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Reeview Article

Ivermectin: Pleiotropic Drug Continues to be Potent Therapeutic Agent

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I N F O

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A B S T R A C T

Aims: Ivermectin is a broad-spectrum antiparasitic agent, primarily deployed to combat parasitic worms in veterinary and human medicine. It has primarily been used in humans as an oral medication for the treatment of filarial diseases. It is used to treat onchocerciasis, strongyloidiasis and scabies in many countries. However, very recently, this drug was used in the management and cure of COVID-19. The aim of the present study is to unveil and focus on various pleiotropic aspects of this wonder drug.

Methodology: Relevant studies were searched by two means: (a) by online database searching using different online search engines and (b) from books, printed journals and government reports available in the library of the National Centre for Disease Control, Varanasi, and the Central Library of Banaras Hindu University, Varanasi, India. The restriction was set to include only those studies and reports which were carried out till 2024 and had information globally. The language of publication was not restricted. Abstracts without published articles were excluded.

Conclusions: Drug delivery mechanisms have impacts upon drug pharmacokinetics, distribution, absorption, metabolism, duration of therapeutic effect and toxicity. The possibility of novel systems for delivering ivermectin has opened up a galore of opportunities for usage of the drug. This unique, multifaceted drug of the past and present has the capability to become a more exceptional drug of the future.

Keywords: Ivermectin, antiparasitic agent, onchocerciasis, pharmacokinetics, COVID-19.

Introduction

Unique microorganisms producing avermectins were discovered by Ōmura in the year 1973.[1] Merck laboratories screened it for possible specialised action as an antihelminthic. Ivermectin is the derivative of avermectin. It was commercialised, for its potential applicability among veterinary, agricultural and aquaculture markets in the year 1981. Later, the drug's potential in human health was confirmed. It was registered in 1987 and immediately provided free of charge (Mectizan) as much as needed for as long as needed with the goal of helping to control

onchocerciasis (river blindness) among poverty-stricken populations across the tropics. Its use to tackle other neglected tropical diseases soon followed. The beneficial global health impact and exciting future potential that ivermectin has to offer to human health globally are the focus of immediate attention. Ivermectin still remains a relatively unknown drug, although few, if any, other drugs can be compared with ivermectin for its beneficial impact on human health and humanity. It is a broad-spectrum antiparasitic agent, primarily deployed to combat parasitic worms in veterinary and human medicine. It has primarily been used in humans as an oral medication for the treatment of filarial diseases. It is effective against other worm-related infections and diseases, several parasite-induced epidermal parasitic skin diseases, and insect infestations. It is used to treat onchocerciasis, strongyloidiasis and scabies in many countries.[1] Recently, this drug was used in the management and cure of COVID-19. The aim of the present study is to unveil and focus on various pleiotropic aspects of this wonder drug.

Materials and Methods

- **Search Strategy**: Relevant studies were searched by two means: (a) by online database searching using different online search engines and (b) from books, printed journals, and government reports available in the library of the National Centre for Disease Control, Varanasi, and the Central Library of Banaras Hindu University, Varanasi, India.
- **Database Searching**: Electronic databases, namely PubMed (http://www.ncbi.nlm.nih.gov/pubmed), World Health Organization library database (http://www.who.int/library/databases/en/), ISI Web of Science (http://wokinfo.com/) and Wolters Kluwer Health (http://www.wolterskluwer.com/Products/Health/Pages/Default.aspx) were searched applying different keyword terms and Boolean operators. Our search was performed until 31st December 2024.
- **Inclusion and Exclusion Criteria for Selection**: The restriction was set to include only those studies and reports which were carried out till 2024 and had information globally. The language of publication was not restricted. Abstracts without published articles were excluded. Only original articles, technical and brief reports were included in this review. The bibliography from included articles was also screened for additional articles relevant to our study objective.

Previous unnoticed success of the drug

Ivermectin is a drug for the world's poor. Approximately 250 million people have been taking this drug annually to combat two of the world's most devastating, disfiguring, debilitating and stigma-inducing diseases onchocerciasis and lymphatic filariasis. The major sections of recipients live in remote, rural and under-resourced communities in developing countries and have virtually limited access to most rudimentary medical interventions. When the avermectins were discovered, they had been designated 'endectocides', used to kill a diverse range of disease-causing organisms as well as pathogen vectors inside as well as outside the body. The avermectin family displayed extraordinarily potent anthelmintic potential. [2,3] Ivermectin is a more potent semisynthetic mixture of two chemically modified avermectins, comprising 80% of 22,23-dihydroavermectin-B1a and 20% of 22,23-dihydroavermectin-B1b.

