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Medical Marijuana-Induced Tacrolimus Toxicity.

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Abstract:

As both recreational and therapeutic marijuana use increases in the US, more attention is being paid to its direct medical and psychoactive effects. One crucial dimension is the potential for marijuana or marijuana-derived therapies to interact with other prescribed medications. Tacrolimus is an immunosuppressant medication prescribed to prevent rejection in patients receiving solid organ and bone marrow transplants. Clinically, it is characterized by a narrow therapeutic index and multiple drug-drug interactions. Constituents in marijuana are known to inhibit cytochrome P-450 3A, which is normally responsible for metabolizing tacrolimus, leading to the potential for a dangerous interaction. Though this phenomenon has been described previously in a stem cell transplant patient[1], we present the case of medical marijuana induced tacrolimus toxicity in a patient who recently received an orthotopic liver transplant.

Keywords:

Transplantation, Cannabis, Tacrolimus, Drug-Drug Interactions, Delirium, Medical Marijuana

Introduction/Literature Review:

Discovered in 1987, tacrolimus was developed as an immunosuppressant medication for use in patients receiving liver transplants and was ultimately broadly adopted for prevention of graft versus host disease in patients following solid organ and hematopoietic stem cell transplants. Tacrolimus has a narrow therapeutic index, requiring close monitoring of serum levels in these patients.[2] At the low end, there is a risk of immune-mediation transplant rejection, while at the high end, tacrolimus toxicity can cause hypertension, acute kidney injury, and electrolyte disturbances in addition to being known for neurobehavioral side effects. These include headache, tremor, coma, delirium and psychosis. High variability in tacrolimus levels has also been associated with worse outcomes clinically, including poorer survival.[3] Common factors that lead to variability in tacrolimus level include protein binding as well as interactions with inhibitors of either CYP3A or P-glycoprotein. Patients receiving liver transplants often require antibiotic and antifungal coverage so there is an increased potential for drug-drug interactions, particularly in the peri-operative period.[4]

Case Summary:

The patient is a 48 year old woman with a history of cholecystectomy complicated by bile duct stricture and multiple hepatic abscesses leading to liver failure and subsequent evaluation for orthotopic liver transplant (OLT). She had a psychiatric history of depression and anxiety, with a brief inpatient hospitalization after cutting her wrists 6 months before her transplant. She then had one month of outpatient therapy. During a pre-transplant psychiatric evaluation, she endorsed no illicit drug use.

Outpatient medications included opioid analgesics and cyclobenzaprine for pain, as well as zolpidem for insomnia secondary to abdominal pain.

The patient was admitted to the hospital and received a tri-segmental OLT on the first day of admission. She was monitored post-operatively in the surgical intensive care unit and started on two agents for immunosuppression (mycophenalate and basiliximab) as well as broad spectrum antibiotics and anti-fungal agents. The pain management service was consulted for post-operative pain control given her dependence on opioid analgesia as an outpatient. Per their recommendations, she was started on a hydromorphone PCA. Her transaminases and coagulation studies were reassuring and the patient was stable enough to be transferred out of the intensive care unit on post-transplant day 3. That same day, she was started on tacrolimus at 2mg q12 hours. A serum tacrolimus level taken the next morning was 7.7 ng/mL which was at goal.

On post-transplant day 5 , the transplant psychiatry service was consulted for agitation and delirium – specifically, she was oriented only to herself, had disorganized speech, was observed to be responding to internal stimuli (speaking to no one in particular while alone in her room) and was exhibiting psychomotor agitation in the form of purposeless shifting and fidgeting. Her vital signs were significant for tachycardia and absence of fever. Laboratory testing revealed a significant increase in tacrolimus level to 17.2 ng/mL despite no changes in dosing. Labs were otherwise stable. An infectious workup was negative and a CT angiogram ruled out pulmonary embolism. The patient's encephalopathy was felt to be secondary to tacrolimus toxicity, though the reason for change in tacrolimus level was initially unclear. The patient's tacrolimus was held at that time, and the psychiatry team recommended low-dose quetiapine as needed for agitation to avoid the use of restraints and mitigate risk of decannulation or removal of other lines. Later that night, the patient's tachycardia, disorientation and confusion worsened, and she required two doses of IV haloperidol.

