Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 99 (2020) 307–309

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Case Report

Treatment of SARS-CoV-2 with high dose oral zinc salts: A report on four patients

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ARTICLE INFO

Article history:
Received 19 May 2020
Received in revised form 2 June 2020
Accepted 3 June 2020

Keywords:
COVID-19
Zinc
Treatment
Case Series

ABSTRACT

Coronavirus 2019 (COVID-19) is a pandemic with substantial mortality and no accepted therapy. We report here on four consecutive outpatients with clinical characteristics (CDC case definition) of and/or laboratory-confirmed COVID-19 who were treated with high dose zinc salt oral lozenges. All four patients experienced significant improvement in objective and symptomatic disease measures after one day of high dose therapy suggesting that zinc therapy was playing a role in clinical recovery. A mechanism for zinc's effects is proposed based on previously published studies on SARS- CoV-1, and randomized controlled trials assessing zinc shortening of common cold duration. The limited sample size and study design preclude a definitive statement about the effectiveness of zinc as a treatment for COVID-19 but suggest the variables to be addressed to confirm these initial findings in future trials.

COVID-19 is a pandemic with substantial mortality and no accepted therapy. Ideally, effective therapy would be both readily available and minimally toxic. Coronaviruses are positive sense RNA viruses of which SARS-Coronavirus-2 (SARS-CoV-2) is the most recently identified member and cause of COVID-19. Previous work has shown that increased intracellular Zn2+ concentrations can interfere with proteolytic processing of polyproteins in many RNA viruses (Lanke et al., 2007). In addition, all coronaviruses are unified in requiring a RNA-dependent RNA polymerase (RdRp) that is a core enzyme in their RNA-synthesizing machinery. Increased Zn2+ levels directly inhibit isolated RdRp complexes and purified recombinant RdRps, SARS-CoV-1 virus replication in tissue culture, and replication of other positive sense RNA viruses (te Velthuis et al., 2010).

It is unknown but plausible that Zn2+ could work by the mechanisms above to inhibit SARS- CoV-2 virus replication. Of note, coronaviruses are part of the larger subset of RNA viruses that cause the common cold. A recent meta-analysis of 7 randomized controlled trials (RCT's) showed that zinc lozenges shortened the mean duration of the common cold by 33% (95% CI, 21-45%) (Hemila, 2017). Zinc has also been proposed to be a helpful cofactor in treatment of COVID-19 with hydroxychloroquine (Skalny et al., 2020; Shittu and Afolami, 2020; Derwand and Scholz, 2020 May; Carlucci et al., 2020).

We asked whether zinc salt lozenges could be therapeutic for COVID-19.

Four consecutive outpatients with clinical characteristics (CDC case definition) of and/or laboratory-confirmed COVID-19 were treated by the author with high dose zinc salt oral lozenges, and clinical symptoms followed on an outpatient basis. Patients only received treatments as specified in each case. All patients provided verbal informed consent and were treated on a compassionate basis. The reported efficiency of zinc lozenges for the common cold ranked zinc acetate > zinc gluconate > zinc citrate (Eby, 2004). Patients 1,2 were treated with zinc citrate lozenges (23 mg of elemental zinc); patient 3, zinc citrate/zinc gluconate(23 mg); patient 4, zinc acetate (15 mg). Patients were started on zinc therapy at different times in their disease course, depending on when they were referred for treatment. They were instructed to take lozenges every 2-4 hours, dissolving lozenges on their tongue over 20 to 30 minutes, but not to exceed 200 mg. Patient 2 did not take the higher dose until day 10 of her illness. No side effects from zinc therapy were reported, other than a chalky taste (case 2). Elemental zinc doses up to 216 mg/day have been well tolerated in clinical trials for the common cold (Eby, 2010), without any significant side effects. Short term zinc use at these doses is considered very safe, with occasional gastric distress and metallic taste being the only reported side effects (Prasad et al., 2000).

Case 1

The subject was a 63-year-old man who developed symptoms 5 days after contact with a household member (A) who had direct exposure to a laboratory-confirmed COVID-19 case. At 5 pm on his first day of illness he developed intensely painful muscle aches in the mid- and lower back, headache, shaking chills and a fever to 100.5 °F/38.1 °C. He assumed he had COVID-19, so he took three 23

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https://doi.org/10.1016/j.ijid.2020.06.006

mg zinc citrate lozenges. Over the next 24 hours, he took a total of 9 lozenges (207 mg). His improvement in fever, headaches, and muscle pain began on day 2. On day 3 he became afebrile. His symptoms continued to improve over the next 10 days while taking 184 mg of Zn^{2+} per day.

