

Chlorpheniramine maleate nasal spray in COVID-19 patients: Case Series

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Case Report

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TITLE

Chlorpheniramine maleate nasal spray in COVID-19 patients: Case Series

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ABSTRACT

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) posted a devastating global health crisis for almost a year already. Very little is known about this virus that scientists, physicians and the medical community struggled to find treatments of this novel virus. The vaccine that can potentially combat this virus is still an unknown reality hence, the repurposing of existing medical treatments such as chlorpheniramine maleate (CPM) could be a possible treatment and is being widely utilized. CPM is a safe and effective antihistamine with potent antiviral activity against various strains of influenza A/B, thus highlighting its great

antiviral potential. We tested the virucidal potential of chlorpheniramine maleate (CPM) in a nasal spray composition currently in development as an anti-allergy medication.

The coronavirus disease 2019 (COVID-19) has a droplet mode transmission with a notably high viral load in the upper respiratory tract, especially the nose. Several studies had already postulated that the nose is possibly the primary route of entry of SARS-CoV-2 owing to the high expression of Angiotensin 2 converting enzyme receptors. We hypothesize that utilizing (CPM) nasal spray as an adjunct treatment to COVID-19 positive patients and reduce their clinical course and hasten their time to negativization via RT-PCR via nasopharyngeal swab. We present a series of four symptomatic patients with mild-moderate risks. CPM nasal spray was added to their current supportive treatment. All four patients showed rapid improvement of their clinical symptoms with a shorter than average time to negativization on repeat nasopharyngeal swab via RT-PCR. No safety issues were encountered during the course of treatment. Given its years of excellent safety profile with remarkable clinical results as shown in this case series, we conclude that CPM nasal spray may be a potential adjunct treatment option in patients with mild to moderate COVID-19 symptoms.

Keywords: COVID19, intranasal, chlorpheniramine maleate, therapeutics, nasal spray, SARS-CoV-2

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) in China, which later rapidly escalated and spread to the rest of the world, led the World Health Organization to recognize it as a global pandemic in March 2020. The cases are on the rise again all over the world, citing the second wave posing a devastating global health crisis. [1]

Effective and safe pre- and post-exposure chemo-prophylactic drugs against SARS-CoV-2 do not exist yet. The main intervention strategy is the control of transmission that the majority of countries have already deployed. The expectancy for vaccines against SARS-CoV-2 has urged scientists to find alternative treatment options to effectively combat COVID-19 with clinical trials focused on investigating the possible effect of potential therapeutic agents and repurposing existing treatments to flatten the curve.

Nasopharynx has been recognized as the port of entry of SARS-CoV-2 and is hence the commonest site for testing, with high viral shedding from the nasal cavity before and after symptoms onset. [2] Nasal secretions are swept by rapid nasociliary clearance into the oropharynx and aspirated into the lower respiratory tract. Respiratory illnesses caused by COVID-19 cover a range of severity. [3]

On the basis of our previously published case report, this study is also focused on understanding the potential effectiveness of nasally delivered chlorpheniramine maleate (CPM) nasal spray in suppressing the replication of SARS-CoV-2 in the nose. [4]

In a study conducted in vitro and then in animal models by Xu et al, it was observed that from the FDA approved drug library, two antihistamine agents, carbinoxamine maleate (CAM) and S-(+)-chlorpheniramine maleate (SCM) have potent antiviral activity against divergent influenza A strains and one influenza B strain which subsequently protect these mice from potentially lethal avian H7N9 influenza virus. These first-generation antihistamine drugs that can penetrate the blood brain barrier, have the ability to inhibit influenza virus infection by targeting the early stage of virus life cycle, viral entry into the host cells possibly the endocytosis process. Application of these agents may also attenuate the inflammatory responses and allergic syndromes caused by viral infection. Additionally, they can be used prophylactically in healthy individuals during an influenza epidemic or pandemic for prevention of influenza virus infection hence demonstrating a great potential in treatment and prevention of influenza virus infection. [5]

We aim to utilize existing medication in COVID-19 positive patients particularly CPM nasal spray by reducing the clinical course of the disease and increasing the time to negativization.

