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Research Paper

Ivermectin Pharmacokinetics and the Danger of Its Use in High Dosage

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***ABSTRACT**: With the pandemic of coronavirus, a run for the discovery of possible medication treatments and prevention started by scientist worldwidly. Ivermectin a drug used firstly in medicine veterinary that soon had it approval for human usage in low doses, as an anti-helminth drug, soon started to be highlighted as a potential off-label drug. In spite of all studies with ivermectin against HIV, Dengue, Influenza and Zika virus be promissor only in-vitro tests were performed, therefore, tests started to be done against SARS-Cov-2. Soon in-vitro tests demonstrated good results and this scientific news started to be announced. Unfortunately, people around the world started to use ivermectin as a prior choice of drug for prevention and/or treatment without medical/ pharmaceutical recommendation. In-vivo tests with ivermectin are not yet finished therefore it already known that this drug in high dosage can cause serious side effects. Even with this danger and no scientific prove, population self- medication it is already notice. The mortality rates only go up proving that COVID-19 is been a difficult disease to control and putts in evidence that ivermectin is not the correct choice for prevention and/or treatment. The damage effects that the wrong use of ivermectin has and in high doses is causing a serious concern between the medical society and scientists.*

***KEYWORDS:** coronavirus, pandemic, SARS-Cov-2, ivermectin, self-medication, side-effects, high dosage.*

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I. INTRODUCTION

Since the emergence of the new SARS-CoV-2 virus pandemic, scientists around the world are looking for alternatives with existing drugs to treat and prevent this infection, such as nitazoxanide, hydroxychloroquine, dexamethasone, azithromycin and ivermectin (1).

Ivermectin is an antiparasitic medication used for the treatment and control of various diseases, including scabies, pediculosis, myiasis and cutaneous larva migrans. This drug has a great safety profile, guaranteeing few adverse effects in its recommended dosage, having as a mechanism of action by the activation of chlorine channels controlled by glutamate, causing hyperpolarization of the plasma membrane and resulting in neuromuscular inhibition of the parasites. Due to the location of the chlorine channels controlled by glutamate in the parasitic pharyngeal muscles, there is also an inhibition of eating behavior (2).

In vitro tests using ivermectin also demonstrates that it occurs an inhibition of import proteins that had the function to recognize signals of nuclear localization of viral proteins which promotes their replication (3). When in vitro ivermectin tests for SARS-CoV-2 RNA were made it reduced the levels of genetic material. However, these levels were with an average maximum inhibitory concentration (IC_{50}) 35 times greater than the maximum plasma concentration (C_{max}) (4).

The incorrect use of medicines is one of the biggest public health problems worldwide and according to the World Health Organization (WHO). The incorrect use of medicines can be very prejudicial as can cause severe side effects moreover it can be notice that half of the medicines are prescribed, dispensed and sold incorrectly (6).

Then causing an increase in adverse reactions to drugs and threatening the population's life (7).Thus, self-medication that a large part of the population is exposing itself to ineffective therapies influenced by incomplete information (8).

During the current pandemic, the rapid transmission of information on possible therapeutic alternatives and the medical culture made the population susceptible to self-medication and the adverse effects of medicines mainly in the use of ivermectin for prevention and/or treatment.

II. IVERMECTIN MECHANISM OF ACTION AND YOUR PROPER USE

Ivermectin at first was developed as veterinary medicine as a treatment to parasitic infection. Its discovery in the late 1970s considered ivermectin as a new class of drug for this type of infection and in short time started to be used in humans with their saved and effectiveness already proven (9).

The original use of ivermectin approved globally and used in many countries is to treat river blindness (onchocerciasis), lymphatic filariasis, strongyloidiasis, entrobiasis, trichuriasisand scabies. This drug is distributed in some countries in mass together with administration campaign as a prevent treatment mainly for onchocerciasis and lymphatic filariasis (10)

It is possible to say that ivermectin became the principal anthelmintic drug as helps to treat Plasmodium falciparum, malaria, therefore it might be point out as the mainly medicine used globally for the control of neglected tropical diseases (11).

Ivermectin is a semi-synthetic drug and the only endectocide medication that has the approval to be used in human. Endectocides drugs presents biological activity against endoparasites, principally the parasitic nematodes; and ectoparasites that acts killing arthropods that feed themselves with blood (12). Your name comes because it is a medical substance derivates from the bacteria Streptomyces avermectinius fermentation (13).

