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RESEARCH ARTICLE

Intranasal Chlorpheniramine Maleate for the treatment of COVID-19: Translational and Clinical Evidence

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ABSTRACT

Recently, the nasal cavity has been highlighted as an ideal route of administration for interventions as it is the portal of entry of the severe acute respiratory syndrome coronavirus (SARS-CoV-2). The present study aimed to demonstrate the feasibility and efficacy of intranasally administered Chlorpheniramine Maleate (CPM) spray to treat coronavirus disease 2019 (COVID-19).

Methods: The present study used a two-phase, non-clinical to clinical approach. The non-clinical phase evaluated CPM's antiviral activity against SARS-CoV-2 delta (B.1.617.2) strain via a highly differentiated three-dimensional *in vitro* model of normal, human-derived tracheal/bronchial epithelial cells. CPM was tested in duplicate inserts of the tissue models of the human airway. Virus yield reduction assays measured antiviral activity on day six after infection. For the clinical phase, COVID-19 symptomatic (polymerase chain reaction positive) patients were recruited and assigned to a 7-day CPM treatment (n=32) or placebo (PLB; n=13). Close safety monitoring of all patients was conducted before and after administering the drug. The primary outcomes monitored were time to symptom resolution (days), progression to hospitalization, emergency room visits, and symptoms of the severity of the disease using a visual analog scale (VAS) on a scale of 1-10 (no symptoms to worst symptoms).

Results: The virus yielded a reduction in the assay such that the CPM solution log reduction value was 2.69 and Remdesivir 0.12, demonstrating much high antiviral activity of CPM. Results of the clinical phase demonstrate that VAS scores between the groups were evident after using CPM for two days (day 3). The CPM group VAS were significantly lower ($P<0.001$) starting from day three compared with day one. In contrast, there were no statistically significant ($P>0.05$) changes in the PLB during the 7-day treatment window. No subjects in the intervention group were hospitalized, while two in the PLB required hospitalization (15.4%; $X2=5.15$, $P=0.023$). Besides some mild discomfort felt by subjects immediately after applying the spray, the participants reported neither adverse reactions nor side effects.

Conclusion: If taken together, the results of the present two-phase study point towards the conclusion that CPM is an antiviral agent that can be administered intranasally to treat COVID-19 effectively.

Keywords: Intranasal Spray, Chlorpheniramine Maleate, COVID-19, SARS-COV-2

1. Introduction

Despite vaccination campaigns and better treatments, coronavirus disease 2019 (COVID-19) remains a significant public health crisis worldwide. COVID-19 is a biphasic clinical syndrome characterized by an initial viremic phase (1-7 days) followed by a hypersensitivity-like hyperinflammatory state (> day 8) mainly driven by mast cell histamine degranulation, and ultimately a cytokine storm [1-4]. One of the primary treatment challenges is to apply effective therapies that can address both phases, particularly in the early stages of the disease, as the viral load is higher in the first week, with the highest peak occurring between days 4-6 after the onset of symptoms. Recently, the nasal cavity has been highlighted as an ideal route of administration for interventions as it is the portal of entry of the severe acute respiratory syndrome coronavirus (SARS-COV-2) [5-8]. Since the nasopharynx has a high expression of angiotensin-converting enzyme-2 receptors (ACE2) (the portal of infection), with the highest viral load, it is plausible to suggest that attacking the virus with intranasal agents having antiviral anti-inflammatory properties could prevent clinical worsening and pulmonary damage associated with the disease.

Recently, various groups (including ours) have identified a drug with promising therapeutic potential against COVID-19, chlorpheniramine maleate (CPM) [9-11]. CPM displays broad-spectrum antiviral properties against COVID-19, influenza, and ebolaviruses, a property that seems to be associated with the drug's ability to block viral adsorption (the viral entry into the host cells) during the early stages of the virus life cycle [11-13]. Recently, early clinical data have shown CPM to be a safe and effective treatment against COVID-19 [14, 15]. Previously, intranasal CPM's safety tolerability and bioavailability were documented (Kirkegaard et al., 1983; Van Toor et al., 2001). A clinical trial showed intranasal CPM's high efficacy and safety for treating allergic rhinitis [16]. However, there is some scarcity of data demonstrating the feasibility and efficacy of CPM to neutralize SARS-COV-2 in respiratory epithelial cells, a more translationally appropriate model, as well as evidence to support its use clinically.

