Austin Journal of Clinical Case Reports

Open Access

Austin Publishing Group

Case Report

Ondansetron in a Paxlovid Intolerant Man

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Received: July 19, 2022; **Accepted:** August 20, 2022; **Published:** August 27, 2022

Abstract

A symptomatic 22-year-old man, unvaccinated and living with high-risk elder parents, was prescribed nirmatrelvir/ritonavir (Paxlovid®) after testing positive for COVID-19. The patient developed persistent moderate to severe nausea after the first dose, progressing to severe nausea and several vomiting episodes after the second dose. To avoid discontinuing Paxlovid, a trial with ondansetron8 mg PO, was initiated, with the first dose given one hour after the last vomiting episode. Due to the improvement in nausea and absence of retching and vomiting, treatment was continued at a dose of 8 mg PO, twice daily, 1-2 hours before each Paxlovid dose, and maintained until completion of the five-day antiviral treatment. No nausea or vomiting was reported during treatment with ondansetron.

In COVID-19 patients intolerant to Paxlovid, due to development of moderate to severe nausea and vomiting, use of ondansetronmay prevent treatment discontinuation, and allow completion of the recommended course of therapy. Ondansetron is not expected to exert drug-interactions with the nirmatrelvir-ritonavircombination.

Background

Paxlovid®, is an orally active antiviral combination of nirmatrelvir and ritonavir.Nirmatrelvir, the anti-SARS-COV-2 component, works intracellularly to inhibit the main viral3CL protease (M^{pro}) interfering with viral replication [1]. Ritonavir prevents nirmatrelvir degradation by Cytochrome 3A4 (1), increasing and sustaining therapeutic nirmatrelvir anti-COVID-19concentrations [2]. Efficacy and safety of nirmatrelvir-ritonavir combination against COVID-19 has been demonstrated [3-5]. In an outpatient, randomized, placebo-controlled trial, of unvaccinated adults with mild-to-moderate COVID-19, initiation of Paxlovid treatment ≤3 days after onset of symptoms, reduced COVID-related hospitalizations, and all-cause deaths [3]. In December of 2021, the FDA granted an Emergency Use Authorization of Paxlovid for the treatment of non-hospitalized adults and pediatric patients aged ≥12 years and weighing ≥40 kg with mild to moderate COVID-19 who are at high risk of disease progression [4]. Recently, the WHO strongly endorsed Paxlovid use in unvaccinated, older and in immunosuppressed individuals with non-severe COVID-19 [5]. Noserioussafety issues have been reported with the nirmatrelvir-ritonavir combination [3-5]. Mild to moderate dysgeusia, nausea, vomiting, and diarrhea, are the most frequently reported side effects [3-5,7]. Adverse effects can lead to medication non-compliance and premature discontinuation of the recommended 5 day course of therapy. Given its novelty, clinicians prescribing Paxlovid must be familiar with the medication side effect profile and gain experience with treatment modalities which may abate symptoms that lead to treatment non-compliance.

Case Presentation

A 22 years old, white Hispanic male, who two days after contact with a COVID-19 positive person, developed intense chills, fever (average 38.3°C), sore throat, nasal congestion, malaise, tiredness, and generalized muscle aches.Symptoms persisted for 36 hours which prompted the patient's presentation for evaluation. On physical examination, the patient's initial vital signs included a blood pressure of 128/64, pulse of 105 beats per minute, oral temp of 38.4^{0}C, respiratory rate of 20 breaths per minute and an oxygen saturation of 98% on room air. The patient was overall well appearing and in no acute distress. The patient's neck was supple with no appreciable lymphadenopathy. The cardiac examination was regular rate and rhythm without murmurs, gallops, or rubs. Distal pulses were 2+ in the radial, dorsal is pedis and posterior tibial arteries. The lung examination was clear to auscultation bilaterally. The abdomen was non tender to palpation and there was no rash appreciated on the skin exam.

On the day of presentation, the patient tested positive for COVID-19 by polymerase chain reaction. Patient had a previous PCR confirmed COVID-19 infection in October of 2020 and had received a single dose of the Pfizer-Biontech vaccine in February 2021.Because the case subject is not fully vaccinated, and is currently living with elder, high-risk parents, isolation and Paxlovid treatment were prescribed.

