



Adverse Effects of Ivermectin in Patients with Sars-Cov-2

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Article History	Abstract
Received: 06 April 2023 Revised: 18 August 2023 Accepted: 21 August 2023	<p>Through a literature review in high impact journals, it was determined that ivermectin, in addition to being a drug widely recognized for its ability to treat and control parasitic infections, has various relevant clinical actions, such as the possibility of eradicating onchocerciasis or "river blindness" Considering this fact as a triumph of humanity for the WHO in 2009. The broad-spectrum antiviral potential of this drug against a variety of RNA viruses is raised, due to its ability to specifically inhibit nuclear-mediated nuclear transport by α / β importine, capable of blocking the nuclear traffic of viral proteins. The proposed anti-SARS-CoV-2 action of ivermectin involves its binding to the IMPα / β1 heterodimer that will bind to the coronavirus burden protein causing the viral load to reduce the host cell's antiviral response, improving the patient's clinical conditions. Several clinical trials of the use of ivermectin in relation to COVID-19 have shown that this drug could produce a slight improvement in its symptoms, so this bibliographic review aims to determine the pharmacokinetics and adverse effects of ivermectin, as possible treatment of SARS-CoV-2.</p>
CC License CC-BY-NC-SA 4.0	Keywords: Ivermectin, SARS-CoV-2, Self-medication

1. Introduction

Emerging and re-emerging infectious diseases are ongoing challenges to global public health (1). The SARS-CoV-2 pandemic has caused serious damage to the population, especially to the most vulnerable groups in society (2). Since the nineteenth century, pathogenic viral outbreaks and their interaction with humans and animals resulted in the transmission of different viruses, threatening human health and safety. (3). In the last two decades, there has been an increase in the different types of coronaviruses identified, such as Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia, severe acute respiratory syndrome coronavirus (SARS-CoV) (4).

The pathological feature of COVID-19 is the rapid replication of SARS-CoV-2, which can trigger an exacerbated immune response, resulting in a cytokine storm that often causes severe inflammatory lung reactions. Disease progression can lead to alveolar damage leading to progressive respiratory failure and possibly death. In addition, monitoring of upper respiratory tract SARS-CoV-2 viral load in critically ill patients has shown that the burden is higher and the persistence of the virus is higher. (5).

Ivermectin is a drug Highly effective antiparasitic is recognized by action as ectoparasitocidal, antiviral and even anticancer, recognizing that certain effects may be secondary to toxic effects on cells (6). Several observational studies describe that patients treated with a single dose of ivermectin and multiple doses of doxycycline for the treatment of COVID-19 showed considerable improvements in symptoms and viral response, while patients who received ivermectin combined with azithromycin and hydroxychloroquine had lower mortality (7).

Considering that there is no drug to cure COVID 19 and its conditions, this research aims to describe the relevant pharmacological aspects of ivermectin as a treatment for SARS-CoV-2.

2. Materials And Methods

A bibliographic review was carried out during May 2021 of 45 scientific articles of which 30 were selected, discarding those that did not comply with ethical guidelines, lacked scientific support or had no clinical relevance. The studies mentioned in the research were selected based on their title, abstract, methodology, conclusions and number of bibliographic references, which have information on ivermectin, its effects, mechanism of action and ivermectin as a treatment for SARS-CoV-2, in addition the studies were published between 2017 and 2021 in high impact journals: Pubmed, Scimedirect, Google Scholar, Scielo, ClinicalTrial, Medline, Nature, medRXiv. Correlating the most relevant facts of each published article determined that there was relevant and scientific information on the clinical use and effects of ivermectin, which was related to a possible treatment for SARS-CoV-2.

3. Results and Discussion

In 1974 Omura's team isolated an organism from the soil sample of avermectins, which turned out to be surprisingly powerful against parasites. Strains of *Streptomyces avermectinius* bacteria from the samples demonstrate strong activity against various intestinal parasites in mouse models, the compound responsible for that activity is called avermectin (8).

Mechanism of Action

Ivermectin, an FDA-approved broad-spectrum antiparasitic usually administered with a single dose of 150 µg/kg orally, is a semisynthetic analogue of avermectin B1a (insecticide obtained for agricultural uses) that acts by interacting with a channel for chlorine in the membranes of nerve and muscle cells, which leads to hyperpolarization of the affected cells, with consequent paralysis and death of parasites (9).

It is widely used to eradicate and resist many different types of infections caused by parasitic nematodes and arthropods that infest livestock and domestic animals. The drug inhibits the reproductive function of the adult female of *O. volvulus* and alters the ability of the microfilariae of this species to evade the host's immune system (10). Specifically inhibit nuclear transport mediated by α/β importin, which blocks nuclear traffic of viral proteins (11).

The hypothesis on the mechanism of action against SARS-CoV-2 of ivermectin involves the binding of ivermectin to $\text{Imp}\alpha / \beta 1$, leading to destabilization of the heterodimer, preventing it from entering the kernel and preventing their binding to viral proteins. $\text{Imp}\alpha / \beta 1$ binds to the Covid-19 loading protein in the cytoplasm and translocates it to the nucleus by means of the nuclear pore complex that will crumble causing the viral load to be able to reduce the antiviral response of the host cell, producing an improved infection (12). Although ivermectin prevents viral proteins from entering the nucleus, reducing the inhibition of antiviral reactions generates pharmacokinetic problems such as high cytotoxicity and low solubility (13).