Accordingly, the present report aimed to examine the feasibility and efficacy of an intranasal CPM formulation for the treatment of COVID-19 infection. To this end, a two-phase study approach was utilized. The first phase (non-clinical / translational) aimed to validate the antiviral efficacy of CPM using an *in vitro* model of respiratory epithelial cells. While on the second phase (clinical), a proof-of-concept pilot clinical was conducted to test the efficacy and tolerability of intranasally administered CPM for the treatment of COVID-19. We hypothesized an intranasally administered CPM formulation would decrease the symptoms associated with COVID-19.

2. Materials and Methods

2.1 Phase 1 (Non-Clinical) - Antiviral Efficacy of CPM Against SARS-COV-2 Infection in Human-Derived Tracheal/Bronchial Epithelial Cells

2.1.1 Test Compounds

The compounds received as solids were dissolved in the MatTek culture medium (AIR-100-MM) and further diluted to the test dilutions. CPM (1%) was diluted to the test dilutions in the culture medium with Remdesivir (MedChemExpress, cat# HY-104077) were tested as the positive control.

2.1.2 Cell Culture

The EpiAirway™ Model consists of normal, human-derived tracheal/bronchial epithelial (TBE) cells which have been cultured to form a multi layered, highly differentiated model which closely resembles the epithelial tissue of the respiratory tract. The cell cultures were made to order by MatTek Life Sciences (https://www.mattek.com) (Ashland, MA) and arrived in kits with either 12- or 24-well inserts each. The TBE cells were grown on 6mm mesh disks in transwell inserts. During transportation the tissues were stabilized on a sheet of agarose, which was removed upon receipt. One insert was estimated to consist of approximately 1.2 x 106 cells. Kits of cell inserts (EpiAirwayTM AIR-100, AIR-112) originated from a single, healthy, non-smoker donor #9831.

Upon arrival, the cell transwell inserts were immediately transferred to individual wells of a 6-well plate according to manufacturer's instructions, and 1 mL of MatTek's proprietary culture medium (AIR-100- MM) was added to the basolateral side. In contrast, the apical side was exposed to a humidified 5% CO2 environment. The TBE cells were cultured at 37°C for a minimum of one day before the start of the experiment. After the equilibration period, the mucin layer, secreted from the apical

side of the cells, was removed by washing with 400 µL pre-warmed 30 mM HEPES buffered saline solution 3X. The culture medium was replenished to the basal side following the wash steps. The tissues were then allowed to rest in a 37°C and 5% CO2 environment for a minimum of 1 hour prior to the assay.

2.1.3 Experimental design

Each compound treatment (140 µ) is applied to the apical side, and culture medium only is applied to the basal side (1 mL), for a 2 h incubation. Virus is then added (140 µL) to the apical side for a 2 h infection period. As a virus control, some of the cells were treated with placebo (cell culture medium only). Following the infection, the apical medium was removed, wells are washed once with media, and fresh test compound is added to the apical side. The basal side was replaced with fresh medium. The cells were maintained at the air-liquid interface. On day 6 (SARS-CoV-2) post-infection, the medium was removed and discarded from the basal side. Virus released into the apical compartment of the TBE cells was harvested by the addition of 400 µL of culture medium that was pre-warmed at 37°C. Triplicate wells were used for virus controls.

2.1.4 Determination of virus titers from each treated cell culture

Samples containing virus were diluted in 10-fold incrementsin infection medium and 200 µL of each dilution was transferred into respective wells of a 96- well microtiter plate. Four microwells were used for each dilution to determine 50% viral endpoints. After 3-7 days of incubation, each well was scored positive for virus if any cytopathic effect (CPE) was observed as compared with the uninfected control. The virus dose that was able to infect 50% of the cell cultures (CCID50 per 0.2 mL) was calculated by the Reed-Muench method [17].

