

CrossMark
click for updates

New hope for treatment of respiratory involvement following COVID-19 by bromhexine

Abdolrazagh Barzegar¹, Masoud Ghadipasha¹, Nima Rezaei^{2,3,4}, Mehdi Forouzesh^{1*}, Rohollah Valizadeh⁵

¹Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran

²Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran &

³Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

⁴Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

⁵Student Research Committee, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article Type:

Epidemiology and Prevention

Article History:

Received: 25 July 2020

Accepted: 7 August 2020

Published online: 12 August 2020

Implication for health policy/practice/research/medical education:

Bromhexine as a fluidifying agent can be investigated in clinical trials to discover its therapeutic effect on respiratory involvement following COVID-19.

Please cite this paper as: Barzegar A, Ghadipasha M, Rezaei N, Forouzesh M, Valizadeh R. New hope for treatment of respiratory involvement following COVID-19 by bromhexine. J Nephroarmacol. 2021;10(2):e11. DOI: 10.34172/npj.2021.11.

Keywords: COVID-19, Bromhexine, Acute kidney injury, transmembrane serine protease 2 (TMPRSS2), Pneumonia, Angiotensin-converting enzyme 2, chronic obstructive pulmonary disease

Currently, the use of mucolytic drugs to dilute respiratory secretions is increasing; among them, bromhexine is considered as one of the most common drugs (1,2). Bromhexine, as a well-tolerated and safe medication introduced in 1963, stimulates the bronchial mucosa and changes the structure of glycoproteins in the secretions, which reduces the adhesion and dilutes the secretions (3). From a long-time ago, bromhexine has been used for treatment of chronic bronchitis (4) and asthma (5). Recently, bromhexine showed an enhancing effect on the lung levels of antibiotics to treat respiratory infections. Additionally, the combination of bromhexine with antibiotics increases the efficacy of medications (6).

Roa and Dantes revealed that a combination of bromhexine and amoxicillin in lower respiratory tract infection enhance clinical effectiveness. Additionally, patients in the group of bromhexine had significantly greater reduction of their symptom scores for symptoms of cough discomfort, cough frequency, ease of expectoration and sputum volume. The patients taking

bromhexine had treated rapidly of pneumonia (7). The role of the mucociliary system in the development of immunity and protection against microorganisms is very important. Bromhexine is also used to treat coughs caused by bronchitis, chronic obstructive pulmonary disease (COPD) or cystic fibrosis (8). According to a study conducted by Cataldi et al on the effect of bromhexine metabolites in children with respiratory disorders, the positive effect of this drug was observed in the treatment of sputum caused by respiratory infections (9). The administration of bromhexine in treatment of adult respiratory distress syndrome (ARDS) was investigated in a study by Kuckelt et al, which showed in patients with ARDS who were treated with bromhexine, pulmonary function is significantly ameliorated (10).

Considering the ability of bromhexine to treat bronchitis, asthma and ARDS, the hypothesis on the possible therapeutic effect of bromhexine is coronavirus disease 2019 (COVID-19) that emerged recently. Bromhexine can inhibit transmembrane serine protease 2 (TMPRSS2), which prevents the virus from entering the body; hence

*Corresponding author: Mehdi Forouzesh, Email: m.forouzesh.forensic@gmail.com

is likely to be beneficial for the treatment of COVID-19. To prevent viral entry, the drug should be an ACE2 (angiotensin-converting enzyme 2)-binding inhibitor or TMPRSS2-specific inhibitor. It is of great importance to conduct some trials on the efficacy of bromhexine as a prophylactic or curative agent in COVID-19 patients (11). The mechanism of bromhexine is inhibition of TMPRSS2, since this pathway showed its effect in patients with the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) some years ago (12). In an ongoing trial, bromhexine hydrochloride is given to COVID-19 patients as a mucolytic agent to suppress cough in patients with suspected COVID-19 in China (13), which shows the effectiveness of this drug to suppress cough (14). Newly, Maggio and Corsini revealed that bromhexine has a main role in the prevention of COVID-19 (14). There is no absolute contraindication reported for bromhexine, except for rare allergy reactions to bromhexine. Meanwhile only few adverse effects of bromhexine are reported such as nausea, vomiting, diarrhea and fever. For these reasons, bromhexine is a safe drug (15). Similarly, the study by Habtemariam et al approved the efficacy of bromhexine as a prophylactic drug against COVID-19 (16). It should be noted that, by preventing the progress of COVID-19 using bromhexine, the renal involvement by SARS-CoV-2 may be indirectly prevented or ameliorated, while acute kidney injury is frequently observed in severe COVID-19 patient (17, 18). Additionally, Markus et al proposed the use of bromhexine as a prophylactic and in a favorable combination with hydroxyl chloroquine as an effective endosomal protease inhibitor for the treatment of moderate to severe COVID-19 cases (19). In summary, it seems that the administration of bromhexine alone or in combination with other adjuvants to facilitate the treatment process in patients with COVID-19.

