Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Schizophrenia Research 223 (2020) 373–375

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the editor

Could the antipsychotic chlorpromazine be a potential treatment for SARS-CoV- 2?

B. Nobile [a,b,*,1], M. Durand [c,1], P. Courtet [a,b,d], P. Van de Perre [c], N. Nagot [c,e], J.P. Molès [c], E. Olié [a,b,d]

[a] Department of Emergency Psychiatry and Acute Care, CHU Montpellier, France
[b] PSNREC, Univ Montpellier, INSERM, CHU de Montpellier, Montpellier, France
[c] Pathogenesis and Control of Chronic Infection, INSERM, EFS, Université de Montpellier, Montpellier, France
[d] FondaMental Foundation, France
[e] Department of Medical Information, CHU Montpellier, France

ARTICLE INFO

Article history:
Received 25 May 2020
Received in revised form 10 July 2020
Accepted 21 July 2020
Available online 25 July 2020

Keywords:
SARS-CoV-2
Chlorpromazine
Clathrin-mediated endocytosis
Viral replication
Sedative medication

A list of drugs with antiviral effects has been suggested against Severe Acute Respiratory Syndrome-Coronavirus type 2 (SARS-CoV-2) (Lythgoe and Middleton, 2020). Until recently, chlorpromazine (CPZ), a cationic amphiphilic drug, has been neglected.

Enveloped viruses, such as SARS-CoV-2, use different ways to enter the host cell. Inoue et al. showed that SARS-CoV (a coronavirus similar to SARS-CoV-2) mainly uses Clathrin-Mediated Endocytosis (CME) (Inoue et al., 2007). During this process, the S protein of coronaviruses (necessary for the fusion between the virus and the cell) is activated by proteases (in a low pH-dependent manner) located in the endosome. Recently, a Chinese study showed that the endocytic pathway is essential for SARS-CoV-2 invasion of host cells, although they could not demonstrate that CME is the major pathway (Ou et al., 2020). CPZ, mainly used as antipsychotic medication, blocks CME by inhibiting the formation of clathrin-coated vesicles (Dyall et al., 2014). In addition, *in vitro* studies demonstrated that CPZ can efficiently inhibit SARS-CoV and MERS-CoV replication (see Table 1 for their description). It was also suggested that CPZ can increase the intra-vesicular pH and consequently inhibit S protein activation due to its cationic amphiphilic properties. Indeed, cationic amphiphilic drugs accumulate in acidic compartments where their tertiary amine groups are protonated. Thus, they act as mild bases, can neutralize the low pH of the acidic environment of endo/lysosomes, and block S protein activation (Dyall et al., 2017).

Moreover, patients with SARS-CoV-2 infection can present a hyper-inflammation phase, called "cytokine storm". High concentrations of inflammatory markers have been associated with poor disease prognosis (Ye et al., 2020). Interestingly, CPZ has also immune-modulatory effects. For instance, in mice, CPZ increases the concentration of the anti-inflammatory cytokines IL-10 and decreases that of pro-the inflammatory cytokines IL-6 and TNFα after administration of endotoxins (Mengozzi et al., 1994; Plaze et al., 2020).

Altogether, CPZ properties suggest that it could be active at different stages of the disease: at the beginning (by inhibiting CME) and later during the hyper-inflammation phase (due to its anti-inflammatory properties).

On the basis of these data, two randomized controlled trials (RCT) have been designed to test CPZ in patients with SARS-CoV-2 infection (*i.e.* either psychiatrics or non-psychiatrics patients): the reCoVery study in France (NTC 04366739) and one study in Egypt (NTC 04354805). Patients' enrollment has not started yet (July 2020).

It is difficult to extrapolate the effective CPZ concentrations needed in patients from *in vitro* studies. Indeed, several factors, such as the proteins in the environment, cell interactions, the molecule distribution volume, and binding to plasmatic proteins, can interfere with the medication action and could change the EC_{50} observed *in vitro*. In psychotic patients, CPZ plasma concentrations are usually below the EC_{50} values observed in *in vitro* studies on its anti-viral effect (*i.e.* from 0.3 to 3 μM) (de Wilde et al., 2014) (Table 1). However, the finding that CPZ concentration is 20- to 200-fold higher in human lungs than in plasma (Forrest et al., 1968; Plaze et al., 2020) suggests that antiviral effective drug concentrations could be reached. Moreover, some studies in cultured cells showed that CPZ at therapeutic concentrations significantly reduces infection by other viruses (*e.g.* JC virus and adenovirus) (Atwood, 2001; Kanerva et al., 2007). Finally, CPZ can pass through the blood brain barrier and diffuses largely in the CNS where SARS-CoV-2 has deleterious effects (*e.g.* encephalitis) with negative consequences for survivors (Nobile et al., 2020).

