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Medical Hypotheses 143 (2020) 109866

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Zinc Iodide in combination with Dimethyl Sulfoxide for treatment of SARS-CoV-2 and other viral infections

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ARTICLE INFO

Keywords:
Zinc Iodide
Dimethyl Sulfoxide
Viral Infection
COVID-19

ABSTRACT

Zinc Iodide and Dimethyl Sulfoxide compositions are proposed as therapeutic agents to treat and prevent chronic and acute viral infections including SARS-CoV-2 infected patients. The therapeutic combinations have a wide range of virucidal effects on DNA and RNA containing viruses. The combinations also exhibit anti-inflammatory, immunomodulating, antifibrotic, antibacterial, antifungal and antioxidative effects. Given the fact that Zinc Iodide has been used as an oral antiseptic agent and DMSO has been already proven as a safe pharmaceutical solvent and therapeutic agent, we hypothesize that the combination of these two agents can be applied as an effective, safe and inexpensive treatment for SARS-CoV-2 and other viral infection. The therapeutic compound can be applied as both etiological and pathogenesis therapy and used as an effective and safe antiseptic (disinfectant) for human and animals as well.

Introduction

COVID-19 pandemic caused by SARS-CoV-2 virus, a type of coronavirus, is posing a worldwide threat with its high infectivity and virulence [1]. Globally, the virus has already caused a costly number of hospitalizations and deaths resulting in many countries taking quarantine actions to limit the spread of infection. The WHO declared the disease the sixth public health emergency, and then declared the coronavirus outbreak a pandemic [2].

There is currently no cure for this disease, meaning there are no approved antiviral drugs or vaccine options available for treatment besides symptomatic managment. Pharmaceutical companies and scientists across the world are dedicating their time and efforts into finding an effective therapy for COVID-19, but this may take far too long. Patients with severe cases are getting supportive care, managing life threatening symptoms of viral pneumonia and acute respiratory distress syndrome (ARDS). Even with medical professionals working day and night, the death toll has been steadily increasing, with more and more countries being infected. There is an urgent need for effective, safe, inexpensive and readily available therapeutic approaches for SARS-CoV-2 and viral infection.

The hypothesis

Given the fact that Zinc Iodide has been used as an oral antiseptic agent and DMSO have already proven as a safe pharmaceutical solvent and therapeutic agent, we hypothesis that the combination of these two agents can be applied as an effective, safe and inexpensive treatment for SARS-CoV-2 and other viral infection.

Evaluation and discussion of hypothesis

Why Zinc?

Zinc as an antiviral agent

Positive-stranded RNA (+RNA) viruses are the single largest group of RNA viruses including many infectious pathogens. They have evolved a variety of replication strategies but share the same mechanism that an RNA-dependent RNA polymerase (RdRp) functions as the core enzyme of their RNA-synthesizing machinery. Given their crucial function in the viral replicative cycle, RdRps are key targets for antiviral research.

Zinc ions and zinc-ionophores, have previously been described as potent inhibitors of various RNA viruses. These compounds have shown efficacy in disrupting the replication pathway, showing antiviral effect. Increasing intracellular Zinc ion and administration of zinc ionophores

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https://doi.org/10.1016/j.mehy.2020.109866
Received 21 March 2020; Received in revised form 4 May 2020; Accepted 21 May 2020

have been shown to impair replication of a wide range of viruses including rhinoviruses [3], influenza [4], coxsackievirus [5], mengovirus [6], picornavirus [6], herpes [7], and even corona viruses [8]. Krenn et al. demonstrated that two metal ion binding compounds (zinc ionophores), pyrithione and hinokitiol causes a rapid import of extracellular zinc into the cytoplasm. Increased intracellular Zn^{2+} concentrations have been shown to efficiently impair replication of RNA viruses by interfering with proteolytic processing of viral polyproteins. A study by Te Velthuis et al. [8] has shown that coronavirus replication can be inhibited by increased Zn^{2+} levels through inhibiting SARS-CoV RdRp activity during the elongation phase of RNA synthesis, without demonstrating detectable cytotoxicity. The mechanism of action is hypothesized that the zinc ions directly affect template binding. However, in other studies, zinc ions seemed to locate into the mitochondria, and the mechanism of inhibition is unclear [6]. Other studies had noted an inhibitory effect of Zn^{2+} on the activity of purified RdRps from rhinoviruses and hepatitis C virus, but not investigated in any detail [9,10].

