Clinical and Experimental Health Sciences

Nasal Sprays Containing Mometasone Furoate Can Be Used Prophylactically in COVID-19 Infection and Related Smell Disorders

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ABSTRACT

Objective: We aimed to emphasize the possible beneficial effects of intranasal sprays containing mometasone furoate, especially for preventive treatment or supportive treatment in patients with olfactory disorders due to damage to the olfactory area, or for regular use in healthcare workers with a high risk of close contact.

Methods: Preventive and therapeutic scientific studies are continuing around the world for viral spread and viral damage associated with the Coronavirus disease 2019 (COVID-19) pandemic. We investigated the attachment of the COVID-19 virus in the nose and entry into the body with the crystal structure of the spike and Angiotensin-Converting Enzyme 2 (ACE-2) proteins, a molecular docking study. This scientific study is the first in-silico study to investigate the possible antiviral effects of Mometasone furoate molecules on spike protein and to show the antiviral effect of mometasone furoate on COVID-19.

Results: We think that nasal sprays containing mometasone furoate can be used prophylactically in patients with COVID-19 infection due to its antiviral effect, and it may be beneficial to use sprays containing mometasone furoate before the symptoms of upper respiratory tract infection begin in patients.

Conclusions: The role of these molecules in the treatment of acute smell disorders associated with COVID-19 infection and their antiviral effects on coronavirus should be investigated by conducting extensive scientific studies on the subject.

Keywords: Anosmia, Coronavirus, Mometasone furoate, Prevention, Olfactory disorders

1. INTRODUCTION

Mometasone furoate (9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,2-dione) is an organic heterocyclic corticosteroid containing functional groups such as hydroxyl, furoate and chlorine. It is used in medicine to treat skin problems such as atopic dermatitis, psoriasis, and allergies. Mometasone furoate is used intranasally in the treatment of patients with allergic rhinitis, and intranasal use has reduced side effects compared to oral use (1). As for pharmacokinetics, no dangerous situation of Mometasone furoate has been reported like other corticosteroids in the literature (2,3). Furoate functional group decreases the possibility of systemic side effects by increasing the destruction of the particles participating in the systemic circulation in the liver. The systemic absorption of mometasone furoate nasal spray has been proven to be minimal and bioavailability <1%. Thus, given that Mometasone furoate has a relatively higher binding affinity to the glucocorticoid receptor than fluticasone furoate and corticosteroids such as Fluticasone propionate, Budesonide and Triamcinolone acetonide, the amount of unbound Mometasone furoate nasal spray in the body has never been detected in plasma (3,4).

Since the COVID-19 pandemic began, many researchers have focused on research into the symptoms of this viral infection, preventing the spread of infection and possible tissue damage associated with coronavirus infection. There are several scientific studies discussing the effects of using nasal sprays containing mometasone furoate on patients with COVID-19 infection and loss of smell, and the possible effects on recovery of olfactory loss (5,6). However, in our current literature review, we did not find any scientific study conducted on humans that directly investigated the antiviral

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effect of mometasone furoate on coronavirus. According to the results of our virtual docking study, we think that the early use or prophylactic use of nasal sprays containing mometasone furoate, especially in patients with COVID-19 infection, can reduce the existing sensory damage with its antiviral effect.

This study aims to investigate the possible antiviral effects of mometasone furoate on the COVID-19 virus, and to use it as a nasal spray in people infected with the COVID-19 virus, besides its known anti-inflammatory effects; It is emphasized that its possible antiviral effects may also be effective in reducing damage to the olfactory mucosa.

The use of mometasone furoate as a nasal spray as soon as the diagnosis is made, without waiting for any smell disorders to occur, can also benefit from its local anti-inflammatory effects as well as its antiviral effect, and reduce the bilateral obstructive inflammation of olfactory clefts. Again, we think that it may be appropriate to use nasal spray forms prophylactically, especially for health personnel who are in close contact with coronavirus, and quarantined individuals with COVID-19 contact.

2. METHODS

In a molecular docking investigation, Autodock Vina v.1.2.0 software (7,8) was used to assess the binding affinity for Mometasone furoate. The spike and ACE-2 proteins' X-ray crystal structures (9) were determined using the X-ray diffraction technique with a resolution factor of 2.45, which was obtained from the RCSB Protein Data Bank (https://www.rcsb.org/). The molecular structure of Mometasone furoate (Deposition Number: 299143) was obtained from the CCDC (https://www.ccdc.cam.ac.uk/) and was used for molecular docking (10). Water molecules were removed from the protein structures and polar hydrogens and Kollman charges were added. Using Discovery Studio Visualizer 2021 v21.1.0.20298 (Dassault Systèmes; San Diego, CA, USA: 2021), the amino acids in the catalytic domain of receptors were determined (11). As a docking engine, the Lamarckian Genetic Algorithm was used, with all docking settings set to default. From ten conformations obtained by docking calculations, the inhibitors with the lowest energy docking score were chosen. For the depiction of 3D figures, UCSF Chimera 1.16 (University of California, CA, USA: 2021) was used (12).

