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Tacrolimus-induced Diabetic Ketoacidosis in a Polymyositis Patient Precipitated by Fluconazole: A Case Report and Review of the Literature

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Abstract Tacrolimus is a reversible calcineurin inhibitor. It is commonly used as an immunosuppressive drug in the treatment of T cell mediated diseases such as polymyositis, graft rejection in solid organ transplant, graft-versus-host disease in hematopoietic stem cell transplant, and is postulated to have diabetogenic potential. Fluconazole, on the other hand, is frequently prescribed antifungal therapy. Fluconazole increases the serum level of tacrolimus into the supratherapeutic range, thus developing drug toxicity if the dose is unadjusted. Diabetic ketoacidosis is a rare adverse drug effect reported with the use of tacrolimus. In this report, we present a case of DKA in a 60-year-old woman with polymyositis on low dose corticosteroids and tacrolimus, precipitated by the use of fluconazole. We highlight the pathophysiologic mechanisms underlying the effect of fluconazole on tacrolimus levels causing an accelerated development of DKA along with the review of literature on this potentially life-threatening condition.

Keywords: *Tacrolimus, Fluconazole, Diabetic Ketoacidosis, Polymyositis*

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1. Introduction

Iatrogenic hyperglycemia from fluconazole-tacrolimus interaction manifesting as diabetic ketoacidosis is a rare clinical entity. Tacrolimus (TAC) inhibits the production of interlukin-2, which promotes the development and proliferation of T cells, suppressing cell mediated and humoral responses. It is an immunosuppressant with a narrow therapeutic index and numerous drug interactions. Most commonly reported side-effects are neurotoxicity and nephrotoxicity [1]. New-onset diabetes is now a well-established and well-studied adverse effect of calcineurin inhibitors, mostly tacrolimus [2]. Azole antifungals are associated with increasing tacrolimus blood levels and occurrences of adverse effects related to tacrolimus toxicity from inhibition of liver cytochrome enzymes and small intestine microsomes [6]. Due to this outcome, it is important that patients on tacrolimus therapy that are also on fluconazole are monitored closely.

2. Case Report

A 60-year-old Asian female presented to our emergency department with malaise and nausea. Her medical history was significant for polymyositis and type 2 diabetes from long-term steroid use, maintained on metformin. She did not have any family history of diabetes. Her symptoms included decreased appetite, generalized fatigue and nausea for a week that got worse over the last 2 days. The patient was on tacrolimus 6 mg BID, azathioprine 200 mg daily, and low dose prednisone 7.5mg, which was tapered down from 20mg daily as her muscle enzymes normalized on her last clinic follow up. Recently, she was started on fluconazole 200mg daily for 14 days for oral and vulvovaginal candidiasis from long-term steroid use. Occasional blood glucose levels, done earlier during follow-up clinic visits, were below 150. Physical exam was remarkable for oral thrush.

Her initial fingerstick was greater than 600. On lab investigations, she was found to have an anion-gap metabolic acidosis attributed to ketoacidosis with bicarbonate levels of 15, gap of 29, potassium 3.9 and glucose 837. Serum beta hydroxybutyrate was elevated. Arterial blood gas showed a pH of 7.29 and PCO2 20. Urinalysis showed ketonuria and glucosuria. Glycated hemoglobin was 7.2%. Tacrolimus trough level was 25. Infectious etiology for hyperglycemia was ruled out.

The patient was started on insulin drip and intravenous fluids, and her electrolytes were corrected. Her acid-base status improved within the next 48 hours. She was switched to subcutaneous insulin and a regular diet on the

floor. Considering the diabetogenic potential of TAC, it was decreased to 2mg BID while continuing fluconazole; background prednisone therapy was discontinued and azathioprine was continued at the same dose. Daily insulin requirements in the hospital were 20 units of long-acting and 3 units of short-acting. The patient was given education about injecting insulin at home and discharged on a diabetic diet and subcutaneous insulin. She was closely followed up upon discharge for monitoring blood glucose levels (Table 1). As the patient completed her fluconazole therapy, her insulin requirements began to decrease drastically.

