CLINICAL VIGNETTE

Acute Tacrolimus Poisoning Treated with Phenytoin

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A 41-year-old female with IgA nephropathy with end stage kidney disease and failed kidney transplant presented to the emergency department with myalgias, diarrhea, and severe headache. Five days prior she developed sore throat, headache, nausea, and fatigue. Two days later she went to urgent care and was diagnosed with COVID. She was prescribed nirmatrelvir/ ritonavir (Paxlovid) and sent home. She took the medications for three days but her symptoms worsened and presented for ED evaluation. Her temperature was 36.6°C blood pressure 139/99, heart rate 100bpm, respiratory rate 18 bpm with 98% O2 saturation on room air. She was alert and orientated but she appeared fatigue. Cardiac and pulmonary exam was normal. She had bilateral hand tremors but no other focal neuro deficits. Laboratory findings included normal white cell count of 6.2. serum creatinine at her baseline of 0.8. Potassium was somewhat low at 3.3 mEq/L, serum CK was normal at 64 and random serum tacrolimus was severely elevated at 82.4 ng/ml. Chest xray was normal. She was admitted and received two liters or normal saline boluses and started on Remdesivir. The Paxlovid was stopped and tacrolimus held for supra-therapeutic level. Her diarrhea, myalgias and severe headache continued. Head CT showed no acute abnormalities, and neurologic exam remained non-focal. The trough serum tacrolimus remained elevated at 78.4ng/ml. Given persistently extremely high tacrolimus levels, she was given 200 mg phenytoin daily for two doses to treat acute tacrolimus poisoning. Over the next 48 hours her serum tacrolimus trough level dropped to 16.2 ng/ml and she had complete resolution of her headache and tremors. She was discharged on her home tacrolimus dose with nephrology follow up scheduled.

Discussion

Tacrolimus poisoning can be a life-threatening emergency. Symptoms vary and are often related to renal failure or neurotoxicity.Common symptoms include headaches, nausea, emesis and hand tremors. Severe symptoms include altered mental status and even cerebral hemorrhage.[1-3] Serum trough levels greater than 30 ng/ml are considered severely elevated and life-threatening.[4,5] Given its large volume of distribution, tacrolimus is not readily cleared by hemodialysis. Serum levels are mainly cleared by the liver through the cytochrome P450 system, specifically CYP3A4.[6] Medications such as protease inhibitors such as Paxlovid inhibit CYP3A4 and can greatly increase tacrolimus levels.[7] On the other hand, medications that induce CYP3A4 can accelerate clearance of tacrolimus. These include phenytoin and phenobarbitol.[8,9]

Our patient presented with an extremely high serum level of tacrolimus of 82.4 ng/ml. We could not find another report with a higher serum level. The high level may have been related to severe diarrhea from her COVID-19 in addition to receiving protease inhibitor. Diarrhea can increase oral bioavailability of tacrolimus due to diarrhea-induced decrease in intestinal p-glycoprotein (PGP) activity.[10] With persistently dangerous levels of tacrolimus in her serum, and neurologic symptoms she was treated with phenytoin to induce metabolism of tacrolimus. She responded very well with her serum levels falling below 20ng/ml in less than 48 hours. Another benefit in using phenytoin is seizure prevention associated with very high tacrolimus serum levels. The exact dose and duration of treatment with phenytoin is not well established. Our case shows that serum levels can decrease dramatically, out of life-threatening levels, with just two doses. Alternatives for induction of CYP3A4 enzyme include rifampin and phenobarbital, but both have more side effects. Reports demonstrating their efficacy are also lacking.

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