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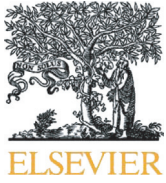


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Letter to the editor

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

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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. In-

deed, 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-inflammatory cytokines IL-6 and TNF α after administration of endotoxins (Mengozi 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 psychiatric or non-psychiatric 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 EC₅₀ observed *in vitro*. In psychotic patients, CPZ plasma concentrations are usually below the EC₅₀ values observed in *in vitro* studies on its anti-viral effect (*i.e.* from 0.3 to 3 μ M) (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 CPZ administration in patients with COVID-19. CPZ use in COVID-19 should be first

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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.

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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.

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