

Cardiovascular Drug Interactions in COVID-19 Patients with Nirmatrelvir/Ritonavir

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Abstract

Symptomatic, non-hospitalized patients with coronavirus disease-2019 (COVID-19) who are at high risk of progressing to severe disease are treated with nirmatrelvir-ritonavir (NMVr). COVID-19 adverse events are more likely to occur in people who have cardiovascular risk factors as well as cardiovascular disease. As a result, they are more likely to receive NMVr. The pharmaceutical enhancer in NMVr, ritonavir, affects the P-glycoprotein pump and is an inhibitor of the CYP450 pathway's enzymes, particularly CYP3A4 and, to a lesser extent, CYP2D6. It is possible for NMVr to interact significantly with medications commonly used to treat cardiovascular conditions, which could result in severe side effects. It is essential to be aware of such interactions and to take preventative measures. In this survey, we examine potential medication drug communications among NMVr and regularly utilized cardiovascular prescriptions in light of their pharmacokinetics and pharmacodynamic properties.

Keywords: Cardiovascular medications • COVID-19 • Drug-drug interactions • Nirmatrelvir-Ritonavir • SARS-CoV-2

Introduction

Despite receiving three doses of an mRNA COVID-19 vaccine, a 57-year-old man with ischemic cardiomyopathy and a history of PCI a month prior presents with symptomatic coronavirus disease-2019 (COVID-19). Aspirin, clopidogrel, high-dose atorvastatin, metoprolol succinate, sacubitril/valsartan, spironolactone, and dapagliflozin are some of his home medications. Nirmatrelvir-ritonavir (Paxlovid, a Pfizer product) is given to him. He calls his cardiologist to inquire about possible drug interactions on the advice of his primary care physician. Aspirin, spironolactone, dapagliflozin, and metoprolol succinate should all be continued by him. Prasugrel replaces clopidogrel. Sacubitril/valsartan and atorvastatin are temporarily withheld. After a 5-day course of NMVr, all cardiovascular medications are resumed, with the exception of atorvastatin, which is resumed three days later [1].

Discussion

As one of the first oral antiviral agents for the treatment of symptomatic adults with mild to moderate SARS-CoV-2 infection who are at high risk for progression to severe disease, Nirmatrelvir-ritonavir (NMVr) received emergency use authorization from the U.S. Food and Drug Administration in December 2021. Compared to placebo, NMVr reduces progression to severe COVID-19 by 89% in nonvaccinated high-risk symptomatic patients. Patients with Najjar-Debbiny et al. retrospectively analyzed outcomes in unvaccinated and vaccinated patients who were prescribed NMVr and demonstrated a combined risk reduction of 46%, with subgroup analysis demonstrating a similar magnitude of effectiveness in both populations. However, real-world data suggest that it may be equally effective in those who have been vaccinated

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against COVID-19. More than a million courses of NMVr have been prescribed thus far, and its use is anticipated to increase with the emergence of SARS-CoV-2 variants that are resistant to monoclonal antibody therapies. The use of NMVr reduces disease progression, the time it takes to achieve a lower viral load, ER visits, hospitalizations, and all-cause mortality. Even though NMVr has been shown to be very effective in patients with pre-existing CVD, it has a lot of drug-drug interactions (DDIs) with cardiovascular medications that are commonly used. Because of this, it's important that all doctors know about those DDIs [2].

The pharmacokinetics and mechanism of action of NMVr Nirmatrelvir prevents SARS-CoV-2 from producing a protease enzyme necessary for viral replication. In antiretroviral therapy for the human immunodeficiency virus, low-dose ritonavir is combined with nirmatrelvir as a pharmaceutical enhancer to delay its hepatic metabolism and extend its duration of action. Ritonavir is an inhibitor of cytochrome P (CYP) 450 enzymes, specifically CYP3A4 and, to a lesser extent, CYP2D6. These enzymes, which are mostly found in hepatocytes, are the ones that are in charge of the oxidative metabolism of a lot of medications. P-glycoprotein (P-gp) is an efflux pump in the intestinal, hepatic, and renal epithelia that facilitates drug transport. Ritonavir also weakens the effects of other CYP450 enzymes, resulting in decreased levels of various medications when administered together. Ritonavir's primary inhibition of P-gp and subsequent induction over time may cause unpredictability in DDIs. In vitro, Nirmatrelvir does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP2D6, but it does inhibit CYP3A4 and P-gp. Because NMVr is a substrate of CYP450 enzymes, it may be rendered ineffective by other potent enzyme inducers. Natural anion carrier polypeptide (OATP) 1B1 is a take-up carrier communicated on the sinusoidal surface of hepatocytes, liable for hepatic take-up of specific medications. NMVr is renally cleared, so it is not recommended for people whose estimated glomerular filtration rate is less than 30 mL/min. NMVr has a weak inhibitory effect on OATP1B1, which can cause relevant DDIs. It is contraindicated in patients with severe liver disease because there are no data on patients with severe hepatic impairment (Child-Pugh class C). Patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) liver dysfunction do not require a dose adjustment [3-5].

Anticoagulants

Unfractionated and low-molecular-weight heparin can be given with NMVr because they are not metabolized by CYP450 enzymes. Warfarin, on the other hand, is broken down differently by various CYP450 enzymes. CYP2C9 is responsible for metabolizing its S-enantiomer, while CYP3A4 and CYP1A2 are responsible for metabolizing its R-enantiomer. Due to the short duration of NMVr, ritonavir is more likely to result in a reduction in international

normalized ratio (INR) and warrants frequent INR monitoring because the initial predominant effect is CYP inhibition followed by CYP induction about a week later [6].

