Cent. Eur. J. Med. • 7(5) • 2012 • 587-590
DOI: 10.2478/s11536-012-0035-7

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Central European Journal of **Medicine**

Interactions between Tacrolimus and Metronidazole in a renal transplant patient

Case Report

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Received 2 April 2011; Accepted 2 January 2012

Abstract: We present a case which reports the occurrence of a potential elevation of Tacrolimus (Tac) plasma levels to toxic values in a renal transplant recipient after adding Metronidazole (Met) to the medication regimen. A 30-year old female, status post living-related renal transplant, who was stabilized on Tac 4.5 mg, twice daily, for 4 months, presented to the clinic with diarrhea. We used Microparticle Enzyme Immunoassay (MEIA) to determine Tac trough concentration (trough concentrations 5-10 ng/ml). After 6 days of Met therapy on 1.5 g/d, Tac trough concentration and serum creatinine (sCr) increased to 20.2 ng/ml and 7.8 mg/dl respectively. Met therapy was discontinued, also one dose of Tac was withheld, while daily dose was decreased to 2 mg/d. Four days after Met discontinuation, Tac concentration dropped to 8.7 ng/ml, sCr to 2.1 mg/dl, warranting Tac dose increase to 3 mg/d. Co-administration of Tac with Met may result in elevated Tac concentrations, possibly leading to tacrolimus nephrotoxicity. Clinicians should be aware of this potential interaction and closely monitor Tac concentration and renal function.

Keywords: *Interactions • Metronidazole • Tacrolimus • Renal transplantation*

1. Introduction

Tacrolimus (Tac) is a potent immunosuppressant widely used in kidney transplantation for prophylaxis of organ rejection as an alternative to cyclosporine. It is primarily metabolized in the liver and intestine by the cytochrome P450 (CYP) enzyme 3A subfamily and P- glycoprotein (P-gp), the protein product of the MDR – 1 gene [1–3]. Due to a difference in intestinal and liver metabolism among patients, the mean oral bioavailability of Tac is approximately 20%, ranging from 6% to 43%. This suggests dosage individualization with a view to achieve the desired systemic exposure. If the concentration is higher than the range (between 5 and 15 ng ml^{-1}), adverse effects will be observed including nephrotoxicity, neurotoxicity and post-transplant diabetes mellitus [3,4]. Because of the role of CYP3A and P-gp in Tac metabolism, many pharmacological interactions have been described between Tac and other medical drugs.

Infections are the leading cause of morbidity and mortality in the early post-transplant period. *Clostridium difficile* is one of the most common infections causing dehydration, hypovolemia, hypoalbuminemia, anasarca, and electrolyte disturbances [5].

Metronidazole (Met) is used to treat anaerobic infections and is recommended as first-line therapy for *Clostridium difficile* infections [6,7]. Also, Met may inhibit CYP3A according to in vitro data and case reports, which are already presented [8–11].

We present a case which reports the occurrence of a potential elevation of Tac concentration to toxic levels in a renal transplant recipient after adding Met to the medication regimen.

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2. Case report

A 30-year-old female, who had undergone kidney transplantation 4 months ago, was complaining of persistent diarrhea, weakness and stomach pain. Results from stool testing were reported and the presence for *Clostridum difficile* was confirmed. A physician from Primary Health Care, initiated therapy with Met, 500 mg 3 times daily for 7 days. The posttransplant immunosuppressant regimen included Tac 4.5 mg twice daily (goal trough concentration of 5–10 ng/ml during the first year post transplant), mycophenolate mofetil 500 mg twice daily and prednisone 20 mg daily. Other medications included carvedilol 6.25 mg twice daily and methyldopa 500 mg 3 times daily.

After 6 days of Met therapy, she was admitted to the emergency department of the nephrology clinic, due to persistent weakness and dehydration. Biochemical laboratory results showed metabolic acidosis hypomagnesemia (0.43 mmol/L), while serum creatinine (sCr) was 7.8mg/dl. The next day, she had Tac circulating concentration determined by Microparticle Enzyme Immunoassay (MEIA). Tacrolimus trough concentration increased to 20.2 ng/ml. During the 4 months after transplantation, sCr level ranged between 1.3 and 2.2 mg/dl, and Tac concentrations between 5 and 10 ng/ml. Liver function tests and blood chemistry did not show any significant change compared to normal values. Due to high level of Tac, Met therapy was discontinued. Also, one dose of Tac was withheld, and tacrolimus regimen was reduced to 2 mg twice daily. Two days after Met discontinuation, the level of Tac was 16.8 ng/ml and sCr was 6.0 mg/dl, and level of magnesium was 0.22 mmol/L. She still had metabolic acidosis. Tacrolimus dosage was changed to 1 mg twice daily. Also the patient was placed on dialysis. Four days after Met discontinuation Tac trough concentration dropped to 8.7 ng/ml, sCr was 2.1 mg/dl, warranting Tac dose increase to 3 mg/d. The entire time during hospitalization she was given oral magnesium. Two days after she was stable, she was released from the hospital. sCr and magnesemia were within normal range. Also, metabolic acidosis was reduced. Tacrolimus trough concentration was within appropriate range.