In invertebrates ivermectin firstly agonizesglutamate-gated chloride channels founded in the ematode nerve or muscle cellscausing hyperpolarisationwhich increases the concentration of intracellular chloride been the principal cause of death and flaccid paralysis, nevertheless, this is characteristic that only invertebrates present (14).

Already, in humans, excellent safety profile is explained by the blood–brain barrier in central nervous system which is responsible to limit the drug access (15). As therapeutic option ivermectin has studies showing activity when combating some viruses mainly HIV, Dengue, Influenza and Zika virus. All scientific data previously studied contrasts only some in-vitro activity through inhibition of IMP α/β1-mediated nuclear import of viral proteins (16).

Others studies suggest that the drug ivermectin can help in the treatment of various types of cancer. It is suggested that IVM can induce the immunogenic cancer cell death (ICD) and also helps is robust T cell infiltration. Still is correspondingly proposed that it can works as an allosteric modulator in the immune cells playing an important role in selectively targets immunosuppressive populations (17).

This antivirus activity has been intriguing but has no in-vivo studies that collaborates with this effectiveness. In the human body it is has been studied that the mechanism of ivermectin is due to the response of the host immunomodulation systems attained when neutrophils are activated. This response occurs when some infection or inflammation are detected by the human body immune system, therefore levels of C-reactive protein and interleukin-6 (IL-6) increases (18).

The plasma cytokine IL-6 in the liver automatic induces the hepatic synthesis of C-reactive protein (CRP). The IL-6 plays a significant role in the immune system as is the prior inflammation mediatorand also responsible to stimulates the acute-phase response. Hence to that response the IL-6 and CRP has an important interplay inflammatory marker (19).

Other way of human body system uses ivermectin against certain types of flavivirus such as dengue, Japanese encephalitis and tick-borne encephalitis virus are when gamma amino butyric acid (GABA)-gated-Cl^- channels are stimulated which leads to cell hyperpolarizationand results in the immobilisation of the infesting organism (20).

III. IVERMECTIN AS POSSIBLE PREVENTION AND/OR TREATMENT FOR SARS-COV-2

Due to COVID-19 pandemic and the numerous tentative of combating the virus many drugs started to been coated as possible drug to fight against the illness. As ivermectin was a drug that already had promising results against some in-vitro viruses it started to be studied as a possible treatment or as a form of the disease prevention.

Nonetheless looking for possible and effective antiviral agents combined with the lack of anti-SARS-CoV-2drugs that has a substantial impact on mortality rates that are increasing rapidly potential antiparasitic

drugs such as ivermectin was point out. Everyday becomes critical the rush of an effective treatment against coronavirus to help to decrease the motility (21)

Since April of 2020 there are many published studies that try to corelates empirically the use of ivermectin and coronavirus however none showsa proved in-vivo efficacy. A study made by Carly (22) confirmed that Ivermectin can combat SARS-CoV-2as acts as a potent in-vitro inhibitor, it shows that play an important role in reducing, after 48 hours,99.8% in viral RNA.

The SARS-CoV-2 virus is the causative of this pandemic, it presents the characteristic of been a positive-sense, single-stranded RNA virus beta-coronavirus (23). It can be highlighted that this is a virus that has similarity to the Severe Acute Respiratory Syndrome (SARS)and Middle East Respiratory Syndrome (MERS), booth caused by human coronaviruses (24).

It is already demonstrated that the 2019-nCoV genome encodes non-structural proteins (3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase) that are key enzymes in the viral life cycle. It is also covered by structural proteins (such as spike glycoprotein) and accessory proteins (23).

This virus has the capacity to cause a severe acute respiratory syndrome coronavirus (SARS-CoV) (22). The mainly studies with SARS-CoV proteins reveals a significant protagonist for IMPα/β1 throughout the infection. It links the signal-dependent nucleocytoplasmic shutting of the SARS-CoV nucleocapsid protein which has a big impact during the host cell division (25).

The ivermectin in-vitro studies suggest that this anti- helminthic drug has anti SARS-CoV-2 action when clinically isolated. The hypothesis in that ivermectin is able to control viral replication by RNA dependent RNA polymerase (RdRp) and/or inhibiting IMPα/β1-mediated nuclear import of viral proteins.It indicates that this could be done in a unique dose of ivermectin within 24-48 hoursinside our biological system which is shown in other RNA viruses' studies (1; 4; 26 and 27).

