

## Metronidazole and Tacrolimus Interaction in a Kidney Transplant Recipient

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### Abstract

We present a 56-year-old male kidney transplant recipient who was hospitalized for acute kidney injury due to gastroenteritis related volume depletion and had kidney function deterioration secondary to rising plasma levels of tacrolimus after metronidazole administration. Tacrolimus dose was decreased and arranged daily by closely drug level monitoring. His creatinine value returned to his basal levels after metronidazole was stopped and his tacrolimus levels were kept in target range. Tacrolimus is metabolized primarily in the liver by CYP3A enzymes and drugs that affect CYP3A functions such as metronidazole can cause elevated tacrolimus plasma levels that results in nephrotoxicity. This case teach us that calcineurin inhibitors should be closely monitored in kidney transplant recipients during metronidazole treatment.

**Keywords:** Renal transplantation; Tacrolimus; Metronidazole; Drug interaction

### Introduction

Tacrolimus which acts via the calcineurin inhibition is an important immunosuppressive drug that is used to prevent rejection in the kidney transplant recipient population. Tacrolimus is metabolized in both liver and intestine by the cytochrome P450 enzyme system and P-glycoprotein. CYP3A especially takes an important role in the tacrolimus metabolism pathway [1,2].

Tacrolimus is not only used in transplantation era but also used in different diseases such as myasthenia gravis, autoimmune disorders, atopic dermatitis, inflammatory bowel disease. Due to the patients who were prescribed tacrolimus were usually multiple drug users and the CYP3A enzyme system can be inhibited or activated by many drugs; tacrolimus related adverse events can be seen frequently. There are many drugs of which interactions with tacrolimus are well known by affecting CYP3A enzymes including antifungal agents (Voriconazole, Itraconazole, Fluconazole, Posaconazole), erythromycin, diltiazem, mibefradil and telaprevir [3].

Blood samples for tacrolimus level assessment must be taken immediately before the next dose. Levels higher than 20 ng/mL are associated with toxicity and in the first three months following the transplantation, it is suggested to keep the plasma level between 10 ng/mL to 15 ng/mL [4].

Herein we present a male kidney transplant recipient who had acute kidney injury due to tacrolimus nephrotoxicity after metronidazole administration.

### Case Report

A 56-year-old male kidney transplant recipient patient admitted to our emergency department with the complaint of watery diarrhea which was started after antibiotic use due to wound infection secondary to inguinal hernia surgery. His stool frequency was 4 to 6 per day and he did not suffer from tenesmus. He said that he had seen mucus but not blood in his stool. Acute kidney injury was detected by his blood biochemistry results (creatinine level: 2 mg/dL). Although the patient was not oliguric, renal ultrasound was performed and a 35 mm × 37 mm sized collection compatible with hematoma which was localized anterior to the bladder was detected and post-renal causes were excluded. He was hospitalized to investigate the etiology of diarrhea and to observe his renal functions.

His past medical history revealed that he had been diagnosed end

stage renal disease in 2013. His renal ultrasound had been consistent with chronic kidney disease with bilateral atrophic kidneys. The cause of chronic kidney disease could not have been found and he had been treated with hemodialysis for 6 months until March 2014 when a kidney was transplanted him from his son. After transplantation, he was discharged from hospital with a creatinine level of 1.2 mg/dL. His immunosuppressive treatment consisting of prednisolone, tacrolimus and mycophenolate mofetil was prescribed. His medical follow-up went on at another hospital till his last emergency department admission. It is learnt that NODAT (New onset diabetes after transplantation) had occured and insulin treatment had been started and his creatinine level had slowly progressed to 1.5 mg/dL by this period.

His physical examination was normal except for decreased turgor pressure. Fractionated Na excretion (FeNa) was calculated as <1%. There was no microscopic hematuria and pyuria in his urine examination. There was 1+ proteinuria by dipstick and spot urine protein to creatinine ratio was 1600 mg/gr while his synchronous serum albumin level was 3.5 mg/dL. He was taking tacrolimus 1.5 mg twice a day and his tacrolimus level was 7 ng/mL. While the clinical condition was accepted as primarily prerenal acute kidney injury due to diarrhea by the lights of physical examination and laboratory findings, intravenous saline infusion was started.

