dose ivermectin and it has been postulated that this lower efficacy may reflect the lack of ovicidal action of the drug [14••]. In addition to common scabies, numerous studies have reported ivermectin's success in the treatment of crusted scabies either as monotherapy or in combination with topical scabicides and keratolytics. Therapy may be effective after a single 200 μg/kg dose, but multiple doses are usually required to achieve cure. In the largest case series to date of 78 Aboriginal patients in Northern Australia with crusted scabies, Roberts and colleagues [15•] used topical scabicides and keratolytic therapy along with a five-dose ivermectin regimen (200 μg/kg/dose) administered on days 1, 2, 8, 9, 15, 22 and 29, and demonstrated a significant decrease in mortality in their patient group. To date, there have been two reported cases of ivermectin resistance in *Sarcoptes scabiei*. Both patients had received >30 doses of ivermectin over 4 years, suggesting the induction of resistance with repetitive treatment [16].

Despite ivermectin's proven efficacy in scabies, questions remain regarding the optimal dosing regimen for both common and crusted scabies and the consequence of extensive use of ivermectin on the emergence of resistant scabies. Presently, there is no general consensus regarding dosage regimens, and standardized protocols of optimal dosage schemes are needed. In addition, there are limited data on the use of topical ivermectin (0.8%) lotion in the treatment of scabies [17•]. Nevertheless, research to date demonstrates that ivermectin can be considered as initial therapy for elderly patients, those with generalized eczema, crusted scabies, HIV-infection, as well as those who may be unable to tolerate or have not responded to a topical scabicide.

Pediculosis

The three major lice that infest humans are *Pediculus humanus capitis* (head louse), *Pthirus pubis* (crab louse) and

Pediculus humanus humanus (body louse). Recent literature suggests that ivermectin has a role in treating both body and crab louse infestation. Foucault and colleagues [18••] demonstrated a significant reduction in prevalence of body lice infestation after three doses of oral ivermectin administered at 7-day intervals in a cohort of homeless men from a shelter in Marseilles, France. Additionally, oral ivermectin has also been advocated for the treatment of *Pthirus pubis* [19]. Although some data exist on ivermectin's efficacy for the treatment of head lice, this area is controversial and more research is needed [20••].

Ivermectin in strongyloidiasis

In recent years, ivermectin has become the drug of choice for the treatment of strongyloidiasis, including disseminated infection [21•,22]. Lately there have been several case reports confirming the efficacy and safety of a parenteral administration of veterinary ivermectin, not currently licensed for human use, as salvage therapy for *Strongyloides stercoralis* hyperinfection syndrome in cases of intestinal ileus or severe hypoalbuminemia [7••,23•–26•]. Varying dosage schedules have been used: 200 μg/kg/day for 14 days [26•], 200 μg/kg/dose every 48 h until resolution of ileus or clearing of larvae from sputum samples, or 200 μg/kg/day repeated on days 2, 15 and 16 [27•]. Subcutaneous administration of ivermectin has been shown to produce higher ivermectin levels than oral administration [7••], yet there are reports of fatal outcomes despite effective clearing of *S. stercoralis* larvae [28••]. At present, there is a need for data on the pharmacokinetics and tolerance of parenteral ivermectin, as well as the signs and symptoms of ivermectin central nervous system toxicity. In addition, clinical trial data assessing the relative efficacy of different dosing regimens for parenteral ivermectin are also crucially needed [29•].

Ivermectin in onchocerciasis

Ivermectin, distributed under the name Mectizan, is the only drug currently recommended for the treatment of *Onchocerca volvulus* for which over 50 million people are currently treated annually (Fig. 2). Despite having little impact on the viability of adult worms, ivermectin is a potent microfilaricide, reducing the levels of skin microfilaria by 96–99% within the first few months of therapy [3].

The most recent literature on ivermectin in onchocerciasis focuses in part on the issue of suboptimal response to ivermectin. Although no unequivocal cases of ivermectin resistance in *O. volvulus* have been described, the recent findings of patients with high microfilarial counts despite many rounds of ivermectin treatment are concerning [30,31]. A comparison of genetic polymorphisms in populations of *O. volvulus* from ivermectin-treated and untreated patients demonstrates evidence of genetic selection by ivermectin on *O. volvulus* [32••], and further work has demonstrated this selection occurring within an ABC transporter gene which functions as an energy-dependent efflux pump, similar to P-glycoprotein [33••]. Nevertheless, the relationship between these genetic polymorphisms and suboptimal clinical response to ivermectin is not clear, and whether these genetic changes are harbingers of developing ivermectin resistance has yet to be determined.

Figure 2 Ivermectin (Mectizan)

Figure courtesy of the Mectizan Donation Program.

As numerous countries have undergone ≥5 years of mass ivermectin distribution, recent studies also demonstrate ivermectin's impact in decreasing onchocerciasis transmission [34•]. Some studies have assessed varying the dose and frequency of administration of ivermectin and have concluded that higher doses of ivermectin (800 μg/kg/day) are associated with an increased frequency of adverse reactions, but that microfilaricidal activity is enhanced with 3-monthly, as opposed to annual, treatments [35,36•].