This case series aims to show how four COVID-19 positive patients who were enrolled in a study utilizing CPM nasal spray with positive outcomes.

CASE PRESENTATION

Case 1

An elderly white female, with a past medical history of hypertension with unknown treatment and asthma treated with desloratadine and albuterol. The patient is a non-smoker, with no past

surgical history, and has tested positive for COVID-19 on September 28, 2020, three days after the beginning of symptoms. She complained of waking up at night due to the coughing episodes , with fever and diarrhea during the first seven days. She consulted a physician and did a COVID-19 antibody test which resulted as IgM positive for SARS-CoV-2. The same day the patient had a COVID-19 RT PCR that was positive. She was then enrolled in this case series and was given the experimental treatment. The patient was instructed to spray two puffs of CPM nasal spray per nostrils two times a day for seven days. The patient continued to use albuterol as needed, and supportive treatment. The patient was followed for seven days and was assessed for symptoms. On day 1, the patient complained of mild runny, itchy and stuffy nose, foreign body feeling in eyes, fever, chest pain, anosmia, ageusia, fatigue, cough. The patient had mild symptoms most of the time on Symptoms Assessment Score (SAS). She rated generalized pain as nine on the Visual Analogue Score (VAS) and the Numerical Rating Scale (NRS). On day 2, oxygenation was 91%. On day 4, an improvement was noted in her symptoms, particularly of runny, itchy and stuffy nose. On day 6, VAS was reported as three. The patient noted an improvement in the overall symptoms and mild to nonexistent congestion. Although mild anosmia was still present, it was markedly improved compared to day 1. On average, the documented resolution of symptoms was two weeks. The patient remained afebrile after the fourth day of the trial. Improvement of symptoms was noted during the trial duration. Patient was tested via nasopharyngeal swab RT-PCR and she tested negative on day 7. A follow-up was done on day 14 and reported mild to non-symptoms with a return to baseline health.

Case 2

A young adult white woman tested positive for COVID-19 on September 28, 2020. She had a past medical history of chronic rhinitis and sinusitis treated with cetirizine. She is a non-smoker with no past surgical history reported. Three days prior, she started experiencing runny and stuffy nose, itchy and painful eyes, anosmia, chest pain, fatigue and fever at 102.2 Fahrenheit (F). She also reported difficulty in sleep due to nasal symptoms and has been using albuterol as needed. No other symptoms were noted. Upon consultation, the patient was tested for COVID-19 RT-PCR via the nasopharyngeal swab. Following the positive COVID-19 test, the patient was subsequently enrolled in the case series experimental group. On day 1, the patient complained of a stuffy nose, sneezing, congestion, sandy and watery eyes, fever 102.2°F, anosmia, and eye

pain. Rated overall symptoms as mild on SAS and generalized pain as nine on VAS. On day 2 and 3, the patient reported fever 100.4° (F) and mid-effort shortness of breath that was worse on day 3 when saturation was 92%. On Day 4, The patient was afebrile and was able to smell strong substances. On day 7, the patient reported all the symptoms were mild or non-existent. The patient remained afebrile starting on day 4. Repeat nasal swab RT-PCR was negative. She returned to baseline health on Day 14.

Case 3

An elderly Hispanic female tested positive for COVID-19 on October 9, 2020. She had a past medical history of chronic rhinitis and allergies treated with cetirizine. She is a non-smoker with no past surgical history reported. The patient went to the physician on day 3 of symptoms and was tested for COVID-19 via nasal swab RT-PCR of which she tested positive. On day 1, she complained of a runny and stuffy nose, anosmia, tiredness, itchy and painful eyes and mild cough. Normal oxygen saturation was detected. On day 3, she noticed an improvement of symptoms in general but with mild presentation of nasal symptoms and persistent eye pain. On day 6, she reported mild eye pain. On day 7, her sense of smell completely recovered. The patient remained afebrile throughout the trial, and was retested on day 7 with a COVID-19 on day 14.

