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.

L'Encéphale 46 (2020) 169–172

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Repurposing chlorpromazine to treat COVID-19: The reCoVery study

Repositionnement de la chlorpromazine dans le traitement du COVID-19 : étude reCoVery

M. Plaze[a,b,*], D. Attali[a,b,c], A.-C. Petit[a,d], M. Blatzer[d], E. Simon-Loriere[e], F. Vinckier[a,b], A. Cachia[f,g], F. Chrétien[d,h], R. Gaillard[a,b,d]

[a] *GHU PARIS Psychiatrie & Neurosciences, site Sainte-Anne, Service Hospitalo-Universitaire, Pôle Hospitalo-Universitaire Paris 15, Paris, France*
[b] *Université de Paris, Paris, France*
[c] *Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Univ Paris Diderot, Sorbonne Paris Cite, Paris, France*
[d] *Institut Pasteur, Experimental Neuropathology Unit, Paris, France*
[e] *Institut Pasteur, G5 Evolutionary Genomics of RNA Viruses, Paris, France*
[f] *Université de Paris, Institut de Psychiatrie et Neurosciences de Paris, INSERM, Paris, France*
[g] *Université de Paris, Laboratoire de Psychologie du développement et de l'Éducation de l'Enfant, CNRS, Paris, France*
[h] *GHU PARIS Psychiatrie & Neurosciences, site Sainte-Anne, Service de Neuropathologie, Paris, France*

ARTICLE INFO

Article history:
Received 30 April 2020
Accepted 11 May 2020
Available online 16 May 2020

Keywords:
Chlorpromazine
SARS-CoV-2
COVID-19
Repurposing of molecules
Clinical trial

ABSTRACT

Objectives. – The ongoing COVID-19 pandemic has caused approximately 2,350,000 infections worldwide and killed more than 160,000 individuals. In Sainte-Anne Hospital (GHU PARIS Psychiatrie & Neuroscience, Paris, France) we have observed a lower incidence of symptomatic forms of COVID-19 among patients than among our clinical staff. This observation led us to hypothesize that psychotropic drugs could have a prophylactic action against SARS-CoV-2 and protect patients from the symptomatic and virulent forms of this infection, since several of these psychotropic drugs have documented antiviral properties. Chlorpromazine (CPZ), a phenothiazine derivative, is also known for its antiviral activity via the inhibition of clathrin-mediated endocytosis. Recent*in vitro* studies have reported that CPZ exhibits anti-MERS-CoV and anti-SARS-CoV-1 activity.
Methods. – In this context, the ReCoVery study aims to repurpose CPZ, a molecule with an excellent tolerance profile and a very high biodistribution in the saliva, lungs and brain. We hypothesize that CPZ could reduce the unfavorable course of COVID-19 infection among patients requiring respiratory support without the need for ICU care, and that it could also reduce the contagiousness of SARS-CoV-2. For this purpose, we plan a pilot, multicenter, randomized, single blind, controlled, phase III therapeutic trial (standard treatment vs. CPZ + standard treatment).
Conclusion. – This repurposing of CPZ for its anti-SARS-CoV-2 activity could offer an alternative, rapid strategy to alleviate infection severity. This repurposing strategy also avoids numerous developmental and experimental steps, and could save precious time to rapidly establish an anti-COVID-19 therapy with well-known, limited and easily managed side effects.

Mots clés :
Chlorpromazine
SARS-CoV-2
COVID-19
Repositionnement de molécules
Essai clinique

RÉSUMÉ

Objectifs. – La pandémie mondiale actuelle de COVID-19 a touché environ 2 350 000 personnes et fait plus de 160 000 morts. Nous avons observé dans le GHU PARIS Psychiatrie & Neurosciences (site Sainte-Anne, Paris, France) une incidence moins importante de formes symptomatiques de COVID-19 chez les patients que dans notre personnel soignant. Notre hypothèse est que les traitements psychotropes pourraient avoir une action prophylactique sur le SARS-CoV-2. Cette hypothèse est cohérente avec les propriétés antivirales connues de plusieurs psychotropes au premier rang desquels la chlorpromazine (CPZ). En plus

* Corresponding author at: GHU PARIS Psychiatrie & Neurosciences, site Sainte-Anne, Service Hospitalo-Universitaire, Pôle Hospitalo-Universitaire Paris 15, Paris, France.
E-mail address: m.plaze@ghu-paris.fr (M. Plaze).

