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Tacrolimus interaction with oral oestrogen in kidney transplant recipients: A case-control study

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Summary

What is known and objective: Oestrogens could inhibit the metabolism of drugs, such as calcineurin inhibitors, that are substrates for cytochrome P-450 microsomal enzymes. This study assessed the potential tacrolimus interaction with oral conjugated oestrogen in kidney transplant recipients who received conjugated oestrogen as prophylaxis against bleeding, before kidney biopsy.

Methods: In this case-control study, 13 kidney transplant recipients who received oral conjugated oestrogen as prophylaxis against uraemic bleeding before allograft biopsy were considered as cases. Thirteen matched kidney transplant recipients with similar immunosuppressive regimen served as controls. In this study, comparisons were made between the groups regarding daily dose, blood trough concentrations and calculated concentration corrected for dose of tacrolimus at three time points of the study.

Results and discussion: All patients in the case group received conjugated oestrogen at a dose of 3.75 mg/day for 4.78 ± 0.83 days. Without any change in tacrolimus dose, the blood concentration of tacrolimus increased during concomitant administration of conjugated oestrogen (from 8.10 ± 2.85 to 12.35 ± 4.62 ng/mL; $P = .11$) and decreased after cessation of conjugated oestrogen (6.07 ± 2.18 ng/mL; $P = .015$). The calculated concentration corrected for dose of tacrolimus increased from 127.04 ± 79.23 to 211.40 ± 146.38 $\frac{\frac{ng}{mL}}{\frac{mg}{kg}/d}$ after conjugated oestrogen administration ($P = .036$). Thereafter, it decreased to 108.55 ± 78.61 $\frac{\frac{ng}{mL}}{\frac{mg}{kg}/d}$ after cessation of oestrogen ($P = .003$). Only one patient experienced nausea while taking oestrogen without any change in her liver enzymes.

What is new and conclusion: Concomitant administration of oral oestrogen increased tacrolimus blood concentration. Hence, it is necessary to monitor tacrolimus blood levels during concomitant oestrogen therapy and for several days after oestrogen withdrawal.

KEYWORDS

drug interaction, kidney transplant, oestrogen, tacrolimus

1 | WHAT IS KNOWN AND OBJECTIVES

In many kidney transplant centres, tacrolimus is the calcineurin inhibitor (CNI) of choice.[1] Tacrolimus is the substrate for cytochrome P450 (CYP 450) microsomal enzymes, mainly 3A5 and to a lesser extent 3A4 isoenzymes, as well as the efflux pump, P-glycoprotein[1]; therefore, its disposition may be influenced by inducers and inhibitors of these systems.

In high-risk individuals, such as those with serum creatinine concentration more than 2 mg/dL, conjugated oestrogen is sometimes used to reduce the risk of bleeding after kidney biopsy.[2-4] Conjugated oestrogen contains 17-β-estradiol which is the substrate for, as well as inhibitor of CYP450 3A4[5,6]; therefore, it may decrease the metabolism of CNIs. On the other hand, CNIs may inhibit estradiol metabolism, delay its clearance and therefore enhance the inhibitory effect of estradiol on CNIs metabolism.[6-10] To date, only one case regarding the drug interaction between tacrolimus and oestrogen has been reported.[11]

This study evaluated the drug interaction between tacrolimus and conjugated oestrogen in kidney transplant recipients who received conjugated oestrogen as prophylaxis of uraemic bleeding before kidney biopsy.

2 | METHODS

2.1 | Study design and setting

This prospective, observational, case-control study was performed in the kidney transplant ward of Imam Khomeini Hospital Complex affiliated to Tehran University of Medical Sciences, Tehran, Iran, from October 2016 to October 2017. In this centre, protocol tissue biopsy is not routine and allograft biopsy is performed if indicated or the patient permits. Here, some nephrologists recommend oral conjugated oestrogen for 3-7 days, starting 1 day before tissue biopsy to prevent bleeding risk after kidney biopsy.

2.2 | Patients

In the first month after transplantation, kidney transplant recipients who were candidates for either indication or protocol allograft biopsy received oral conjugated oestrogen and their whole blood trough concentrations were available before, during and after conjugated oestrogen therapy were included as case group. Each case was matched with a control kidney transplant recipient who had a similar immunosuppressive regimen and underwent allograft biopsy within the first month after transplantation without receiving oral conjugated oestrogen. An attempt was made to match controls with cases for sex, age, number and interval of assessment of tacrolimus whole blood levels (Figure 1).

Patients were excluded from the study if they received any other drugs with the potential to inhibit or induce tacrolimus metabolism.