Ivermectin has a broad spectrum of activity, is highly efficacious, and acts robustly at low doses against a wide variety of nematodes, insects and parasites.[4,5] It has been proved to be extremely effective against most common intestinal worms (excepting tapeworms) and can be administered orally, topically or parenterally. It quickly became used worldwide to combat filarial and other infections/infestations in livestock and pets. In 1987, as it got registered for human use, ivermectin was immediately donated as Mectizan tablets to control Onchocerciasis is a skin-disfiguring and blinding disease caused by infection with the filarial worm *Onchocerca volvulus*. To control this disease in endemic areas, annual or semi-annual mass drug administration of ivermectin is carried out, and only 21–22 million people (almost exclusively in Africa) remain infected with *O. volvulus*. [6] On account of its use in control efforts, ivermectin has been so successful that it has now been switched from disease control to worldwide disease elimination. [7]For most afflicted countries, onchocerciasis elimination is within reach, and there is hope that the global elimination target of 2025 will be achieved. [7] In the mid-1990s, ivermectin proved to be an excellent treatment for lymphatic filariasis, leading to the donation programme being extended to cover this disease in areas where it co-exists with onchocerciasis. Ivermectin mass drug administration endows significant secondary community-wide health and socioeconomic benefits due to its impact on non-target infections. Very surprisingly, despite many years of unmatched global success proven by widespread intensive scientific studies, scientists are still not certain about the exact phenomena of action of ivermectin.

Present therapeutic uses of the drug

Mechanism of action: Ivermectin acts by disrupting glutamate-gated chloride channels and affecting γ-aminobutyric acid (GABA) receptors. It disrupts neurotransmission in nerve and muscle cells, leading to hyperpolarisation of the neuronal membrane, inducing paralysis of somatic muscles(pharyngeal pump), killing the parasite. GABA-related channels are common throughout nematodes and insects. In mammals, GABA receptors and neurones are restricted to the central

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nervous system. Ivermectin is quite safe for vertebrates because it cannot cross the blood–brain barrier. Adult filarial worms (microfilariae), once paired, do not require substantial movement or pharyngeal pumping. As a result, ivermectin treatment causes a rapid and almost total (98%) reduction in dermal-dwelling immature worms (microfilariae),[8] but has only a limited sterilising effect on female microfilariae.[9] There is a disparity between maximum plasma concentrations after ivermectin administration and the concentrations needed to induce paralysis in microfilariae. Studies have shown the evidenced-based hypothesis that the clearance of microfilariae is governed by immunoregulatory processes. Ivermectin treatment causes microfilariae to quickly disappear from the peripheral skin lymphatics. Due to the high lipid solubility of the drug, it results in wide distribution throughout the body. On oral administration, mean peak plasma concentration occurs approximately 4 hours after dosing, with a second peak at 6–12 hours probably due to enterohepatic recycling of the drug, with the plasma half-life of ivermectin being around 12 hours. [10,11,12] Studies have indicated that glutamate-gated chloride channel activity is solely expressed in musculature surrounding the filarial excretory–secretory vesicle.[13] It is believed that the rapid microfilarial clearance following ivermectin dosing occurs not from the direct impact of the drug but via suppression of the parasite's ability to evade the host's natural immune defence mechanism. [14]

Possible future potential of the drug

Ivermectin is acknowledged for human use primarily to treat onchocerciasis and strongyloidiasis, and, in combination with albendazole, to combat lymphatic filariasis. It is being increasingly used 'off-label' to combat a variety of other diseases. Ivermectin has now been used for over three decades to treat parasitic infections in mammals.[15]

