JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Can Levamisole be used in the treatment of COVID-19 patients presenting with diarrhea?

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, on Jan 7, 2020. Over the following months, the virus rapidly spread throughout the world. Coronavirus Disease 2019 (COVID-19) can involve the gastrointestinal tract, including symptoms like nausea, vomiting and diarrhea and shedding of the SARS-CoV-2 in feces. Angiotensin-converting enzyme 2 (ACE2) protein, which has been proven to be a cell receptor for SARS-CoV-2, is expressed in the glandular cells of gastric, duodenal, and rectal epithelia, supporting the entry of SARS-CoV-2 into the host cells. According to the literature, rates of COVID-19 patients reporting diarrhea were between 7 - 14%. Diarrhea in the course of COVID-19 disease can cause dehydration and hospitalization. Although no antiviral drug was specifically designed for the treatment of diarrhea, several molecules could have beneficial effects by reducing viral replication. In this letter, we discussed the Levamisole, which is an anthelmintic agent with immunomodulatory effects, could be used effectively both for antiviral therapy and especially in COVID-19 patients with diarrhea.

Key words: Levamisole; COVID-19; diarrhea.

J Infect Dev Ctries 2020; 14(8):844-846. doi:10.3855/jidc.13101

(Received 21 May 2020 – Accepted 20 July 2020)

Since the novel coronavirus (SARS-CoV-2) was identified in China at the end of 2019, Coronavirus Disease 2019 (COVID-19) outbreak subsequently spread to become a global pandemic.

Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging. In addition to respiratory symptoms, gastrointestinal symptoms (eg, nausea and diarrhea) have also been reported in onset or during COVID-19. In an analysis, 17.6% of patients with COVID-19 had gastrointestinal symptoms and the prevalence of diarrhea was 13% [1]. In a systematic review and meta-analysis, rates of COVID-19 patients reporting diarrhea were 7.4% [2]. Although real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) of upper respiratory samples (naso/oro- pharyngeal) typically has been used to confirm the clinical diagnosis, the virus can be detected in specimens from other sites, and therefore potentially transmitted in other ways than by respiratory droplets, is unknown [3]. SARS-CoV-2 RNA has also been detected in stool specimens. This raises the problem of viral gastrointestinal infection and fecal-oral transmission route. Xiao *et al*. analyzed stool samples from 73 COVID-19 patients to assess the clinical significance of measuring SARS-CoV-2 RNA in the feces. Diarrhea was found in 26 patients and the fecal test remained positive until 12 days after the disease onset and in 17 patients (23.3%) the stool test was still positive despite negative respiratory tests [4].

Angiotensin-converting enzyme 2 (ACE2) which is known to be a cell receptor for SARS-CoV, has been shown to be a co-receptor for viral entry for SARS-CoV-2 that it has a role in the pathogenesis of COVID-19. ACE2 has a broad expression pattern in the human body with strong expression noted in the gastrointestinal system, heart, and kidney with more recent data identifying expression of ACE2 in type II alveolar cells in the lungs [5]. It has shown that ACE2 protein, which has been proven to be a cell receptor for SARS-CoV-2, is expressed in the glandular cells of gastric, duodenal, and rectal epithelia, supporting the entry of SARS-CoV-2 into the host cells [4]. However, the mechanism of diarrhea formation could not be fully explained.

Diarrhea in the course of COVID-19 disease can cause dehydration and hospitalization. Despite our growing experience about COVID-19, diarrhea is still not well characterized and data on the characteristics (number, consistency) and duration of symptoms are not available. In our practice, we noticed COVID-19 patients either reporting diarrhea presenting with the symptom or during the disease. We test the patients for the general pathogenic culprits and give the treatment according to the results. If we have not detected any active pathogen, we often use loperamide and hydration for the treatment of diarrhea. There is no evidence of the effectiveness of antidiarrheal drugs, but, as with all diarrheal patients, adequate rehydration and potassium monitoring should be performed. China's National Health Commission recommended the use of probiotics for the treatment of patients with severe COVID-19 to maintain intestinal balance and to prevent secondary bacterial infections [6]. Although no antiviral drug was specifically designed for the treatment of diarrhea, several molecules could have beneficial effects by reducing viral replication such as camostat mesylate, lopinavir-ritonavir, remdesivir, chloroquine and hydroxychloroquine [7]. However, there is insufficient real-life data associated with these agents.

We thought of a new agent that could be used effectively both for antiviral therapy and especially in COVID-19 patients with diarrhea: Levamisole.

Levamisole (LMS) is an anthelmintic agent with immunomodulatory effects, successfully used as monotherapy or in addition to treatment in various diseases. Since 1990, combination therapy of LMS and fluorouracil (5-FU) has played an important role in the adjuvant treatment of stage III colon cancer [8]. LMS shows its effects on the immune system through cholinergic activity on T lymphocytes. LMS enhance T-cell responses by stimulating T helper-1 cells with upregulation of interleukin-2, interleukin-12, and interferon-γ (IFN-γ). LMS also potentiate monocyte and macrophage functions including phagocytosis and chemotaxis, and increase neutrophil mobility, adherence, and chemotaxis [9].

Due to its immunomodulatory effects, LMS has been studied in the treatment of various immune-mediated diseases and used in the reatment of parasitic, viral and bacterial infections including leprosy, collagen vascular diseases, inflammatory skin diseases and children with impaired immune a variety of reasons. It has also been used in combination with other drugs for treating a number of dermatologic disorders, e.g. recalcitrant warts, lichen planus, erythema multiforme and aphthous ulcers of the mouth [10].

It is reported that the immunomodulating dose of LMS can stimulate certain antiviral immune markers by increasing concentrations of IFN-γ, nitric oxide (NOx), and total immunoglobulin G (IgG); prevents the gut injury; and reduces fecal consistency and dehydration scores in rotavirus type A (RVA)-positive piglet diarrhea [11].

On April 2, 2020, a double-blinded, parallel, randomized clinical trial has started with a new strategy for the treatment of COVID-19 which consists of local anti-inflammatory and systemic immune stimulant drugs. It hypothesis that LMS as an immunostimulant, can increase lymphocytes and empower the immunity of the body. According to the study description; LMS can also bind to Papaine Like Protease (PL-pro) of the shell of the virus which is necessary for virulence of COVID-19 and also can decrease the level of TNF α and IL-6, and as a chemical adjutant can introduce the virus to the immune system [12]. In addition, with the same thought, two new clinical trials have been initiated with LMS being used in both prophylaxis and therapeutic treatment in COVID-19 patients, and results are expected [13,14].

Consequently, LMS, which has an immunomodulatory effect, should be kept in mind as an agent that can be used in treatment, especially in patients with COVID-19 who have diarrhoea.

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Conflict of interests: No conflict of interests is declared.