3. RESULTS

Mometasone furoate was tested on spike protein, one of the most critical proteins of the coronavirus, using the *in-silico* method. Two calculations were performed, namely the spike protein and its contact with the ACE-2 receptor, and the results were compared (Figure 1).

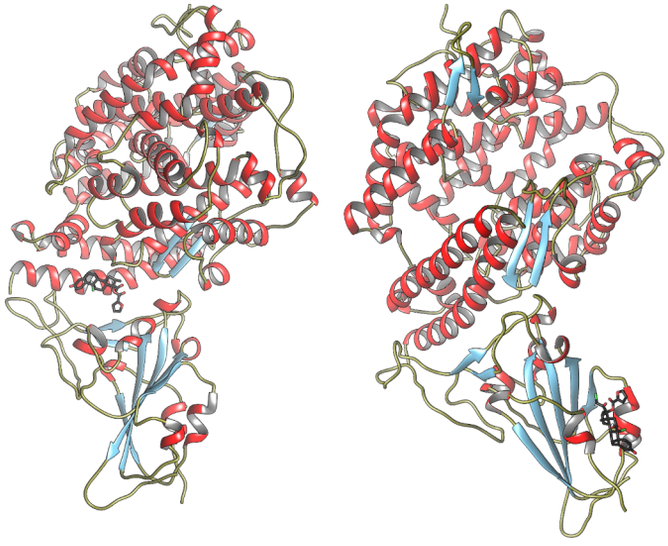

Figure 1. *Demonstration of the interaction of mometasone furoate with both the spike protein and its contact site with ACE2.*

When the spike protein results were evaluated, the binding affinity of the macrocyclic mometasone furoate to the enzyme was – 7.00 kcal/mol and it formed conventional hydrogen bond type interactions with the catalytic domain. One of these conventional hydrogen bond interactions is between ASN343 (Asparagine) and the carbonyl, and the length of the interaction is 2.29Å. again, one of the hydrogen bonds is between SER371 (Serine) and the carbonyl close to the furan ring, and the length of the interaction is 2.15Å (Figure 2).

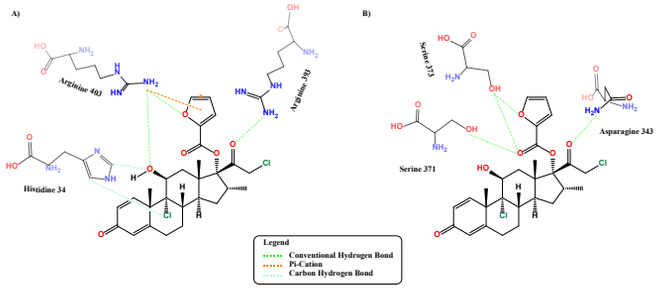

Figure 2. *Mometasone furoate and amino acid interactions diagram. A) Contact zone, B) Spike S1.*

According to the spike protein and ACE-2 contact site docking results, the binding affinity is – 8.2 kcal/mol. In this catalytic region, the carbonyl group of mometasone furoate formed two conventional hydrogen bond interactions with ARG403 (Arginine), and the furan ring formed a π-cation interaction. And again, it formed a conventional hydrogen bond interaction with ARG393 (Arginine). The HIS34 (Histidine) carbons, on the other hand, tend to carbon-hydrogen bonds with the hydroxy and chlorine atoms of mometasone furoate. All conventional hydrogen bond interactions have lengths in the 2.24 – 2.72Å range. π-cation bond electrostatic interaction length is 3.56Å. The carbon-hydrogen bond lengths are 3.53 and 3.64Å, respectively.

4. DISCUSSION

In the current literature, the effect of intranasal corticosteroids on the prevention of olfactory loss associated with COVID-19 infection or the treatment of emerging olfactory loss is not clear. There are limited studies evaluating the treatment of olfactory disorders after COVID-19 infection with intranasal corticosteroid spray therapy (13,14).