https://doi.org/10.1016/j.encep.2020.05.006
0013-7006/

de ses effets antipsychotiques classiques, plusieurs études *in vitro* ont également démontré une activité antivirale de cette phénothiazine via l'inhibition de l'endocytose dépendante des clathrines. Récemment, des études ont révélé un effet anti-MERS-CoV et anti-SARS-CoV-1 de la CPZ.
Méthodes. – Dans ce contexte, l'étude reCoVery, basée sur le repositionnement de la CPZ – molécule avec un excellent profil de tolérance et une biodistribution très élevée dans la salive, les poumons et le cerveau – vise à tester l'hypothèse que la CPZ pourrait diminuer l'évolution défavorable de l'infection COVID-19 chez des patients oxygénorequérants sans nécessité de soins en réanimation mais aussi réduire la contagiosité du SARS-CoV-2. Nous allons réaliser pour cela un essai thérapeutique pilote de phase III multicentrique, randomisé, contrôlé (traitement standard vs CPZ + traitement standard) et en simple insu.
Conclusion. – Le repositionnement de la CPZ comme antiviral anti-SARS-CoV-2 offre une stratégie alternative et rapide pour atténuer la propagation du virus ainsi que la gravité et la létalité du COVID-19.

Introduction

The current COVID-19 pandemic has so far affected approximately 2,350,000 people and killed more than 160,000 [1]. It is the third and the most serious coronavirus epidemic after SARS-CoV-1 in 2003 and MERS-CoV in 2012. In the GHU PARIS Psychiatrie & Neurosciences (Sainte-Anne hospital, Paris, France) we have observed a lower incidence of symptomatic forms of COVID-19 among patients (around 4% in the Pôle Hospitalo-Universitaire de Psychiatrie Paris 15) than among our healthcare staff (around 14% of nurses and doctors in these same wards). Similar observations have been reported by other COVID units in psychiatric wards in France, Spain and Italy. These observations led us to hypothesize that psychotropic treatments administered to patients could have a prophylactic action towards SARS-CoV-2 and protect patients from the symptomatic and virulent forms of this infection.

This hypothesis is consistent with the known antiviral properties of several psychotropic drugs commonly used in psychiatry, and in particular chlorpromazine (CPZ). This phenothiazine, synthesized in 1951 by Rhône Poulenc, has been used in psychiatry from 1952 when Jean Delay and Pierre Deniker, two psychiatrists at Sainte-Anne hospital, discovered its antipsychotic properties [2]. From the 1980s, *in vitro* antiviral properties of this molecule against various RNA and DNA viruses were also reported: influenza virus [3], HIV [4], JC virus [5], Japanese encephalitis [6], HCV [7] and alphaviruses (Chikungunya, Semliki Forest Virus [8]).

Potential benefit of chlorpromazine against COVID-19

The effects of Chlorpromazine against earlier coronaviruses

CPZ anti-coronavirus activity was first documented in 2014, when two independent studies highlighted the *in vitro* inhibition of viral replication of coronaviruses [9,10]. In the first study, de Wilde et al. showed the anti-viral activity of CPZ and three other molecules against MERS-CoV and SARS-CoV-1 from an *in vitro* screening of 348 molecules [9]. The authors concluded that CPZ is one of the most promising molecules for inhibiting coronaviruses in human cells. The second study highlighted the effectiveness of 27 molecules, including CPZ, to inhibit viral replication of MERS-CoV and SARS-CoV-1 among the 290 molecules tested [10]. More recently, Cong et al. confirmed the efficacy of CPZ in inhibiting viral replication of SARS-CoV-1 and MERS-CoV in monocyte cell lines derived from human macrophages [11]. The efficacy of CPZ is greater than that of toremifene and chloroquine, two other molecules tested in this study.

Regarding the cellular mechanisms, CPZ affects clathrin-dependent endocytosis through an interaction with dynamin [12,13]. These clathrin-dependent endocytosis mechanisms are essential for coronaviruses to enter the cell [14]. Very recently, a review of the literature highlighted the interest of a therapeutic strategy targeting the pathway of clathrin-dependent endocytosis to inhibit viral replication of SARS-CoV-2 [15]. Other mechanisms of action of CPZ could be involved, since CPZ has been shown to also inhibit MERS-CoV replication in both the early and late stages of cell entry [9]. Overall, CPZ appears to possess broad-spectrum inhibition potential against coronaviruses [9,10].