2.2- Phase-2 (Clinical) Pilot to demonstrate safety and efficacy of intranasally administered CPM: Proof of Concept

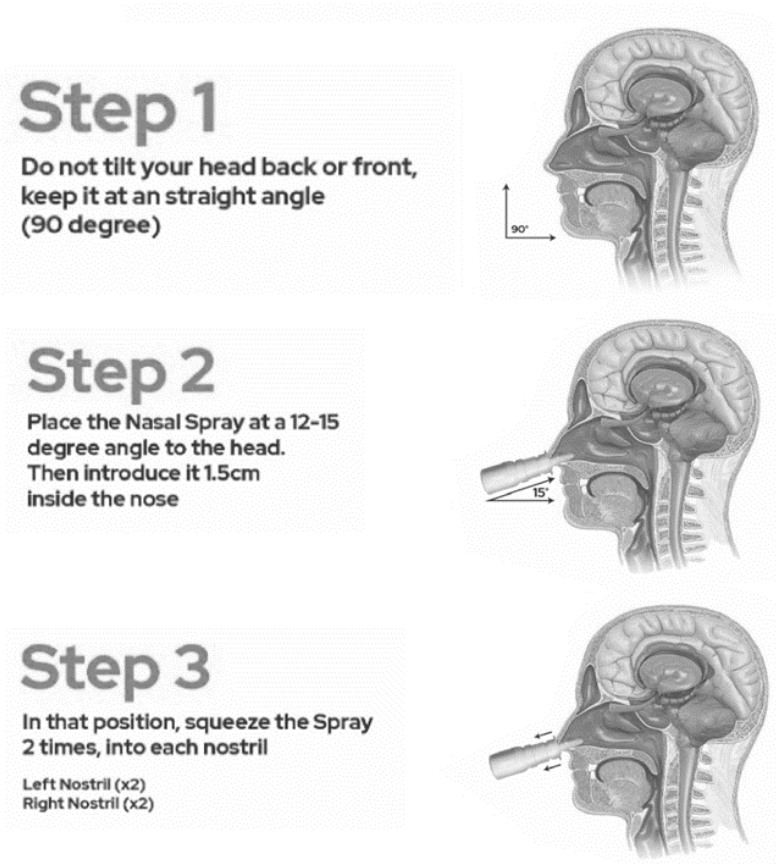
2.2.1 Trial Design

In a randomized, double-blind, placebo-controlled fashion, a 7-day pilot (proof of concept) was conducted. Randomization and matching were performed by someone not associated with the care or assessment of the patients using a computer-generated random number table (with a 20% random element) using an allocation ratio of 1:1. Monitoring during the trial for each subject was conducted during and after administration of the treatment to assess any adverse reaction including drowsiness, dry mouth, nose and throat, nausea, vomiting, loss of appetite, constipation, headache, increased chest congestion, and nasal irritation.

2.2.2 Subjects

After proceeding with informed consent, a total of 45 patients were assigned to the CPM (n=32) spray or nasal saline placebo (PLB; n=13). Both treatments were administered in two spray doses in each nostril (~100 µL of the solution per nostril three times a day 0.4% CPM solution). The total daily dose from the CPM was 4.8 mg a day, corresponding to prominently a quoter of the daily maximum oral recommended amount (24 mg). Subjects were instructed to use the atomizer following a 12-15° angle to optimize the medication distribution in the nasopharynx (Figure 1) [18, 19]. The present study was approved following the statutes of the Declaration of Helsinki by the Institutional Ethics Committee at the Department of Education and Research, Vargas Hospital in Caracas, Venezuela.

Figure 1. Patients were instructed to use the atomizer to optimize drug delivery in the nasopharynx, adapted from Basu 2021 [18].



The inclusion criteria comprised of adults aged 18 to 65 years of either sex, positive polymerase chain reaction positive (PCR) confirmed SARS-COV-2 infection by nasopharyngeal swab, mild symptoms: minimal or asymptomatic respiratory symptoms in addition to a positive test, and light symptoms including respiratory symptoms such as cough, fever, no oxygen desaturation (Room air SpO2 <92%). The exclusion criteria included: patients with more than seven days of symptoms and more than five days positive for a nasopharyngeal PCR test, hypoxemia (Room air SpO2 <92% plus severe polypnea (not included), hospitalized patients (usually seriously ill), subjects with known hypersensitivity to Chlorpheniramine and any of the inactive ingredients, subjects receiving therapy with Monoamine oxidase inhibitors (MAOIs; rasagline, selegiline, isocarbonboxasid, phenelzine, tranylcypromine.), and issues with narrow-angle glaucoma, urinary retention, severe hypertension or severe coronary heart disease.

