CASE REPORT

Effect of diarrhoea on Tacrolimus trough level in a post liver transplant patient

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SUMMARY

Tacrolimus, which bonds to an immunophilin, FK506 binding protein (FKBP) has emerged as one of the most widely used immunosuppressant post solid organ transplantation. It offers excellent patient survival rates post-transplantation and a lesser number of acute rejections as compared to cyclosporine.

Tacrolimus has a narrow therapeutic window with overexposure leading to acute and chronic forms of nephrotoxicity. Remarkably few data have been published on the overexposure to tacrolimus following mild diarrhoea in post-transplant patients who received treatment with tacrolimus. We observed a post-liver transplant patient with increased trough level of tacrolimus during severe diarrhoea with no complications following a timely adjustment on the dose of tacrolimus.

INTRODUCTION

The immunosuppressant tacrolimus, which is a calcineurin inhibitor, is used widely in post organ transplant patients. Diarrhoea is a frequent adverse event in patients treated with tacrolimus, and diarrhoea imposes a significant impact on the pharmacokinetics of tacrolimus.

CASE REPORT

We report herein a male patient with biliary atresia who underwent Kasai procedure at the age of six weeks old. Subsequently, he underwent living-donor liver transplantation aged 23-year-old. Post-operatively, immunosuppression was achieved with tacrolimus in combination with mycophenolate mofetil and prednisolone. The latter two regimens were gradually tapered due to neutropenic side effect. The tacrolimus dosage was adjusted accordingly by maintaining tacrolimus therapeutic level at 8-10µg/L. When tacrolimus dosage was gradually increased from 1mg twice a day to 3mg twice a day, the patient developed a low-grade fever and acute diarrhoea. There was a surge in FK506 level from 5.1µg/L to 16.3µg/L.

Possible infections including cytomegalovirus, stool ova and cysts tested negative. The patient was not given any comedication that may affect the level of tacrolimus. Subsequently, two doses of tacrolimus were omitted on the first day of diarrhoea and restarted at 2mg/day on the following day. The FK506 level was found reduced to 9.3µg/L with spontaneous resolution of diarrhoea and fever. Figure 1 shows tacrolimus trough concentrations and daily tacrolimus doses administered during hospitalization. After a temporary reduction of the FK 506 dosages and symptomatic therapy for diarrhoea, the patient recovered rapidly.

DISCUSSION

Few studies have described the elevated trough levels of tacrolimus (FK 506) during diarrhoea in liver transplant recipients, but most of the studies were carried out among the paediatric group of patients.[1,2]

The pharmacokinetic profile of tacrolimus shows considerable variability in drug bioavailability, contributing a clinical challenge in maintaining therapeutic concentrations.[3] Factors affecting the pharmacokinetics of tacrolimus, including age or gender of the patient, liver impairment, genetic variances in the cytochrome P450 (CYP) enzymes and P-glycoprotein expression. Furthermore, the blood levels of tacrolimus are affected by exogenous factors such as diarrhoea and comedications.

In our patient, diarrhoea preceded the rise in tacrolimus blood trough level, indicating the diarrhoea is the cause of the increment of tacrolimus exposure and not as a consequence. The increase in tacrolimus exposure during severe diarrhoea could have several causes.

Firstly, the bioavailability of tacrolimus may be raised by the reduced enzymatic activity of the CYP3A system or P-gp in enterocytes that are damaged by intestinal inflammation and infection. Secondly, there is shortened ileal transit time to the duodenum during diarrhoea, a higher amount of tacrolimus may be delivered to the colon, where the lower metabolic activity of CYP3A could result in increased absorption. Besides, the increased exposure to tacrolimus during diarrhoea can be explained by the hemoconcentration, reduced hepatic metabolism, and fasting.[4-6]

Tacrolimus is a low-clearance drug with an extraction ratio of <3% of hepatic blood flow. Tacrolimus has poor aqueous solubility and extensive plasma protein binding; hence it is not dialyzable in the event of tacrolimus intoxication.

CONCLUSION

The intra-individual variability in tacrolimus exposure resulting in fluctuations in their measured FK506 level.

This article was accepted: 08 August 2020
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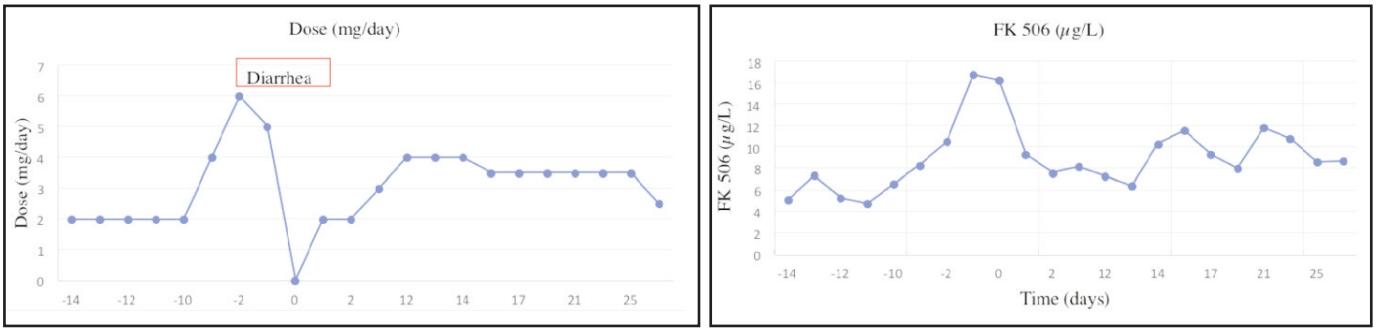

Fig. 1: Doses and trough levels of tacrolimus during episodes of diarrhea.

Hence, individualized dosing is needed based on the measured trough concentrations. As a clinician, we should be aware of the potential raised in tacrolimus trough level during diarrhoea in post organ transplant patients. Therapeutic drug monitoring (TDM) should be performed to prevent tacrolimus intoxication.

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