Case 2

A 57-year-old female partner of case 1. She developed mild symptoms of diarrhea, fatigue, and low grade fever (under 100.5), 7 days after contact with household member A. She took only one or two 23 mg zinc lozenges daily. On day 5 she developed a dry, nonproductive cough, sore throat. chest tightness and with mild dyspnea while walking. On day 10, she suddenly developed severe dry cough, chest pain, intense neck muscle pain, fever, headache, and shortness of breath at rest. Over the next 5 hours, she took a 23 mg lozenge every hour. After a total of 7 zin. lozenges (161 mg), her cough and shortness of breath was much improved. On day 11, she had reduced her zinc dose to two daily and her cough started again. After 3 more lozenges her coughing decreased. She increased her regimen to taking 5 lozenges (115 mg) daily for 10 days, during which time she gradually improved.

Case 3

A 41-year-old female healthcare worker developed body aches, cough and sinus pain on day 1. On day 3 she had a fever to 101.5, severe body aches, worsening cough and tested positive for COVID-19. On day 4 her PaO_2 dropped to 94% on room air, (Figs. 1 and 2). On day 6 she developed shortness of breath (PaO_2- 93/94%) and was started on hydroxychloroquine, 200 mg po bid. On days 7-9 she experienced an overall worsening in her cough, body aches and shortness of breath.

On the evening of day 9, she started zinc, 23 mg, q 4 hours,138 mg daily. On day 10 she felt better; her PaO_2 and fever began improving one day after zinc was initiated(Figs. 1 and 2). She continued zinc q 4 hours and was well by day 19.

Case 4

A 26 year-old female acquired COVID-19 through direct contact with an infected health care worker. During week 1 she had fever, cough and severe body aches. In the second week she developed shortness of breath and severe fatigue. During week 3 her fever abated but she had a significant cough, fatigue and body aches, and slept more than 14 hours daily. After three weeks of symptoms the patient began 15 mg of zinc, q 2 hours, 10 lozenges a day, 150 mg daily for 14 days. One day later the cough and body aches and fatigue began to improve, and two weeks later she felt fully recovered.

We report four consecutive outpatients with clinical characteristics of and /or laboratory-confirmed COVID-19 who were treated with high dose zinc salt lozenges. Two cases lacked laboratory confirmation but had direct exposure to confirmed cases and had characteristic clinical features (CDC case definition). To the best of our knowledge, this is the first report of COVID-19 cases treated with high dose zinc salts. In all 4 cases symptomatic and objective measures of disease began to improve within 24 hours after initiation of zinc lozenges.

Twenty percent of common colds are caused by coronaviruses. Zinc acetate and zinc gluconate appear to be the most effective in RCT's to treat common colds (Eby, 2004; Eby, 2010), and they also have the most theoretical effectiveness as they release the most free Zn^{2+}. The effectiveness also appears to be influenced by the time course of dissolution of the lozenge on the tongue, and exact chemical composition of the lozenge (Eby, 2004; Eby, 2010). In successful zinc clinical trials, total ionic zinc release from lozenges was found was to be highly correlated ($P < 0.001$) with reduction in common cold symptoms (Eby, 2010).

In this uncontrolled case series, initiation of high dose zinc salt lozenges was followed by symptomatic and objective improvement in 4 consecutive patients with clinical signs and symptoms and/or laboratory confirmation of COVID-19. However, the limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment. The day within the disease course that each patient initiated zinc therapy varied, and due to difficulty in obtaining zinc lozenges during the pandemic, three different zinc salts were used. Therefore, controlled clinical trials with single formulation will be required to properly assess the role of zinc therapy in CoVID-