Zinc as an immune supporter

Zinc is an essential trace element for humans and serves as a cofactor in many transcription factors and enzymes that play critical roles in growth and development, metabolism, immune function, and wound healing [11]. This micronutrient is found throughout the body, in the cells, and is needed as the central ion for over > 300 enzymes to work [12]. Additionally, it plays a huge part in normal immune function. This micronutrient is crucial for maintaining homeostasis of both innate and adaptive immune systems and its deficiency is correlated with compromised immune cell development and functions [13]. One of the major clinical symptoms in zinc deficient patients is depressed immunity, which leads to adverse clinical outcomes including increased infections and frequency of disease [13].

Studies have shown that zinc plays important roles in regulating the activity of immune mediators including cytokine and chemokine activities, contributing to membrane stabilization, and regulating lymphocyte apoptosis [13]. Clinically, the use of zinc has been proven effective against infectious diseases in the human population. After supplementing zinc in the elderly population, there was a significant decrease of infections in 12 months compared to the placebo group [14]. Randomized double blinded placebo-controlled trials have shown that daily zinc supplementation can reduce the incidence and duration of chronic diarrhea by 25–30% [15], reduce rates of acute respiratory infection up to 45% [16], and can even decrease the duration of the common cold [17].

Zinc as an anti-inflammatory and antioxidative modulator

Clinical trials have demonstrated decreased oxidative stress biomarkers and decreased inflammatory cytokines in the elderly with zinc supplementation.[14] In the experimental model of zinc deficiency, the investigators showed that zinc deficiency *per se* increased the generation of IL-1β and its mRNA in human mononuclear cells following LPS stimulation. Zinc supplementation also upregulates A20, a zinc containing transcriptional factor, which inhibits the activation of NF-κB [18] which is the prototypical proinflammatory signaling pathway in cellular responses [19]. Downregulating this pathway leads to a decreased generation of inflammatory cytokines. Controlling oxidative stress and chronic inflammation is important because they are contributing factors for several chronic diseases attributed to aging, such as atherosclerosis and related cardiac disorders, cancer, neurodegeneration, immunologic disorders and the aging process itself.[20]

Why Iodine?

Iodine is an extremely effective broad-spectrum antiseptic with low toxicity [21]. Iodine has very high germicidal activity targeting bacterial exotoxins and enzymes [22], making developing resistance difficult [23]. Fischer et al. [24] demonstrated that after a single dose of oral potassium iodide to a human subject increased serum I^- concentrations and resulted in the increase of I^- in the upper airway secretion. The increased concentration of iodide demonstrated robust activity against two major respiratory viral pathogens, adenovirus, and RSV. This study suggests that iodide compound contributing to airway antiviral defense is through the activation of the lactoperoxidase/I_2/H_2O_2 system. The delivery of I^- to airway mucosa may augment innate antiviral immunity.

Iodine is one of the essential nutrients. There have been many historical reports of immune deficiencies among populations of iodine-deficient people [25]. A lack of iodine is widespread in modern dietary and lifestyle, with high dietary perchlorate, glucosinolate, thiocyanate, calcium nitrate, cobalt and rubidium interfere with iodine metabolism and may increase iodine requirements [26]. Household hygiene products such as chlorine containing beach and fluoride in water and toothpaste further depletes iodine in our body [27]. Leukocyte myeloperoxidase enzyme uses iodine in cell-mediated immunity and iodine is an important component of many immune cells [28]. Additionally, iodides also have many other biologic effects including regulating inflammation, improving immune cell bacteria phagocytosis, and boosting the innate immune functions [26]. Iodine is highly instable and tends to sublimate. The development of unique iodine complexes that provide better availability to the human and animals is very important.

Why Dimethyl Sulfoxide?

