The Open Dermatology Journal

Content list available at: https://opendermatologyjournal.com

REVIEW ARTICLE

Intranasal Ivermectin Spray, the Sunscreen to COVID-19

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Abstract:

Throughout the battle against SARS-CoV-2 (COVID-19), various medications have been repurposed in hopes of finding a successful treatment modality to combat the global pandemic. One medication that has recently begun to show promising advancement in clinical trials is the well-known anti-parasitic medication, ivermectin. In this review, we delve into ivermectin and its use as a therapeutic agent against COVID-19. The foundation of how ivermectin treats COVID-19 lies in its ability to inhibit the viral replication process. After assessing the mechanism, pharmacokinetic properties, and current uses of ivermectin, we hypothesized that administering ivermectin intranasally would best capitalize on the inhibitory qualities while avoiding dangerous dosages that would be achieved with oral treatment. Therefore, we propose early use of ivermectin to limit viral replication and severity, as well as prophylactic administration of ivermectin to protect those in high-exposure environments.

Keywords: Ivermectin, COVID-19, Pharmacology, Preventative medicine, Infectious disease, Pharmacokinetics.

Article History	Received: February 14, 2022	Revised: February 28, 2022	Accepted: March 17, 2022

1. INTRODUCTION

Two years and nearly 50 million cases and 808,000 deaths later, SARS-CoV-2 (COVID-19) continues to be a dominating concern for the United States of America [1]. Over the past year, numerous treatment modalities tried to curb the devastating effects of this new virus. This has allowed for innovations in medicine, as well as the opportunity to explore unique treatment modalities that are normally reserved for distinct specialties. In particular, the field of dermatology has contributed many of its tried-and-true medications as possible mechanisms to treat the unwieldy virus. Early in the course of treatment attempts, providers utilized hydroxychloroquine. Dermatologists use this medication for a wide array of conditions based on its anti-inflammatory, immunomodulating, and photoprotective abilities [2]. This drug also offers antimalarial activity, allowing for the bridging of a common dermatologic pharmaceutical into the management of infectious diseases. In relation to the treatment of COVID-19 specifically, hydroxychloroquine combats the virus in three major ways. Hydroxychloroquine interferes with glycosylation of ACE2 and prevents viral fusion with the host cell, blocks the transport of the virus from early endosomes to endolysosomes, and partially prevents the cytokine storm due to its anti-inflammatory properties [2]. In more recent research and literature, the utilization of ivermectin, another well-known dermatological treatment, has come into favor. Ivermectin possesses many important attributes including antiparasitic activity, antiviral effects, and immunomodulation [3]. Recent clinical trials revealed ivermectin to be a promising form of treatment, which provides hope for a more effective and standardized plan of management for COVID-19. Ivermectin may potentially have prophylactic properties that can be used in tandem with widespread immunization campaigns.

1.1. History of Ivermectin

The story of ivermectin begins with its discovery in the mid-1970s thanks to Satoshi Omura, a microbiologist at Tokyo's Kitasako Institute [4]. He sampled soil in search of new antibacterial properties and sent them to Merck Research Labs in New Jersey where his collaborator, William Campbell, tested their effectiveness against various parasitic worms [4]. One culture grew *Streptomyces avermitilis* which demonstrated a potent response against helminthes substances. The biologically active component, avermectin, needed minor chemical modifications to increase its safety and activity. It was later renamed the compound we know today, ivermectin. Ivermectin was initially only used by veterinarians to treat parasitic infections in animals. It wasn't until 1987, when William Campbell urged for a trial of ivermectin as a treatment

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for onchocerciasis, that ivermectin began being prescribed for humans [4]. Since it's initial utilization for onchocerciasis, ivermectin continues to be used in unique ways to treat a variety of conditions and now is known as the mainstay treatment for head lice and scabies.

2. PHARMACOKINETICS OF IVERMECTIN

Ivermectin is currently only approved for use in humans *via* the oral route. However, other routes of administration have been assessed, with intranasal spray becoming popular since the development of COVID-19.