Discussion

Infections are the leading cause of morbidity and mortality in the early post-transplant period. *Clostridium difficile* is one of the most common hospital-acquired (nosocomial) infections causing antibiotic-associated colitis. *Clostridium difficile* infections are treated with oral Met for 15 days or until diarrhea subsides [5].

Two cases have been published in which Met addition to the immunosuppressant regimen with Tac caused a threefold increase in Tac concentrations [11,12]. Also, these cases reported a significant increase in sCr, approximately two-fold . In one case report, the Tac levels of a kidney transplant patient increased 100% nine days after the addition of Met (400 mg three times a day). His sCr was also increased. Both Tac and sCr declined following a decrease in the dosage of Tac by more than 50%. After completion of the 2-week course of Met, Tac concentrations became subtherapeutic and an increase in the Tac dosage was necessary. [13].

Our patient had a 3-fold increase in Tac level with a 4-fold increase in sCr, after 5 days of Met treatment. This led to one tacrolimus dose being withheld and to a decrease of Tac daily dose. This action was performed in order to avoid Tac nephrotoxicity. The mechanism which can explain possible pharmacokinetic interaction is the change in pre-systemic metabolism of Tac associated with CYP3A4 and P-gp. In vitro data suggest that Met may be responsible for inhibition of CYP3A4 and other mixed function oxidases [10]. Because, Tac is among drugs that are substrates for CYP3A4, it is plausible that Met interacts with Tac in this manner. This can be confirmed by other reports, which introduce interaction between Met and other CYP3A4 substrates, such as cyclosporine, carbamazepine, and quinidine [8,9,14,15].

P-gp, may be the target site of the tacrolimus – metronidazole interaction. It is located throughout the epithelial cells of the jejunum, kidney, pancreas, and liver and has significant role in Tac metabolism [16,17]. There is no evidence that confirms that Met may be an inhibitor or substrate of P-gp, but, according to previous reports, Met may interfere with Tac clearance [11]. If the P-gp efflux pump is inhibited by Met, this can increase Tac trough concentration [16] Page et al. assumed that, mucosa permeability may be changed as a result of intestinal infection. They based their assumption on the fact, that *Clostridium difficile* can invade and rupture the intestinal epithelium and change the permeability of the mucosa in this manner. Also, Page indicated that Tac trough concentration may remain elevated from 2 weeks to 4 months after resolution of diarrhea and infection [11]. Our case can not support this conclusion due to the fact that our patient was dialyzed and this action caused a decrease in Tac trough concentrations. Also, our patient did not continue with Met, so we couldn't have checked possible interaction.

We have done the Naranjo probability scale, which can indicate a probable adverse drug reaction. Score was 6, which is indicative of interaction between drugs [18].

We have insufficient data that Met is an inhibitor of CYP3A4 or P-gp [19,20]. Michalets et al., suggest that Met, among the other drugs, is a CYP3A4 inhibitor and it should be avoided in coadministration with other CYP3A4 substrates, but there is no confirmation from in vivo studies [21]. Based on detailed research of available database (FDA, EMA, Drugs), according to isolated case reports, Met does not significantly inhibit CYP3A4 activity. Nevertheless, the possible elevation effect of Met on Tac in kidney transplant patients has been reported although its mechanism is still unknown. Most probably the mechanism is CYP3A4 inhibition due to specific pharmacokinetics in certain types of patients [13,22,23]. Furthermore, Tac has a narrow therapeutic range thus increasing the risk of toxicity.

As we said earilier, in vitro studies confirmed potentional inhibitory activity of Met, which indicates that further research in the field of Met metabolism is needed.

3. Conclusion

The occurrence of infectious complications is closely related to immunosuppressive treatment, so it is likely that an anti-infective agent would be administered to a patient. Every drug indicated during immunosuppressant therapy should be monitored carefully with all possible safety for patient health. Co-administration of Tac with Met may result in elevated Tac trough concentration, possibly leading to tacrolimus nephrotoxicity. Clinicians should be aware of this potential interaction and closely monitor Tac trough concentrations and renal function. Further research in a field of pharmacokinetic interactions is needed, especially concerning the mechanisms of drug biotransformation.

Acknowledgment

This case report was supported by grant of Ministry of Science and Technological Development - project number 41018.

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