Case 4

A young adult white female, with a history of chronic rhinitis treated with desloratadine. Patient tested positive for COVID-19 on October 9, 2020. She is a non-smoker, with no past surgical history. She reported fatigue, restless, runny, itchy and stuffy nose, anosmia and eye pain, fatigue, shortness of breath with minimum physical activity, eye pain, runny nose, anosmia, ageusia and diarrhea two days prior. A consultation was pursued followed by a COVID-19 RT-PCR test which was positive. The patient was enrolled in this case series and was given the experimental treatment. On day 1, she complained of a stuffy nose, anosmia, ageusia, tiredness, cough, and congestion. She reported mild symptoms on SAS, rated generalized pain as nine on the VAS and the NRS. She had diarrhea on day 3 and day 4. Improvement of symptoms was

noted on day 7 and a repeat COVID-19 RT-PCR via nasopharyngeal swab was done with negative results. She reported return to baseline health by day 14 on follow up.

DISCUSSION

The above-mentioned cases are showing the potential efficacy of utilizing CPM containing nasal spray as a possible adjunct treatment against COVID-19 and augment the time to negativization on nasal RT-PCR. Although this does not guarantee definite proof of efficacy, this case series provides a framework for initiating a broader scope randomized placebo-controlled clinical trial in the potential efficacy of chlorpheniramine nasal spray in COVID-19 patients.

Patients in this case series reported several risk factors that could potentially increase morbidity and mortality in COVID-19 infected individuals. Patient 1 was an elderly, and had hypertension and asthma, patient 2, 3 and 4 had chronic rhinitis and sinusitis. Although relatively healthy, these patients had more than average risk of morbidity and mortality of COVID-19. [6] All patients had a benign course of disease and all showed improvement of symptoms with the use of chlorpheniramine.

Patients were asked to spray two puffs of CPM nasal spray per nostrils two times per day for seven days. A study conducted on SARS-cov-2 stock to highlight the virucidal potential of CPM showed a reduction of 99.7% in viral load in Vero 76 infected cells. [7]

Mostafa et al in a study on FDA approved drugs that have potent antiviral activity against SARS-CoV-2 concluded that besides antimicrobial drugs like Azithromycin, Niclosamide, and Nitazoxanide, several antihistamines and anti-inflammatory drugs could reduce SARS-CoV-2 replication in vitro. Of these, Chlorpheniramine maleate, a competitive histamine H1 receptor antagonist, exhibited strong virucidal activity against a broad spectrum of influenza viruses.[8]

In addition, CPM is generally safe and effective for use with the main side effect being drowsiness. However, several studies showed that intranasal delivery showed high efficacy with minimal to no side effects. [9] A study also reviewed the systemic bioavailability and overall

safety of a nasal spray solution that delivers doses of 1.12 and 2.24 mg CPM intranasally (0.4% nasal spray) and has found no adverse events. [9]

Lastly, the improvement of symptoms and time to negative PCR test are important to highlight. A study conducted by Vaira, L.A. found that olfactory and gustatory dysfunctions are common symptoms in COVID-19 patients. [9] The average resolution of these symptoms had a mean of 6.89 day. [10] Furthermore, Al-Ani RM et al. also highlighted that patients who have nasal and paranasal problems have longer time in recovery from the smell because of interference with air current from reaching the olfactory epithelium to the roof of the nose. In addition, Speth et. Al stated that patients with diseases such as allergic rhinitis, chronic rhinosinusitis, and asthma, have increased severity in symptoms. [11] In this case series, resolution of symptoms was notable as early as Day 4 with no progression to severity. Furthermore, when patients were tested via nasal RT-PCR on Day 7, all of them tested negative, a 50 % reduction to negativization as opposed to the average 14-day course of the disease. [12]

CONCLUSION

In summary, the four cases reported in this case series, who have minimal to moderate morbidity and mortality risk from COVID-19 showed a significant improvement in symptoms and a 50% reduction in the clinical course with the use of CPM nasal spray as an adjunct to their supportive treatments. This could potentially pave the way in improving clinical outcome and reduce clinical burden in areas heavily affected with COVID-19. While it is relatively safe for general use, we recommend larger randomized, placebo-controlled clinical trial studies be utilized which could further shed light on this potential treatment.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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