The pharmacological activity of Ivermectin can be explained by the presence of a macrocyclic lactones, produced by the filamentous bacterium *Streptomyces avermitilis*, which shows broad-spectrum antiparasitic effect (28). Ivermectin has no proven of clinical efficacy against coronavirus described yet, studies only previously demonstrate that this substance is able to inhibit the in vitro replication of the virus (29).

As some countries that already try to use ivermectin as treatment and/or prevention continue to have high numbers of mortality of coronavirus disease. This can point out that ivermectin is not a game changer in this fight and demonstrates to be a drug with low efficacy against SARS-COV-2 at any dosage.

IV. IVERMECTIN PHARMACOKINETIC

Ivermectin is prescriptions are based in weight reaching maximus of 200 µg/kg in a single oral dose (30). Therefore, has its approval as a safe treatment based in the drug safety sheet when it is used as it follows: 150 µg/kg once yearly for onchocerciasis, 200 µg/kg single dose for strongyloidiasis, and 150 to 200 µg/kg twice yearly or 300 to 400 µg/kg once yearly in endemic areas for lymphatic filariasis (31).

The greatest experience with human use of ivermectin is in the dose ranges of 150 to 200 µg/kg (32). Pharmacokinetic of a drug is correlated to its absorption, bioavailability, distribution, metabolism, and excretion.Ivermectin presents as pharmacokinetic characteristic rapid oral absorption, high liposolubility. It is a drug which is widely distributed in the body and has a plasma half-life about 12 to 56 hours.The peal reaches plasma levels after between 3to 5 hours after ingested (28).

The concentrations found in the plasma are nearly proportional to the dose acquired. It is also already known that your metabolization happens in the liver and gut by cytochrome P450 system and CYP3A4 (33). Its metabolites are almost exclusively excreted by the bile and the faeces in around 12 days, nevertheless with < 1% is lost unchanged in the urine (34).

Side effects when this drug is used in the safe precautions are uncommon and limited. Reported side effects with greater than 1% occurrence included, elevation in ALT/AST, anorexia, nausea, constipation, diarrhea, vomiting and abdominal distention (35).

It is also reported peripheral edema, tachycardia, increased hemoglobin, dizziness, prolonged prothrombin times, pruritus, anaemia and decreased leukocyte count and eosinophilia (36). Ivermectin is highly lipophilic drug which has a high degree of protein binding (37).

V. THE DANGER OF IVERMECTIN IN HIGH DOSAGE

In doses proven by pharmacokinetic tests, this drug has the possibility of causing nausea, diarrhea, reduced leukocyte count, peripheral edema, tachycardia, dizziness and itching. When exposed to significant doses of ivermectin there is evidence of side effects such as skin lesions, hives, swelling, headache, dizziness, lack of disposition, nausea, vomiting, abdominal pain, diarrhea, convulsions, altered balance and shortness of breath (38).

Doses above the safety limit of ivermectin in humans have been associated with different adverse effects, such as abdominal pain, asthenia, hypotension, edema, tachycardia, dizziness, headache, hyperthermia, insomnia, depression, ataxia, psychosis, confusion, seizures, drowsiness, dizziness, itching, skin rash, hives, diarrhea, nausea, vomiting, eosinophilia, leukopenia, myalgia, blurred vision, mild conjunctivitis, spot opacity, fever and lymphadenopathy (39). The dose of ivermectin is considered safe for therapeutic use in humans ≤ 200 μg / kg, it uses in high dosage for long periods can even cause central and peripheral nervous disorders such as encephalopathy, headache, abnormal gait. More serious damages to the human body as even coma or liver transplant can be needed. It is also possible to experience more rare side effects such as seizures, hypotension and worsening asthma, in addition to being contraindicated for patients with a history of allergy, liver disease and asthma (40).

VI. CONCLUSION

Despite ivermectin be a drug discovered a long time ago for veterinary medicine soon it could be used by humans with effectiveness as an anti-helminthic drug. It did not take a long time to started a diversified study of other types of use due to its capacity of immune modulation. Studies included the use as antiviral drug, as cancer targeting, against HIV, dengue, Influenza and Zika virus and lately has been suggest as a potential drug against SARS-CoV-2. Unfortunately, even with all efforts that are been made by the scientific society only in-vitro tests shows that ivermectin could be a promisor drug in the fight beyond of parasites. The increased numbers of mortality can demonstrate that it is a drug with low efficacy beyond that there is no study that can corroborate with this theory as no in-vivo tests were done. Nevertheless, the population still uses as a prevention/treatment drug and the high dosage of ivermectin is proven to be very danger to the human organism.

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