บทบาทของฟลูว็อกซามีนในโรคโควิด-19
Fluvoxamine and Its Role in COVID-19

นิพนธ์ปริทัศน์

Review Article

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บทคัดย่อ

การระบาดของโรคอุบัติใหม่โควิด-19 ทำให้เกิดแบบแผนการรักษาเพื่อการกำจัดเชื้อโควิด-19 และการดูแลรักษาผู้ป่วย ยาเดิมที่ประกอบด้วยข้อบ่งใช้ใหม่เป็นทางเลือกที่เร็วที่สุดในการจัดการกับโรคระบาด ปัจจุบันพบว่ายาฟลูว็อกซามีนมีประสิทธิภาพในการรักษา โควิด-19 ซึ่งเป็นยาในกลุ่มต้านการซึมเศร้า มีข้อมูลเภสัชจลนศาสตร์และเภสัชพลศาสตร์ที่ชัดเจน สะดวกต่อการสั่งใช้ยา กลไกของยาฟลูว็อกซามีน ในการรักษา โควิด-19 คือ ป้องกันการแบ่งตัวของไวรัสและลดการสร้างสารไซโตไคน์ที่ก่อให้เกิดการอักเสบ อย่างไรก็ตาม ข้อมูลในปัจจุบันยังมีค่อนข้างจำกัด อาจต้องรอผลการศึกษาวิจัยทางคลินิก เพื่อพิสูจน์สมมติฐานในการรักษา โควิด-19 ของยาฟลูว็อกซามีน

คำสำคัญ : โควิด-19, ฟลูว็อกซามี, ยาต้านซึมเศร้า, ไซโตไคน์

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Abstract

With the advent of the COVID-19 pandemic era, new treatments are needed to eradicate its spread and to heal human society. Familiar medications with new indications may be the fastest way to cope with the pandemic. Fluvoxamine is one such medication that has promising potential. It is a well-known antidepressant with pharmacokinetic and pharmacodynamics properties that make it convenient to use. Its mechanisms of action against virus replication and inflammatory cytokines have been well reviewed, but more clinical trials are needed to prove the hypothesis about its potential role in treating COVID-19.

Keywords: COVID-19, fluvoxamine, antidepressants, cytokines

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Introduction

Over the past few years, the Coronavirus 2019 (COVID-19) outbreak has led to a near collapse of healthcare, social, and economic systems worldwide as the world has struggled to cope with the resulting pandemic. Various measures have been applied to cope with the pandemic; particularly, mass vaccination, but also the use of curative medications. There is some evidence suggesting that fluvoxamine has potential effectiveness for patients with COVID-19 in the early stage and may prevent clinical deterioration and reduce the need for hospitalization. Consequently, this study aimed to review the data on the pharmacokinetics and pharmacodynamics of fluvoxamine and its role in COVID-19 treatment.

Pharmacodynamics and pharmacokinetics of Fluvoxamine

Fluvoxamine is a non-sedating antidepressant that acts as a potent selective serotonin reuptake inhibitor (SSRI). Fluvoxamine has been commercially available since 1983, and it was first investigated in patients with depression in the 1970s.[1] The structure of fluvoxamine is based on a benzene substituted by a (1E)-N-(2-aminoethoxy)-5-methoxypentanimidoyl group at the 1 position and a trifluoromethyl group at the 4 position (Figure 1).[1]

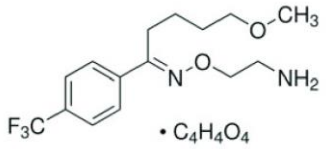

Figure 1 Structure of fluvoxamine.