Divergent disease-fighting potential identified for ivermectin

- **Trichinosis:** Ivermectin kills *Trichinella spiralis. The* first site of infection of Trichinella spiralis is the small intestine (first 1-4 weeks), then the larvae migrate through the bloodstream and encyst within striated muscle cells such as the diaphragm, tongue, and biceps.[16]
- **Asthma:** Studies have shown the impact of ivermectin on allergic asthma symptoms in mice. It significantly curtailed recruitment of immune cells, production of cytokines in the bronchoalveolar lavage fluids and secretion of ovalbumin-specific IgE and IgG1 in the serum. Mucus hypersecretion by goblet cells is found to be suppressed by ivermectin. Thus, it may be useful in treating allergic asthma and other inflammatory airway diseases.[17]
- **Disease vector control:** Ivermectin is highly effective in killing a broad range of insect vectors. It has been proved toxic to vectors of malaria and critical neglected tropical diseases such as leishmaniasis and trypanosomiasis. At sub-lethal doses, ivermectin inhibits feeding and disrupts mating behaviour, oviposition and egg hatching.[18]
- **Leishmaniasis:** Ivermectin is a possible rodent-bait feed-through insecticide to help control the Phlebotomine sandfly vectors that transmit Leishmania parasites. [19] In cutaneous leishmaniasis, ivermectin is more effective than other drugs in killing *Leishmania tropica* parasites in vitro. [20]
- **African trypanosomiasis (sleeping sickness):** Tsetse flies (*Glossina palpalis*) fed on ivermectin-treated animals have been shown not to survive more than 5 days, demonstrating that ivermectin has promise to help control these African trypanosomiasis vectors. [21]
- **Malaria Mosquitoes:** *Anopheles gambiae* that transmit *Plasmodium falciparum* may be killed by the ivermectin present in the human bloodstream after a standard oral dose. [22]
- ***Myiasis***: It is an infestation of fly larvae that grow inside the host. Surgical removal of parasites is often the only remedy. Oral myiasis has been treated with ivermectin. [23] The drug is effective against orbital myiasis, a rare and preventable ocular morbidity. [24]
- **Epilepsy:** Nodding syndrome (NS) is a mysterious and problematic form of epilepsy. The condition has serious socioeconomic implications and generates profound social stigma. The cause of NS remains unclear, but there exists an unexplained link with Onchocerciasis infection. [25]
- **Bedbugs:** Bedbugs are parasitic insects of the Cimicidae family; they feed exclusively on blood. *Cimex lectularius* is the common one and feeds on human blood. Its infestation is increasing significantly in poor households. Ivermectin is highly effective against bedbugs. [26]
- **Antibacterial effect*:*** Reports have shown that ivermectin has the capability of preventing infection of epithelial cells by the bacterial pathogen *Chlamydia trachomatis*. [27] In 2013, researchers showed the bactericidal effect of ivermectin against a range of mycobacterial organisms, including multidrug-resistant and extensively drug-resistant strains of *Mycobacterium tuberculosis*. [28]
- **Schistosomiasis:** Schistosoma species are the causative agents of schistosomiasis. Praziquantel is the sole drug available for controlling schistosomiasis. Ivermectin is a potent agonist of glutamate-gated chloride channels, whereas glutamate signalling has been recorded in schistosomes. [29]

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- ***Neurological disease:*** Many neurological disorders, such as motor neurone disease, appear due to cell death initiated by excessive levels of excitation in central nervous system neurones. Novel therapy for these disorders involving silencing excessive neuronal activity using ivermectin has been proposed by some studies. Because of its action on P2X4 receptors, ivermectin has potential for the prevention of alcohol use disorders as well as for motor neurone disease. In humans, Cys-loop neurotransmitter receptors activated by GABA mediate rapid synaptic transmission throughout the nervous system and are crucial for intercellular communication. They are key factors in fundamental physiological processes, such as learning and memory. Further understanding of the stereochemistry of ivermectin binding will facilitate the development of new lead compounds as anthelmintics as well as treatments for a wide variety of human neurological disorders. [30]
- ***Anticancerous effect:*** Ivermectin has been looked for as having substantial value in the treatment of a variety of cancers. Avermectins are known to have pronounced anti-tumour activity,[31] as well as the ability to potentiate the anti-tumour action of vincristine on Ehrlich carcinoma, melanoma B16 and P388 lymphoid leukaemia.[32,33] It exhibits both anti-cancer and anti-cancer stem cell properties. An in silico chemical genomics study indicated that ivermectin may be useful in tackling glioblastoma, lung and breast cancer. Breast cancer is the most common cancer among women around the world. Activation of cytostatic autophagy, disrupting cellular signalling in the process, probably by reducing PAK1 expression by ivermectin, suppresses breast cancer. Ivermectin-induced cytostatic autophagy causes suppression of tumour growth in breast cancer xenografts, catching the attention of researchers to believe there is scope for using ivermectin to inhibit breast cancer cell proliferation. Several studies revealed that ivermectin induces chloride-dependent membrane hyperpolarisation and cell death in leukemia cells, and it has also been suggested that ivermectin synergises with the chemotherapy agents cytarabine and daunorubicin to induce cell death in leukaemia cells.

Conclusions

Drug delivery mechanisms have impacts upon drug pharmacokinetics, distribution, absorption, metabolism, duration of therapeutic effect and toxicity. There is a co-existing necessity for more improved and nascent novel mechanisms to target the delivery of drugs. A focus on working upon efficacious therapeutic concentrations and durations of drug delivery is required. Ivermectin is one of the most extensively used anti-parasitic agents globally. Minor variations in its formulation may have fruitful impacts upon plasma kinetics, biodistribution, and efficacy. The possibility of novel systems for delivering ivermectin has opened up a galore of opportunities for usage of the drug. It also helps in realising its potential to combat a totally new range of diseases. The drug ivermectin is under various in-depth studies to find its role in the cure and care of metabolic-related diseases, such as hyperglycaemia, insulin resistance, hypertriglyceridemia, hypercholesterolaemia, diabetes and obesity. This unique, multifaceted drug of the past and present has the capability to become a more exceptional drug of the future.

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