Case-1: Preanalytical Challenges in Tacrolimus Monitoring

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Summary

A 37-year-old woman experienced a significant increase in blood tacrolimus levels after starting Clarithromycin for an H. Pylori infection. Tacrolimus, used in organ transplant patients, has a narrow therapeutic index requiring close monitoring. The concurrent use of Clarithromycin, a CYP3A4 inhibitor, led to a dramatic spike in tacrolimus levels, causing signs of potential toxicity, such as elevated serum creatinine. This case highlights the critical importance of awareness of drug-drug interactions, especially involving CYP3A4 inhibitors, to prevent adverse effects and ensure patient safety. Clinicians should closely monitor tacrolimus levels when prescribing such medications.

Keywords- CYP3A4; Tacrolimus; Clarithromycin; Drug Interaction

Introduction

Tacrolimus is an immunosuppressive drug that inhibits T-lymphocyte activation by inhibition of the phosphate activity of calcineurin. It is highly bound to the erythrocytes. Absorption from the gastrointestinal tract is variable and irregular. Peak blood concentrations are achieved at 1.5 to 3.5 hours. The elimination half-life from whole blood is about 11 hours in transplant patients. It has a narrow therapeutic index range; high tacrolimus concentrations are associated with toxicity, whereas low concentrations are associated with an increased risk of graft rejection. Although dose adjustments based on therapeutic drug monitoring are performed, unexpected large variations in tacrolimus concentration are sometimes encountered.

Case Presentation

We received a request from physician to recheck blood tacrolimus level for a 37 years lady who received renal transplantation 8 years back. Her blood tacrolimus level was 36.7µg/L and on rerunning the same sample, the result was 36.1µg/L. We informed the same result to the physician. However, physician admitted his disagreement with the report because he had not increased the dosage for tacrolimus and requested for repeating the test in new sample next day. On the subsequent day, the blood tacrolimus level was 39.8µg/L and there was also rise in serum creatinine to 1.5 mg/dl which was 1.0 mg/dl 2 weeks back. Physician was informed about the result.

Careful inspection for potential source of error in all analytical steps was done. We receive around 350 blood tacrolimus samples in a month at our center. We measure blood tacrolimus using Abbott Architect i1000 (Abbott, USA). Architect tacrolimus assay is designed to have a correlation coefficient of 0.90 for samples with result between 2.0 - 30.0 µg/L when compared to LC/MS/MS.

The reagent, calibrator, internal quality control graphs and instrument were checked to identify presence of any analytical error, however no abnormality was found. There was no recent maintenance of instrument and no issues with other parameters. We confirmed the delta check for tacrolimus results in other patients and none of them were suspicious.

We decided to inquire directly with the patient. There was no change in tacrolimus dosage and any recent major illness or hospital admission. Patient denied changing the brand for tacrolimus and confirmed that she provided blood samples on empty stomach 15 minutes before her next dosage. There was no history of biliary disease and recent diarrhea which are known to increase trough tacrolimus level. On further inquiring she admitted that she was recently prescribed triple therapy by the different physician for *H.Pylori* infection after her urea breath test was positive. The therapy consisted amoxycillin 1 grams twice day, clarithromycin 500 mg twice a day and pantoprazole 40 mg twice a day for 14 days. We reviewed the literature and found that there were few case reports on drug-drug interaction between tacrolimus and clarithromycin. After contacting physician, clarithromycin was stopped and azithromycin was initiated. The subsequent blood tacrolimus dropped down to 23.1 µg/L and to 4.0µg/L within 4 days after stopping clarithromycin (Figure 1). The result-date graph (Figure 1) is directly taken from the laboratory information system.

Discussion

Tacrolimus inhibits T-lymphocyte activation by binding to an intracellular protein, FKBP-12 and complexes with calcineurin dependent proteins to inhibit calcineurin phosphatase activity. Its metabolism is mediated by cytochrome CYP3A 4/5 thus making it potential substrate for clinically significant interaction. Clarithromycin is a macrolide antibiotic used for H.Pylori eradication and is a potent CYP3A inhibitor. A reversible rise in trough concentration in tacrolimus level, due to pharmacokinetic interaction with clarithromycin, associated with nephrotoxicity as evidenced by temporary rise in serum creatinine is presented in the index case. Wolter et al. reported the first case of tacrolimus-clarithromycin interaction where a renal transplant patient whose tacrolimus level increased from 9 to 29 ng/ml 3 days after the initiation of oral clarithromycin 500 mg twice daily for suspected pneumonia. (1)