Pharmacodynamics

The mechanism of fluvoxamine is a potent serotonin inhibitor of brain neurons for the subtypes of sigma (σ)-receptors, which is also the main mechanism for the

management of psychosis and aggression.[2] The activity of fluvoxamine for the management of depression is initiated by inhibition of serotonin transporter at the presynaptic cleft, resulting in an enhanced serotonin activity at the postsynaptic terminal, together with some effects on dopamine and norepinephrine.[3] This process may lead to primary and secondary changes in the receptors and rates of firing and the release of neurotransmitters, which may result in a decrease in depressive symptoms.[1]

Pharmacokinetics

The absolute bioavailability of immediate- release fluvoxamine tablets is 53%, while that of extended-release capsules is 84%. Fluvoxamine is 80% bound to plasma protein. The metabolism of fluvoxamine takes place in the liver via oxidative demethylation and deamination. Fluvoxamine is excreted through the renal system, with the excretion of 94% of the drug- related products. However, the clearance of fluvoxamine is reduced by 50% in elderly patients (Table 1).[1]

Table 1 Pharmacokinetics of fluvoxamine.

Process	Properties
Absorption	• The absolute bioavailability of immediate-release tablets is 53% and that of extended-release capsules is 84%.
	• Food slightly increases the mean AUC and C_{max} but does not significantly affect the absorption.
Distribution	• Fluvoxamine is 80% bound to plasma protein.
	• The distribution volume of fluvoxamine is 45 L/kg.
Metabolism	• Fluvoxamine is metabolized in the liver via oxidative demethylation and deamination.
	• Fluvoxamine is as an inhibitor of CYP 1A2 (potent), CYP2C9, CYP 2C19, and CYP 3A4. Moreover, it is also a weak inhibitor of CYP 2D6 *in vitro*.
Excretion	• The renal excretion of fluvoxamine is 94% of the drug- related products, while 2% is excreted unchanged in the urine.
	• There is a 30% decrease in fluvoxamine clearance in patients with hepatic dysfunction. In the elderly, the clearance of fluvoxamine is reduced by 50%.
Elimination half-life	• The mean plasma half-life of 100 mg fluvoxamine at a steady state from immediate- release tablets is 15.6 hours and 16.3 hours from extended-release capsules.

Indication and dosage

The fluvoxamine dosage for depression is 50 – 300 mg/day, while the dosage for obsessive–compulsive disorder and social society issues is 100 – 300 mg/day. The initial dosage is 50 mg/day orally, which may then be increased by 50 mg/day every week during the first month of therapy. If little or no response is seen in the first 4 weeks, the dosage is increased weekly or biweekly up to the maximum dosage tolerated, maintaining the treatment for a period of at least 4 to 6 weeks at the highest comfortably tolerated dosage. The maximum dosage is 300 to 450 mg/day.[1]

Adverse effects

The accumulative dosage of fluvoxamine increases the risk of late adverse effects, which may include cardiotoxicity. However, fluvoxamine does not appear to have adverse effects in healthy patients. The most common adverse events are nausea and vomiting (37% of patients), mostly due to the effects of increased serotonin on the gastrointestinal and central nervous system. Headache and sexual dysfunction, including erectile dysfunction, are also side effects of SSRIs.

SSRIs may present central nervous system impairment and abnormal sleep patterns. In contrast, fluvoxamine has no effect on cognition or psychomotor speed. Moreover, fluvoxamine can improve sleep quality and post- traumatic stress disorder (PTSD) symptoms including insomnia and nightmares. Children taking SSRIs may experience decreased appetite and weight loss including through taking fluvoxamine.[1] Moreover, fluvoxamine has been reported to increase the resting metabolic rate, which can result in less weight gain compared to drug-free periods.[2,4] de.

Fluvoxamine and COVID-19

COVID-19 is caused by the novel RNA virus (SARs-CoV-2) and can lead to acute respiratory disease. Evidence has revealed that SARs- CoV- 2 has deleterious effects on the central nervous system (CNS) resulting in neurological and psychiatric symptoms in patients with infection.[5] The repurposing of a drug is a process that is carried out to identify new therapeutic uses for existing drugs. It is considered a promising approach for the COVID- 19 pandemic because of the high speed and low costs required for treatment development and approval.[5]

Evidence has suggested that the use of fluvoxamine might be associated with a reduced risk of clinical deterioration in SARS-CoV-2-infected patients, especially fluvoxamine. There are several mechanisms of fluvoxamine in potentially treating COVID- 19. The most likely mechanisms of action are described below.