2.3 | Immunosuppressive regimen

Based on the centre protocol, all patients received rabbit thymoglobulin, 1 mg/kg/day initiated 1 hour before allograft reperfusion and continued daily until achieving a cumulative dose of 3-4 mg/kg, methyl prednisolone 500 mg as pulse therapy at the time of transplantation followed by 250 mg and 125 mg for the first and second days after transplantation surgery. Methyl prednisolone changed to oral prednisolone, 1 mg/kg on the third day after transplantation with rapid tapering to reach 5 mg/day at the end of the first month after transplantation. Maintenance immunosuppressive regimen included tacrolimus (whole blood trough level of 8-10 ng/mL during the first 3 months after transplantation) and mycophenolate mofetil 1-1.5 g/day, as well as oral prednisolone.

All patients received prophylaxis against *Pneumocystis jirovecii*, cytomegalovirus and candida infections using co-trimoxazole, ganciclovir/valganciclovir and clotrimazole troche, respectively, for a defined duration based on the centre's protocol.

Based on biopsy results or clinical assessment, the treatment of acute cellular or antibody-mediated rejection consisted of methyl prednisolone pulse, thymoglobulin, IVIG, plasmapheresis or rituximab.

2.4 | Measurements

Patients' demographic data (age, sex, weight and height), daily dose (mg/kg) and whole blood trough concentration (ng/mL) of tacrolimus were collected from the patients' medical records. Patients were monitored for any signs and symptoms of possible hepatotoxicity including nausea, vomiting, abdominal pain or icterus. Based on the ward's protocol, liver function tests were assessed in patients with clinical signs or symptoms of liver dysfunction.

The measurements of tacrolimus concentrations were taken at the steady state that was at least 48-72 hours after any change in the tacrolimus dose in both groups. In the case group, tacrolimus levels were gathered from the patients' medical report before the administration of conjugated oestrogen, during oestrogen therapy (at least 3 days after starting conjugated oestrogen) and 1 week after cessation of conjugated oestrogen. The levels were marked as first, second and third times of evaluations, respectively. In the control group, tacrolimus blood levels at three time points with intervals of at least 3-6 days were used, to be matched for intervals between tacrolimus blood concentrations in the case group. Tacrolimus blood concentrations were assessed by the chemiluminescent microparticle immunoassay method (i2000, Abbott, USA).

2.5 | Outcomes

Comparisons were made between the groups regarding the total daily doses, whole blood trough concentrations and calculated concentration corrected for dose of tacrolimus at three time points of evaluations. The calculated concentration corrected for dose of tacrolimus was computed by dividing the tacrolimus

trough concentration (ng/mL) by tacrolimus daily dose (mg/kg of ideal body weight per day).

2.6 | Ethical Considerations

The Local Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran, approved the study protocol (IR.TUMS.PSRC.REC.1394.6). All patients signed written consent forms and agreed to the use of data from their medical records.

2.7 | Statistical analysis

Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 21.0; SPSS Inc., Chicago, Illinois, USA). The results are expressed as mean ± standard deviations (SD), median (min-max) or percentage. The Kolmogorov-Smirnov test was used to assess the normal distribution of quantitative variables.

Using independent Student's *t* test or Mann-Whitney *U* test, quantitative variables at the point of initiation of the study were compared between the two groups. Repeated measure ANOVA was used to compare the total daily dose of tacrolimus, tacrolimus trough concentrations and calculated concentration corrected for dose of tacrolimus at three scheduled times of evaluations between the two groups. Categorical variables were compared between groups using Chi-square test. *P*-values of less than .05 were considered as statistically significant.

3 | RESULTS

Thirteen patients from each group completed the study (Figure 1). There was no significant difference between the two groups regarding demographic data such as age, sex, weight, height and baseline variables (Table 1). All patients in the case group received oral conjugated oestrogen at a daily dose of 3.75 mg for the mean duration of 4.84 ± 0.55 days (range 4 to 6 days).