Treatment and Outcome

Paxlovid treatment was started approximately 38 hours after the initiation of symptoms. Approximately two-hours after the first dose, the patient started complaining of severe nausea (VAS: 7/10) [8], food aversion and dysgeusia, which persisted for rest of the dose interval. One hour after the second dose, the intensity of the nausea increased (VAS 10/10), followed by two vomiting episodes. Due to the persistence and exacerbation of the severe nausea and vomiting, the patient requested an alternative treatment to Paxlovid. After discussing pros and cons of treatment discontinuation, a trial with ondansetron, 8 mg PO, was initiated, with the first dose administered one hour after the vomiting episodes. After the first dose of ondansetron, nausea intensity ameliorated (VAS 3/10), and no new

Citation: Cubeddu LG, Dalley TM and Cubeddu LX. Ondansetron in a Paxlovid Intolerant Man. Austin J Clin Case Rep. 2022; 9(4): 1254.

episodes of retching or vomiting were reported. Due to the favorable response, ondansetron, 8 mg PO, was administered twice daily, 1-2 hours before each of Paxlovid doses, and continued until completion of the five-days antiviral treatment. The nausea disappeared after second dose of ondansetron, appetite improved, and no further nausea or vomiting was reported through the rest of the Paxlovid treatment. The taste alteration, although milder, persisted throughout the treatment period. No jaundice, abdominal pain, diarrhea, or any other new symptoms were reported. Finger oximetry SpO2 averaged 98%.Covid-related symptoms gradually subsided, no chills or fever were present after the fourth day, with residual occasional cough and tiredness at day 8 of symptoms onset. The patient is currently asymptomatic (day 12) and in good health.

Discussion

The efficacy of ondansetron against the nausea and vomiting associated with Paxlovid treatment, may add to the list of off label uses of ondansetron [9]. Ondansetron, a selective 5-HT3 receptor antagonist, was developed for the prevention and treatment of highly and moderately emetogenic chemotherapeutic regimes [9,10]. These regimes induce massive degranulation of enterochromaffin cells releasing large amounts of serotonin, which acting on 5-HT3 receptors on enteric vagal afferents, signal the emetic reflex [10]. Ondansetron has also shown antiemetic efficacy for cyclophosphamide-based regimens, and radiation-induced and postoperative nausea and vomiting [9,11]. Off label use ondansetron in acute gastroenteritis, drug overdose, and in pregnancy and hyperemesis gravidae, has also been reported [9,12,13].

Ritonavir is a potent inhibitor of cytochrome P-450 3A4, increasing the risk of clinically significant drug interactions. Noteworthy, ondansetron can be safely administered combined with nirmatrelvir-ritonavir, because ondansetron is not selectively metabolized, and is neither an inducer nor an inhibitor of cytochrome P-450 3A4 [13]. Ondansetron is metabolized by several of the cytochrome P450 isoforms, CYP1A1, CYP1A2, CYP2D6, and the CYP3A, with no preference for a single form, which minimizes clinically significant interactions. Medications with a narrow margin of safety, and that that are metabolized via the cytochrome P450 3A4, such as ranolazine, amiodarone, dronedarone, flecainide, colchicine, lurasidone, clozapine, and midazolam, among others, should be avoided or their dose reduced, if combined with Paxlovid [15,16].

Summary

In summary, we report an additional novel application of ondansetron in a patient with COVID-19 who developed severe nausea and vomiting episodes upon treatment initiation with Paxlovid. Addition of ondansetron allowed completion of the full 5-days treatment with the antiviral combination pills. Although, nausea, may also be a symptom of a COVID-19 infection (16), the observation that the nausea and vomiting developed not before, but promptly after the first dose and intensified promptly after the second dose, suggests that these symptoms were likely induced by the antiviral medication.

Learning Points

- Nirmatrelvir-ritonavir (Paxlovid) is the first oral medication to receive FDA Emergency Use Authorization (EUA) for the treatment of COVID 19. Mild to moderate dysgeusia, nausea, vomiting, and diarrhea, are the most frequently reported side effects.
- Given its novelty, clinicians prescribing Paxlovid must be familiar with the medication side effect profile and gain experience with treatment modalities which may abate symptoms that lead to treatment non-compliance.
- Ondansetron, a selective 5-HT3 receptor antagonist, may provide relief of the nausea and vomiting associated with Paxlovidtreatment in patients with COVID 19, allowing treatment completion and full anti-COVID efficacy.Ondansetron can be safely administered combined with nirmatrelvir-ritonavir becauseondansetron is not selectively metabolized, and is neither an inducer nor an inhibitor of cytochrome P-450 3A4.

Contributors

LGC, MD and LCX contributed equally to the planning, conduct, concept, and authorship of the paper and are requesting to join first authorship.

Funding

No specific grants for this research were requested from any funding agency in the public, commercial or not-for-profit sectors.

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