Activation of sigma-1 receptor activity

SARs- CoV- 2 virus enters cells via the spike glycoprotein and binds to the angiotensin- converting enzyme 2 (ACE2) receptor, which subsequently activates endocytosis. SARs-

CoV-2 replication takes place in the endoplasmic reticulum (ER). This replication causes ER stress, which may contribute to inflammatory events, such as cytokine storms, which result in severe symptoms of acute respiratory distress syndrome and are accompanied by high mortality. Fluvoxamine acts as a potent sigma-1 receptor agonist, which decreases SARs-CoV-2 replication via sigma-1 chaperone activity and may attenuate ER stress. This results in blocking inflammatory events and delaying clinical deterioration in SARs-CoV-2 (Figure 2).[5,6]

Platelets aggregation

Innate immunity, such as neutrophils, monocytes, eosinophils, and dendritic cells affect adaptive immunity and modulate B-cells and T-cells by secreting various granule proteins, such as serotonin (5-HT) and platelet factor 4 (PF4). Moreover, platelets cause lysosomal degradation of the viral coat and activation of the pathogen-associated molecular pattern receptor Toll-like receptor 7 (TLR7) signals though protein kinase B (AKT). Direct platelet–SARs-CoV-2 interactions may be significant in the prothrombotic response, whereby platelet reactions to the signal arising from the injury may contribute to thrombosis. 5-HT becomes a vasoconstrictor when the endothelium is damaged, leading to an aggregation process. In this process, 5-HT is taken up from plasma and stored in platelet granules, and is then released into the blood and activates 5-HT_{2A} receptors on the platelet membranes, which enhances platelet aggregation. Moreover, 5-HT promotes the recruitment of neutrophils. Fluvoxamine inhibits serotonin transporter (SERT) and elevates plasma 5-HT levels, resulting in a decrease in platelet aggregation. In addition, fluvoxamine may increase the bleeding time and reduce neutrophil recruitment, which may attenuate platelet aggregation and blood clotting (Figure 2).[6-8]

Mast cell degranulation

Mast cells can recognize viruses by several mechanisms, including Toll-like receptor 3 (TLR3) for detecting viral double-stranded ribonucleic acid (RNA), viral sphingosine-1-phosphate (S1P) binding to S1P receptors, and retinoic acid by inducing the gene I (RIG-1) recognition of uncapped viral RNA, and then expressing ACE2, which is a principal receptor of SARs-CoV-2. Thus, mast cells could become hosts of the virus. Fluvoxamine can stabilize mast cells, such that fluvoxamine can reduce histamine release from mast cells as well as reduce cytokine storms in COVID-19 (Figure 2).[6,9]

Melatonin

An *in vitro* study of human epithelial cells and macrophages found that fluvoxamine decreases the expression of intracellular cell adhesion molecule-1 (ICAM-1), cyclooxygenase 2 (COX-2), vascular cell adhesion molecule-1 (VCAM-1), and inducible nitric oxide synthase (iNOS) in epithelial cells that are inflammatory genes.[5] Therefore, fluvoxamine was studied in SARS-CoV-2-infected patients.