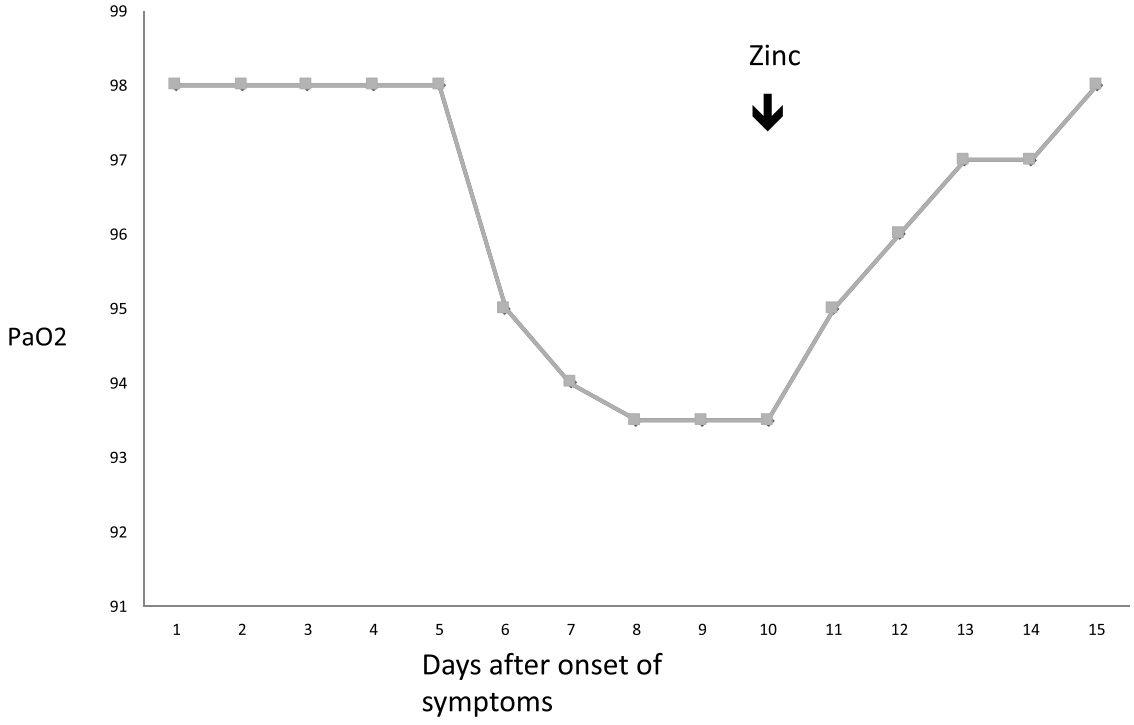

Fig. 1. Case 3 self-monitored her Pa02 by pulse oximetry. The arrow shows the start of high dose zinc lozenges.

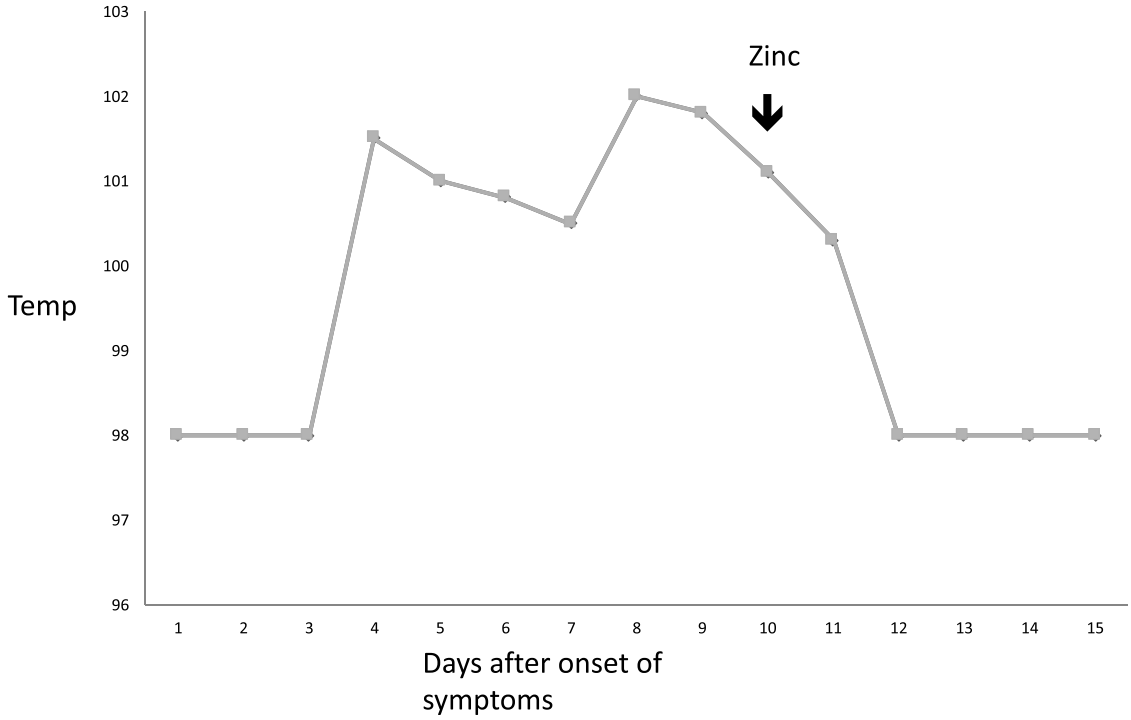

Fig. 2. Case 3 self-monitored daily oral temperature. The arrow shows the start of high dose zinc lozenges.

19. Particular care is needed in the selection of zinc lozenges such that sufficient ionic zinc is released. In addition, frequent dosing (i.e- q 2-4 hours), adequate dosing (i.e. close to 200 mg daily), and slow dissolution on the tongue (20 −30 min) will be essential for meaningful trials (Eby, 2004; Eby, 2010).

Given the low toxicity and ease of administration of zinc lozenges it would seem prudent to begin testing of zinc in a controlled setting as a potential therapy for COVID-19.

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.

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Funding

No funding was provided for this study.

Declaration of interests

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.

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