Table 1. Blood glucose levels with subsequent insulin requirements in a patient on fluconazole therapy

Timeline	Random blood glucose levels	Insulin requirement
1st week of fluconazole	277	None
2nd week of fluconazole	837	Insulin drip tapered down to lantus 20 units and aspart 3 units
Post 2-week course of fluconazole	152	Lantus 10 units
Day 42 after initiation of fluconazole	140	Lantus 5 units

3. Discussion

Tacrolimus can affect glucose metabolism in two different ways. First, high levels reduce insulin secretion by causing structural damage to pancreatic beta cells. Second, it also decreases insulin transcription by reversible inhibition of calcineurin [5]. Calcineurin is known to participate in T-cell signaling, but has been found in other cells, including in HIT-T15 pancreatic beta cells. Investigation of this cell line demonstrated that tacrolimus binds to FK506-binding protein-12, which then inhibits calcineurin activation and thereby is thought to interrupt gene transcription. Inhibition of this complex induced a reversible time- and dose-dependent decrease in insulin mRNA levels and expression of human insulin promoter-chloramphenicol acetyltransferase reporter gene, thus suggesting that insulin gene transcription and insulin secretion are reversibly inhibited [3]. Vacuolization and degranulation noted in beta cells after they have been exposed to excessive levels of tacrolimus suggest cell toxicity [5].

On the other hand, a 2-year follow-up cohort study on kidney transplant patients with new-onset diabetes demonstrated higher blood insulin levels to be the primary cause of insulin resistance whereas the C-peptide levels were similar in both groups [8]. Another in-vivo study that investigated the mechanism of diabetogenic potential of TAC attributed hyperglycemia to impaired glucose tolerance and/or higher glucose intestinal absorptive capacity. Elevation in blood glucose levels seen on glucose tolerance tests during TAC administration in a dose dependent manner led to sustained hyperglycemia and eventually hyperinsulinemia. With excess circulating levels of insulin higher than expected for levels of glucose, insulin receptors become less sensitive to insulin, thus impairing overall metabolism [7]. Insulin requirement varied in hepatic and renal transplant patients that were chronically on tacrolimus for more than 3 months. At 6 months, 20% of patients required insulin but as few as 5.5% required it after 1 year [1].

Decreased insulin requirements after completing fluconazole therapy indicate that toxic levels of tacrolimus may cause transient and apparently reversible pancreatic damage [2]. A small study of 20 transplant patients who were given tacrolimus and fluconazole reported a dose related effect of each other. In these patients, highest trough concentration along with an increase in half-life of FK506 was seen within three days after the introduction of fluconazole therapy. This happened due to decreased FK506 elimination through hepatic metabolism by cytochrome P-450 enzymes, which fluconazole is known to inhibit. Another possibility could be fluconazole-mediated inhibition of FK506 metabolism in the gut and therefore an increase in the extent of absorption [9]. Interestingly, tacrolimus is found to have some antifungal activity as well. The underlying mechanism of immunosuppression and antifungal action is predicted to be similar. However, the profound effect of immunosuppression causing fungal proliferation at higher doses outweighs the antifungal properties of the drug [4]. Major risk factors for the development of new-onset diabetes in patients receiving calcineurin inhibitors include African ethnicity, obesity, family history of diabetes, increased age, increased number of transplants and the use of prednisone [5]. Our patient had two of these risk factors: age and steroid use. Both glucocorticoids and tacrolimus increase the risk of hyperglycemia. What predisposed our patient to DKA was the recently started fluconazole that inhibited liver CYP3A4, resulting in an increased tacrolimus concentration. Tacrolimus trough levels were significantly lower after fluconazole discontinuation.

4. Conclusion

When starting patients receiving steroids and tacrolimus on azoles in treating fungal infections, care should be exercised to monitor blood glucose levels in preventing life threatening complications. It is also another call for attention on the side effect profile of this potent calcineurin inhibitor. Therefore, it is recommended to adjust tacrolimus dosage with co-administration of azole antifungals. Ideally the dose of tacrolimus should be halved when an azole is co-administered and TAC levels should be checked more often to maintain therapeutic range and avoid one of the major adverse outcomes of severe hyperglycemia.

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