In oral administration, there appears to be an initial rise in ivermectin levels followed by a short-term drop, and then a tendency for the second rise in plasma levels. This cycling of the drug occurs between 6 and, 12 hours after the dose and suggests an enterohepatic method of drug recycling [5]. In those with compromised oral absorption, such as individuals with disseminated strongyloidiasis, a parenteral route *via* subcutaneous administration (not licensed in humans) enabled accumulation of the metabolite and provided a sustained antiparasitic effect [5]. Most recently, the development of intranasal administration demonstrated high levels of ivermectin absorbed in the nasopharynx and lung both immediately, at 6 hours, and at 24-hour time intervals respectively. When compared to the oral administration route, the intranasal modality in humans provided fast, high, and persistent ivermectin concentration at the nasopharynx area in much lower doses. However, lung concentrations were found to be higher in oral administration after 6 hours when compared to intranasal administration [6].

After absorption, ivermectin distributes broadly throughout the body due to its highly lipophilic nature. This pharmacokinetic feature proves particularly beneficial in the respiratory tract where there is a large presence of lipids. Ivermectin also binds strongly to plasma proteins and can reach notable levels in the breast milk of a healthy woman [5].

Although the estimated half-life of ivermectin is approximately 1 day, the antiparasitic effects after one dose can last several months [5]. Metabolization is suggested to be driven by human liver microsomes in the cytochrome P450 system, more specifically, the cytochrome P-4503A4 [5]. This cytochrome P450 isoform breaks down ivermectin into various metabolites *via* hydroxylation and demethylation. These metabolites are then primarily excreted in feces, and a mere 1% are excreted in the urine [5].

These pharmacokinetic properties suggest an avenue for ivermectin to be utilized as a lipophilic nasal spray. It also poses a unique idea for ivermectin to be used as a rapid preventative treatment *via* nasal spray prior to entering a COVID-19 exposed environment.

2.1. Mechanism of Action of Ivermectin

Apart from its antiparasitic activity, ivermectin has several other effects including anti-inflammatory, antibacterial, and anticancer properties. Among these various actions, ivermectin's antiviral properties continue to gain traction for further investigation due to the continued prominence of the COVID-19 global pandemic.

The fundamental mechanism of ivermectin and its treatment of parasitic infections, scabies, and lice, stems from its ability to inhibit glutamate Cl− channels. Glutamate Cl− channels are expressed in the musculature of invertebrates, and consequently inhibition of these channels causes paralysis and eventual organism death [7]. Fortunately, for humans, as vertebrates, these channels are not present in the core musculature and are only accessible after crossing the blood-brain barrier, which ivermectin is unable to do. In addition to paralysis, other mechanisms surrounding the effects of glutamate Cl− channel inhibition have been identified. Specifically, with microfilarial infections such as onchocerciasis, inhibition of glutamate Cl− channels demonstrated a decrease in excretory-secretory vesicle secretion of proteins which resulted in the parasite's inability to evade the host's natural immunologically mediated TH2 response [7]. Thus, demonstrating ivermectin's versatility in treatment with its fundamental mechanism.

The treatment of another skin condition, dermatitis, led to the discovery of the anti-inflammatory mechanisms of ivermectin. Studies performed by Ventre *et al*. and Barańska-Rybak & Kowalska-Olędzka applied topical ivermectin to various inflammatory skin conditions, including allergic dermatitis and perioral dermatitis, and successfully demonstrated sustained decreases in inflammation [8, 9]. The proposed mechanism involves the reduction in the activation of allergen-specific T-cells, and diminished production of inflammatory cytokines. Ivermectin accomplishes this by inhibiting phosphorylation of the mitogen-activated protein kinases (MAPK) p38, extracellular -signal-regulated kinase (ERK) n1/2, and c-Jun N-terminal kinase (JNK). Consequently, this results in inhibition of iNOS, and COX2 gene expression, which suppresses the inflammatory mediator's NO and prostaglandin E2 (PGE2) [9].