With constant daily doses of tacrolimus, changes in tacrolimus trough concentrations from baseline to the time of oestrogen administration in the case group did not statistically differ with matched assessments in the control group (Table 2). In comparison with the matched time point concentrations in the control group, tacrolimus

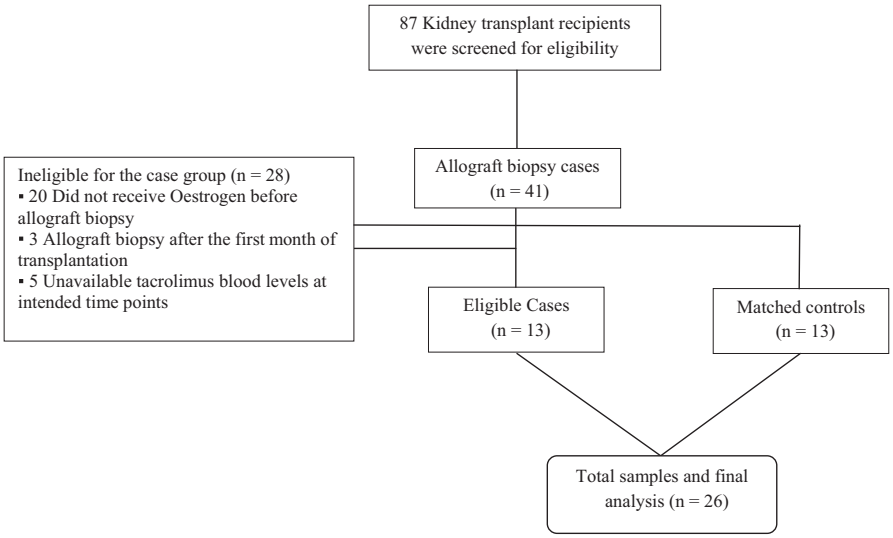

FIGURE 1 Patients' screening and enrolment

TABLE 1 Baseline characteristics of study population

Parameters	Control group (n = 13)	Case group (n = 13)	*P*
Age (years)	46.92 ± 14.36	39.62 ± 13.77	.198
Sex [Male, n (%)]	8 (61.54)	7 (53.85)	.691
TBW (kg)	65.15 ± 12.10	60.54 ± 18.19	.464
Height (cm)	[165 (150-183)]	[160 (154-174)]	.687
Baseline tacrolimus daily dose (mg/kg)	0.08 ± 0.01 [0.08 (0.07-0.10)]	0.08 ± 0.04 [0.07 (0.03-0.16)]	.750
Baseline tacrolimus whole blood trough level (ng/mL)	7.72 ± 5.46 [7.00 (2.10-19.40)]	8.10 ± 2.85 [8.90 (1.50-12.00)]	.827
Baseline calculated concentration corrected for dose of tacrolimus $\left(\frac{\frac{ng}{mL}}{\frac{mg}{kg/d}}\right)$	94.47 ± 74.14 [77.78 (27.50-277.14)]	127.04 ± 79.23 [113.75 (34.38-296.67)]	.186

TBW, Total body weight.

TABLE 2 Daily dose, whole blood trough concentration and calculated concentration corrected for dose of tacrolimus over the study periods across the groups by repeated measure ANOVA

Parameters	Control group (n = 13)			Case group (n = 13)			P
	First time of evaluation	Second time of evaluation	Third time of evaluation	First time of evaluation	Second time of evaluation	Third time of evaluation	
Tacrolimus daily dose (mg/kg)	0.08 ± 0.01 [0.08 (0.07-0.10)]	0.09 ± 0.02 [0.09 (0.06-0.12)]	0.09 ± 0.02 [0.09 (0.04-0.13)]	0.08 ± 0.04 [0.07 (0.03-0.16)]	0.08 ± 0.04 [0.08 (0.02-0.16)]	0.08 ± 0.04 [0.07 (0.02-0.16)]	.604[a]
Tacrolimus whole blood trough level (ng/mL)	7.72 ± 5.46 [7.00 (2.10-19.40)]	8.29 ± 5.38 [7.70 (2.60-21.90)]	7.33 ± 2.41 [7.00 (2.10-10.50)]	8.10 ± 2.85 [8.90 (1.50-12.00)]	12.35 ± 4.62 [11.90 (6.30-24.60)]	6.07 ± 2.18 [6.00 (2.00-10.80)]	.027[a] .112[b] .015[c]
Calculated concentration corrected for dose of tacrolimus $\left(\frac{\frac{ng}{mL}}{\frac{mg}{kg}/d}\right)$	94.47 ± 74.14 [77.78 (27.50-277.14)]	101.76 ± 70.333 [85.56 (28.89-243.33)]	95.28 ± 58.89 [82.50 (35.00-260.00)]	127.04 ± 79.23 [113.75 (34.38-296.67)]	211.40 ± 146.38 [180.00 (57.27-595.00)]	108.55 ± 78.61 [91.43 (25.00-275.00)]	.009[a] .036[b] .003[c]

Data have been presented as mean ± SD and median (min-max).
[a]Represent interaction between time and group, adjusted by Bonferroni test.
[b]Represent the difference of measured values between groups over the first and second times of evaluation.
[c]Represent the difference of measured values between groups over the second and third times of evaluation.

trough concentration significantly decreased by 46.92 ± 22.08% [median: 52.38%, range 76.02%-13.83%] after cessation of conjugated oestrogen ($F_{(1,24)}$ = 6.82, P = .015; Table 2 and Figure 2) in the case group.

