Coronavirus disease 2019 (COVID-19) has had a major impact on global communities and healthcare. Paxlovid (nirmatrelvir/ritonavir) is an oral drug for the treatment of COVID-19 that has been approved by the U.S. Food and Drug Administration. In Korea, Paxlovid is the first-line drug for patients who are >60 years old or using immunosuppressants, or those who are >40 years old with chronic diseases such as obesity, diabetes, chronic kidney disease, or hypertension. One caveat of Paxlovid treatment is the potential risk of drug interaction as it is a strong cytochrome P450 (CYP) 3A and P-glycoprotein inhibitor. Tacrolimus is the key immunosuppressant used in kidney transplant (KT) recipients; however, it is metabolized by CYP 3A enzyme, which is strongly affected by Paxlovid. Here, we introduce a case of successful management of severe acute kidney injury (AKI) in a KT patient resulting from tacrolimus overdosage after Paxlovid; AKI was successfully reversed by phenytoin administration to induce CYP3A enzyme.

A 65-year-old man presented to the emergency room with headache, nausea, abdominal pain, and peripheral neuropathy after taking Paxlovid for 3 days. He received a living donor KT 2 years prior from his wife due to focal segmental glomerulosclerosis. Maintenance immunosuppressants were tacrolimus of 4.5 mg twice a day, mycophenolate mofetil of 360 mg twice a day, and prednisone of 5 mg once a day. After 3 days of Paxlovid treatment, which was prescribed at a local clinic after diagnosis of COVID-19, the patient questioned us through his wife about how to take Paxlovid and immunosuppressants during quarantine. Considering tacrolimus toxicity, we recommended discontinuing tacrolimus immediately while completing 5 days of Paxlovid treatment. On the 3rd day after tacrolimus discontinuation and on the 1st day after completing Paxlovid treatment, the patient visited the emergency room. Trough concentration of tacrolimus was >30 ng/mL, creatinine was 9.57 mg/dL, aspartate transaminase/alanine transaminase 19/9 IU/L, and urine dipstick value was 1+. In the previous 3 months, his average tacrolimus trough level was 8.13 ng/
mL and creatinine was 1.4 mg/dL. The symptoms were suspected to be due to tacrolimus-related neurotoxicity and nephrotoxicity, and we administered phenytoin to rapidly decrease the concentration of tacrolimus by inducing the CYP3A enzyme. The patient took phenytoin for 3 days (day 1, 200 mg three times; day 2, 200–100 mg twice; day 3, 100 mg once) (Fig. 1). Phenytoin trough level was evaluated one day after the first dose at 7 AM, measuring 3.73, 4.26, 2.29, and <0.5 µg/mL on the 2nd, 3rd, 4th, and 5th days of administration, respectively. Phenytoin treatment led to a reduction in tacrolimus trough levels from >30 ng/mL to 16.6, 8.2, and 3.5 ng/mL on 1st, 2nd, and 3rd days after admission, and creatinine decreased to 1.92 mg/dL. Headache, gastrointestinal symptoms, tingling sensation, and kidney function improved 1 day after taking phenytoin and resolved by day 3. The patient restarted tacrolimus at 90% of the baseline daily dose 1 day after discontinuing phenytoin. His tacrolimus trough level was 8.2 ng/mL and creatinine concentration was 1.52 mg/dL at discharge.

In KT patients, a combination of three immunosuppressants is mainly used, of which calcineurin inhibitors (CNI) are metabolized by CYP3A [1]. In Korea, oral antiviral medication for COVID-19 is prescribed at a designated local clinic if there are no contraindications according to Ministry of Health and Welfare guidelines. Although not a contraindicated drug, CNI concentration increases in serum with Paxlovid treatment.

In a previous study, tacrolimus and mammalian target of rapamycin (mTOR) inhibitors were stopped and cyclosporine was reduced by 80% empirically when starting Paxlovid. CNI doses were reassessed on day 3 and day 6–7 when beginning Paxlovid. Next, immunosuppressants were resumed by serum concentration. Guidelines recommend that recent transplant patients or those who have experienced rejection try to avoid a subtherapeutic level of immunosuppressant [2,3]. However, during the pandemic, it was difficult to measure CNI level over a short period and reset the concentration to resume accordingly. Some authors recommended skipping or reducing tacrolimus in solid organ transplant recipients receiving Paxlovid;

| Figure 1. Serum creatinine, tacrolimus (FK), and phenytoin levels during hospital stay (HD). |
| Admin, administration; con., concentration; tid, three times a day; qd, once a day. |
however, there have been no reports on the rapid reversal of Paxlovid-induced nephrotoxicity after tacrolimus overdosage in a real-world setting. One case reported a gradual reduction in tacrolimus level over 8–10 days [4–6].

This patient experienced undesirable systemic tacrolimus toxicity from Paxlovid. After taking phenytoin, systemic symptoms of tacrolimus toxicity resolved and the trough level of tacrolimus decreased to nontoxic range within 3 days. Phenytoin drug level was undetectable after a 1-day withdrawal, and there were no observed side effects (hypotension, arrhythmia) from phenytoin. There was no rebound tacrolimus trough level spike after tacrolimus re-administration.

Physicians should be cautious when prescribing Paxlovid to KT recipients due to potential drug interactions with CNIs. Phenytoin, a CYP3A inducer, can be used to rapidly resolve tacrolimus over dosage.

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Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization, Investigation, Methodology: KEJ, JCJ
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