In addition to the mechanisms of treating dermatological conditions, researchers have successfully discovered the utilization of ivermectin in anti-bacterial and anti-cancer treatments. Lim *et al*. found that ivermectin, as well as other avermectins, elicits a bactericidal effect that successfully treats most drug-resistant *M. tuberculosis* clinical isolates and *M. tuberculosis* laboratory strains [10]. Ashraf *et al*. provided findings that further support this notion with their demonstration of ivermectin's potent anti-staphylococcal activity [11]. More recently, Juarez *et al*. identified ivermectin's anti-cancer properties that included its ability to modulate multidrug resistance proteins (MDR), the Akt/mTOR and WNT-TCF pathways, the purinergic receptors, the PAK-1 protein, certain cancer-related epigenetic deregulators such as SIN3A and SIN3B, RNA helicase activity, and the ability to down-regulate stemness genes to preferentially target cancer stem-cell like populations [12]. All of these innovations demonstrate ivermectin's untapped potential as a therapeutic modality.

These studies support the future of ivermectin and its antiviral properties, as well as highlight its ability to fight against COVID-19. One known antiviral property of ivermectin is its ability to inhibit nuclear transport mediated by

the importin α/β1 heterodimer, and consequently prevent the translocation of viral proteins necessary for replication [13]. This mechanism directly affect several RNA viruses including Dengue Virus 1-4 (DENV), West Nile Virus (WNV), and Venezuelan Equine Encephalitis Virus (VEEV), and Influenza [14 - 17]. Therefore, with the identification of COVID-19 as an RNA virus, it was inferred a similar mechanism might apply. Errecalde *et al*. recently confirmed this mechanism to be true in COVID-19 with their pig model assessment of intranasal ivermectin [6]. Furthermore, preliminary studies in humans identify an earlier clearance of COVID-19 in those treated with a 5-day course of ivermectin compared to placebo [18]. Thus, supporting the claim of ivermectin's ability to combat COVID-19 successfully, and warranting continued investigation of harnessing ivermectin's importin α/β1 heterodimer antiviral mechanism to combat the virus in other ways.

2.2. Indications for Ivermectin

As we look to integrate ivermectin into the arsenal of treatment methods for COVID-19, it is imperative to learn from current indications of ivermectin use. In dermatology, ivermectin treats scabies with a 200 mcg/kg single oral dose and may be repeated in 14 days if necessary. It can also be prescribed for Gnathostomiasis, a parasitic infection with creeping eruptions, a 200 mcg/kg as a single oral dose. Off-label ivermectin treats head lice with a 200 mcg/kg single oral dose that may require 1-2 additional doses repeated after 7 days. Another off-label use of ivermectin treats blepharitis with a 200 mcg/kg single oral dose followed by a repeat dose once in 7 days. Topical 1% ivermectin cream off-label treats resistant rosacea and resistant dermatitis.

Other indications for ivermectin use include strongyloidiasis of the intestinal tract and river blindness (Onchocerciasis) and off-label uses for filariasis due to *Mansonella Ozzardi* and filariasis due to *Mansonella Streptocerca.* Dosing for strongyloidiasis ranges from 3-200mcg/kg single oral dose and only needs a repeat dose if stool examinations demonstrate a lack of eradication of infection. Dosing for onchocerciasis ranges from 3-150mcg/kg single oral dose that can be repeated in 3-12 months based on clinical symptoms. Dosing for filariasis due to *Mansonella Ozzardi* is 6mg as a single oral dose and for filariasis due to *Mansonella Streptocerca* 150mcg/kg as a single oral dose.