The changes in the calculated concentration corrected for dose of tacrolimus were significantly different between the case and control groups ($F_{(1.39,33.25)}$ = 6.54, P = .009). The calculated concentration corrected for dose of tacrolimus increased by 85.62 ± 98.54% [median: 38.10%, range −5.5 to 326.67%] by concomitant administration of conjugated oestrogen compared to the baseline values ($F_{(1,24)}$ = 4.94, P = .036; Table 2). After cessation of conjugated oestrogen, the calculated concentration corrected for dose of tacrolimus decreased by 46.60 ± 21.12% [median 51.24%, range 9.33-73.63%] ($F_{(1,24)}$ = 10.52, P = .003; Table 2). Figure 3 presents changes in the calculated concentration corrected for dose of tacrolimus in each group, during the three phases of the study.

Only one patient reported nausea while taking conjugated oestrogen without any change in her liver function chemistries.

FIGURE 2 Comparing means (±SD) of the tacrolimus whole blood trough concentration in the case and control groups over the time courses of evaluations

FIGURE 3 Comparing means (±SD) of the calculated concentration corrected for dose tacrolimus in the case and control groups over the time courses of evaluations

4 | DISCUSSION

This is the first case-control study to evaluate the drug interaction between oral conjugated oestrogen and tacrolimus in kidney transplant recipients. In this study, higher tacrolimus trough concentrations and higher calculated concentration corrected for dose of tacrolimus were detected in the presence of conjugated oestrogen compared to the control group. The results showed a median increase of about 38% in the calculated concentration corrected for dose of tacrolimus when conjugated oestrogen was administered concomitantly, followed by a median decrease of 51% in the calculated concentration corrected for dose of tacrolimus, after cessation of conjugated oestrogen.

Previously, an in vitro study using human and animal hepatic and intestinal microsomes showed that ethinylestradiol inhibits tacrolimus metabolism by inhibiting CYP 3A4.[9] The same effect of estradiol on cyclosporine (another CNI) metabolism was reported.[12-14] On the other hand, experimental studies using human or recombinant hepatic microsomes have revealed that cyclosporine and tacrolimus (to a lesser extent compared with cyclosporine) inhibit phase I metabolism of estradiol (hydroxylation). Tacrolimus also inhibits the phase II metabolism of estradiol (glucuronidation) by about 80%.[6,7]

Deray et al reported a case of drug interaction between cyclosporine and oral contraceptive (OCP) containing 150 μg of levonorgestrel and 30 μg of ethinylestradiol, in a patient who was treated with cyclosporine 5 mg/kg/day for idiopathic uveitis. This interaction resulted to an increase in the plasma level of cyclosporine from 110 ng/mL before administration of the OCP to 249 ng/mL during the concomitant administration of that OCP with cyclosporine. This interaction resulted in cyclosporine-induced symptomatic hepatotoxicity with elevation of serum aminotransferases, alkaline phosphatase and bilirubin, besides a slight increase in the serum creatinine concentrations. About 2 weeks after cessation of OCP, the cyclosporine trough level was 153 ng/mL with a daily cyclosporine dose of 4 mg/kg that reduced to 111 ng/mL about 4 weeks later with the same cyclosporine dose. With the re-initiation of that OCP, there was an increase in the cyclosporine trough level to 222 ng/mL.[15] As can be computed from the data (provided by the authors in the article), the calculated concentration corrected for dose of cyclosporine increased from 22 $\frac{\frac{ng}{mL}}{\frac{mg}{kg}/d}$ before OCP initiation to 49.8 $\frac{\frac{ng}{mL}}{\frac{mg}{kg}/d}$ during concomitant OCP administration and decreased to 38.25 and 27.75 $\frac{\frac{ng}{mL}}{\frac{mg}{kg}/d}$ about 2 and 6 weeks after OCP withdrawal. The calculated concentration corrected for dose of cyclosporine increased from 27.75 to 55.5 $\frac{\frac{ng}{mL}}{\frac{mg}{kg}/d}$ following re-initiation of the same OCP. These data showed 100%-126.4% increase in the calculated concentration, corrected for dose of cyclosporine with concomitant administration of OCP.[15]