The SARS-CoV-2 coronavirus involved in the current COVID-19 epidemic belongs to the 2b coronavirus family [16] and has many phylogenetic similarities with SARS-CoV-1 [17]. It is therefore very likely that a molecule with efficacy against MERS-CoV and SARS-CoV-1 would also have anti-SARS-CoV-2 activity. In order to confirm the hypothesis of an antiviral action of CPZ on SARS-CoV-2, a preclinical *in vitro* study started in April 2020 at the biosafety level 3 laboratory at Institut Pasteur in collaboration with the GHU PARIS Psychiatry & Neurosciences.

The immunomodulatory effects of chlorpromazine

In cases of severe COVID-19, several elements suggest a dysregulation of the immune system, although the precise mechanisms have not yet been elucidated [18]. The search for immunomodulatory treatments, driven by different mechanisms and on different cell types, is therefore of major interest. Since the 1990s, several studies have highlighted the immunomodulatory effects of CPZ [19], in particular by increasing blood levels of IgM [20]. In mice, CPZ has been shown to have a protective effect against septic shock induced by the injection of bacterial endotoxins, and to cause a concomitant decrease in IL-2, IL-4, IFN alpha, TNF and GM-CSF pro-inflammatory cytokines, as well as an increase in IL-10, an anti-inflammatory cytokine [21–24].

Chlorpromazine biodistribution, a possible advantage against COVID-19

One of the advantages of CPZ compared to other antivirals lies in its biodistribution. Indeed, it has been shown in animal experiments that after a single injection of CPZ, the highest concentrations of this molecule and its metabolites are detected in the lungs, with CPZ levels 20 to 200 times higher than in the blood [25,26]. This result was confirmed in humans in a post-mortem study on schizophrenia patients treated with CPZ [27]. Because of the respiratory tropism of SARS-CoV-2 [28], this marked pulmonary distribution could be of major interest for COVID-19 treatment. CPZ is also highly concentrated in saliva, with concentrations 30 to 100 times higher than in plasma in humans [29]. These high concentrations of CPZ in the salivary glands could decrease the salivary viral load and therefore reduce the contagiousness of SARS-CoV-2.

Finally, due to its lipophilic nature, CPZ can cross the blood-brain barrier [30] and could therefore have a therapeutic or prophylactic effect on the neurological forms of COVID-19 [31]. This cerebral CPZ distribution, known for a long time and underpinning both the antipsychotic action and the side effects of this molecule, was documented in the 1960s in animals and in humans [32,33]. Using isotopic labeling, CPZ was detected in the brain tissue 15 min after a single intravenous injection, in different brain areas including the cortex, the caudate nucleus, the putamen and the thalamus [32,33]. In chronic administration in rats, CPZ concentrations in the brain have been found to be up to 25 times higher than in the plasma [34,35].

Repurposing chlorpromazine, a molecule widely used for almost 70 years

The current health crisis urgently needs ready-to-use molecules to reduce the contagiousness, the severity and the lethality of the COVID-19 pandemic. The repurposing of already existing, FDA-approved drugs is an interesting alternative strategy to the discovery of new molecules. Indeed, repurposing eliminates many stages of development and testing required for new molecules, by deploying a drug whose side effects are already known.

CPZ, widely used in psychiatry, has an excellent tolerance profile. Its side effects are known: anticholinergic effects (sedation, dry mouth, constipation, urinary retention), QT increase and malignant syndromes in rare situations. It is also easy to manage. The FDA indications are the management of manifestations of psychotic disorders and manic-depressive illness. The non-psychiatric FDA-indications are control of nausea and vomiting, relief of restlessness and apprehension before surgery, relief of intractable hiccups and acute intermittent porphyria. CPZ is used in clinical routine among vulnerable patients, including pregnant women with drug-resistant nausea and vomiting [36] and patients with advanced cancer [37], as well as for the treatment of headache in various neurological indications [38,39].

The critical question of the CPZ dosage required to achieve a clinically relevant anti-SARS-CoV-2 effect in humans is still unsolved because:

- it is difficult to extrapolate effective *in vivo* dosages from effective*in vitro* dosages and;
- there is no *in vivo* animal data on the anti-coronavirus effect of CPZ.