Another major question concerns the timing of CZP administration in patients with COVID-19. CPZ use in COVID-19 should be first

* Corresponding author at: Inserm-U1061, Hôpital La Colombière, 39, avenue Charles Flahault, BP 34493, 34093 Montpellier cedex 5, France.
E-mail address: benedicte.nobile@gmail.com (B. Nobile).
[1]These authors have equally contributed to the manuscript.

https://doi.org/10.1016/j.schres.2020.07.015

Table 1
In vitro studies on CPZ effect against coronavirus infection (Cong et al., 2018; Dyall et al., 2014, 2017; de Wilde et al., 2014).

Title	First author and year of publication	Tested virus (MOI[a])	Cell line (s)	Starting time of incubation with CPZ	CPZ and viral incubation length	Significant inhibition of viral replication	EC_{50}	Cytotoxicity at EC_{50} or CC_{50}
Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted	Inoue et al., 2007	SARS-CoV (MOI: 1)	Human hepatoma HepG2	1 h before infection	36 h	Yes (20 μM)	Approximately 7 μM	Not evaluated
Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection	Dyall et al., 2014	MERS-Cov (MOI: 0.1) and SARS-CoV (MOI: 1)	Vero E6	MERS-CoV: 1 h before infection SARS-CoV: 2 h before infection	2 days for both	Yes	MERS-CoV: 9.5 μM; SARS-CoV: 12.9 μM	Cytotoxicity at $EC_{50} < 25\%$
Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture	de Wilde et al., 2014[b]	MERS-CoV (MOI: 0.005) and SARS-CoV (MOI: 0.005)	Huh7 and Vero E6	1 day after infection	2 days (with Huh7 cells) and 3 days (with Vero E6 cells)	Yes	MERS-CoV: 4.9 ± 1.2) μM SARS-CoV: 8.8 ± 1.0) μM	MERS-CoV: Huh7: 21.3 (1.0) μM SARS-CoV: 24.3 (1.1) μM
Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture	de Wilde et al., 2014 (Bis)[b]	MERS-CoV (MOI: 1)	Huh7 and Vero	1 h before infection or 1 h after infection	1 day	Yes	2 log reduction of virus progeny titers (CPZ administered 1 h before infection) 0.5 to 1 log reduction (1 h after infection)	
MERS-CoV pathogenesis and antiviral efficacy of licensed drugs in human monocyte-derived antigen-presenting cells	Cong et al., 2018	MERS-CoV (MOI: 0.1)	Human MDM and MDDC Vero E6	1 h before infection	2 days	Yes	13.58 μM in MDM and MDDC 9.5 μM in Vero E6	CC_{50}: 25.64 μM in MDM and MDDC Cytotoxicity at $EC_{50} < 25\%$ in Vero E6

[a] MOI: multiplicity of infection; ACE2: angiotensin-converting enzyme 2; MDM: monocytes-derived macrophages; MDDC: monocyte-derived dendritic cells.
[b] In the study by de Wilde et al., two types of experiments were performed, thus we used two lines to describe them.

investigated: i) in hospitalized patients with mild or moderate disease at the beginning of the infection (as proposed by the reCoVery study with a dosage of 300 mg/day) to reduce the viral load and decrease the risk of disease worsening; ii) in patients in intensive care units to reduce inflammation, with or without corticoids (to date, no RCT on CPZ in this population), and also to reduce confusion or during extubation. In a second time, CPZ could also be considered as a pre-exposure prophylaxis, or to prevent the long-term neurological consequences.

Obviously, CPZ use could expose patients to adverse effects (*e.g.* QT interval elongation). Yet, if the recommendations of use (electrocardiogram before prescription, and treatment under medical supervision only) are respected, side effects can be rapidly corrected by clinicians. Furthermore, CPZ is used not only for psychiatric patients, but also in anesthesia, and in pregnant women with treatment-resistant nausea; its use is safe (Plaze et al., 2020).

Given the emergency of the situation worldwide, several drugs are considered for repurposing on the basis of *in vitro* data. CPZ is readily available and inexpensive and might be worth testing. Moreover, collecting clinical data on the SARS-CoV-2 infection rate and disease severity among psychiatric patients currently on CPZ could be useful. The results of the newly launched RCTs will give robust information on CPZ place in COVID-19 management.

Funding

None.

Authors contributions

Emilie Olié initiated this review and supervised the redaction of the paper. Mélusine Durand and Bénédicte Nobile performed the bibliographic research and wrote the manuscript. Jean-Pierre Molès supervised the redaction of the paper. Philippe Courtet, Philippe Van de Perre and Nicolas Nagot actively revised the manuscript. All authors have contributed to the manuscript and have accepted the final version of the paper.

