Brief Report

Pharmacokinetic interaction between corticosteroids and tacrolimus after renal transplantation

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Abstract

Background. Tacrolimus is an immunosuppressive drug that is a substrate of cytochrome P450 3A (CYP3A) enzymes and P-glycoprotein (P-gp). After transplantation, many pharmacological interactions have been described. Corticosteroids induce both CYP3A and P-gp activity. This study was designed to investigate the presence of a clinically significant interaction between steroids and tacrolimus after renal transplantation.

Methods. We studied 83 renal transplant recipients receiving tacrolimus after transplantation. Patients were divided into three groups, according to steroid dose (low: 0–0.15 mg/kg/day; intermediate: 0.16–0.25 mg/kg/day; and high: >0.25 mg/kg/day). All other medications, including those known to interact with CYP3A and/or P-gp, were recorded. Steroid dosage, tacrolimus dosage, tacrolimus trough concentration (C₀) and tacrolimus concentration/dose ratio [C₀ divided by the 24 h dosage (mg/kg)] were assessed for each dosage group after 1 and 3 months of tacrolimus treatment.

Results. The three groups were not different as regards the use of non-immunosuppressive treatments or clinical events. At 1 and 3 months, the tacrolimus doses and concentration/dose ratios differed significantly in the three steroid dosage groups. With the higher doses, higher tacrolimus doses were needed to achieve the blood tacrolimus targeted trough level.

Conclusions. We demonstrated that pharmacokinetic interaction occurs between steroids and tacrolimus in renal transplant patients. The higher the steroid dosage, the higher the dosage of tacrolimus needed to achieve target trough levels in these patients. The most likely interaction mechanism is specific enzymatic induction of CYP3A and/or P-gp. Interaction is present, even when the steroid dosage is low. The clinical events liable to occur during steroid sparing or tapering must be taken into account because it may be associated with episodes of tacrolimus-related nephrotoxicity.

Keywords: drug interaction; pharmacokinetics; renal transplantation; steroids; tacrolimus

Introduction

Tacrolimus, a calcineurine inhibitor, is used to prevent allograft rejection in solid organ transplantation, and is therefore a basic component of immunosuppressive therapy in transplant recipients. The clinical management of tacrolimus is difficult, because of its narrow therapeutic index and the large inter- and intra-individual variations in its pharmacokinetic characteristics. This management is particularly difficult after renal transplantation, because of the dose-related nephrotoxicity observed with tacrolimus. Like cyclosporine, many clinically relevant pharmaceutical interactions have been described between tacrolimus and other drugs used after transplantation [1].

Cytochrome P450 3A (CYP3A) and P-glycoprotein (P-gp) both reduce the intracellular concentration of various xenobiotics. CYP3A enzymes constitute the major phase one drug-metabolizing enzyme family in humans [2]. P-gp, the product of the multidrug-resistance (MDR-1) gene, is responsible for the transmembrane efflux of many drugs. Many CYP3A and P-gp substrates are also known to increase or reduce drug activity. The variations in the intra-individual metabolism of various xenobiotics may be partially due to their interactions with concomitantly administered drugs, and may have important clinical consequences.
CYP3A and P-gp are involved in the metabolism of both tacrolimus [3,4] and steroids. Steroids are also known inducers of P-gp and/or CYP members in animal models and in vitro studies [5–7]. Dexamethazone, at doses similar to those used in clinical practice, has been shown to increase CYP3A4 activity in both healthy volunteers and human hepatocyte cultures [8]. High-dose steroid therapy was also recently shown to lower tacrolimus blood levels in the rat, as a result of the induction of P-gp and CYP3A in the intestine and liver [9]. The combined use of steroids and P-gp and/or CYP3A substrates may change the pharmacokinetic characteristics of the drug combinations in the patient, leading to changes in their efficacy or side effects. Possible drug interactions have been extensively studied in patients treated with a combination of cyclosporine and steroids after organ transplantation. However, the results reported are conflicting [10]. Little information is available on the pharmacokinetic interactions between tacrolimus and steroids after renal transplantation.