The frequency of smell disorders in COVID-19 varies widely between studies. The frequency of anosmia in COVID-19 patients ranges from 22% to 68% (15). However, patients who reported smell disorders were significantly more likely to test positive for COVID-19. As part of the pretest screening of suspected patients, it may be appropriate to use smell disorders as a highly specific manifestation of COVID-19 (5,6-13,14). There are two proposed mechanisms by which COVID-19 causes anosmia. Coronaviruses are known to infect the olfactory epithelium. The human angiotensin-converting enzyme 2 receptor, the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor, is present on olfactory epithelial cells, particularly sustentacular cells, within the olfactory cleft. Inflammation of the olfactory cleft mucosa can reduce airflow, causing conductive ophthalmic disorder (16).

According to the results of our study, we think that nasal sprays containing Mometasone furoate can both reduce edema in the olfactory area by reducing mucosal inflammation in this region with their local anti-inflammatory effects and reduce viral damage due to its reducing effect on viral binding.

Dr. Abdelalim *et al*. emphasized that, unlike other studies, the use of mometasone furoate nasal spray as a topical corticosteroid in the treatment of post-COVID-19 anosmia did not provide superiority over olfactory training regarding olfactory scores, anosmia duration, and recovery rates (6).

Dr. Rashid *et al*. emphasized that the use of nasal betamethasone drops in the treatment of smell disorders associated with COVID-19 infection is beneficial (17). Dr. Singh et al. emphasized that the use of fluticasone nasal spray may be beneficial for smell disorders (18).

Dr. Kasiri *et al*. emphasized that when mometasone furoate nasal spray was used, there was a higher improvement in severe chronic anosmia with COVID-19, as a result of their scientific study on adult patients with COVID-19 infection who developed severe microsomia or anosmia within two weeks (5).

The SARS-CoV-2 virus uses the spike protein S1, which allows the virion to interact with the host ACE2 receptor and adhere to the cell membrane. ACE-2 is a functional receptor for SARS-CoV-2, and its expression and distribution in the nervous system indicate that SARS-CoV-2 can directly or indirectly cause neurological manifestations (19).

The cell surface protein ACE-2 and the protease Transmembrane protease, serine 2 (TMPRSS2) are expressed in sustentacular cells of the olfactory epithelium, but absent or much less in most olfactory receptor neurons. These data show that sustentacular cells are involved in SARS-CoV-2 virus entry and impaired sense of smell in COVID-19 patients (20). According to our study result, nasal sprays containing mometasone furoate can reduce the sustentacular cell damage associated with COVID-19.

Dr. Eliezer *et al*. stated that there may be the sudden and complete loss of smell as a possible symptom in COVID-19 infections, and they emphasized the bilateral inflammatory occlusion of the olfactory clefts in computed tomography and Magnetic resonance imaging (MRI) in patients who described the loss of smell after coronavirus. In the scientific study they published, they defined bilateral obstructive inflammation or inflammation of olfactory clefts while olfactory bulbs are normal (21). In their study, although it was emphasized that corticosteroids should be avoided in patients infected with SARS-CoV-2; according to the results of our virtual docking study, we think that nasal sprays containing mometasone furoate should be used in the early period, especially in patients with acute coronavirus infection, before the symptoms of viral upper respiratory tract infection begin, due to their anti-inflammatory effects and antiviral properties.

Coronaviruses can invade the brain through the cribriform plate, which is close to the olfactory bulb and olfactory epithelium. In this case, there may be some structural changes in the olfactory bulb that cannot be detected in MRI results (19,20). In addition, Yao *et al*. reported that olfactory bulb volume decreased in patients with postinfectious olfactory loss and was inversely related to the duration of olfactory loss (22).

It has recently been emphasized that inhaled corticosteroids not only have anti-inflammatory effects but also have antiviral effects. While ciclesonide and mometasone suppress the *in vitro* replication of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle East respiratory syndrome coronavirus (MERS-CoV); It was determined that dexamethasone, cortisone, prednisolone, and fluticasone had no antiviral effects (13) Dr. Miyazawa emphasized that clinical studies are required to determine the preventive effects of nasal mometasone sprays in the treatment of early-stage COVID-19 (23). Since Mometasone has a smaller particle size than other molecules, it may be possible to reach small alveoli as an inhaler (24) and it can also be used as an inhaler in treatment due to its possible antiviral properties. Therefore, there is a need for comprehensive scientific studies on the subject. In the current literature, we did not find any other scientific study that directly evaluated the antiviral effects of mometasone furoate on the COVID-19 virus.

5. CONCLUSION

According to the results of our study, we think that nasal sprays containing mometasone furoate can be used prophylactically in patients with COVID-19 infection due to its antiviral effect, and it may be beneficial to use sprays containing mometasone furoate before the symptoms of

upper respiratory tract infection begin in patients. The role of these molecules in the treatment of acute smell disorders associated with COVID-19 infection and their antiviral effects on coronavirus should be investigated by conducting extensive scientific studies on the subject.

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