Suggested indications for ivermectin use in the treatment of COVID-19 should originate with its mechanism of impeding viral replication. One possible indication is an immediate one-time oral dose in newly infected individuals to suppress further increases in viral load, which in turn would reduce the duration and severity of infection. Another possible indication for ivermectin utilization in COVID-19 is for individuals suffering from a severe inflammatory response due to the infection. These individuals could benefit from one or more oral doses of ivermectin to not only diminish the viral load but also exploit the anti-inflammatory properties of the drug to lower cytokine levels. Although administration of parenteral ivermectin is not approved yet, intranasal use of ivermectin provides another unique vector that needs to be considered. Errecalde *et al*. found in a 60 kg body weight person, higher ivermectin concentrations in nasopharyngeal tissue were attained with 4 mg intranasally (2 spray doses 12 h apart) than giving 12 mg orally (1 dose 0.2 mg/kg) [6]. They also found two sprays elicited significantly higher concentrations of ivermectin than one spray. This suggests that the intranasal administration of ivermectin in humans can provide faster and higher levels of ivermectin for longer periods when compared to oral administration. As a result, intranasal treatment could potentially provide enhanced protection against COVID-19, a virus that enters through the nasopharynx. COVID-19 patients treated with intranasal ivermectin had a greater rate of two consecutive negative PCR nasopharyngeal swabs (94.7% *vs.* 75.4% P=0.004) and shorter periods for a nasopharyngeal swab to be negative (8.3± 2.8 days versus 12.9 ± 4.3 days; P = 0.0001) compared to COVID-19 patients treated as per the standard Egyptian protocol [19]. They also found shorter durations of fever, cough, dyspnea, and anosmia between the two groups (fever, 5 ± 1.7 days versus 13.6 ± 2.7 days; cough, 5 ± 1.9 days versus 14 ± 2.6; dyspnea, 4.4 ± 2.7 days versus 10.1 ± 3.4; anosmia, 0.5 ± 0.9 versus 1.6 ± 3.2, with P = 0.0001 for all) [19].This evidence supports a new application of ivermectin as a treatment for COVID-19. It is important to note that some studies demonstrate dissimilar and contradictory results. However, the intent of this article is not to evaluate the merit of ivermectin's effectiveness as a treatment in the literature, but rather to highlight a potential new treatment modality for COVID-19. More specifically, we suggest a once-daily administration of intranasal ivermectin for health care workers to ensure protection against COVID-19 in the nasopharyngeal tissue. Errecalde *et al*. also assessed intranasal ivermectin concentrations in the lung, and found that although there is notable distribution in the lung after intranasal administration, concentrations measured at 6h post-treatment were higher in those receiving oral ivermectin [6]. Therefore, we also suggest that an indication of oral ivermectin might be preferred for protection against more severe pulmonary infections, while intranasal administration might be prioritized for rapid preventative purposes and nasal mucosa protection. Nevertheless, parenteral uses of ivermectin and warrant further investigation, especially when considering many patients suffering from COVID-19 are intubated and cannot receive oral ivermectin. Furthermore, the plethora of possible indications of ivermectin as a modality of treatment for COVID-19 identifies the value it can bring to healthcare as a proactive defense against the global pandemic.

2.3. Drug interactions and Safety of Ivermectin

When considering repurposing ivermectin as a treatment for COVID-19, one must assess drug interactions. Of particular interest, drug interactions with other medications currently being used to treat COVID-19. Dexamethasone is one of the drugs widely used to treat COVID-19 due to its anti-inflammatory properties. Areskog *et al*. assessed dexamethasone's interactions with ivermectin in calves and demonstrated significantly lower plasma levels of ivermectin in the group concomitantly treated with dexamethasone compared to the group treated with only ivermectin [20]. They concluded that dexamethasone altered the pharmacokinetics of ivermectin

and impaired its efficacy. Therefore, optimal treatment of COVID-19 with ivermectin likely requires cessation of dexamethasone.

Another medication that currently treats COVID-19 patients is the antiviral agent, remdesivir. Remdesivir had been previously thought to depend on p-glycoprotein for transportation, which posed a concern if used in conjunction with ivermectin. These concerns included inhibitory effects causing increased plasma concentration of either ivermectin or remdesivir, as well as alterations of the pharmacokinetics of remdesivir due to ivermectin's functionality as both a substrate and an inducer of p-glycoprotein [21]. However, alternative preclinical studies indicate that remdesivir is not a substrate of CYP2C8, CYP2D6, or CYP3A4, and is not "significantly" transported by ABCB1/Pgp or the OATP type drug transporters [22]. This conclusion alleviates concerns that ivermectin and remdesivir will have drug-drug interactions. Telbisz *et al*. also addressed concerns of other antivirals inhibiting ivermectin's P-glycoprotein efflux pumps at the blood-brain barrier and potentially causing neurotoxicity [22]. To do this, they identified a recent analysis of ivermectin-related neurotoxic adverse events reported to the WHO Program for International Drug Monitoring that showed only one case out of 1,668 reports in which, concomitant use of antivirals and ivermectin was associated with neurotoxicity [22]. Consequently, one can surmise that ivermectin and remdesivir are safe to utilize together in the treatment of COVID-19. Of note, Telbisz *et al*. brings to light concerns that the ivermectin plasma concentrations required to reach an in vitro antiviral efficacy (about 2–10 μM) are highly toxic, and very high oral doses would be needed for antiviral use. These concerns were previously identified but left with the caveat that animal models show up to a 3-fold higher ivermectin level in pulmonary tissue than in plasma, and leave the potential for targeted increases in concentration to possibly circumvent toxic level doses [23]. Thus, illuminating the recommendation of an ivermectin nasal spray since it can reach these required antiviral concentration levels in the nasopharynx without inducing toxic plasma levels. Further investigation into whether or not the same P-glycoprotein transporters and pharmacokinetics apply to nasal administration of ivermectin is recommended for optimal safety.