We examined here the effect of steroid dosage on tacrolimus dosage and trough levels in a large group of renal transplant recipients. The resulting pharmacokinetic interactions may have clinically significant consequences, especially during steroid tapering or high-dose therapy for acute rejection after transplantation.

**Subjects and methods**

**Study population**

All renal graft recipients transplanted in our centre between 1997 and 2001 and treated with tacrolimus were invited to participate in this retrospective study. In all, 84 recipients were included. Their demographic characteristics are shown in Table 1. The use of all medications known to interfere with either CYP3A or P-gp function was recorded for all patients. None of the drugs that may interact with P-gp and/or CYP3A at therapeutic doses was used in the studied patients. Among these drugs, the more frequently used in transplantation were calcium antagonists. When necessary, amlodipine, which does not interact with CYP3A or P-gp at therapeutic doses, was deliberately chosen. When oral contraception was needed, we chose the progestative drug chlormadinone for doses, was deliberately chosen. When oral contraception was needed, we chose the progestative drug chlormadinone for which no significant interaction is described.

**Immunosuppressive regimen**

Induction therapy with monoclonal or polyclonal agents was used when delayed graft function was anticipated (n = 43). All patients were treated with an initial tacrolimus daily dose of 0.2 mg/kg. This daily dose was thereafter adapted according to the blood trough concentrations (12 h post-dose) of tacrolimus. During the first 3 months, the target blood trough concentration was 10–15 ng/ml, measured by a semi-automated microparticle enzyme immunoassay (Abbott, Rungis, France). All patients received a purine inhibitor, which was either mycophenolate mofetil (n = 48) or azathioprine (n = 35). Regarding the use of steroids, the standard dosage was 500 mg intravenous (i.v.) methylprednisolone at transplantation, 125 mg i.v. the following day, and then 20 mg prednisone daily. Oral prednisone was then progressively tapered to 5 mg daily at 3 months post-transplantation.

**Data collection**

Patients had clinical and laboratory assessments at 1 and 3 months after tacrolimus initiation. Clinical evaluation included body weight and all the concomitant medications with possible CYP3A and/or P-gp interaction. The daily doses, in milligrams, of both tacrolimus and steroid were recorded, and the weight-adjusted tacrolimus and steroid dosages were calculated (mg/kg/day). Laboratory tests included measurement of blood tacrolimus trough concentrations (ng/ml). The concentrations measured were dose-normalized, using the tacrolimus concentration/dose ratio, obtained by dividing the tacrolimus trough concentration by the corresponding 24 h dose, on an mg/kg basis. The value obtained is the tacrolimus dose needed to obtain a given trough level. Lastly, we explored the correlations between the weight-adjusted tacrolimus doses and concentration/dose ratios on the one hand, and the steroid dosages on the other. Steroid dosages, expressed in mg/kg/day, were classified as low, intermediate and high (<0.15, 0.16–0.25 and >0.25 mg/kg/day, respectively).

**Statistical analysis**

After confirmation of the normal distributions, all results were expressed as means ± SD. When necessary, the median and range are given. The pharmacokinetic values between the steroid dosage groups at different times post-transplantation were compared by non-parametric tests. The Mann–Whitney U-test was used for comparison of two groups, and the Kruskal–Wallis test for comparison of the three dosage groups. P-values of <0.05 were considered significant.

**Results**

The demographic characteristics of the patients in the three daily steroid dosage groups were not different (Table 1). Mean recipient age was 42 ± 11.3 years.

**Table 1. Demographic characteristics of the study population**

<table>
<thead>
<tr>
<th>Steroid dose at 1 month</th>
<th>Steroid dose at 3 months</th>
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<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Gender (n, female/male)</strong></td>
<td>4/8</td>
</tr>
<tr>
<td><strong>Ethnic group (n, black/Caucasian)</strong></td>
<td>3/9</td>
</tr>
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Mean recipient body weight was 62.5 ± 13.7 kg. Eighteen patients (21.7%) presented with diabetes in our study population, 12 with type I, and six with type II diabetes. Eighteen percent of patients experienced at least one episode of acute rejection during the first year post-transplantation. Apart from corticosteroids, no patient was given any drug known to interact with either CYP3A or P-gp.