Since Apixaban is a substrate of both CYP3A4 and P-gp, administering it with NMVr increases the risk of bleeding. When administered concurrently with ritonavir, the dosage of apixaban should be decreased by 50% for patients taking 10 mg or 5 mg twice daily. For patients taking 2.5 mg twice daily for extended venous thromboembolism (VTE) prophylaxis, it is reasonable to continue taking apixaban at the same dose with the expectation that this will likely achieve therapeutic levels of anticoagulation for 8 days after initiating NMVr due to the interaction with riton. Case-by-case management is advised for patients with atrial fibrillation (AF) taking 2.5 mg twice daily. Metabolism and excretion of rivaroxaban involve CYP3A4, CYP2J2, and P-gp. In patients with a high risk of thrombosis, apixaban should be withheld for 12 to 24 hours, then initiation of both NMVr and an alternative anticoagulant, such as enoxaparin, should be continued for 3 additional days after NMVr treatment completion (total of 8 days), before switching back to. When taking ritonavir, the AUC of rivaroxaban rises to 153% over time. As a result, it is best not to give rivaroxaban and NMVr at the same time. A physiologically based pharmacokinetics modeling study suggested that a decreased dose of 10 mg daily of rivaroxaban during NMVr treatment and 3 days after completion of treatment could ensure safe systemic levels of rivaroxaban.⁸ If NMVr treatment is required, rivaroxaban should be withheld for 24 to 36 hours based on its elimination half-life. After that, both NMVr and an alternative anticoagulant (such as enoxaparin) can be. Edoxaban, which is a substrate of P-gp, was found to increase the risk of bleeding in elderly patients and those with at least moderate renal impairment¹⁴. In the ENGAGE AF-TIMI 48 (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] vs. Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48), Ritonavir inhibits P-gp and may potentially increase the concentration of edoxaban. In the NCT00781391 study, the dose of edoxaban was decreased by 50% in patients taking other P-gp inhibitors. Ritonavir was not included in the study. For patients on 60 mg edoxaban every day for AF, the portion can be decreased by half for a sum of 8 days from the outset of NMVr. When prescribed for acute or recent VTE, edoxaban should be stopped and enoxaparin should be started while on NMVr for a total of eight days. Switching to an alternative anticoagulant, such as enoxaparin, while on 30 mg daily is a viable option. Edoxaban can be taken again three days after NMVr is finished [7,8].

Treatment for heart failure Angiotensin-converting enzyme inhibitors like lisinopril, enalapril, quinapril, and captopril are safe to continue because they are excreted unchanged in the urine. Because ritonavir is a weak inducer of CYP2C9, it could reduce the antihypertensive effects of irbesartan, which is oxidized by CYP2C9. Losartan, on the other hand, is converted to its active metabolite through the CYP2C9 pathway, and when taken with NMVr, it can cause hypotension. However, since ritonavir's inducing properties are delayed, no dose adjustment is recommended. Weak inhibition of the hepatic uptake transporter OATP1B1 by NMVr may increase the concentration of both valsartan and the active metabolite of sacubitril, necessitating close monitoring of blood pressure. For this reason, discontinuing sacubitril and valsartan for a short period of time while taking NMVr Olmesartan 30 and candesartan 29 do not interact with NMVr and are excreted unchanged in the urine. Telmisartan isn't utilized by the CYP450 chemicals and in this way, has no connection with NMVr. Azilsartan is essentially processed by CYP2C9. As a weak CYP2C9 inducer, ritonavir may theoretically lower azilsartan plasma levels, but its clinical utility is unknown [9].

Antiarrhythmic drugs

CYP3A4 is the enzyme that breaks down antiarrhythmic drugs like amiodarone, dofetilide, dronedarone, and quinidine. CYP2D6 is what breaks down flecainide. Propafenone is utilized by CYP2D6 and, less significantly, CYP3A4. Sotalol is renally cleared and safe to co-administer with NMVr. If NMVr therapy is deemed essential, agents such as dofetilide, propafenone, and quinidine, which have a relatively short half-life, can be withheld for 2.0 to 2.5 days (4 to 5 half-lives) before NMVr is initiated. Coadministration of ritonavir with these agents is contraindicated due to an increased risk of life-threatening arrhythm. However, due to the risk of recurrent arrhythmias while therapy is

interrupted, the need for hospitalization to restart certain antiarrhythmics, and the time required to initiate NMVr, which reduces its effectiveness, this strategy may not be practical. Flecainide, dronedarone, and amiodarone cannot be interrupted because their elimination time is longer than 5 days, beyond which NMVr may not be effective; NMVr should therefore be avoided (Central Illustration) [10].

Conclusion

The numerous known and potential DDIs between NMVr and various cardiovascular medications have been discussed. The significance of prescription compromise before commencement of NMVr can't be overemphasized to keep away from serious DDIs. During the course of NMVr treatment and three to five days after it is finished, cardiovascular medications may need to be stopped or their doses may need to be adjusted. NMVr should be avoided and other treatments used if co-administration with certain cardiovascular medications is not recommended or if their temporary discontinuation is impractical. Clinicians are able to offer patients who are unable to take NMVr because of DDIs alternative treatment options because they are aware of and have access to other COVID-19 therapies like molnupiravir, remdesivir, and anti-SARS-COV-2 monoclonal antibodies.

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Conflict of Interest

None.

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