Other pertinent interactions to consider with the use of ivermectin to treat COVID-19 include alcohol and fruit juices. The data of the pharmacokinetic effects of these beverages on ivermectin, although minimal, demonstrates significantly elevated plasma concentrations of ivermectin when co-administered with 750ml of beer when compared to water, and a decreased plasma concentrations when co-administered with orange juice when compared to water [24, 25]. The drug interference mechanism is suggested to be related to GABA with regards to the alcohol and the effect of fruit juices on drug transporters. Although not direct medications administered in a hospital, the general population commonly consumes both of these beverages, and practitioners should make a note when assessing the appropriate administration of ivermectin.

Drug resistance and safety are the final aspects to address in the discussion of repurposing ivermectin as a modality to treat COVID-19. Despite 40 years of continued use of ivermectin, and billions of doses administered for various parasitic and dermatological conditions, there is minimal evidence of drug resistance. This is not to say that expanding ivermectin's use as a treatment modality will not potentially lead to the development of drug resistance. However, until the prominent evidence of drug resistance develops, safety precautions against possible effects of ivermectin should be the primary focus. The main safety concern with ivermectin use is neurotoxicity due to high doses causing the activation of GABA-gated chloride channels in the mammalian central nervous systems [23]. In addition, patients with genetic defects in p-glycoprotein channels are at a higher risk of neurotoxicity [22]. Another effect to monitor is prolonged prothrombin times due to the reduced factor II and factor VII levels [5]. Although patients in this study did not suffer any bleeding complications, and mass treatment was deemed unjustified, it is suspected that ivermectin interferes with Vitamin K metabolism and therefore requires monitoring in higher risk populations. The involvement of other organ systems is minimal, but mild to moderate ocular events were noted in patients receiving higher doses of ivermectin [26]. The safety concerns with ivermectin use are not entirely negligent, but low enough to consider it as a safe drug to use in the treatment of COVID-19 and even possibly the drug of choice to treat the new variants due to its non-existent drug resistance profile.

CONCLUSION

The continued dominance of COVID-19 and its variants has allowed for the utilization of many drugs to attempt to combat the infective capability of the SARS virus, as well as to prevent the systemic cytokine storms that occur as the result of infection. Two prominent dermatologic drugs that have contributed to these treatment attempts are hydroxychloroquine, and more recently, ivermectin. Although ivermectin has been found to have a quite significant variability in dosing and drug-drug interactions with other medications, the positive contributions to minimizing inflammation and viral replication are essential to the successful treatment of COVID-19 positive patients. Current clinical trials are exploring the utilization of ivermectin in the oral form, but more importantly, the nasal form. Ivermectin nasal spray would allow for the protection of the nasopharyngeal mucosa from viral attachment and replication, as well as allow for some systemic absorption. Nasal administration also prevents the required high dosing scheme that is experienced with oral administration, which lessens the side effect profile of the medication. The possibility of using ivermectin as a daily preventative modality offers the opportunity for ivermectin to be likened to one of the most prominent preventative measures of all time, sunscreen.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Dr. Craig Burkhart is the EIC of The Open Dermatology Journal.

FUNDING

None.

ACKNOWLEDGEMENTS

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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