

Cationic drugs and COVID-19

Oreste Vittore Brenna^{1,2*}, Sara Torretta^{3,4} ,
Lorenzo Pignataro^{3,4} and Federica Di Bernardino^{3,4*}

International Journal of
Immunopathology and Pharmacology
Volume 34: 1–3
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2058738420966078
journals.sagepub.com/home/iji



Abstract

Given the sharp spreading of COVID-19 pandemic all around the world, our attention was brought to consider that many cationic drugs (i.e. those characterized by the presence, at physiological pH value, of one or more cationic groups, both primary, secondary, tertiary and guanidinic aminic groups) could have any effect in impairing SARS-CoV2 entry in the host cell. This could open to new therapeutic chances against COVID-19.

Keywords

cationic drugs, COVID-19, emergency, infection, pandemic

Date received: 6 July 2020; accepted: 22 September 2020

Regarding the possibility of overcoming the COVID-19 pandemic disease, the World Health Organization has noted some critical points, namely that it may be impossible to quickly produce an effective coronavirus vaccine; people can be re-infected with the virus and there is a doubt that immunity to the virus could not be long lasting. Therefore, it becomes important and necessary to be able to fight the disease with other weapons, for example with the use of drugs already used to fight other viruses or other diseases, which involve the slightest adverse effects. Some of these express their activity on the process of the binding of the virus to the target cell, interacting with one or more of the steps required for infection. These include enzyme inhibitors involved in the process, such as camostat, nafamostat, 4-(2-aminoethyl)-benzenesulfonyl fluoride chloridrate (AEBSF) that inhibit serinic proteases, particularly Serin Protease Trans Membrane 2 (TMPRSS2).¹ Other drugs, already under examination, are antivirals and antimalarials and, more recently, it has been suggested that some type 2 diabetes drugs may be used as inhibitors of dipeptidyl peptidase-4 (DPP4),² another serinic protease, already identified as a receptor for the spike protein of the MERS Co.V.³

Some researchers have tried to find other drugs to use, but of course you can't test in vivo hundreds of compounds, unless you have plausible guidelines that can rationally reduce your choice.

A recent paper reported a cluster of drugs chosen by chemoinformatics, searches and specialist knowledge among approved drugs, investigational new drugs and pre-clinical candidates.⁴

A fact to keep in mind is that many viruses, including many human pathogens and SARS-CoV2, bind cell surface glycans during the initial steps of infection.⁵ Viral glycan receptors, such as

¹Department of Food, Environmental and Nutritional Sciences, Università degli Studi di Milano, Milan, Italy

²Retired Professor

³Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

⁴Università degli Studi di Milano, Department of Clinical Sciences and Community Health, Milan, Italy

*These authors contributed equally to write this article.

Corresponding author:

Sara Torretta, Otolaryngology and Head and Neck Surgery Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico and Department of Clinical Sciences and Community Health, University of Milan, Via F Sforza 35, Milano 20100, Italy.
Email: sara.torretta@unimi.it



glycosaminoglycans and sialic acid-containing carbohydrates, are negatively charged.

This, in our opinion, can be a crucial fact in simplifying the drug screening.

In fact, if we consider the structural formula of drugs so far used in the various trials, one fact clearly stands out: practically all are characterized by the presence, at physiological pH value, of one or more cationic groups, both primary, secondary, tertiary and guanidinic aminic groups.

To remember a few of those already under trials: camostat, nafamostat, bromhexine, ambroxol, chloro- and hydroxychloroquine, zanamivir, oseltamivir, misenovir, proguanyl, metformin, aloglyptin. Although some of these drugs express their activities as inhibitors of serinic proteases or of DPP4, the presence of at least one positive charge can affect the microenvironment in which the proteases act.⁶ Lately, it has been proposed the hypothesis that nicotine, fixing itself on the cell receptor also used by the coronavirus, can block its penetration into cells.⁷ Nicotine, on the other hand, belongs to the class of alkaloids, such as quinine, and contains two positively charged amino groups.

The unifying function of the activity of all these drugs and compounds toward COVID-19, apart from the intrinsic properties for which they are used in clinical practice, may also be due to their potential to ionically react with anionic groups of sialic acid-containing carbohydrates of the cell surface glycans since all of them have one or more guanidinic aminic groups, which are cationic at physiologic pH.

Although not all of these groups can realistically be involved with the binding of the virus to cells, they can certainly interfere with the virus attack through the known pathway, that is, the interaction between the virus spike protein and ACE.⁸

Furthermore, the Sars-CoV-2 spike protein has undergone mutations compared to the original one; the main one and the most contagious is the genetic variant D614G.⁹ In this mutation, the strains with glycine (G) instead of aspartic acid (D) infect human cells 3 to 6 times more. The new spike protein has one less negative (aspartic) charge, so in total it has a more positive net charge than before and can attach itself more strongly to the negative surface of the sialic acid of the target cell, in particular to the ACE2 receptor.⁹ This observation supports the hypothesis that it is

necessary to mislead the virus by not making it recognize the receptor which can occur either with ACE2 receptor inhibitors or with steric hindrance caused by cationic drugs that compete for sialic with spike proteins.

Conclusion

Since some of the drugs studied, such as hydroxychloroquine, are antimalarial drugs, the therapeutic practice with these drugs should follow the protocol used in their primitive use, which requires their intake before, during and following the period when a traveler has to attend areas of the world where there is a possibility of being affected by malaria.

Recently, time-of-addition experiment confirmed that hydroxychloroquine effectively inhibited the entry step, as well as the post-entry stages.¹⁰

It would also be useful to be able to correlate the data that have certainly been recorded for all infected subjects and the severity of their symptoms, from asymptomatic or pauci-asymptomatic (with positive COVID-19 test), sick people who have healed without having been under ventilation and intubated or not, or even deceased.

Some interesting drugs to test, always containing cationic groups, could be chosen from those widely used for other clinical situations, such as Enalapril, an ACE inhibitors, antidepressants like imipramine or fluoxetine, the last acting as an inhibitor of nicotinic acetylcholine receptors, or tamsulosin used to treat benign prostatic hypertrophy or betahistine, used in the treatment of Ménière's disease and vertigo.

Due to the fact that these drugs are widely prescribed, it would be extremely interesting to find out that their intake may have somehow influenced the course of the COVID disease.

This could be of great help if, as happened in the case of AIDS disease, an efficient vaccine for COVID-19 cannot be obtained.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sara Torretta  <https://orcid.org/0000-0002-8461-6042>

References

1. Shen LW, Mao HJ, Wu YL, et al. TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections. *Biochimie* 2017; 142: 1–10.
2. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? *Diabetes Research and Clinical Practice* 2020; 162: 108125.
3. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013; 495(7440): 251–254.
4. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; 583(7816): 459–468.
5. Varki A and Gagneux P. Multifarious roles of sialic acids in immunity. *Annals of the New York Academy of Sciences* 2012; 1253(1): 16–36.
6. Ohkuma S, Chudzik J and Poole B. The effects of basic substances and acidic ionophores on the digestion of exogenous and endogenous proteins in mouse peritoneal macrophages. *The Journal of Cell Biology* 1986; 102(3): 959–966.
7. Farsalinos K, Niaura R, Le Houezec J, et al. Editorial: Nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system. *Toxicology Reports* 2020; 7: 658–663.
8. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181(2): 271–280.e8.
9. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 spike: Evidence that D614G increases infectivity of the COVID-19 virus. *Cell* 2020; 182(4): 812–827.
10. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery* 2020; 6(1): 16.