2.2.3 Outcomes

The expected outcomes are: Nasopharynx negative for SARS-COV-2 from initial swab and confirmed by PCR test on day 14; Time to symptom resolution (days); Progression to hospitalization; Emergency room visits; Symptoms of the severity of the disease, measurements to be used: At 10 cm from the visual analogue scale (VAS), the tap is recommended to be handmade with a mark on the scale of 1-10 to represent the "no symptoms" and the "worsening of symptoms."

2.2.4 Statistical analyses

Statistical analyses were performed using SPSS Version 26.0 (IBM Corp., Armonk, NY, USA) to calculate descriptive and inferential statistics. Independent samples t-test and Chi-Square (X^2) tests were used to compare the groups (CPM vs. PLB) in continuous variables and categorical variables, respectively. The effects of CPM and PLB were evaluated using a 2 x 7 repeated-measures ANOVA (analysis of variance) with Bonferroni alfa

adjustment for time effects from day 1: treatment (CPM vs. PLB) x time (day 1 vs. day 2 vs. day 3 vs. day 4 vs. day 5 vs. day 6 vs. day 7).

3. Results

3.1 Phase 1: Non-clinical Results

The results of the viral inactivation assays demonstrate a high efficacy of CPM against SARS-CoV-2 with minimal or no toxicity reported as summarized in Table 1

Table 1. Antiviral efficacy of Chlorpheniramine Maleate against SARS-CoV-2 strain USA/PHC658/2021 (B.1.617.2;delta).

Test Compounds	Concentration	[a]Log_{10} $CCID_{50}$ virus per 0.2 mL	[b]LRV
Chlorpheniramine Maleate	1% 1%	2.30 2.50	2.69
Remdesivir	5 µM 0.5 µM 0.05 µM	0.67 2.50 5.00	[c]EC90 0.12 SI >42
Virus Control SARS-CoV-2 USA/PHC658 /2021 (B.1.617.2; delta)	MOI 0.02	5.30 5.30 4.67	Avg. 5.09

Each well was scored positive for virus if any cytopathic effect was observed as compared to the uninfected control.

aTiter results from the virus yield reduction assay.

bLRV (log reduction value) is the average virus reduction compared to the average virus control.

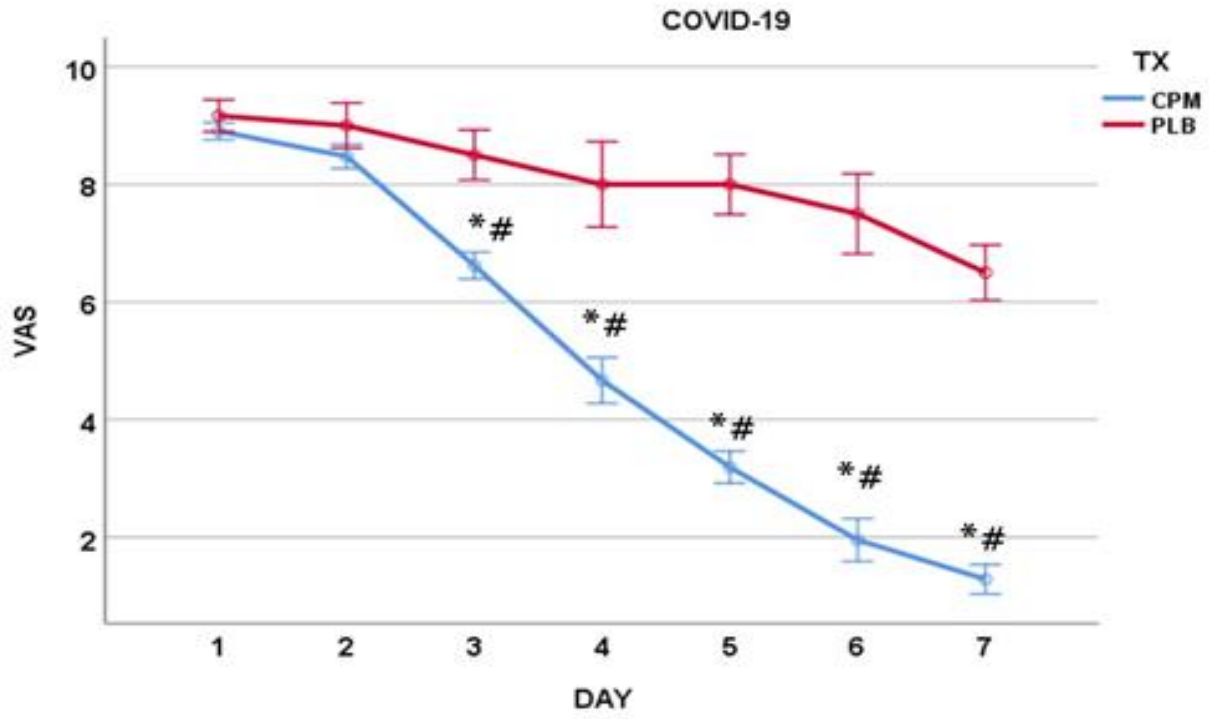
cEC90 = 90% effective concentration (reduce virus yield by 1 on log10 scale) as determined by regression analysis.