The index patient had mild nephrotoxicity owing to sudden rise in serum tacrolimus level that led to temporary increase in serum creatinine. However no other toxicity was recorded. Many factors contribute to the development of tacrolimus nephrotoxicity which includes exposure to metabolites of tacrolimus, local renal P-glycoprotein and renin angiotensin system activation resulting in vasoconstriction of the afferent and glomerular arterioles. (2) Since tacrolimus use is typically in combination with other immunosuppressant's, target levels usually decrease as post-transplant time increases to minimize calcineurin inhibitor-mediated nephrotoxicity and adverse effects. There was alarming rise in tacrolimus level in our patient after 8 years of transplant which raised concern from the physician.

CYP3A 4/5 genetic polymorphism are widely accepted to play an important role in tacrolimus metabolism and its allele mutation might be different in different races. Therefore, tacrolimus toxicity and interaction with other drugs differs among races. For an example CYP3A-5 genotype dependent drug interaction was found between tacrolimus and nifedipine in Chinese renal transplant patient. (3) Therefore personalized therapy accounting for CYP3A4/5 genotype detection as well as therapeutic drug monitoring is necessary for renal transplant patients.

After diagnosis of clarithromycin induced tacrolimus toxicity, physician advised to use azithromycin, another macrolide antibiotic, which is an alternative to clarithromycin because this antibiotic has a very similar microbiological spectrum and it does not interact significantly with CYP 3A4 enzyme. Therefore, clinicians should be aware that other drugs which are metabolized via the same enzyme system should also be used with caution for patients on tacrolimus (Table 1). (4, 5)

Conclusion

Vigilant monitoring and awareness of tacrolimus drug interaction is essential to prevent its toxicity with its narrow therapeutic window.

Acknowledgement

None

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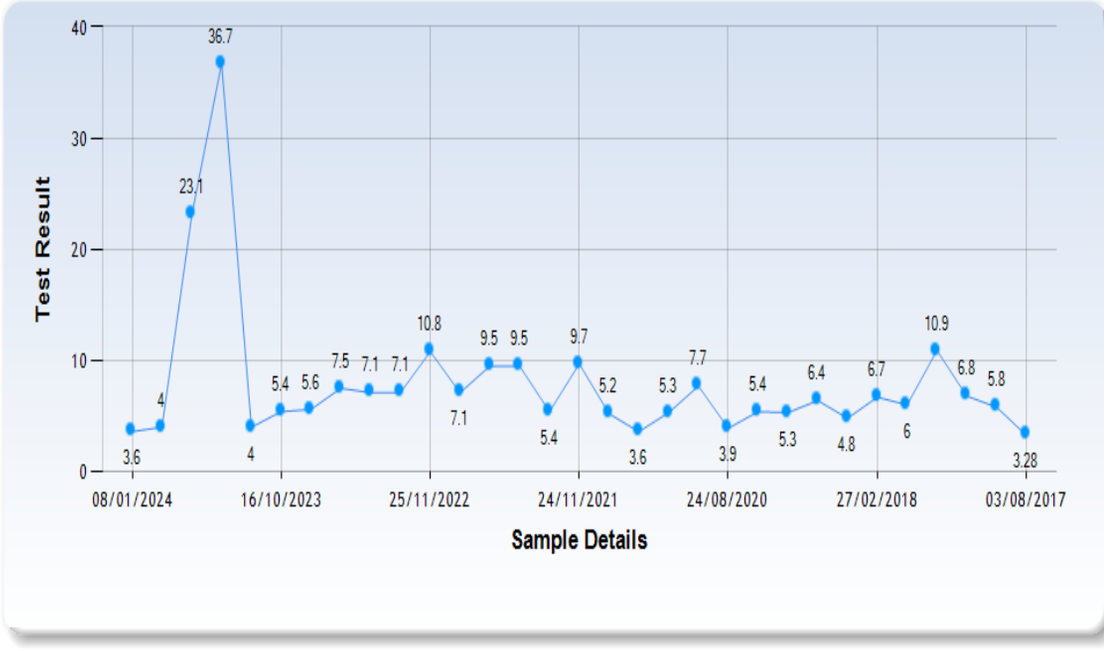

Figure 1: Tacrolimus (Y-axis) level versus date of test (X-axis)