



REASON FOR USING IVERMECTIN IN COVID-19-A REVIEW

Dr. J. Jayasheela	Assistant Professor, Department of Pharmacology, Sri Lakshmi Narayana Institute Of Medical Sciences.
Dr. G. Somasundaram*	Professor &Hod Department of Pharmacology, Sri Lakshmi Narayana Institute Of Medical Sciences. *Corresponding Author
Dr. DS. Disha sheoran	2 nd year MBBS, Sri Lakshmi Narayana Institute of Medical Sciences.

ABSTRACT COVID-19 is an emerging, rapidly evolving situation worldwide. It is a contagious respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) which spreads through air (droplet infection) when an infected person sneezes or coughs. The SARS CoV-2 is a 50 nm, positive sense single stranded RNA virus and it is diagnosed from a nasopharyngeal swab by real-time Reverse Transcriptase Polymerase Chain Reaction test (RT-PCR). It produces symptoms like fever, fatigue, dry cough, breathing difficulties and loss of smell and taste. It can cause both Upper and Lower Respiratory tract infections. Although there are many clinical trials going on worldwide to test possible therapies there are a few older, FDA approved drugs that can fight COVID-19. One of these drugs is Ivermectin, used to treat parasitic infections. It has in vitro antiviral effects and has shown to inhibit replication in SARS CoV-2. Ivermectin is a safe, FDA approved drug which has high efficacy. Therefore, it could serve as potential treatment for mild to moderate SARS CoV-2 infections.

KEYWORDS : Ivermectin, COVID-19, Antiviral, Ionophore.

INTRODUCTION

The novel coronavirus disease causing organism, SARS CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) has so far caused more than 1.2 million deaths worldwide. This disease can be asymptomatic or symptomatic. Symptoms can be fever, dry cough, myalgia etc. It has become a global threat and has been declared a pandemic. To deal with this pandemic, many potential treatments were proposed which are undergoing clinical trials right now. One of these drugs is Ivermectin.

Ivermectin is an FDA approved, antiparasitic agent. It was discovered in the 1970s and approved in 1981 for animal use^[1]. It was discovered and developed by William C. Campbell and Satoshi mura who received a Nobel Prize in 2015 for this^[2]. It is obtained from *Streptomyces avermitis*^[3]. It is an extremely potent semi synthetic macrocyclic lactone. It belongs to Avermectin (22, 23 Dihydroavermectin B) classification of drugs^[4]. It is on the World Health Organization's list of Essential Medicines due to its broad spectrum of actions^[5]. Ivermectin is a versatile drug which acts through a variety of mechanisms on parasites, mammals, arthropods etc^[2]. It is an approved drug for many conditions like roundworm infestations (river blindness, filariasis, ascariasis, strongyloidiasis), conditions caused by ectoparasites and rosacea. The antiviral properties of Ivermectin were documented progressively from 2012 onwards, towards both RNA and DNA viruses such as HIV-1, Flavivirus, Zika virus, Pseudorabies, Adenovirus^[4]. Apart from being an antiviral and antiparasitic agent, it also shows anticancer properties as it does not allow cancer cell proliferation^[2]. Despite having so many actions and properties, many of its mechanisms are still unknown.^[2] Ivermectin can be used to treat early stage COVID-19 infections as it has the potential to convert a positive RT-PCR to negative.^[6]

Chemical Structure

Ivermectin is assumed to have Ionophore property. Ionophore is a molecule containing a hydrophilic pocket, constituting the binding site for cations and a hydrophobic surface therefore, allowing complex to cross cell membranes.^[1] The Ivermectin formula is made up of two structures, B1a (C₄₈H₇₄O₁₄) and B1b (C₄₇H₇₂O₁₄). [Fig 1]

It is hypothesized that the head and tail of the two molecules reacting with each other can be considered to create a suitable ionophore. This ionophore property causes ionic imbalance which affects the hydro-electrolyte balance due to which the virus is neutralized at an early stage. This Ionophore hypothesis is only concerned with viruses that do not contain a proteic capsid since it resists osmotic pressure. The SARS CoV-2 virus does not have a proteic capsid, it only has a phospholipid envelope which encloses its genetic material.^[1]

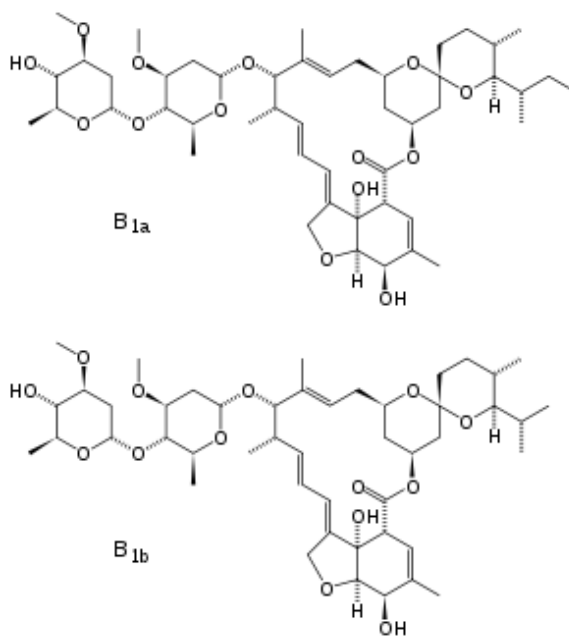


Figure 1-Chemical Structure of Ivermectin

Mechanism Of Action

According to a recent in vitro study, COVID-19 infected Vero/hSLAM cells were exposed to Ivermectin and the results showed that a single dose of Ivermectin caused a ≈ 5000 fold reduction in viral load within 48 hours.^[2] After assessing, it was acknowledged that the drug inhibits Importin (IMP; a Karyopherin-type protein) α /B1 receptor which is responsible for viral replication. The IMP α /B1 receptor acts by transmitting proteins from virus to the nucleus of the host cell. Also, SARS CoV-2 accessory protein ORF6 which is located on the Rough Endoplasmic Reticulum/Golgi Membrane antagonizes the activity of STAT-1 Transcription Factor by sequestering IMP α /B1 on RER/GM. It binds to the Nuclear Import Complex and disrupts its formation by tethering IMP α /B1 to the membrane^[7,8].