There are several future research and programmatic needs regarding ivermectin's role in onchocerciasis. First, there is an urgent need to better understand suboptimal response, its relationship to ivermectin treatment efficacy and associated changes in parasite genotype. If suboptimal response becomes a growing issue, trials of combination chemotherapy to mitigate against the development of drug resistance will be increasingly important. Although there is initial evidence that demonstrates no increase in adverse reactions with ivermectin in individuals co-infected with onchocerciasis and HIV-1, more research in this area is needed, as HIV-1 infection is common in many places where onchocerciasis is hyperendemic [37••]. Lastly, there remains a need for new drug development, particularly a macrofilaricide that can destroy adult *O. volvulus* worms and is safe for mass

distribution. Moxidectin, an avermectin similar to ivermectin, is presently undergoing trials for macrofilaricidal activity, and anti-Wolbachia antibiotics such as doxycycline and azithromycin are also being evaluated [38•]. Albendazole has been shown to interfere with embryogenesis, but whether a more potent benzimidazole may be macrofilaricidal is unknown.

Ivermectin in lymphatic filariasis

Ivermectin is microfilaricidal in *Wuchereria bancrofti* infection and the combination of ivermectin and albendazole has been adopted for mass treatment by The Global Programme for the Elimination of Lymphatic Filariasis in sub-Saharan Africa, where onchocerciasis is co-endemic. There are numerous studies of the effects of ivermectin alone or in combination with albendazole or diethylcarbamazine on *W. bancrofti* infection. A recent systematic review of the available drug trial data involving 57 randomized studies concluded that administration of combined drug regimens, particularly ivermectin and albendazole or diethylcarbamazine and albendazole, demonstrated greatest efficacy in decreasing circulating *W. bancrofti* microfilaria [39••]. Nevertheless, a recent Cochrane review concluded that there is inadequate evidence to verify an added benefit of albendazole to ivermectin's or diethylcarbamazine's microfilaricidal efficacy in humans, although entomologic data suggest that the combination of ivermectin and albendazole is superior to ivermectin alone for reducing the frequency of *W. bancrofti* infection in mosquitoes [40••,41•]. Recent data have also demonstrated that long-term biannual ivermectin treatment can significantly reduce *W. bancrofti* microfilaremia in populations [42•]. Presently, there remains a need for more comprehensive comparative drug studies for *W. bancrofti* that better define optimal frequency of dosing, duration and treatment endpoints. In addition, similar to onchocerciasis, a means for detecting the potential development of resistance in *W. bancrofti* will be essential [43••].

Ivermectin in loaisis

The administration of ivermectin to patients with extreme elevations in *Loa loa* microfilaremia (>20 000/μl) has been associated with severe posttreatment encephalopathy, sometimes resulting in fatalities. The etiology of post-ivermectin serious adverse reactions is poorly understood, yet these adverse events have affected activities of the African Programme for Onchocerciasis Control (APOC) in areas where loaisis and onchocerciasis are co-endemic. Risk factors for posttreatment encephalopathy have recently been shown to include male gender, advanced age and a high level of exposure to infective larvae [44•]. More research is needed to understand the mechanisms of action of ivermectin on *L. loa* microfilaria as well as to find methods to reduce *L. loa* microfilaria to levels at which subsequent ivermectin administration would be safe.

Other uses of ivermectin

There are numerous reports of ivermectin's effectiveness in a variety of other parasitic infections. Ivermectin has been used in several intestinal helminth control programs given its efficacy against *Ascaris lumbricoides*, *Trichuris trichiuria*, and hookworm [9••,45]. Ivermectin has also been used on an off-label basis for many years to treat cutaneous larva migrans [46]. Recent literature indicates that ivermectin may have a role in the treatment of *Enterobius vermicularis* infection, both as oral and as topical therapy [47•]. Single-dose ivermectin has also been used in the treatment of cutaneous gnathostomiasis. Although one study found it less effective than 21 days of albendazole, the sample size was small [48]. In addition, there are case reports of destructive rhino-orbital myiasis and external ophthalmomyiasis successfully treated with ivermectin prior to surgical extraction [49•,50].

Ivermectin resistance

The molecular basis of putative resistance to ivermectin is presently not well understood. It has been hypothesized that with intensive ivermectin use and drug selection pressure, mutations of P-glycoprotein encoding genes or of genes encoding glutamate-gated or γ-aminobutyric acid (GABA)-gated chloride ion channels may lead to ivermectin resistance in both intestinal helminths and arthropods [6•,16,51•]. Although ivermectin-resistant parasites have emerged as a major problem in several intestinal nematodes of goats, sheep and cattle [52], there have been no reports of ivermectin-resistant *Dirofilaria immitis* or ivermectin-resistant strongyloides thus far [4•]. More recent data suggest that ivermectin-insensitivity may exist in *Onchocerca volvulus*, although the pharmacologic or genetic demonstration of this phenomenon has not yet been made [30]. At present, there is a pressing need to develop field-based assay systems to test the in-vitro efficacy of ivermectin and the benzimidazoles against clinical helminth isolates showing in-vivo drug resistance [53•]. The ability to assay drug sensitivity in helminth populations will be important for the future of both the onchocerciasis and lymphatic filariasis elimination programs among others.

Conclusion

The history of ivermectin, from discovery in Japanese soil to widespread veterinary utilization and subsequent public health application, demonstrates how a scientific advance can be transformed into the keystone of several of the most important public health programs in recent history. The donation by Merck & Co. for onchocerciasis and lymphatic filariasis elimination constitutes one of the earliest and most successful examples of public–private partnerships. The future requires developing a

more thorough understanding of ivermectin's mechanism of action, including the pathogenesis of ivermectin-induced adverse effects, the basis of ivermectin resistance, as well as studies that better define optimal ivermectin dosing regimens for varying diseases. Despite these challenges, universal treatment with ivermectin has helped make the elimination of onchocerciasis and lymphatic filariasis an achievable goal and is presently benefiting millions of the world's poorest people.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 655–656).

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