Early interaction between tacrolimus and rifampin

Interaction précoce entre tacrolimus et rifampicine

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RÉSUMÉ

Les interactions médicamenteuses sont inévitables et doivent être proactivement identifiées et prises en charge, en particulier, l'effet inducteur de la rifampicine sur le tacrolimus dont les données sur la puissance et la durée sont limitées.

Nous rapportons le cas d'un transplanté rénal traité par tacrolimus dont les concentrations sanguines résiduelles (C0) étaient en moyenne de 7,9 +/- 2 ng/mL. Le patient a présenté une tuberculose ganglionnaire nécessitant sa mise sous rifampicine. Un jour plus tard, la C0 était de 2,6 ng/mL sous 5 mg/jour. La créatininémie était normale. Neuf jours après, la C0 était de 1,6 ng/mL sous 7 mg/j.

Dans le cas rapporté, l'interaction entre le tacrolimus et la rifampicine était survenue un jour seulement après l'introduction de la rifampicine nécessitant un suivi thérapeutique précoce des C0.

Mots-clés

Suivi thérapeutique pharmacologique - Transplantation - Tacrolimus - Rifampicine - Interaction

SUMMARY

Drug interactions are unavoidable and need to be proactively identified and managed, in particular, the inductive effect of rifampin on tacrolimus whose potency and duration data are limited.

We report the case of a renal transplant patient who was prescribed tacrolimus with preserved tough blood levels (C0) of 7.9 +/- 2 ng/mL. He presented ganglionic tuberculosis and started rifampin. One day later, C0 was 2.6 ng/mL with 5 mg/day. The serum creatinin was normal. Nine days later, C0 was 1.6 ng/mL with 7 mg/day.

In this case-report, the tacrolimus-rifampin interaction occurred just one day after rifampin introduction necessitating early C0 monitoring.

Key-words

Therapeutic drug monitoring - Transplantation - Tacrolimus - Rifampin - Interaction

INTRODUCTION

Calcineurin-inhibitors metabolism through the hepatic cytochrome P450 (CYP) systems is influenced by multiple drugs (1,2). Tacrolimus is metabolized by CYP3A5 and CYP3A4 in both of the liver and the small intestine. Rifampin is a well-known inducer of CYP3A4 in vivo and may induce significant interactions with tacrolimus. In transplant patients, the prevalence of tuberculosis is estimated to 2.5 case/1000 persons/year (3,4). Tacrolimus-rifampin drug interaction needs to be proactively identified and appropriately managed. Studies of the effect of rifampin on the pharmacokinetics of drugs metabolized by CYP3A4 showed that full induction of these enzymes was reached at one week after starting treatment with rifampin (5). Information about the extent, duration, and potency of the rifampin-tacrolimus interaction is limited. This interaction sometimes results in an allograft dysfunction leading to a tenfold increase in the daily dose requirement (6,7).

We present a case of an early rifampin-tacrolimus interaction in a renal transplant patient.

CASE PRESENTATION

We report the case of a 25-year-old renal transplant man since 2.5 years. The patient was prescribed tacrolimus, prednisone and mycophenolate mofetil. The tacrolimus trough blood levels (C_0) were measured by an immunoanalysis technique, performed by the automat Architect from Abbott Laboratories (the low limit of detection of tacrolimus C_0 was 0.3 ng/mL). These C_0 were preserved varying between 5.3 and 11.4 ng/mL (mean of 7.9 ng/mL +/- 2 ng/mL) with a tacrolimus C_0 target of 5 to 10 ng/mL and there was no need to change the tacrolimus dosage (mean 7.1 +/- 1.2 mg/day). He presented an abdominal pain. After investigation, the diagnosis of ganglionic tuberculosis was established. The patient started four anti-tuberculous drugs including isoniazid 300 mg/day, rifampin 600 mg/day, ethambutol 900 mg/day and pyrazinamid 3 g/day. The last C_0 before anti-tuberculous drugs introduction was 7.9 ng/mL.

He was prescribed 5 mg/day of tacrolimus, regularly taken. One day after anti-tuberculous drugs' introduction, C_0 was 2.6 ng/mL (Table 1). Nine days later, C_0 was 1.6 ng/mL with 7 mg/day of tacrolimus. Eight months after rifampin withdrawal, C_0 was 11.1 ng/mL with 7 mg/day of tacrolimus (Figure 1). The serum creatinin was normal in each control varying between 93 and 99 µmol/L.

Table 1: Tacrolimus blood levels variations in time before and after rifampin coadministration

Date	Tacrolimus daily dose (mg/day)	Tacrolimus tough blood levels (ng/mL)
25/11/2010	6	5.3
05/05/2011	6	9.3
10/05/2011	5	7.9
Day 0: 11/05/2011	1st day of rifampin administration	
Day 1: 12/05/2011	5	2.6
Day 9: 21/05/2011	7	1.6
07/01/2012	7	11.1