Cytokine storms and the inflammatory process induce the apoptosis of epithelial cells and endothelial cells, as a result of vascular leakage, and lead to acute respiratory distress syndrome (ARDs) or acute lung injury (ALI). Melatonin has indirect anti-viral actions with anti-inflammation, anti-oxidant, and immunomodulation mechanisms. The anti-inflammatory effect of melatonin involves the suppression of nuclear factor kappa-B (NF-kB) activation in ARDs, and the downregulation of NF-kB activation in T-cells and lung tissue. Melatonin reduces the elevated production of cytokines and chemokines. Melatonin presents anti-oxidative effects, by upregulating anti-oxidative enzymes, downregulating pro-oxidative enzymes, and by directly interacting with free radicals. The role of melatonin in immunomodulation is to regulate the NOD-like receptor 3 (NLRP3) inflammasome, which is part of the innate immune response that is correlated to lung injury, allergic airway inflammation, and oxygen-induced ALI, leading to reducing the infiltration of macrophages and neutrophils into the lungs.[10] Fluvoxamine increases melatonin levels via the inhibition of CYP 1A2 and by inhibiting melatonin degradation, ultimately reducing the inflammatory effects from the SARs-CoV-2 virus (Figure 2).[6]

Clinical Studies of Fluvoxamine and COVID-19

The preliminary study of adult outpatients with symptomatic COVID-19 was performed as a double-blind, randomized, clinical trial. This study compared 80 patients who received fluvoxamine 100 mg three times daily and 72 patients who received a placebo. The eligible study participants were community-living, non-hospitalized adults

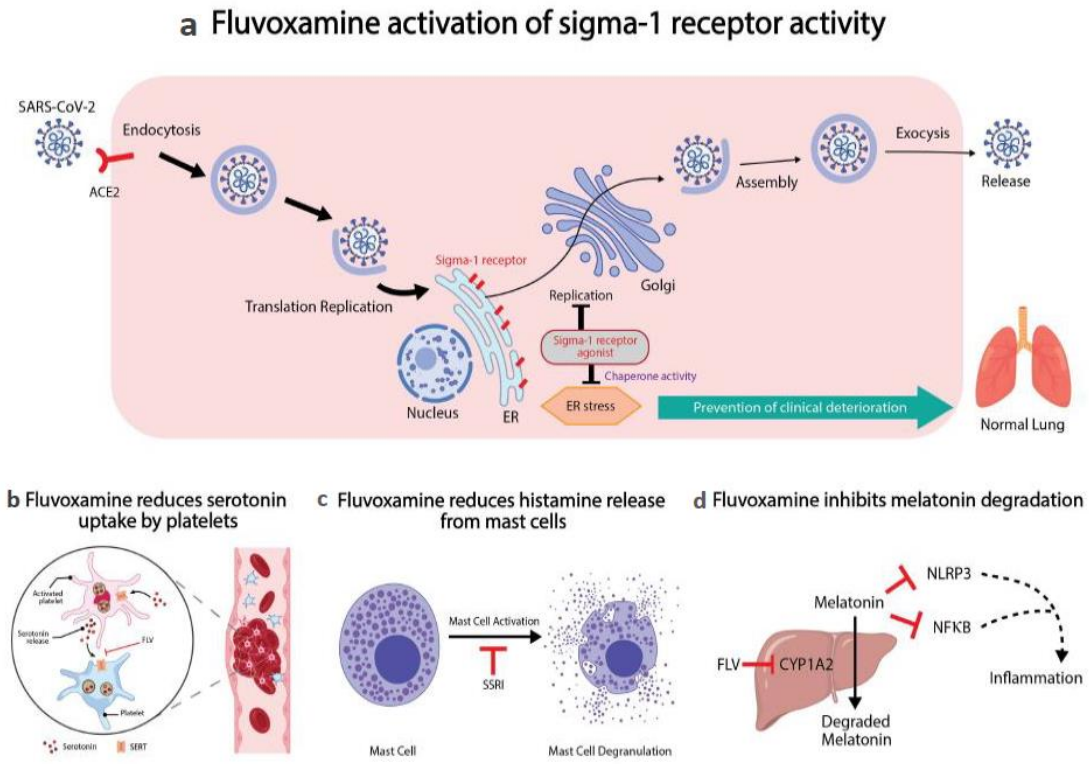

Figure 2 Mechanisms of fluvoxamine in potentially treating COVID-19.

Note:

2a) Fluvoxamine activates sigma-1 receptor activity, which decreases SARs-CoV-2 replication via sigma-1 chaperone activity and may attenuate ER stress.