However, it is important to note that the effective *in vitro* dosage for inhibiting viral replication of the MERS-CoV and SARS-CoV-1 coronaviruses were non-toxic doses for cells [9–11]. In addition, an *in vivo* animal study has shown antiviral efficacy (against adenoviruses) of CPZ at dosages used in humans [40]. Finally, the observation of the low prevalence of SARS-CoV-2 among our patients with psychiatric disorders suggests an effective dosage in humans similar to the dosage used for antipsychotic purposes.

Pilot study on the efficacy of chlorpromazine against COVID-19

Objectives of the reCoVery study

In this context, our hypothesis is that CPZ, if administered at the onset of respiratory signs, could limit the unfavorable evolution of COVID-19 infections and reduce the contagiousness of SARS-CoV-2. To test this hypothesis, we designed the reCoVery project ("repurposing of chlorpromazine in COVID-19 treatment"), a pilot, phase III, multicenter, single-blind, randomized controlled therapeutic trial. We will recruit oxygen-requiring patients with COVID-19 without the need for intensive care. Patients requiring or having required mechanical ventilation in intensive care will not be included in this study. The mechanisms of action of CPZ (*i.e.* inhibition of clathrin-dependent endocytosis) target the entry of the virus into the cell, blocking viral replication at the early stage of infection, which suggests greater effectiveness of this molecule at the start of the disease. In addition, the reduction in the prevalence of symptomatic and virulent forms of COVID-19 among our patients compared to clinical staff supports the hypothesis of an efficacy of CPZ in the early stages of the disease.

Patients will be randomized in two groups, one receiving standard COVID-19 treatment (standard-of-care, SOC) and the other receiving SOC in combination with CPZ (CPZ + SOC). Patients in the CPZ + SOC group will receive up to 300 mg P.O. per day of CPZ until the recovery criteria are met [41], with a maximum of 21 days of treatment.

The main objective of the reCoVery study is to demonstrate a shorter time to response to treatment (TTR) in the CPZ + SOC group than in the SOC group. Response to treatment is defined by the reduction of at least one level of severity on the WHO Ordinal Scale for Clinical Improvement (WHO-OSCI, [42]).

The secondary objectives are to demonstrate in the CPZ + SOC group compared to the SOC group:

- a greater clinical improvement;
- a greater decrease in the biological markers of viral attack by SARS-CoV-2 (PCR, viral load);
- a greater decrease in inflammatory markers (*e.g.*CRP and lymphopenia);
- a greater decrease in parenchymal involvement (chest CT) at the seventh day post-randomization;
- to define the optimal dosage of CPZ and its tolerance;
- to evaluate the biological parameters of response to treatment, in particular the involvement of inflammatory cytokines.

The reCoVery study design and its objectives are in line with WHO recommendations for conducting pilot studies in the therapeutic management of COVID-19 [42].

The expected benefit for people participating in this study is a reduction of the unfavorable course of COVID-19 disease, *i.e.* a reduction in the duration of the disease, of hospital care, of oxygen therapy, of mechanical or non-invasive ventilation and a reduction in mortality. Another possible benefit is a decrease in the anxiety commonly associated with COVID-19 dyspnea.

Safety of patients included in the study

The possible risks of this study are the well-known side effects of CPZ. These risks will be limited by clinical monitoring at the hospital over the whole period of CPZ treatment with specific monitoring of its potentially severe side effects: regular titration of CPK to detect neuroleptic malignant syndrome, daily clinical examinations, regular ECG. Also, as mentioned above, CPZ is already used at high dosages in non-psychiatric indications and sometimes in frail or vulnerable populations, in particular in the treatment of drug-resistant vomiting in oncology or hematology, and among patients with sepsis and organ failure [37]. The dosages used can then be up to 100 mg IV every 4 h [37]. Finally, it is important to note that since CPZ is not a respiratory depressant, this drug is not contraindicated for patients with acute respiratory distress syndrome (ARDS), unlike other anxiolytics such as benzodiazepines.

Conclusion

The originality of the reCoVery study is based on the repurposing of CPZ – a molecule discovered 68 years ago, widely used in psychiatry and with an excellent tolerance profile – for use in the current COVID-19 pandemic for which a treatment is still lacking. The potential therapeutic benefit of CPZ against COVID-19 is based on both the observation of a lower incidence of symptomatic forms of COVID-19 among patients in psychiatric wards and on several studies providing virological evidence.