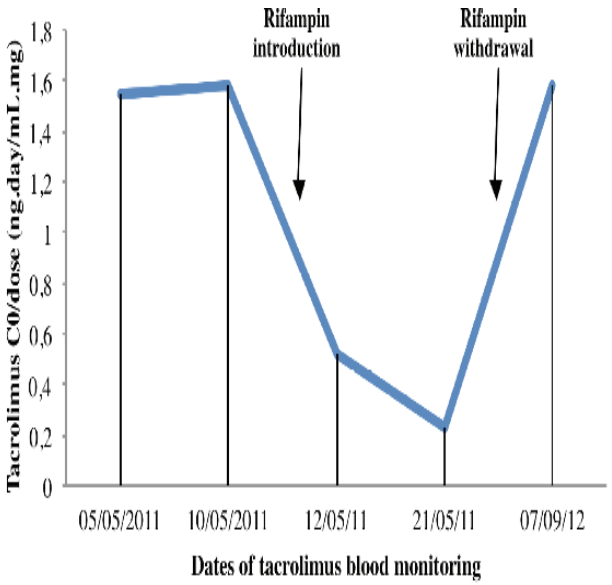

Figure 1: Variation of the ratio of tacrolimus C0/dose in time

DISCUSSION

In this case-report, tacrolimus C_0 decreased 3 to 5 times the initial C_0, respectively one to nine days after anti-tuberculous drugs' introduction. Tacrolimus has a narrow therapeutic index (5-10 ng/mL) (8) and a large interpatient variability in its pharmacokinetics. Tacrolimus pharmacokinetics may be influenced by multiple factors, including graft type, hepatic and renal functions, use of concomitant medications such as rifampin, time since transplantation, patient's age, ethnic background, hematocrit and albumin concentrations, food intake and diarrhea (9). Pro-inflammatory cytokines may decrease

production of CYP450 enzymes (10) but inflammatory biomarkers were not explored in our patient.

In renal transplant patients, polymorphisms of genes coding for enzymes (CYP3A4 and 3A5) and transport proteins involved (ABCB1, encoding the transport protein P-glycoprotein) in the metabolism of tacrolimus have been thoroughly studied demonstrated interindividual variation in tacrolimus metabolic capacity (11-13). However, only CYP3A5 polymorphisms influence on the pharmacokinetics of tacrolimus is well established. In fact, CYP3A5*1 allele carriers or high expressors require larger doses of tacrolimus to reach target C_0 than homozygous carriers of the CYP3A5*3 allele or low expressors (14-17). The reported case illustrated the potent and rapid effects of rifampin on tacrolimus metabolism in only one day after rifampin introduction necessitating an early C_0 monitoring and dose adjustment. In fact, rifampin induces the expression of a number of drug metabolism–related genes as ABCB1 and CYP3A4, uridine diphosphate–glucuronosyltransferases, monoamine oxidases, and glutathione S–transferases. Drugs that depend on these enzymes for their metabolism are prone to drug interactions when co-administered with rifampin as tacrolimus and mycophenolate mofetil (18). Our patient pharmacogenetics profile was unknown. But, we may hypothesize that the early interaction between tacrolimus and rifampin could be explained by a high expression of CYP3A5*1 allele. Rifampin may induce the hepatic CYP3A4 system and the oxidative metabolism mediated by this system in the gut necessitating the use of large doses of tacrolimus (19). Herbert et al found that with co-administration of rifampin, the clearance of tacrolimus increased nearly 50% and theoral bioavailability decreased 50% (5). In the literature (19-23), transplant recipient patients in whom tacrolimus and rifampin were prescribed presented a subsequent C_0 decrease of 3 to 6.6 times in two to 6 days and a two to 12-fold increase in the tacrolimus dose was needed to maintain pre-rifampin C0 (Table 2). In similar cases, CYP3A4 inhibitors may be added or rifampin discontinued (19, 20).

In our patient's renal function remained unchanged from baseline throughout his course in hospital but mycophenolate mofetil dose adjustment and mycophenolic acid (MPA) plasmatic levels were not reported. In fact, rifampin induces the expression of a number of drug metabolism–related genes interacting on the metabolism of co-administered drugs as mycophenolate mofetil. In the study of Kuypers et al, this interaction resulted in a MPA dose–corrected AUC0–12 after rifampin withdrawal versus before rifampin withdrawal change of 221% (18).

CONCLUSION

In this case-report, the tacrolimus-rifampin interaction occurred just one day after rifampin introduction. Close monitoring of C_0 and frequent dose adjustments are

Table 2 : Characteristics of Reported Cases of Rifampin–Tacrolimus Interactions

Reference	Days between rifampin introduction and tacrolimus trough blood concentration decrease	Tacrolimus trough blood concentration decrease	Target tacrolimus trough blood concentration (ng/mL)	Maximum (increase)	Rifampin Dose(mg/day)	CYP3A4 Inhibitors
Bhaloo et al (6)	5 days	_	10–15	5.33-fold	600	Clarithromycin, diltiazem, fluconazole
Chenhsu et al (19)	_	3 to 5-fold	5–8	12-fold	600	None
Mori et al (20)	_	> 2-fold	5–10	2-fold	300	Itraconazole
Moreno et al (21)	2 days	6.6-fold	5–10	2-fold	Unknown	None
López-Montes et al (22)	_	2.2 to 3.2-fold	10–15	3.75-fold	600	None
Naylor et al (23)	4 days	3-fold	5–8	2.25-fold	600	None
This case	One day	3 to 5-fold	5-10	1.4-fold	600	None

required to optimize allograft function. With advancement of knowledge, the therapeutic drug monitoring can emerge optimizing the management of pharmacokinetic interindividual drug interactions assisted by the identification of functional SNPs in genes encoding for drug metabolizing enzymes.

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