2b) Fluvoxamine reduces serotonin and neutrophil recruitment, which may attenuate platelet aggregation.

2c) Fluvoxamine reduces histamine release from mast cells as well as reduces cytokine storms.

2d) Fluvoxamine increases melatonin levels via the inhibition of CYP 1A2 and by inhibiting melatonin degradation.

with severe acute respiratory syndrome coronavirus 2 infection, with the onset of COVID-19 symptoms within 7 days and an oxygen saturation of 92% or greater. The duration offollow-up assessment was 30-day post-randomization. The results showed that clinical deterioration was found in none of the fluvoxamine-treated COVID-19 patients and 6 of the 72 (8.3%) patients in the placebo group [absolute difference = 8.7% (95%CI = 1.8% – 16.4%)] by survival analysis, log rank χ^2 = 6.8 and p = 0.009]. The fluvoxamine group showed 1 serious and 11 other adverse events, while the placebo group showed 6 serious and 12 other adverse events. In spite of the promising results, several limitations were noted. It was a small study that was conducted within a single geographic area with the small number of end point events. The differences in clinical deterioration may have been a consideration of the comparative baseline distributions of oxygen saturation rather than an effect of treatment. This study had a short follow-up duration and almost 20% of participants stopped the survey. The study did not measure the effect of fluvoxamine on persistent symptoms or late deterioration.[11]

The TOGETHER trial was another major study and involved a placebo-controlled, randomized, adaptive platform trial done in high-risk symptomatic patients. The patients were randomly assigned into two groups: fluvoxamine 100 mg twice daily for 10 days or the placebo group. The primary endpoint was a composite endpoint of hospitalization, which was defined as either retention in a COVID-19 emergency setting under observation for more than 6 hours or transfer to a tertiary hospital due to COVID-19 for up to 28 days post-random assignment on the basis of an intention to treat. The eligible criteria were patients older than 18 years old, presenting to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date or a positive rapid test for SARS-CoV-2 antigen done at the time of screening or a patient with a positive SARS-CoV-2 diagnostic test within 7 days of symptom onset. The proportion of high-risk COVID-

19 patients who transferred to a tertiary hospital as a result of COVID-19 was lower for the fluvoxamine group than the placebo group: 79 (11%) of 741 vs. 119 (16%) of 756 [relative risk = 0.68%; 95% Bayesian credible interval (95% BCI) = 0.52 – 0.88]. The study found no significant distinction in the number of treatment emergent adverse events among patients in the fluvoxamine and placebo groups. Therefore, the use of fluvoxamine in the fluvoxamine group (100 mg twice daily for 10 days) in high-risk outpatients with early diagnosed COVID-19 decreased the necessity of hospitalization. This study greatly suggests that the use of fluvoxamine can create an effective, inexpensive, safe, and relatively well tolerated option for ambulatory COVID-19 patients. The major limitation of the study was related to the challenges of doing trials in COVID-19 cases when no standard of care exists for early treatment. Moreover, there is a highest risk of disease progression from COVID-19 as some patients with numerous risk factors might quickly recover while others with less established risk factors might not. The adherence might also be associated to tolerability, as 84 and 64 participants stopped treatment with fluvoxamine and placebo, respectively. Eventually, when the study began, vaccines were not available. Therefore, the study modified the eligible criteria and authorized vaccinated patients to enter during the trial.[12]

Conclusion

COVID-19 treatment is the key to ending the Coronavirus pandemic. Fluvoxamine is a familiar medication that has well-known pharmacokinetics and pharmacodynamics properties. It acts as a Sigma-1 receptor agonist, in which its distinctive mechanisms of action modulate innate and adaptive immunity. Further, it facilitates anti-platelet and mast cell stabilization, which may prevent cytokine storm. Although the mechanism is promising, more clinical trials are still needed to prove the concept of using fluvoxamine to treat COVID-19.

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