Opinion

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A Drug Interaction between Tacrolimus and Nirmatrelvir/Ritonavir was Treated with Phenytoin

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Description

The SARS-CoV-2 or COVID-19 pandemic, also known as the novel severe acute respiratory syndrome coronavirus 2, has had a significant impact on health systems. A treatment for this virus has been developed with a lot of effort. New antiviral medications are being developed and released rapidly by pharmaceutical companies using Emergency Use Authorizations (EUA). Many pharmacologic aspects of these medications, such as side effects and drug–drug interactions, are unknown prior to authorization because of the medications' rapid approval. In December 2021, Pfizer's nirmatrelvir/ritonavir (PaxlovidTM) received approval from the Federal Drug Administration (FDA) *via* a EUA for the treatment of mild to moderate cases of COVID-19 with a high risk of progression to severe COVID-19, which could result in hospitalization or death. Nirmatrelvir, a SARS-CoV-2 main protease inhibitor, and ritonavir, an HIV-1 protease inhibitor, are the two antiviral medications that make up Nirmatrelvir/ritonavir. Although ritonavir does not have any antiviral properties, it is a well-known CYP3A4 inhibitor a cytochrome P450 enzyme that helps nirmatrelvir reach and maintain therapeutic concentrations.

Acute Tacrolimus Toxicity

Patients undergoing immunosuppression following a solid organ transplant take the calcineurin inhibitor tacrolimus. Because it is a substrate of P-glycoprotein and is primarily metabolized by CYP3A4, tacrolimus is susceptible to numerous drug–drug interactions. Among the many possible signs and symptoms of acute tacrolimus toxicity are gastrointestinal issues, nephrotoxicity, and neurotoxicity. Due to its propensity for these interactions and narrow therapeutic index, Tacrolimus requires therapeutic drug monitoring. Patients with a history of solid organ transplant who test positive for COVID-19 are considered to be at high risk for progression to severe disease due to their immunosuppression and are therefore candidates for nirmatrelvir/ritonavir under the EUA. The goal level is 3–12 ng/mL for the majority of transplant patients. Tacrolimus plasma concentrations are expected to rise as a result of ritonavir's ability to block CYP3A4. It has been reported that giving tacrolimus and nirmatrelvir/ritonavir together can quickly raise tacrolimus concentrations to toxic levels. Nephrotoxicity (increase in serum creatinine or decrease in urine output) and neurotoxicity (headache, confusion, vision changes, tremors, extremity numbness, seizures, and coma) are the clinical signs and symptoms of tacrolimus toxicity. Although the exact cause of nephrotoxicity is still unknown, vasoconstriction in afferent arterioles and thrombotic microangiopathy may be to blame. Tacrolimus-induced neurotoxicity is described in a few case reports. When this medication is given in conjunction with ritonavir, careful monitoring of both the medication's therapeutic effects and its side effects is advised.

In this case, tacrolimus and nirmatrelvir/ritonavir were given to a patient with a history of orthotopic heart transplant in the context of COVID-19. Due to the use of tacrolimus and nirmatrelvir/ritonavir simultaneously, the patient presented with tacrolimus toxicity. After that, phenytoin was used as a CYP3A4 inducer to quickly lower the tacrolimus level above therapeutic levels. A 67-year-old woman was recently diagnosed with COVID-19 when she presented to an outside Emergency Department (ED) with cough and dyspnea symptoms. Due to familial cardiomyopathy, chronic kidney disease (baseline creatinine 1.5 mg/dL), hypertension, hyperlipidemia, hypothyroidism, and chronic obstructive pulmonary disease, her prior medical history is significant for an orthotopic heart transplant in 2004. The COVID-19 vaccine was not given to her. Azathioprine, carvedilol, diphenoxylate-atropine, hydrochlorothiazide, levothyroxine, losartan, pravastatin, tacrolimus, and temazepam were among the medications she was taking prior to admission. The patient's home tacrolimus regimen consisted of 3 mg in the morning and 2 mg in the evening, with her target level of 4–6 ng/mL.

Supratherapeutic Tacrolimus Drug Level

With a prescription for nirmatrelvir/ritonavir, the patient was initially discharged from the outside emergency department. The prescriber claims that the patient was not told to alter her tacrolimus regimen. The patient presented to the outside emergency department three days later with sluggish speech, fatigue, weakness, and a loss of appetite. The patient had completed four days of nirmatrelvir/ritonavir treatment at this point. After that, she was moved to our facility for better care.

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Her tacrolimus level was 176.4 ng/mL when she was admitted, and she had an acute kidney injury (BUN 111 mg/dL, serum creatinine 2.5 mg/dL). The patient was alert throughout the hospitalization but did not know the date or time. Her care was made possible by the toxicology, transplant, and neurology services. Other than the presence of encephalopathy, her neurologic exam was not particularly noteworthy. An Electroencephalogram (EEG) and brain MRI were recommended by neurology. Although the MRI was negative, the EEG showed evidence of toxic/metabolic encephalopathy, with generalized periodic discharges and triphasic waves and diffuse slowing; these findings were attributed by the neurology team to uremia and her supratherapeutic tacrolimus drug level.

Throughout her admission, her immunosuppressants, azathioprine and tacrolimus, were withheld. Because of its CYP3A4-inducing properties, the team decided to start her on oral phenytoin 150 mg twice daily on the first day of her hospitalization. Phenytoin was given to her in seven different doses. Her tacrolimus level had risen to 6.1 mg/mL, slightly above her target range, five days after she was admitted. She was disoriented for several days, but it went away when the tacrolimus level got lower. At her neurologic baseline, the patient was discharged from the hospital on day seven. Shortly after her discharge, Tacrolimus was restarted, with close monitoring by her primary care physician. Due to follow-up at a different institution, the patient's restarted tacrolimus dose is unknown. In accordance with JMT policy, consent to publish this case was obtained and provided to the journal. Change in the level of tacrolimus in relation to the pattern of administration of phenytoin and serum creatinine during hospitalization. This case demonstrates that drug–drug interactions can precipitate and even reverse tacrolimus toxicity, which has a high morbidity. Due to the drug's large volume of distribution and 99 percent protein binding, hemodialysis is ineffective for tacrolimus toxicity. As a result, supportive care is the primary treatment option. Although there is a lack of information on how to treat tacrolimus toxicity, phenytoin's CYP3A4-inducing properties are mentioned in several case reports. Phenytoin is a CYP-P450 inducer that increases the expression of the induced enzyme at higher doses. Although it is unknown how phenytoin reduces tacrolimus levels *via* CYP3A4, it is likely that receptor transcription factors are activated.