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Safely prescribing Paxlovid: Avoiding drug-drug interactions

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Story from the front lines

A 72-year-old man called his primary care provider (PCP) with two days of throat pain, myalgia, mild shortness of breath, and fever. A home COVID-19 antigen test was positive. He had received 3 doses of the BNT162b2 vaccine (Pfizer BioNTech COVID-19 vaccine), the most recent dose was 6 months ago. Considering a history of recent coronary artery bypass graft (CABG), hypertension, diabetes, and age, his PCP prescribed Nirmatrelvir and Ritonavir (Paxlovid) for 5 days. The patient called his PCP after two days with active complaints of worsening myalgia. On medication review, the patient's active medications included atorvastatin 80 mg daily, metformin 1000 mg twice a day, aspirin 81 mg daily, and dapagliflozin 10 mg daily.

The patient was advised to stop Paxlovid, hold atorvastatin and check creatinine kinase (CK) levels. The patient's CK levels came back within normal limits. With rest and over-the-counter analgesics, the patient's symptoms improved without further interventions. His COVID-related symptoms resolved within 5 days. He was restarted on atorvastatin one week after finishing Paxlovid with no recurrence of myalgias.

Teachable moment

Nirmatrelvir and Ritonavir (Paxlovid) were approved for emergency use authorization by the (Food and drug administration) FDA in December 2021 for the treatment of mild-to-moderate COVID-19 in adults who are also at high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid use in unvaccinated high-risk patients showed a significant reduction (89%) in progression to severe COVID-19[1]. In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the Infectious Disease Society of America guideline panel suggests nirmatrelvir/ritonavir to be initiated within five days of symptom onset irrespective of the vaccination

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status. Since approval, as of Sep 18, 2022, 4,799,532 courses of Paxlovid have been prescribed in the US[2].

As mentioned, Paxlovid consists of two medications: nirmatrelvir and ritonavir. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro) and Ritonavir is as an inhibitor of cytochrome P450 3A4 (CYP3A4) which decreases nirmatrelvir metabolism and thus increase its serum levels. As Ritonavir is a CYP3A4 inhibitor, ritonavir has significant and complex drug-drug interactions leading to increased levels and toxicities of some commonly used drugs.

It is estimated that of all reported adverse drug events, 26% are due to drug-drug interactions[3]. Generally, drug interactions are classified under risk ratings which consist of 5 groups. A provider should be vigilant for interactions with risk ratings of C (monitor therapy), D (consider drug modification), and X (avoid combination). CYP3A4 is a member of the cytochrome P450 superfamily of enzymes. Cytochrome P450 enzymes metabolize approximately 60% of prescribed drugs, with CYP3A4 responsible for about half of this metabolism[4]. With medications like Paxlovid which has a CYP3A4 inhibitor, a prescriber should be vigilant to check for interactions. Common drug interactions with Paxlovid are mentioned in Table 1.

Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications. The CYP3A4 isoenzyme is responsible for the metabolism of statins and hence strong CYP3A4 inhibitors like protease inhibitors (e.g. Ritonavir) can increase levels of drugs metabolized by CYP3A4 pathway leading to harmful side effects. One of the major side effects related to statin use is muscle toxicity which can be of varying severity. About 15% of patients on Statin therapy develop myalgias, however true statin-induced myopathy is thought to occur in less than 1% of patients. Statin related myopathy, when it does occur, is often due to drug-drug interaction. It is estimated that 60% of cases of statin-induced rhabdomyolysis (most severe presentation of myopathy) are due to drug interactions. In cases where myopathy is due to a reversible etiology, a statin can be restarted with close monitoring once the etiology is resolved[5].

The FDA Paxlovid emergency use authorization factsheet for healthcare providers recommends temporarily discontinuing medications metabolized by CYP3A4, such as atorvastatin, during treatment with nirmatrelvir/ritonavir. Statins can often be restarted 3–5 days after discontinuing Paxlovid, or another CYP3A4 inhibitor, since these drugs will be metabolized by that time.

As this case illustrates, Paxlovid has significant interactions with many commonly prescribed drugs (Table 1). Our teachable moment emphasizes two things. First, Paxlovid has significant benefit for high-risk patients, as it can substantially reduce their risk of progressing to severe disease or death. Thus, rather than avoiding prescribing Paxlovid altogether for high-risk patients, clinicians should simply consider drug-drug interactions and understand how to temporarily modify the dosing of drugs or hold them preemptively for the duration of Paxlovid administration. Second, drug-drug interactions provide an important rationale for avoiding the use of Paxlovid in low-risk patients (e.g., a healthy

patient under age 40 years who is fully vaccinated). For our patient, the best approach may have been to prescribe a full 5-day course of Paxlovid and asking him to hold atorvastatin for the next 8–10 days.

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Table 1.

Common drug interactions with Paxlovid

Drug	Affect with Paxlovid	Action needed	Interaction category
Inhaled Beta agonists			
Salmeterol	Risk for arrhythmia	Avoid this combination	X
Oral Anticoagulants			
Rivaroxaban	Increased bleeding risk	Avoid this combination	X
Apixaban	Increased bleeding risk	Decrease dose of apixaban by 50%[¶]	D
Warfarin	Unpredictable INR effects	Close monitoring of INR [*]	C
Alpha and Calcium channel blockers			
Tamsulosin	Risk for orthostatic hypotension	Dose reduction/temporarily hold dose	X
Calcium channel blockers	Increased risk for hypotension and bradycardia	Consider reduced dose for duration of Paxlovid therapy.	C
Steroids and hormones			
Hormonal contraceptive	Contraceptive failure	Use alternate contraception	D
Steroids (inhaled and systemic)	Increased drug levels	Monitor for increased steroid-related adverse effects	C
Benzodiazepines and Atypical antipsychotics			
Quetiapine	Increased drug levels	Reduce Quetiapine dose to 1/6th for duration of Paxlovid therapy	D
Alprazolam, Clonazepam, Diazepam	Risk for sedation, respiratory depression	Dose reduction.	D

C = Monitor therapy X = Avoid combination D = Consider therapy modification

[*] INR= International normalized ratio

[¶]-Hold apixaban if dose is 2.5 mg twice a day