A case of liver transplant recipient on cyclosporine 200 mg twice daily who received OCP containing 50 μg ethinylestradiol daily for 1 week to manage severe menorrhagia developed symptomatic intrahepatic cholestasis. The patient's trough serum cyclosporine levels were between 95 and 295 ng/mL before starting ethinylestradiol, 110 and 195 ng/mL during ethinylestradiol consumption and declined to 55 and 95 ng/mL after withdrawal of ethinylestradiol. During that study, there was no specified change in the dose of cyclosporine. Withdrawal of oestrogen resulted in the relief of patient's symptoms and normalization of the liver function test. The patient showed similar manifestations with re-challenge of oral ethinylestradiol, but not with transdermal ethinylestradiol. Due to the first pass effect of oral oestrogens, the authors concluded that treatment with oral oestrogen in transplant recipients who take cyclosporine might result in cholestasis.[16]

Cyclosporine and tacrolimus, the two available CNIs, share similar metabolizing systems but with some differences. Cyclosporine is mostly a substrate for CYP450 3A4 isoenzyme while tacrolimus is mainly metabolized by CYP 3A5[1]; therefore, their drug interactions may differ somewhat. There is only one case report on drug interaction between tacrolimus and oestrogen. It was by Migali et al *who* reported that a kidney transplant recipient experienced an increased tacrolimus plasma level, following administration of 0.5 mg/day of dermal oestrogen gel. Plasma tacrolimus level with the daily tacrolimus dose of 9 mg increased from 5.0-7.5 ng/mL before receiving oestrogen to 14.2-18.3 ng/mL during oestrogen administration. The daily dose of tacrolimus was reduced by 60% to reach therapeutic plasma concentrations of about 6.4 ng/mL.[11] Therefore, the authors concluded that even by avoiding first pass hepatic effect through the use of transdermal administration of oestrogens, small amounts of oestrogens are also able to interact with tacrolimus metabolism that necessitates tacrolimus level monitoring in kidney transplant recipients who take oestrogens by any route.[11] Oestrogen-induced increase in tacrolimus concentration in Migali's study is comparable to our results. The differences in average increase in tacrolimus concentrations may be due to the different biological media in which the concentrations of tacrolimus were assessed and the route of oestrogen administration. Migali et al measured the concentrations of tacrolimus in the plasma but in the present study, whole blood tacrolimus levels were assessed.

In a retrospective analysis on 15 liver transplant recipients taking CNIs-containing immunosuppression (13 patients tacrolimus and 2 patients cyclosporine) who received transdermal or oral contraceptive containing 20 μg ethinylestradiol, no case of graft rejection or significant changes in aminotransferases and bilirubin were reported. In this study, changes in the daily dose of CNIs and concentration were unspecified.[17]

Similarly, the use of a contraceptive vaginal ring delivering 15 μg/day ethinylestradiol for 12 menstrual cycles in 9 kidney and 8 liver transplant recipients on tacrolimus or cyclosporine therapy resulted in no change in their renal and liver functions or need for change in the immunosuppressive regimens.[18]

The major limitations of the present study are the small sample size and no assessment of the area under the concentration-time curve of tacrolimus, as a marker of tacrolimus bioavailability.

5 | WHAT IS NEW AND CONCLUSION

In conclusion, the concomitant administration of oral oestrogen increased tacrolimus blood concentrations in kidney transplant patients. This finding necessitates the close monitoring of the concentrations of tacrolimus in the blood during concomitant oestrogen administration and for several days after the discontinuation of oestrogen therapy. The small sample size and no daily monitoring of tacrolimus blood levels made the authors unable to recommend preventive dose reduction in tacrolimus coincided with the start of oral oestrogen in kidney transplant recipients. Due to the absence of any remarkable tacrolimus side effects during the few days of increased tacrolimus blood levels, more frequent monitoring of tacrolimus blood levels (for example twice weekly) during oestrogen therapy and for at least 1 week after the withdrawal of oestrogen administration and appropriate tacrolimus dose adjustment may be recommended.

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CONFLICT OF INTEREST

No conflict of interests have been declared.

AUTHORS' CONTRIBUTION

Maryam Ghadimi contributed in acquisition, analysis and interpretation of data, drafting the article and final approval of the version to be published. Simin Dashti-Khavidaki contributed in trial conception and design, analysis and interpretation of data, drafting the article and final approval of the version to be published. Mohadesseh Shahali contributed in data acquisition and final approval of the version to be published. Mojdeh Gohari contributed in data acquisition and analysis and final approval of the version to be published. Mohammad-Reza Khatami contributed in trial design, data interpretation, drafting the article and final approval of the version to be published. Azam Alamdari contributed in data acquisition and analysis, and final approval of the version to be published.

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