Declaration of competing interest

None.

Acknowledgements

None.

References

Atwood, Walter J., 2001. A combination of low-dose chlorpromazine and neutralizing antibodies inhibits the spread of JC virus (JCV) in a tissue culture model: implications for prophylactic and therapeutic treatment of progressive multifocal leukencephalopathy. J. Neurovirol. 7 (4), 307–310.

Cong, Yu, Hart, Brit J., Gross, Robin, Zhou, Huanying, Frieman, Matthew, Bollinger, Laura, Wada, Jiro, Hensley, Lisa E., Jahrling, Peter B., Dyall, Julie, Holbrook, Michael R., 2018. "MERS-CoV pathogenesis and antiviral efficacy of licensed drugs in human monocyte-derived antigen-presenting cells" edited by S. Pöhlmann. PLoS One 13 (3), e0194868.

Dyall, Julie, Coleman, Christopher M., Hart, Brit J., Venkataraman, Thiagarajan, Holbrook, Michael R., Kindrachuk, Jason, Johnson, Reed F., Olinger, Gene G., Jahrling, Peter B., Laidlaw, Monique, Johansen, Lisa M., Lear-Rooney, Calli M., Glass, Pamela J., Hensley, Lisa E., Frieman, Matthew B., 2014. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob. Agents Chemother. 58 (8), 4885–4893.

Dyall, Julie, Gross, Robin, Kindrachuk, Jason, Johnson, Reed F., Olinger, Gene G., Hensley, Lisa E., Frieman, Matthew B., Jahrling, Peter B., 2017. Middle East respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. Drugs 77 (18), 1935–1966.

Forrest, I.S., Bolt, A.G., Serra, M.T., 1968. Distribution of chlorpromazine metabolites in selected organs of psychiatric patients chronically dosed up to the time of death. Biochem. Pharmacol. 17 (10), 2061–2070.

Inoue, Yuuki, Tanaka, Nobuyuki, Tanaka, Yoshinori, Inoue, Shingo, Morita, Kouichi, Zhuang, Min, Hattori, Toshio, Sugamura, Kazuo, 2007. Clathrin-dependent entry of

severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted. J. Virol. 81 (16), 8722–8729.

Kanerva, Anna, Raki, Mari, Ranki, Tuuli, Särkioja, Merja, Koponen, Jarmo, Desmond, Renee A., Helin, Aija, Stenman, Ulf-Håkan, Isoniemi, Helena, Höckerstedt, Krister, Ristimäki, Ari, Hemminki, Akseli, 2007. Chlorpromazine and apigenin reduce adenovirus replication and decrease replication associated toxicity. The Journal of Gene Medicine 9 (1), 3–9.

Lythgoe, Mark P., Middleton, Paul, 2020. Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol. Sci. 41, 363–382.

Mengozzi, M., Fantuzzi, G., Faggioni, R., Marchant, A., Goldman, M., Orencole, S., Clark, B.D., Sironi, M., Benigni, F., Ghezzi, P., 1994. Chlorpromazine specifically inhibits peripheral and brain TNF production, and up-regulates IL-10 production, in mice. Immunology 82 (2), 207–210.

Nobile, B., Durand, M., Olié, E., Guillaume, S., Molès, J.P., Haffen, E., Courtet, P., 2020. Clomipramine could be useful in preventing neurological complications of SARS-CoV-2 infection. J. NeuroImmune Pharmacol.

Ou, Xiuyuan, Liu, Yan, Lei, Xiaobo, Li, Pei, Mi, Dan, Ren, Lili, Guo, Li, Guo, Ruixuan, Chen, Ting, Hu, Jiaxin, Xiang, Zichun, Zhixia, Mu, Chen, Xing, Chen, Jieyong, Hu, Keping, Jin, Qi, Wang, Jianwei, Qian, Zhaohui, 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat. Commun. 11 (1).

Plaze, M., Attali, D., Petit, A.C., Blatzer, M., Simon-Loriere, E., Vinckier, F., Cachia, A., Chrétien, F., Gaillard, R., 2020. Repositionnement de la chlorpromazine dans le traitement du COVID-19: étude reCoVery. L'Encéphale 46 (3), 169–172.

de Wilde, Adriaan H., Jochmans, Dirk, Posthuma, Clara C., Zevenhoven-Dobbe, Jessika C., van Nieuwkoop, Stefan, Bestebroer, Theo M., van den Hoogen, Bernadette G., Neyts, Johan, Snijder, Eric J., 2014. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob. Agents Chemother. 58 (8), 4875–4884.

Ye, Qing, Wang, Bili, Mao, Jianhua, 2020. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. J. Infect. 80 (6), 607–613.