The median daily doses of steroid were 0.25 mg/kg (range 0–0.93 mg/kg) 1 month after tacrolimus initiation, and 0.17 mg/kg (range 0–1.1 mg/kg) after 3 months ($P < 0.0001$). At 1 and 3 months, the daily steroid dose was low (<0.15 mg/kg) for 12 and 33 patients, respectively, intermediate (0.16–0.25 mg/kg/day) in 33 and 44 patients, and high (>0.25 mg/kg/day) in 38 and six patients.

Fig. 1. Distribution in 84 renal transplant patients of the daily doses of tacrolimus needed to obtain the target trough level after 1 month (A) and 3 months (B) of tacrolimus treatment.
One and 3 months after transplantation, there was no difference in tacrolimus blood levels within the three steroid groups (13.4 ± 2.2, 11.8 ± 2.3 and 12.2 ± 4.6 ng/ml at 1 month and 10.7 ± 2.7, 11.5 ± 3.9 and 11.1 ± 4.5 ng/ml at 3 months for the low, intermediate and high steroid dose groups, respectively; \(P = \text{NS}\)). These values were within the desired target range. As expected, there were wide inter-individual variations in the tacrolimus dose required to obtain the target trough level (range 0.05–0.39 mg/kg/day at 1 month and 0.03–0.38 at 3 months; Figure 1). The median daily dose was significantly higher 1 month after tacrolimus initiation than 3 months thereafter (0.18 vs 0.12 mg/kg/day, \(P < 0.0001\)).

Next, we studied the effect of steroid dosage on tacrolimus therapy. The tacrolimus trough levels were not different in the three steroid dosage groups after 1 and 3 months of tacrolimus treatment. Nevertheless, the tacrolimus doses correlated with the daily steroid dose at both 1 and 3 months (\(P < 0.05\), Kruskal–Wallis test; Figure 2A and C). The higher the dose of steroid, the higher the daily dose of tacrolimus needed to achieve target trough blood concentrations.

At 1 month, the median tacrolimus dose required to reach the target concentration was significantly higher in patients given the highest steroid dose than in those given the intermediate and the lowest doses (0.21, 0.17 and 0.15 mg/kg/day, respectively; high vs intermediate dose, \(P = 0.05\); high vs low dose, \(P = 0.03\); intermediate vs low dose, \(P = \text{NS}\)). At 3 months, these values were, respectively, 0.18, 0.15 and 0.10 mg/kg/day (high vs intermediate dose, \(P = \text{NS}\); high vs low dose, \(P = 0.02\); intermediate vs low dose, \(P = 0.0001\)). Lastly, we evaluated the median tacrolimus concentration/dose ratios. These ratios differed significantly in the three steroid dosage groups, both after 1 month of tacrolimus treatment (\(P = 0.05\), Kruskal–Wallis test; Figure 2B) and after 3 months (\(P = 0.001\), Kruskal–Wallis test; Figure 2D).

Discussion
After renal transplantation, immunotherapy has to continue throughout the graft’s lifetime. The initial
immunosuppressive regimen is based on a combination of several drugs, which often include steroids and a calcineurin inhibitor such as tacrolimus. Because of the role of CYP3A and P-gp in the tacrolimus metabolism, many pharmacological interactions have been described between tacrolimus and other medical drugs [1]. These interactions may be of great importance when they involve other immunosuppressive therapies used after organ transplantation. Many attempts to spare or stop steroids have indeed been reported using tacrolimus-based immunosuppression [11,12]. Underestimation of pharmacological interactions during these manoeuvres may lead to either under-immunosuppression or immunosuppressant-induced nephrotoxicity.