Dimethyl sulfoxide (DMSO), discovered in 1963, is an all-natural substance derived from wood pulp. It could penetrate the skin and other membranes without damaging them and could carry components into the biological system. DMSO is commonly used as a solvent to dissolve water-insoluble drugs or test samples in both *in vivo and in vitro* experiments. DMSO can readily induce oxidative stress, raise oxygen levels, and act as an antiviral agent [29,30]. This compound has shown to revise septic conditions associated with viral infection-induced dysregulated immuno-inflammatory responses [31,32]. Mechanistically, DMSO is a potent antioxidant that can regulate transcription factor activation in septic animals, and act as a carrier for other drugs. Several studies have been done on the effect of DMSO infusion for patients with cancer, showing efficacy with limited side effects [33]. Intra-venous infusion of DMSO with sodium bicarbonate brought on symptomatic relief in patients with metastatic prostate cancer [34], and demonstrated better pain control for refractory cancer pain [35].

Zinc Iodine-DMSO therapeutic compound for COVID-19 and viral infections

Morbidity, mortality, infectiveness and spread of infectious diseases are dependent on the host-pathogen relationship. Given the lack of effective and safe antiviral drugs for COVID-19, we should place more attention in supporting host immune defense, cytoprotection, and immunoregulation. We propose using a combination of Zinc Iodide (ZnI_2) with Dimethyl Sulfoxide for the prevention and treatment of viral infection and sepsis. The therapeutic compound combines the two ingredients ZnI2 and DMSO might have strong synergetic efficacy in controlling symptoms, preventing, and treating all types of viral infections.

Conclusion

Viral infections such as SAR-CoV-2 (COVID-19), influenza, RSV, and many others are usually associated with increased oxidative stress leading to oxidative cellular and tissue damages resulting in multi-organ failure. The proposed therapeutic combination of Zinc Iodide-DMSO can be used effectively for the treatment of SARS-CoV-2 infected

patients by suppressing viral replication and virulence, decreasing inflammation and reducing organ damages. Zinc Iodide-DMSO might also be used as a preventive agent for respiratory viral infections including SARS-CoV-2 by boosting the innate immune defense and reducing pathogen infectiveness.

Further clinical trials are needed to validate the effectiveness and develop an optimal therapeutic protocol for possible application of Zinc Iodide-DMSO in patients with viral infections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109866.