Side Effects

WHO has demonstrated its efficacy and safety by clinical studies, at different doses for endoparasites and ectoparasites, no cases of lethality have been reported even at its maximum dose of 24 mg/kg/weight (14).

Table 1. Adverse effects of the drug ivermectin

IVERMECTIN SIDE EFFECTS	
General Side Effects	Side effects in onchocerciasis treatment
<ul style="list-style-type: none"> • Hypersensitivity reactions • Dizziness • Nausea • Vomiting • Stomach pain or swelling • Diarrhoea • Constipation • Weakness • Sleepiness • Chest discomfort 	<ul style="list-style-type: none"> • Swelling of the eyes, face, arms, hands, feet, ankles, or lower legs • Joint pain and swelling • Pain and swelling of the glands in the neck, armpits, or crotch • Fast heart rate • Eye pain, redness, or watering • Swelling of the eyes or eyelids

Taken from Medline – Ivermectin, Natl Libr Med (US) (15).

Ivermectin In SARS-CoV-2

Ivermectin is part of the drugs analyzed and proposed as part of the treatment of SARS-CoV-2, such is the case of the Ministry of Health of Peru, where MINSA recommended the early use of Ivermectin despite doubts about the effectiveness and efficacy of this drug against COVID-19 due to the few clinical trials that support its use (2).

Although administration of 5 µM ivermectin reduced SARS-CoV-2 RNA levels 5,000-fold in vitro (9), demonstrating its partial antiviral properties, this drug received limited early attention in Europe and the United States due to the inability of currently approved oral doses to reach lung tissue levels, since the average maximum inhibitory concentration for SARS-CoV-2 is 35 times higher than the maximum plasma concentration, so to reach HF50 at the lung level, It should be used more than 25 times the approved dose weekly (9)(10).

Ahmed Sabeena, investigated the use of ivermectin alone or in combination with doxycycline in the treatment of adult patients with COVID-19 with mild symptoms, hoping that in the course of infection viral load would decrease, the duration of illness would be reduced and transmission would stop (15).

A randomized, double-blind clinical trial compared single-dose ivermectin with placebo in patients with non-severe COVID-19, to evaluate ivermectin use with a tendency to reduce viral loads and IgG titers that may reflect milder disease and clinical benefit in the cardinal symptoms of COVID-19 associated with tissue damage: anosmia / hyposmia and cough (16).

Our study aimed to determine the efficacy of ivermectin as a possible treatment for SARS-CoV-2, so the frequency of adverse effects of the drug was estimated by relating them to the factors that cause its appearance. (15), demonstrating that the side reactions obtained not only depend on the dose but also on the pathology presented by the patient and the interaction of ivermectin with another medicinal product generating serious adverse effects (17).

It is important to emphasize that despite the urgent need for effective drugs to treat or reduce the viral load of SARS-CoV-2, there is no specific antiviral treatment. Even so, several studies have demonstrated the antiviral effects of ivermectin against several RNA viruses, so the proposed anti-SARS-CoV-2 action with this drug would focus on the fact that treatment with this drug could be related to a decrease in mortality rate. (18).

Because ivermectin seems to have the ability to inhibit nuclear transport mediated by α / β importin, it is proposed that this could cause an improvement in the clinical conditions of the patient, by reducing the antiviral response of the host cell, But the clinical interest of ivermectin is also that it regulates the decrease in the expression of several pro-inflammatory genes, including those of IL-8, TNF- α and cathelicidin LL-37, the latter being particularly important, as it directly influences different pro- and anti-inflammatory pathways, including stimulating the production of IL-18 and IL-1 β , as well as

having a chemotactic effect for neutrophils and eosinophils. This effect could inhibit the expression of the gene hCAMP18, which encodes the precursor LL-37 so it is possible that the inhibition of importins favoring the immune regulatory effect (19).

If the mechanism of action of ivermectin against COVID-19 has to do with a nicotinic effect, inhibitory concentrations of this receptor could be reached in lung tissue in a short period of time with oral administration and for much longer periods with nebulized therapy, applying its influence on the reversal of anosmia. But before considering the most optimal dose for this case, it is necessary to study further the potential of ivermectin metabolites in any observed effect (10).

4. Conclusion

The positive results obtained in in vitro studies, in conjunction with various clinical trials with ivermectin, provided hope for the use of this drug in a clinical setting, proposing that this drug could be potentially useful for the therapy of COVID-19; However, with the present investigation it was determined that in addition to the recognized safety profile, Easy administration and evidence of good tolerance

The clinical interest of ivermectin as a possible treatment for SARS-CoV-2, is due to its ability to inhibit nuclear transport mediated by α / β importin so it could cause an improvement in the clinical conditions of the patient, by reducing the antiviral response of the host cell, as long as the drug is used in an early phase of the disease and with a dosage higher than the maximum recommended by the FDA, because the adverse effects of ivermectin such as nausea, dizziness and transient tachycardia, occur frequently in COVID-19 patients treated with this medicine, taking into account that the severity and number of side reactions obtained not only depend on the dose but also on the pathology suffered, the interaction of ivermectin with another medicine and the patient's immune system.

Clinical trials conducted demonstrated a reduction in viral load, a tendency to reduce IgG titers that may reflect milder disease, and a clinical benefit in the cardinal symptoms of COVID-19 associated with tissue damage: anosmia/hyposmia and cough. But because the samples were not significant, the use of ivermectin on a large scale as a treatment for SARS-CoV-2 needs more studies to certify its efficacy and safety with respect to this pathology.

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