Authors' contribution

AB, MG and MF; Concept, design and manuscript draft. RV and NR conducted final revision. All authors read and signed the final paper.

Conflicts of interest

The authors declare that there is no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Satoskar RS, Rege N, Bhandarkar SD. Pharmacology and pharmacotherapeutics. India: Elsevier; 2017.
2. Pospíšilová M, Polásek M, Jokl V. Determination of ambroxol or bromhexine in pharmaceuticals by capillary isotachopheresis. *J Pharm Biomed Anal.* 2001;24:421-428. doi: 10.1016/s0731-7085(00)00448-9
3. Tripathi KD. Essentials of medical pharmacology. JP Medical Ltd; 2013.
4. Christensen F, Kjer J, Ryskjaer S, Arseth-Hansen P. Bromhexine in chronic bronchitis. *Br Med J.* 1970; 4:117. doi: 10.1136/bmj.4.5727.117-a
5. Brogan TD, Ryley HC, Hutt H, Neale L. The effect of bromhexine on sputum from patients with chronic bronchitis and asthma. *Br J Dis Chest.* 1974;68:28-34.
6. Deretic V, Timmins GS. Enhancement of lung levels of antibiotics by ambroxol and bromhexine. *Expert Opin Drug Metab Toxicol.* 2019;15:213-218. doi: 10.1080/17425255.2019.1578748
7. Roa CC Jr, Dantes RB. Clinical effectiveness of a combination of bromhexine and amoxicillin in lower respiratory tract infection. A randomized controlled trial. *Arzneimittelforschung.* 1995;45:267-272.
8. Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. *Nat Rev Microb* 2004;2:95-108.
9. Cataldi M, Sblendorio V, Leo A, Piazza O. Biofilm-dependent airway infections: a role for ambroxol? *Pulm Pharmacol Ther* 2014;28:98-108.
10. Kuckelt W, Dauberschmidt R, Scharfenberg J, Winsel K, Lachmann B, Frenzke H, et al. Application of bromhexine metabolite VIII (NA 872) and bromhexine-glucose in treatment of adult respiratory distress syndrome; experimental and clinical results. *Respiration.* 1980;39:264-271. doi: 10.1159/000194226
11. Depfenhart M, de Villiers D, Lemperle G, Meyer M, Di Somma S. Potential new treatment strategies for COVID-19: is there a role for bromhexine as add-on therapy? *Intern Emerg Med.* 2020. doi: 10.1007/s11739-020-02383-3
12. Shen LW, Mao HJ, Wu YL, Tanaka Y, Zhang W. TMPRSS2: a potential target for treatment of influenza virus and coronavirus infections. *Biochimie.* 2017;142:1-10.
13. ClinicalTrials.gov. Evaluating the efficacy and safety of bromhexine hydrochloride tablets combined with standard treatment/standard treatment in patients with suspected and mild coronavirus pneumonia (COVID-19) Available from: <https://clinicaltrials.gov/ct2/show/NCT04273763>
14. Maggio R, Corsini GU. Repurposing the mucolytic cough suppressant and TMPRSS2 protease inhibitor bromhexine for the prevention and management of SARS-CoV-2 infection. *Pharmacol Res.* 2020;157:104837. doi: 10.1016/j.phrs.2020.104837.
15. Bhagat A, Rachana R. Bromhexine: A Comprehensive Review. *Int J Bio Med Res.* 2018;9:6455-9.
16. Habtemariam S, Nabavi SF, Ghavami S, Cismaru CA, Berindan-Neagoe I, Nabavi SM. Possible use of the mucolytic drug, bromhexine hydrochloride, as a prophylactic agent against SARS-CoV-2 infection based on its action on the Transmembrane Serine Protease 2. *Pharmacol Res.* 2020;157:104853. doi: 10.1016/j.phrs.2020.104853.

17. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.* 2020;97:829-38. doi:10.1016/j.kint.2020.03.005
18. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. *Intensive Care Med.* 2020;46:1339-48. doi: 10.1007/s00134-020-06153-9
19. Markus D, Gottfried L, Markus M, Marina R, Dario B, de Villiers D. A SARS-CoV-2 Prophylactic and Treatment; a Counter Argument Against The Sole Use of Chloroquine. *Am J Biomed Sci & Res.* 2020;8(4):248-251. doi: 10.34297/AJBSR.2020.08.001283 .

Copyright © 2021 The Author(s); Published by Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.