

SARS-Cov-2, The Covid-19 Pandemic Reminds us of the Antiviral Properties of Chlorpromazine

Peter Lepping^{1*}, Erwin Kirchler², Markus Huber²

¹Betsi Cadwaladr University Health Board/Bangor University, Wales and Mysore Medical College and Research Institute, India

²Department of Psychiatry, General Hospital Bruneck, South Tyrol, Italy

***Corresponding Author:** Dr. Peter Lepping, Betsi Cadwaladr University Health Board/Bangor University, Wales and Mysore Medical College and Research Institute, India, E-mail: PETER.LEPPING@wales.nhs.uk

Received: 01 June 2020; **Accepted:** 10 June 2020; **Published:** 23 June 2020

In vitro studies have established the classic antipsychotic drug chlorpromazine (CPZ) as an effective antiviral agent against various viruses, including corona viruses [1]. Also, SARS-CoV-2, the cause of the current Covid 19 pandemic, is inhibited by CPZ [2].

CPZ is known to act on clathrin-mediated endocytosis (CME), which affects the formation of clathrin-coated pits on the plasma membrane [3]. This pathway is one of the most important entry routes of viruses, more precisely virions, into host cells. Studies on the antiviral effect of CPZ have shown that it influences different mechanisms of virus formation, including post-entry effects. CPZ belongs to the group of cationic amphiphilic drugs (CADs), which have the propensity to interact with various cell structures, especially membranes. They accumulate in intracellular compartments (acidic), such as early and late endosomes/lysosomes crucial for virus formation (e.g. particle coating, assembly or budding) [4]. In the case of corona viruses (SARS-CoV), CPZ inhibits the cell entry chiefly by CME [5]. However, CPZ it is also known to inhibit membrane fusion processes at the plasma membrane or at an intracellular location following virus uptake by endocytosis. Among them, CME and cathepsin mediated S protein cleavage are two critical steps for viral entry and infection of corona viruses (all coronaviruses are enveloped viruses with a long single-plus stranded RNA) [6]. Notably, SARS-CoV and SARS-CoV-2 use exactly the same attachment receptor (ACE2) and serine protease (TMPRSS2/S protein priming) for cell entry [7]. However, the exact nature of the viral entry is context-dependent, including the type of the virus and the type of the host cells. As mentioned above, SARS-CoV-2 utilizes the ACE2-receptor (angiotensin converting enzyme II) for viral entry into the host cells. ACE2 transcripts was originally only found in heart, kidney and testis of humans. However, it was later found that ACE2 protein expresses abundantly in the epithelia of the human lung, small intestine and brain [8].

The understanding of such mechanisms is important in the search for antiviral agents (therapeutics) with broad-spectrum properties. CPZ, as a typical phenothiazine-derivative, interacts with multiple cellular targets. Phenothiazine, characterized by a Sulphur-containing tricyclic amine (formula: $S(C_6H_4)_2NH$), is known as an important lead structure for a large number of drugs with different biological activities, due to its multicyclic structure. Paul Ehrlich (Nobel laureate 1908 in medicine), was the first to recognize the antimicrobial effect of the phenothiazine derivative “methylene blue” in malaria infections. Today, we know that phenothiazine derivatives, besides their antipsychotic activity, have antiviral, antibacterial, antiprotozoal, antifungal, insecticidal, antipiron, anticancer, antiinflammatory, anticonvulsant, analgesic, immunosuppressive and multidrug resistant reversal properties [9]. CPZ itself was discovered in the 1950s by Paul Charpentier in Paris. However, the beginning of its use as an antipsychotic is considered as the milestone in modern psychotropic drug therapy.

At present, no clinical use of CPZ in antiviral treatment (repurposing) has been reported. However, it may be a timely coincidence that the first clinical study on the antiviral effect of CPZ has just started in Paris (April 29, 2020) [10]. The study (Randomized Interventional Model/Parallel Assignment) evaluates the effects of the addition of CPZ to the standard therapeutic protocol in COVID-19 patients for respiratory symptom management.

Since CPZ in vitro has demonstrated its potential as a broad-spectrum antiviral drug clinical trials are urgently needed, either as a single therapy or in combination with other antiviral drugs. Importantly, the inhibition of SARS-CoV-2 by CPZ was achieved in VeroE6 cell lines at a range of IC₅₀ values (half maximal inhibitory concentrations) at non-cytotoxic concentrations [2]. In addition, CPZ is a clinically proven antipsychotic that easily crosses the blood-brain barrier, which could be of immense benefit in SARS-CoV-2 cases with neurological complications [8]. The dosage of CPZ as antipsychotics is broadly diversified and can be administered orally, intramuscularly and intravenously.

The Covid-19 pandemic has highlighted the need for antiviral drugs with broad-spectrum effectiveness. It has emerged worldwide as a significant global public health threat and economic challenge. The reasons why there are no selective drugs on the market for viruses are complex. Their business potential may have appeared to be limited because so far, the affected population groups often had a poor socio-economic background. Regardless of whether SARS-CoV-2 can be effectively treated, the next unknown virus will certainly appear in the near future. We need to validate antiviral drugs with broad-spectrum efficacy that are ready at the first signs of a new outbreak. We await the results from the trial in Paris with some anticipation and congratulate our colleagues for their foresight in selecting CPZ (for the first time) for a clinical trial against a SARS-CoV-2 virus.

Contributions

PL, EK and MKH conceptualised, researched, drafted and finalised the submission equally.

References

1. Pietschmann T. Clinically Approved Ion Channel Inhibitors Close Gates for Hepatitis C Virus and Open Doors for Drug Repurposing in Infectious Viral Diseases. *J Virol* 91 (2017): e01914-16.
2. Weston S, Haupt R, Logue J, et al. FDA approved drugs with broad anti-coronaviral activity inhibit SARS-CoV-2 in vitro. *BioRxiv preprint* doi: <https://doi.org/10.1101/2020.03.25.008482>. this version posted March 27, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. It is made available under a CC-BY-NC-ND 4.0 International license.
3. Yang N, Shen HM. Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19. *Int J Biol Sci* 16 (2020): 1724-1731.
4. Salata C, Calistri A, Parolin C, et al. Antiviral activity of cationic amphiphilic drugs. *Expert Rev Anti Infect Ther* 15 (2017): 483-492.
5. Inoue Y, Tanaka N, Tanaka Y, et al. Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. *J Virol* 81 (2007): 8722-8729.
6. Wang H, Yang P, Liu K, et al. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. *Cell Res* 18 (2008): 290-301.
7. 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* 181 (2020): 271-280.e8.
8. Chen R, Wang K, Yu J, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *BioRxiv preprint* doi: <https://doi.org/10.1101/2020.04.07.030650>. this version posted April 9, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. It is made available under a CC-BY-NC-ND 4.0 International license.
9. Varga B, Csonka Á, Csonka A, et al. Possible Biological and Clinical Applications of Phenothiazines. *Anticancer Res* 37 (2017): 5983-5993.
10. Plaze M (Principal Investigator). Repurposing of Chlorpromazine in Covid-19 Treatment. <https://clinicaltrials.gov/ct2/show/NCT04366739>; Study Start Date: April 29 (2020).

Citation: Peter Lepping, Erwin Kirchler, Markus Huber. SARS-Cov-2, The Covid-19 Pandemic Reminds us of the Antiviral Properties of Chlorpromazine. *Journal of Psychiatry and Psychiatric Disorders* 4 (2020): 101-103.



This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC-BY\) license 4.0](https://creativecommons.org/licenses/by/4.0/)