We demonstrated here, in a clinical setting, that steroid tapering reduces tacrolimus requirements in renal transplant recipients. If a steroid–tacrolimus interaction is not recognized and the tacrolimus dosage is not appropriately adjusted, episodes of acute renal dysfunction secondary to nephrotoxicity may occur. Such an interaction may explain some of the episodes observed during steroid-tapering as suggested by Kuyper and Vanrenterghem [12].

Our results are consistent with the occurrence of a clinically relevant pharmacokinetic interaction between glucocorticoids and tacrolimus in renal transplant patients. The impact of an inducer drug gradually increases over time. Our data are in accordance with this mechanism, because the correlations found between steroid doses and pharmacokinetic parameters of tacrolimus are closer after 3 months of tacrolimus treatment than after 1 month. The most likely mechanism is therefore enzymatic induction.

Potential sites of pharmacokinetic drug interactions include the gastrointestinal tract, protein- and tissue-binding sites, drug-metabolizing enzymes, the drug transport system, biliary excretion, enterohepatic recirculation and renal excretion. However, the most important mechanisms reported for such interactions are either the inhibition or induction of the CYP3A-mediated metabolism of tacrolimus [1]. Since CYP3A is responsible for more than 90% of the metabolic elimination of tacrolimus, the inhibition or induction of CYP3A will lead to a clinically significant pharmacokinetic drug interaction [13]. The induction of CYP3A diminishes oral drug bioavailability and accelerates tacrolimus elimination, thus increasing the need for higher daily doses. Although traditionally the liver was considered to be the main site of pharmacokinetic drug interactions, the importance of gut metabolism was recently stressed and high levels of CYP3A enzyme expression were indeed recently reported in the gut [14]. In addition, evidence has emerged that the P-gp efflux pump, largely expressed in the enterocytes, may play an important role in the variability of tacrolimus absorption [14,15].

Glucocorticoids are known substrates and inducers of CYP3A enzymes [16]. The regulation of these enzymes, particularly CYP3A4, has been extensively studied [2]. Synthetic glucocorticoids such as dexamethasone, prednisone or prednisolone have been shown to transactivate the CYP3A4 gene through several signalling pathways. These pathways involve nuclear receptors such as the pregnane X, glucocorticoid and the constitutive androstane receptors [17]. Many drugs and steroid hormones have also been shown to induce P-gp expression. This induction appears to take place at the transcriptional level. The MDR-1 gene may be transactivated by the nuclear receptor PXR [18]. The induction of CYP3A and P-gp by dexamethasone in rat liver has also been described [5,6].

Although corticosteroids have been shown to be inducers of CYP3A and P-gp, little information is available on the pharmacokinetic interactions between tacrolimus and low dose steroids in clinical practice, especially after organ transplantation. In rat studies, tacrolimus blood concentrations were lowered by dexamethasone [13]. In a pharmacokinetic study, the relative clearance of tacrolimus was shown to correlate with the mean oral steroid dose during maintenance therapy [19]. More recently, a decrease in the tacrolimus blood concentration was reported in a liver transplant patient after high-dose steroid therapy for acute graft rejection [9].

Genetic polymorphisms in the pseudogene CYP3AFL, correlated with the CYP3A5 activity, and in the multidrug resistance-1 gene (encoding for P-gp) have been recently associated with tacrolimus requirements [20]. This suggests that the large inter-individual variations in tacrolimus pharmacokinetics may be the sum of genetically determined variability and epigenetic factors such as pharmacokinetic interactions. A better knowledge of all of these interfering parameters may lead to an improvement in tacrolimus management in transplant patients.

In summary, we demonstrated here that a pharmacokinetic interaction does occur between glucocorticoids and tacrolimus in renal transplant patients. Its most likely mechanism is enzymatic induction of CYP3A and/or P-gp. This interaction is present even when low-dose steroids are used. The clinical events that may occur during steroid sparing or tapering must be taken into account. Special attention must be paid to tacrolimus blood concentrations during these manoeuvres.

Conflict of interest statement. None declared.

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