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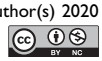

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Psychiatry and COVID-19: The Role of Chlorpromazine

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The coronavirus has turned society upside down and changed reality with the application of containment and social distancing to slow the rate of transmission. Psychiatric patients must be considered as a vulnerable population. Psychiatrists do know this. They know psychopharmacology as well, in particular a drug that revolutionized psychiatric care: chlorpromazine (CPZ). CPZ is a phenothiazine used to treat psychotic disorders such as schizophrenia. It is also used in adults to treat nausea and vomiting, anxiety before surgery, chronic hiccups, acute intermittent porphyria, and tetanus symptoms. Less is known about its antiviral potential. Almost 300 compounds for activity against MERS-CoV were screened from a library where agents are Food and Drug Administration (FDA) approved or in an advanced clinical development. Seventy-two compounds that had activity against MERS-CoV were subsequently screened against both MERS-CoV and SARS-CoV. Twenty-seven compounds showed a 50% inhibition activity against both viruses, and CPZ is one of them.[1,2]

The global spread of SARS-CoV-2 creates an urgent need to find effective therapies. The repositioning of drugs already approved in humans is a useful tool to seek new therapeutic options, especially in the current global crisis. This is what sparked, for example, the heated debate around hydroxychloroquine. Existing drugs with potent antiviral efficacy can be directly and quickly applied to treat COVID-19, as we know their deleterious effects.

The mechanism of action of CPZ is related to the formation of clathrin-coated pits inhibiting clathrin-mediated endocytosis.[3-5] Coronaviruses are enveloped, single-stranded positive genomic RNA viruses and are responsible for SARS, MERS, and COVID-19. A key component of viral infection is the process of viral entry into host cells. The endocytic pathway and the autophagy process in viral entry and replication are important. As a result, the endocytic pathway comprising the endosome and the lysosome has become important targets for drug development in the fight against diseases caused by coronavirus. The early stages of viral infection are critical events in the course of the viral cycle. In particular, viral entry is the first step in the interaction between a virus and a cell that can initiate, maintain, and spread the infection. Therefore, this stage constitutes a major target of the host's adaptive immune response.

The formation of clathrin-coated vesicles requires the concerted action of several dozen proteins. The necessary steps are sorting and concentration of receptors, deformation of the plasma membrane and recruitment of the clathrin mantle to form a depression, and finally the cleavage of the vesicle from the cell surface. The main proteins involved in these stages are the AP2 adapter, the clathrin triskeles, the mechano-enzyme dynamin, and many so-called accessory proteins with various functions such as sorting aid selective receptor or plasma membrane deformation. CPZ causes the redistribution of AP-2 blocks and blocks clathrin-dependent endocytosis. In the case of a SARS-CoV infection, viral entry would require a low pH in the intracytoplasmic vesicles; however, little is known about how SARS-CoV invades these compartments.

Thus, CPZ inhibits the replication of alphaviruses, hepatitis C virus, SARS-CoV, and MHV-2. However, studies suggest that CPZ inhibits the replication of MERS-CoV also at a later stage, implying that an effect on clathrin-mediated endocytosis is probably not the only antiviral mechanism. The plasma concentrations of CPZ in patients treated for

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psychotic disorders are slightly lower than those observed in viral experiments.

Based on the review of the antiviral mechanisms of action, there is indirect evidence to suggest CPZ might have antiviral properties. There is no evidence to date suggesting that this evidence can meaningfully translate into the clinical use of CPZ for anti-COVID treatment. However, a pandemic for which there is no treatment necessitates considering treatments and approaches that fall outside the normal course of action. Nonetheless, in a pandemic, we must adhere to practices and standards of evidence when considering using agents for very off-label use like CPZ for anti-COVID. The CPZ is widely used as an antipsychotic agent and is relatively safe to treat psychosis. The availability of information related to CPZ, such as pharmacokinetics, pharmacodynamics, safety, and toxicity, is an important advantage. To my knowledge, there is no epidemiological or observational studies exploring the clinical status of COVID-19 patients under CPZ treatment. CPZ could be efficacious to treat COVID-19 patients provided that adequate and good clinical trials are conducted. So, if the CPZ has anti-coronavirus properties in human, it is necessary to conduct rigorous quality clinical trials. Carefully constructed observational studies or large registry study are possible to look at relative rates of infection among individuals treated with CPZ versus those who are not. Randomized control trial (RCTs) and the usual procedure for approving drugs for clinical trials, with the caveat that these take time should be conducted. The various ways in which CPZ might have antiviral properties relative to COVID would be helpful. It would be interesting for psychiatry to come to the rescue of virology.

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