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Letter to Editor

Ammonium Chloride as a Potential Candidate for the Treatment and Controlling of Covid-19

Kargar Kheirabad A[1*], Nourozi M[1, 2]

1. Virology Department, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
2. Clinical Virology Research Center

Dear Editor,

Coronaviruses are pathogens with a zoonotic potential which are positive sense single-stranded RNA viruses. SARS Corona-virus-2, the cause of Covid-19 infection, is from the betacoronavirinea subfamily, which has close genomic and proteomic similarity to SARS Coronavirus-1 (1). Given the genomic proximity of these two viruses, studies on SARS Coronavirus-1 can be used to control or detect SARS Coronavirus-2. The cellular receptor of the virus is ACE-II, which virus binds to it through S protein (2). S Protein plays a major role in the pathogenesis of the virus by reducing the levels of the ACE-II receptor in the infected cells, disrupting the renin-angiotensin system and affecting the tropism. Therefore, S protein is one of the important proteins in the pathogenesis of the virus and is an appropriate target for treatment (3, 4).

S Protein is a trimer spike on the surface of the virion consisting of S1 and S2. The virus binds to the cell receptor via the surface globule (S1) and then enters the cell through receptor-mediated endocytosis. Cathepsin-L enzyme is an important cysteine peptidase in the endosome. Within the endosome (lysosome) with the effect of Cathepsin-L enzyme, S protein is cleaved in S1/S2 junction. As a result, the fusion peptide at the S2 is exposed to the lysosomal membrane, which is followed by the virus nucleocapsid release to the cytosol and beginning of the viral replication. The higher the affinity of the S protein to the receptor, the higher the severity of the disease (4, 5).

Important Notes:

1. It appears at least some of the treatment strategies provided for Covid-19 are based on preventing the virus from being released from the endosome by inhibiting the cleavage of the S protein within the endosome.
2. The Cathepsin-L enzyme, which is important in the process of virus replication, functions at pH=4.7 and is inactivated at higher pH (5, 6).
3. In SARS Coronavirus-1, inhibition of S1/ 2 cleavages prevents the virus replication (5, 6).
4. S1/S2 cleavage can be prevented in several ways:

4.1. **Lysosomotropic agents**, which are weak bases, increase the pH of the lysosome upon their entry into the lysosomes. As a result of increased pH, the Cathepsin-L enzyme is deactivated, preventing the fusion of the endosome membrane and the virus envelope which prevents the release of the virus nucleocapsid. These drugs include Chloroquine and Ammonium Chloride. In the clinical trial, the efficacy of Chloroquine in the management of Covid-19 infection has been confirmed and this drug has been widely used to treat this infection in China and Iran. On the other hand, many experiments have confirmed the effectiveness of Ammonium Chloride (7, 8).

4.2. **Cathepsin-L protease inhibitors** can prevent the cleavage of S1/S2 in two manners:

4.2.1. **Competitive inhibitors such as peptides.** Cathepsin-L can be inhibited by different

[*]**Corresponding author:** Ali Kargar Kheirabad Virology Department, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Email: kargarapgv@gmail.com
Tel: (+98) 21-88992660

types of peptides that have the enzyme cleavage site (9).

4.2.2. **Non-competitive inhibitors such as viral protease inhibitors.** These drugs have also been used to treat Covid-19 infection in hospitalized patients, and their efficacy has been confirmed, e.g. Kaletra (9).

5. SARS coronavirus-1 virions infectivity reduces significantly in the weak acidic environment (1, 10).

5.1. When Ammonium Chloride is metabolized in the liver, acidosis occurs in the lungs (11). Acidosis in the intracellular environment could inactivate the virus after proliferation and inhibit the initiation of the next cycle of infection in the patient (severity of the disease) or its infectivity (transmission and spread of the infection among individuals). Thus, besides the treatment of the disease, it could be effective in the control of Covid -19 infection.

6. The severity of the infection in cases of reinfection and the mildness of the disease in children indicate that immune responses play an important role in complicating the infection (12).

Diphenhydramine compound is a generic drug used to control the clinical symptoms of respiratory infections. This drug has diphenhydramine, a competitive inhibitor of histamine-1, which has a positive effect on the treatment of respiratory diseases. It also contains Ammonium chloride. Ammonium chloride will be effective in the control and treatment of Covid-19 infection in the following ways:

A. By increasing the lysosomal pH and inhibiting the Cathepsin-L enzyme, it prevents the initiation of the virus replication cycle in the cell.

B. By decreasing the pH of the intracellular environment in the patient's lung and inducing acidosis, it could inactivate new viruses, which replicated in the host, in addition to controlling infection in the patient, is likely to reduce the spread of infection in the population.

C. Covid-19 is associated with dry cough. Increased sputum is also effective in the treatment of pneumonia, which greatly helps to relieve the symptoms. Ammonium Chloride as a sputter can also help in this matter. This is a preliminary suggestive report which requires further clinical investigation before being used in human. Obviously, the results of viral informatics and clinical evaluations of this study will be published soon.

Editorial view

This suggestive report requires further investigation to determine its effectiveness and the extend of its side effects must be done in collaboration with clinicians. The editors take no responsibility for the use of this compound in clinical cases.

Conflict of Interest

The authors declare that they have no conflict of interest.

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