It was also found that both Ivermectin and Doxycycline bind with the viral proteins but Ivermectin binds better than Doxycycline and is hence more effective^[9]. Overall, all these reports suggest that Ivermectin's ability to inhibit nuclear transport can be effective against SARS CoV-2.

Pharmacokinetics

Ivermectin is orally well absorbed. It has high lipid solubility therefore; it is widely distributed in the body.^[10] It is metabolized extensively in the liver by CYP3A4.^[11] The plasma half life of Ivermectin is 12-36 hours and it is 93.2% bound to plasma proteins.^[10,12]

Dosage and preparation of ivermectin for sars cov-2 infection according to various studies and trials.

Currently, there are several clinical trials underway to test whether Ivermectin is suitable as treatment for SARS CoV-2 infection, all over the world. According to these studies and clinical trials, dosages of Ivermectin ranging from 200-1200 mcg/kg for 3-7 days were administered and have shown significant improvement in symptoms and also decrease in viral load. Recent in vivo studies have also shown that the combination of Ivermectin and Doxycycline given to patients had better success than the combination of Hydroxychloroquine and Azithromycin, in terms of symptomatic relief, adverse effects and patient compliance.^[9]

Pharmaco-economics And Availability

Ivermectin is a cost effective and easily available drug. The complete course costs <Rs1000.^[8] Ivermectin, if approved for COVID-19 drug therapy, could become the cheapest and safest cure for SARS CoV-2 infections.^[13]

Adverse Drug Reaction, Drug Interactions And Contraindications

Ivermectin is generally well tolerated. Mild side effects may be observed in very few people.^[6] Interactions can be possible with drugs that are metabolized by CYP3A4.^[11] Also, due to its GABA action, alcohol ingestion is not recommended.^[10] It is contraindicated in Children <15 kg, Pregnant females; since safety is not established and lactating mothers; since it is excreted in breast milk.^[14]

CONCLUSION

Ivermectin has antiviral properties which are mediated via targeting the Importin α /B1 receptor. The chemical structure of Ivermectin is assumed to have ionophore property which can neutralize the virus at an early stage. Ivermectin, alone or in combination therapy can prove to be helpful in prevention of further disease progression, if given at early stages and decrease transmission from one person to another. A dosage of 12mg BD for 5-7 days of Ivermectin, alone or in combination with Doxycycline, maybe a safe therapeutic option to treat mild- moderate or severe COVID-19 infections. Ivermectin can also prove useful as prophylaxis for COVID-19 as it can prevent development of infection after exposure to the infectious agent.

REFERENCES

- 1) Emanuele R, 'Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action' *Naunyn-Schmiedeberg's Archives of Pharmacology* 2020; 393:1153–1156
- 2) Heidary F, Gharebaghi R. 'Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen' *The journal of antibiotics*, 2020; 73: 593–602
- 3) Khan S et al. 'Ivermectin, a new candidate therapeutic against SARS-CoV-COVID-19' *Annals of clinical microbiology and antimicrobials* 2020; 23
- 4) Jans D, Wagstaff K. 'The Broad-spectrum host directed agent- Ivermectin as an antiviral for SARS CoV-2?' *Biochem Biophys Res Commun* 2020
- 5) World Health Organization (2019). 'World Health Organization model list of essential medicines: 21st list 2019'. Geneva: *World Health Organization*. Hdl:10665/325771
- 6) Vora A, Arora V.K, Behera D. 'White paper on Ivermectin as a potential therapy for COVID-19. 2020
- 7) Caly L., Druce J.D., Catton M.G., Jans D.A., Wagstaff K.M. 'The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro' *Antiviral Res.* 2020; 178.
- 8) Frieman M, Hount B, Heise M, Bromberg S, Palese P, Baric R., June 2007 'Severe Acute Respiratory Syndrome Coronavirus ORF6 Antagonizes STAT1 Function by Sequestering Nuclear Import Factors on the Rough Endoplasmic Reticulum/Golgi Membrane' *Journal of Virology*. 2007
- 9) Pandey S, Pathak S et al, Sept 2020 'Ivermectin in COVID-19: What do we know?' *Elsevier public health Emergency collection* 2020; 14(6): 1921–1922
- 10) Canga A et al. 'The Pharmacokinetics and Interactions of Ivermectin in Humans—A Mini-review' *Journal of American Association of Pharmaceutical Scientists*. 2008; 10(1): 42–46
- 11) The Pharmacological basis of Therapeutics by Goodman and Gilman; 12th edition; Chapter 51, pg1455
- 12) Crump A, Omura S, Feb 2011 'Ivermectin, Wonderdrug from Japan: The human use perspective' *Proceedings of Japan Academy Series B*. 2011; 87(2):13–28.
- 13) Alok Dixit, Ramakant Yadav, and Amit Vikram Singh 'Ivermectin: Potential Role as Repurposed Drug for COVID-19. *Malays J Med Sci*. 2020 Jul; 27(4): 154–158.
- 14) Patricia Nicolas, MSc, Marta F Maia, PhD, Prof Quique Bassat, et.al 'Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis,' *The lancet*. 2020; 8(1).