Microscopic evaluation of the stool sample revealed a lot of leukocytes and erythrocytes suggesting bacterial gastroenteritis. There were no amip and parasitic ovas in microbiological evaluation and *Clostridium difficile* toxin PCR result was negative. Stool sample was sent for culture and metronidazole was started. Owing to patient's past medical history included similar diarrhea attacks; mycophenolate mofetil was switched to azathioprine and prednisolone dose was increased to 10 mg per day. Although his creatinine level was minimally decreased from his admission level while he was taking enough enteral and parenteral fluids and his stool frequency was decreased; his creatinine levels raised up to 4.2 mg/dL progressively in two days after metronidazole administration.

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There were no Schistocytes in his peripheral blood smear and his complete blood count was normal, therefore hemolytic uremic syndrome was excluded. Due to his kidney function deterioration occurred after metronidazole administration, calcineurin nephrotoxicity was suspected as causative factor. It was detected that his tacrolimus level was raised to 15.3 ng/mL from the level of 7.6 ng/mL which was evaluated before metronidazole initiation. Tacrolimus was stopped, drug level was monitored daily and added lower dose again when its level decreased under the target range. His diarrhea was stopped and creatinine value was returned to the baseline level in the ongoing days. The patient was discharged after his metronidazole treatment course had been completed.

## Discussion

Rejection is an important and one of the most common causes of graft loss after kidney transplantation. In most centers; triple immunosuppressive drug combination regimen usually consisting of corticosteroids, calcineurin inhibitors and an antiproliferative agent is preferred for rejection prevention. This regimen yielded a very low rejection rates. There are two calcineurin inhibitors (tacrolimus and cyclosporine) which are used in kidney transplantation era. It is shown by clinical trials that tacrolimus is better for rejection prevention than cyclosporine [5].

Gonwa et al. randomized deceased donor recipients into three immunosuppressive regimens (all consisted corticosteroids); tacrolimus plus azathioprine, tacrolimus plus mycophenolate mofetil and microemulsion cyclosporine plus mycophenolate mofetil. Although acute rejection rates were similar in each group ( $\leq 20\%$ ), the incidence of corticosteroid resistant rejection was lower in the tacrolimus arms. A 3-year follow-up found no statistically significant difference in renal function, patient or overall graft survival, but improved graft survival in recipients with delayed graft function in the tacrolimus arms [6]. The Elite Symphony trial also demonstrated that the low dose cyclosporine is not as effective as low dose tacrolimus on the rejection prevention [7]. As a result of these trials, the KDIGO Clinical Practice Guidelines suggest that tacrolimus should be the preferred calcineurin inhibitor for renal transplant recipients (Level of recommendation 2A) [8].

Metronidazole which consists 5-nitroimidazole compound is effective on protozoan and anaerobic bacterial infections. It is widely used to treat gastroenteritis suspected to have an infectious origin. Metronidazole is associated with gastrointestinal (nausea, vomiting, metallic flavour in the mouth etc.) and neurological (headache, optic neuritis, peripheral neuropathy etc.) adverse events when it is used for a long period or administered high dose [9].

Metronidazole is metabolized in the liver via CYP 450 enzyme system but specific isoforms which have a role in the drug's metabolism is not known. CYP2C9 inhibiting effect of metronidazole is well described in the literature but although there are some case reports that reveal increased serum levels of CYP3A substrates during metronidazole use, inhibition of the CYP3A enzymes by metronidazole couldn't be demonstrated by basic and clinical researches yet. Interactions between CYP3A substrates and metronidazole must include other mechanisms rather than direct inhibition of the enzyme system by metronidazole [10].

## Conclusion

To conclude; as occurred in our case, clinicians should be aware of metronidazole administration to a kidney transplant recipient who is under treatment with a calcineurin inhibitor consisting immunosuppressive regimen and should monitor the drug level and kidney functions closely.

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