CPZ, whose French commercial name, Largactil, was chosen in reference to its broad action (or "*large action*", in French) has a very broad spectrum of properties, including antipsychotic, anxiolytic, antiemetic, and antiviral properties, inhibition of clathrin-dependent endocytosis, modulator function on the blood-brain barrier, immunomodulatory effects, etc. CPZ has already demonstrated *in vitro* antiviral activity against SARS-CoV-1 and MERS-CoV. The immunomodulatory effects of CPZ could also open new perspectives for the treatment of not only early but also late and severe forms of COVID-19.

The discovery of the properties of CPZ, as with many other molecules in psychiatry, is the result of both serendipity and careful clinical observations. In this context of the COVID-19 pandemic, the field of mental illness could provide innovative therapeutic avenues in the fight against SARS-CoV-2.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors wish to thank the Fondation Pierre Deniker for its support, as well as Laetitia Canivet.

References

[1] Situation update worldwide, as of 20 April 2020. European Centre for Disease Prevention and Control.
[2] Delay J, Deniker P, Harl JM. [Therapeutic use in psychiatry of phenothiazine of central elective action (4560 RP)]. Ann Med Psychol (Paris) 1952;110:112–7.
[3] Krizanová O, Ciampor F, Veber P. Influence of chlorpromazine on the replication of influenza virus in chick embryo cells. Acta Virol 1982;26:209–16.
[4] Hewlett I, Lee S, Molnar J, Foldeak S, Pine PS, Weaver JL, et al. Inhibition of HIV infection of H9 cells by chlorpromazine derivatives. J Acquir Immune Defic Syndr Hum Retrovirol 1997;15:16–20.
[5] Pho MT, Ashok A, Atwood WJ. JC virus enters human glial cells by clathrin-dependent receptor-mediated endocytosis. J Virol 2000;74:2288–92.
[6] Nawa M, Takasaki T, Yamada K-I, Kurane I, Akatsuka T. Interference in Japanese encephalitis virus infection of Vero cells by a cationic amphiphilic drug, chlorpromazine. J Gen Virol 2003;84:1737–41.
[7] Blanchard E, Belouzard S, Goueslain L, Wakita T, Dubuisson J, Wychowski C, et al. Hepatitis C virus entry depends on clathrin-mediated endocytosis. J Virol 2006;80:6964–72.
[8] Pohjala L, Utt A, Varjak M, Lulla A, Merits A, Ahola T, et al. Inhibitors of alphavirus entry and replication identified with a stable Chikungunya replicon cell line and virus-based assays. PLOS ONE 2011;6:e28923.
[9] de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, et al. 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 2014;58:4875–84.
[10] Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother 2014;58:4885–93.
[11] Cong Y, Hart BJ, Gross R, Zhou H, Frieman M, Bollinger L, et al. MERS-CoV pathogenesis and antiviral efficacy of licensed drugs in human monocyte-derived antigen-presenting cells. PLOS One 2018;13:e0194868.
[12] Daniel JA, Chau N, Abdel-Hamid MK, Hu L, von Kleist L, Whiting A, et al. Phenothiazine-derived antipsychotic drugs inhibit dynamin and clathrin-mediated endocytosis. Traffic 2015;16:635–54.
[13] Wang LH, Rothberg KG, Anderson RG. Mis-assembly of clathrin lattices on endosomes reveals a regulatory switch for coated pit formation. J Cell Biol 1993;123:1107–17.
[14] Burkard C, Verheije MH, Wicht O, Kasteren SIv, Kuppeveld FJv, Haagmans BL, et al. Coronavirus Cell Entry Occurs through the Endo-/Lysosomal Pathway in a Proteolysis-Dependent Manner. PLOS Pathogens 2014;10:e1004502.
[15] Yang N. Targeting the Endocytic Pathway and Autophagy Process as a Novel Therapeutic Strategy in COVID-19. Int J Biol Sci 2020;16:1724–31.
[16] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
[17] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
[18] Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host Microbe 2020 [Online ahead of print].
[19] Pollmächer T, Haack M, Schuld A, Kraus T, Hinze-Selch D. Effects of antipsychotic drugs on cytokine networks. J Psychiatric Res 2000;34:369–82.