3.2 Phase 2: Clinical Results

None of the patients were vaccinated for SARS-CoV-2, while there was no difference in subjects characteristics between the groups for weight (M ± SEM; 72.1 ± 2.5kg), age (44.5 ± 12.2 years), and a number of comorbidities (1.1 ± 0.2). ANOVA with repeated measures revealed a significant treatment-by-time interaction such that the CPM group had a significant decrease ($P < 0.05$) in VAS (Δ-7.2 ± 2.0) compared to PLB after 7 days (end of treatment (Figure 2). The difference in VAS scores between the groups was evident after using CPM 2 days (day 3). The CPM group VAS were significantly lower ($P < 0.001$) starting from day 3 compared with day 1 whereas there were no statistically significant ($P > 0.05$) changes in the PLB during the 7-day treatment window.

None of the subjects in the intervention group were hospitalized, while two patients in the PLB (2/13 15.4%; X2 = 5.15, P=0.023) required hospitalization. Besides some mild discomfort felt by subjects immediately after applying the spray, the participants reported neither adverse reactions nor side effects.

Figure 2: Changes in Visual Analogue Scale (for covid symptoms) in response to Chlorpheniramine Maleate and Placebo



Note: Data are Mean ± 95%CI. # P 0.01 vs Placebo. * P<0.001 vs. Day 1.
CPM, Chlorpheniramine Maleate; PLB placebo.

4. Discussion

The present two-phase study sought to examine the feasibility and efficacy of a CPM intranasal fromulation for the treatment of COVID-19. Results demonstrate *in vitro* efficacy of the CPM against SARS-CoV-2 (non-clinical), which translated into faster clinical recovery and potentially fewer hospitalizations when used early in the course of COVID-19, as observed in the clinical phase of the study. Intranasally administered CPM could be an additional effective therapeutic option for the early treatment of COVID-19.

Previously, our group demonstrated the efficacy of CPM intranasal solution (0.4%) as an antiviral agent against SARS-CoV-2 *in vitro*. Moreover, we tested CPM's virucidal activity using viral stock of SARS-CoV-2, USA-WA1/2020 strain in Vero 76 infected cells. After 25 minutes of contact time, the CPM nasal spray reduced the levels of the virus from 4.2 to 1.7 log10 CCID50 per 0.1 mL, a statistically significant 2.5 log reduction value or 99.7% reduction in the viral load [10]. CPM has displayed strong antiviral activity against SARS-CoV-2 in two independent studies [10,11]. It seems that CPM inhibits SARS-CoV-2 by blocking viral adsorption (the viral entry into the host cells) [12, 20], apparently by interfering with SARS-CoV-2 spike protein interactions via ACE2 and sigma-1 receptor binding blockade [21]. As expected, CPM demonstrated antiviral activity (Log Reduction Value = 2.69) against the prevalent variant (Delta) in the non-clinical phase of the present study. Interestingly, the approach of the present study took advantage of a more translationally adequate model via human-derived TBE cells that closely resemble the respiratory tract's epithelial tissue in both structure and function. It can be argued that a three-dimensional lung tissue TBE model may be more high throughput and accessible route for drug validation studies for newly emerged viral pathogens than small animal models, as suggested by Zarkoob et al. 2021 [22]. It is worth mentioning that the nasal cavity, the nasopharynx, and the upper respiratory tracts are the portals of entry of SARS-CoV-2. Hence, intranasal therapies such as the CPM could rapidly inactivate viral particles before spreading to the lungs avoiding pulmonary