References

[1] Jernigan DB. Update: Public Health Response to the Coronavirus Disease 2019 Outbreak—United States, February 24, 2020. MMWR. Morbidity and Mortality Weekly Report. 2020;69.
[2] Luttikhuizen DT, Harmsen MC, Van Luyn MJ. Cellular and molecular dynamics in the foreign body reaction. Tissue Eng 2006;12:1955–70.
[3] Korant B, Kauer J, Butterworth B. Zinc ions inhibit replication of rhinoviruses. Nature 1974;248:588–90.
[4] Oxford J, Perrin D. Inhibition of the particle-associated RNA-dependent RNA polymerase activity of influenza viruses by chelating agents. J Gen Virol 1974;23:59–71.
[5] Lanke K, Krenn B, Melchers W, Seipelt J, Van Kuppeveld F. PDTC inhibits picornavirus polyprotein processing and RNA replication by transporting zinc ions into cells. J Gen Virol 2007;88:1206–17.
[6] Krenn B, Gaudernak E, Holzer B, Lanke K, Van Kuppeveld F, Seipelt J. Antiviral activity of the zinc ionophores pyrithione and hinokitiol against picornavirus infections. J Virol 2009;83:58–64.
[7] Kaushik N, Anang S, Ganti KP, Surjit M. Zinc: a potential antiviral against hepatitis E virus infection? DNA Cell Biol 2018;37:593–9.
[8] Te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6.
[9] Ferrari E, Wright-Minogue J, Fang JW, Baroudy BM, Lau JY, Hong Z. Characterization of soluble hepatitis C virus RNA-dependent RNA polymerase expressed in Escherichia coli. J Virol 1999;73:1649–54.
[10] Hung M, Gibbs CS, Tsiang M. Biochemical characterization of rhinovirus RNA-dependent RNA polymerase. Antiviral Res 2002;56:99–114.
[11] Dardenne M. Zinc and immune function. Eur J Clin Nutr 2002;56:S20–3.
[12] McCall KA, Huang C-c, Fierke CA. Function and mechanism of zinc metalloenzymes. J Nutrition 2000;130:1437S–46S.
[13] Maares M, Haase H. Zinc and immunity: An essential interrelation. Arch Biochem Biophys 2016;611:58–65.
[14] Prasad AS, Beck FW, Bao B, et al. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. A J Clinical Nutrition 2007;85:837–44.
[15] Yazar AS, Güven Ş, Dinleyici EÇ. Effects of zinc or synbiotic on the duration of diarrhea in children with acute infectious diarrhea. Turk J Gastroenterol 2016;27:537–40.
[16] Rerksuppaphol S, Rerksuppaphol L. A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children. Pediatric Reports 2019;11.
[17] Singh M, Das RR. Zinc for the common cold. Cochrane Database Systematic Rev 2013.
[18] Prasad AS. Clinical, immunological, anti-inflammatory and antioxidant roles of zinc. Exp Gerontol 2008;43:370–7.
[19] Lawrence T. The nuclear factor NF-κB pathway in inflammation. Cold Spring Harbor Perspect Biol 2009;1:a001651.
[20] Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. Current Opinion Clinical Nutrition Metabolic Care 2009;12:646–52.
[21] Kelly FC. Iodine in medicine and pharmacy since its discovery— 1811–1961. SAGE Publications; 1961.
[22] Klossner BL, Widmer H-R, Frey F. Nondevelopment of resistance by bacteria during hospital use of povidone-lodine. Dermatology 1997;195:10–3.
[23] König B, Reimer K, Fleischer W, König W. Effects of Betaisodona® on parameters of host defense. Dermatology 1997;195:42–8.
[24] Fischer AJ, Lennemann NJ, Krishnamurthy S, et al. Enhancement of respiratory mucosal antiviral defenses by the oxidation of iodide. Am J Respir Cell Mol Biol 2011;45:874–81.
[25] Black R. Micronutrient deficiency: an underlying cause of morbidity and mortality: SciELO. Public Health 2003.
[26] Bilal MY, Dambaeva S, Kwak-Kim J, Gilman-Sachs A, Beaman KD. A role for iodide and thyroglobulin in modulating the function of human immune cells. Front Immunol 2017;8:1573.
[27] Rogan W, Paulson J, Baum C, et al. Iodine deficiency, pollutant chemicals, and the thyroid: new information on an old problem. Pediatrics 2014;133:1163–6.
[28] Klebanoff SJ, Kettle AJ, Rosen H, Winterbourn CC, Nauseef WM. Myeloperoxidase: a front-line defender against phagocytosed microorganisms. J Leukoc Biol 2013;93:185–98.
[29] Huang S-H, Wu C-H, Chen S-J, Sytwu H-K, Lin G-J. Immunomodulatory effects and potential clinical applications of dimethyl sulfoxide. Immunobiology 2020;151906.
[30] Chang CK, Albarillo MV, Schumer W. Therapeutic effect of dimethyl sulfoxide on ICAM-1 gene expression and activation of NF-κB and AP-1 in septic rats. J Surg Res 2001;95:181–7.
[31] Chang CK, Llanes S, Schumer W. Inhibitory effect of dimethyl sulfoxide on nuclear factor-κB activation and intercellular adhesion molecule 1 gene expression in septic rats. J Surg Res 1999;82:294–9.
[32] Guo Q, Wu Q, Bai D, et al. Potential use of dimethyl sulfoxide in treatment of infections caused by Pseudomonas aeruginosa. Antimicrob Agents Chemother 2016;60:7159–69.
[33] Hoang B, Levine AS, Shaw GD, et al. Dimethyl sulfoxide as an excitatory modulator and its possible role in cancer pain management. Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy) 2010;9:306–12.
[34] Hoang BX, Le BT, Tran HD, et al. Dimethyl sulfoxide–sodium bicarbonate infusion for palliative care and pain relief in patients with metastatic prostate cancer. J Pain Palliative Care Pharmacotherapy 2011;25:350–5.
[35] Hoang BX, Tran DM, Tran HQ, et al. Dimethyl sulfoxide and sodium bicarbonate in the treatment of refractory cancer pain. J Pain Palliative Care Pharmacotherapy 2011;25:19–24.