[20] Zucker S, Zarrabi HM, Schubach WH, Varma A, Derman R, Lysik RM, et al. Chlorpromazine-induced immunopathy: progressive increase in serum IgM. Medicine (Baltimore) 1990;69:92–100.
[21] Bertini R, Garattini S, Delgado R, Ghezzi P. Pharmacological activities of chlorpromazine involved in the inhibition of tumour necrosis factor production in vivo in mice. Immunology 1993;79:217–9.
[22] Gadina M, Bertini R, Mengozzi M, Zandalasini M, Mantovani A, Ghezzi P. Protective effect of chlorpromazine on endotoxin toxicity and TNF production in glucocorticoid-sensitive and glucocorticoid-resistant models of endotoxic shock. J Exp Med 1991;173:1305–10.
[23] Mengozzi M, Fantuzzi G, Faggioni R, Marchant A, Goldman M, Orencole S, et al. Chlorpromazine specifically inhibits peripheral and brain TNF production, and up-regulates IL-10 production, in mice. Immunology 1994;82:207–10.
[24] Tarazona R, González-García A, Zamzami N, Marchetti P, Frechin N, Gonzalo JA, et al. Chlorpromazine amplifies macrophage-dependent IL-10 production in vivo. J Immunol 1995;154:861–70.
[25] Bickel MH, Graber BE, Moor M. Distribution of chlorpromazine and imipramine in adipose and other tissues of rats. Life Sci 1983;33:2025–31.
[26] Sgaragli GP, Valoti M, Palmi M, Frosini M, Giovannini MG, Bianchi L, et al. Rat tissue concentrations of chlorimipramine, chlorpromazine and their N-demethylated metabolites after a single oral dose of the parent compounds. J Pharm Pharmacol 1995;47:782–90.
[27] Forrest IS, Bolt AG, Serra MT. Distribution of chlorpromazine metabolites in selected organs of psychiatric patients chronically dosed up to the time of death. Biochem Pharmacol 1968;17:2061–70.
[28] Chu H, Chan JF-W, Yuen TT-T, Shuai H, Yuan S, Wang Y, et al. Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: an observational study. Lancet Microbe 2020;1, e14-23.
[29] May PR, Van Putten T, Jenden DJ, Cho AK. Test dose response in schizophrenia: chlorpromazine blood and saliva levels. Arch Gen Psychiatry 1978;35:1091–7.
[30] Rundle-Thiele D, Head R, Cosgrove L, Martin JH. Repurposing some older drugs that cross the blood–brain barrier and have potential anticancer activity to provide new treatment options for glioblastoma. Br J Clin Pharmacol 2016;81:199–209.
[31] Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020 [Online ahead of print].
[32] Comar D, Zarifian E, Verhas M, Soussaline F, Maziere M, Berger G, et al. Brain distribution and kinetics of 11C-chlorpromazine in schizophrenics: positron emission tomography studies. Psychiatry Res 1979;1:23–9.
[33] Sjöstrand SE, Cassano GB, Hansson E. The distribution of 35S-chlorpromazine in mice studied by whole body autoradiography. Arch Int Pharmacodyn Ther 1965;156:34–47.
[34] Tsuneizumi T, Babb SM, Cohen BM. Drug distribution between blood and brain as a determinant of antipsychotic drug effects. Biol Psychiatry 1992;32:817–24.
[35] Wiesel FA. The distribution and metabolism of chlorpromazine in rats and the relationship to effects on cerebral monoamine metabolism. Eur J Pharmacol 1976;40:263–72.
[36] Committee on Practice B.-O. ACOG Practice Bulletin No. 189: Nausea And Vomiting Of Pregnancy. Obstet Gynecol 2018;131:e15–30.
[37] Gupta M, Davis M, Walsh D, LeGrand S, Lagman R, Parala-Metz A. Nausea and Vomiting in Advanced Cancer—The Cleveland Clinic Protocol (TH310). J Pain Symptom Manage 2013;45:338–9.
[38] Marmura MJ, Silberstein SD, Schwedt TJ. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. Headache 2015;55:3–20.
[39] Weinman D, Nicastro O, Akala O, Friedman BW. Parenteral Treatment of Episodic Tension-Type Headache: A Systematic Review. Headache 2014;54:260–8.
[40] Kanerva A, Raki M, Ranki T, Särkioja M, Koponen J, Desmond RA, et al. Chlorpromazine and apigenin reduce adenovirus replication and decrease replication associated toxicity. J Gene Med 2007;9:3–9.
[41] HCSP. Coronavirus SARS-CoV-2 : critères cliniques de sortie d'isolement des patients infectés. Paris: Haut Conseil de la Santé Publique; 2020.
[42] WHO | Coronavirus disease (COVID-2019) R&D. WHO; 2020.