By post-transplant day 7, the patient's encephalopathy began to resolve, with improving orientation and less psychomotor agitation. Her serum tacrolimus level was down-trending to 7.3ng/mL and she was restarted at a dose of 1mg q12hrs. At this time, the patient's family mentioned that since her pre-operative pain was poorly controlled by various opioids, she had sought pain management from a medical marijuana clinic in a neighboring state where medical marijuana was legalized. A urine drug screen confirmed her use of cannabinoids. The patient produced a bottle of medical marijuana lozenges from her purse at bedside. The bottle indicated that each lozenge contained 10mg of THC and 1mg CBD. She had filled the bottle 10 days prior to admission, and reported taking 2-4 lozenges per day up until her transplant, though she denied taking any during admission. She denied any other previous marijuana use. On post-transplant day 9, her level was stable at 3.4 ng/mL and her dose was titrated to 2mg q12hrs.

The patient was advised to discontinue cannabis usage due to concern for drug-drug interactions. Her post-operative care has been uncomplicated by subsequent mental status issues. Her tacrolimus dosage is stable at 3 mg po q 12 and her level has remained at goal, most recently 7.4 mg/mL.

Discussion:

Marijuana is the most commonly used illicit substance in the US. In the past decade alternative formulations of its active ingredients have become adopted in many states for the treatment of various medical conditions, including various types of chronic pain.[5] In this case, our patient was seen in a medical marijuana clinic by a pain specialist who was registered with the New Jersey Medical Marijuana Treatment Program. Under this program, patients must be found to have an "approved debilitating medical condition" that has either been demonstrated to be treatable by cannabis or has not responded to conventional treatment. Our patient met criteria for "chronic pain of visceral origin." She was able to obtain the lozenges at a licensed dispensary affiliated with her doctor's office.

Anecdotal reports of marijuana use leading to decreased reliance on opioid pain medications have led to new investigations into its analgesic effects. One case study from 2016 described the use of marijuana to wean opioid use in a patient who had received OLT.[6] Additionally, while many proponents of marijuana's analgesic properties distinguish between the potential therapeutic effects of its two major ingredients, tetrahydrocannabinol (THC) and cannabidiol (CBD), it is unclear whether their pharmacokinetics differ meaningfully.[7] In vitro studies have demonstrated THC and CBD to be CYP 3A4 substrates and there is some evidence that they act as inhibitors as well.[1,8] A case report from 2006 described myocardial infarction in an otherwise healthy 41-year-old man after concomitant use of sildenafil and marijuana, thought to be due to 3A4 inhibition.[9] Additionally, constituents in marijuana have been shown both to inhibit or induce P-glycoprotein, which could then interfere with the absorption and distribution of medications like tacrolimus.[10] As mentioned above, the resultant variability in tacrolimus levels not only leaves potential for neurotoxicity, but is also associated with worse graft survival.[3]

The evaluation and treatment of encephalopathy in post-transplant patients are similar those for delirium in the general post-operative patient, with the additional consideration of immunosuppression as a unique factor. While haloperidol and quetiapine are 3A4 substrates, they are not known to interfere with the metabolism of tacrolimus, and their metabolism is not impaired in patients with poor liver function when used conservatively. There is one case report of QT prolongation leading to arrhythmia in a patient receiving both tacrolimus and haloperidol, though tacrolimus is less likely to prolong QT independently when compared to other immunosuppressants.[11]

The increased prevalence of both recreational and medical marijuana use represent challenges to safe immunosuppression in post-transplant patients. Since medical marijuana is not consistently monitored between states and is not thought of universally as a legal medication, it can easily be overlooked as part of medication reconciliation. Additionally, as medical marijuana therapy remains a controversial topic among providers, there is significant stigma attached to its use.[12] In one study, 10.4% of transplant candidates used cannabis, and were found to be less likely to receive a transplant despite similar survival rates to those who did not.[13] The perception that disclosing marijuana use (though it was sanctioned by a medical professional) could hurt her chances at a receiving a transplant was likely a factor in our patient not disclosing it to her transplant team.

Emerging research on cannabinoids suggest that they offer immunosuppressive effects independently[14] which further complicates their use in patients where tightly controlled immunosuppression is necessary for healthy recovery.

Conclusion:

In treating patients who are candidates for or who have received OLT, it is important to screen both for recreational as well as prescribed marijuana use due to the potential for drug-drug interactions between marijuana and tacrolimus in particular. In addition, patients seeking medical marijuana prescriptions should be screened for conditions leading to organ failure that may require transplantation. The dangers of marijuana use in patients receiving tacrolimus include tacrolimus toxicity which is associated with increased morbidity and prolonged recovery from transplant. Treatment of marijuana induced tacrolimus toxicity includes cessation of marijuana, holding tacrolimus while measured levels are above goal range, in addition to treating any resulting agitation or delirium.

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