complications associated with the poor clinical course of COVID-19 [5,7,8].

Early reports to test the feasibility of using intranasally administered CPM to inhibit histamine-induced (provocation test) rhinitis symptoms were documented by Kirkegaard et al. 1983 [23]. In addition, Kirkegaard et al. demonstrated a significant topical (local) effect induced by intranasal CPM, which inhibited the histamine-induced tickling sneezing and discharged symptoms typically experienced by COVID-19 patients [24-26]. Van Toor et al. 2001 [27] investigated the bioavailability of single doses of CPM when administered intranasally (0.4%). Interestingly, Van Toor et al. emphasized that the lower doses used in the nasal cavity were associated with reducing systemic exposure without affecting efficacy. Still, the effective concentration was similar to those administered orally. Our group has recently followed the same approach by exploring the safety and efficacy of a 0.4% CPM intranasal solution to treat allergic rhinitis. The intranasal solution of CPM effectively decreased symptoms associated with allergic rhinitis, while patients did not report drowsiness in the treatment group without affecting the efficacy of the intervention [16]. In the present study, a higher daily dose of CPM was administered owing to the acute nature of COVID-19 such that outpatients in the CPM group reported a fast clinical recovery and avoided hospitalizations. It is important to note that COVID-19 may induce an important release of histamine with the associated hyperinflammatory response, which is not atypical for many respiratory viruses, and hence CPM may play a role in reducing such responses to prevent COVID-19 complications [28-30].

Mechanistically, there are potentially some pathways associated with the faster recovery of patients in the CPM group. First, CPM antiviral actions rapidly neutralized the viral load counts, leading to a decrease in viral titers and infection rate. Although controversy exists on the role of viral and infection in COVID-19, a reduction of the viral shedding could be associated with the results observed in the clinical phase of this study [31]. Viral load was not measured, which is a limitation of the clinical portion of the study. However, taste 2 bitter taste receptors (T2R) have been recently identified as essential mediators of COVID-19 patients outcomes. Taha et al. demonstrated that using a therapeutic protocol that stimulates (agonists) the T2R had a better clinical prognosis than those not using such an approach [32]. Interestingly CPM has been identified as a potent stimulator of T2R, which can improve innate immune function, increase nitric oxide secretion, stimulate viral elimination, and prevent mast cell degranulation and essential aspect of the hypersensitivity like phase of COVID-19 [33,34]

We are aware that this two-phase study has some limitations. Despite current standards, we only tested for the time-relevant variant in the non-clinical studies and did not test for other variants of concern. However, the three-dimensional model of TBA cells seems to be a better translational model than the typically used (Vero cells). The associated limitations come with a relatively small clinical sample size as some of the findings cannot be generalized to other populations. Interestingly, none of the patients were vaccinated against SARS-CoV-2, which is considered a high-risk population. This study might be replicated in double-blind clinical trials among large and diverse groups and possibly evaluate several COVID-19 variants, yielding the most clinically relevant data.

5. Conclusion

This two-phase study has established the CPM's non-clinical in vitro antiviral activity against COVID-19 via a more translationally sound model of TBE cells. Results demonstrated the feasibility and efficacy of intranasally administered CPM against COVID-19 among human subjects. This is significant because CPM is a cost-effective, already established, and safe drug with proven anti-allergy and anitflamatory efficacy. Thus, intranasally administered CPM could be included as a safe and effective option in addressing COVID-19 infection to prevent hospitalizations and associated complications.

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