Co-administration of ketoconazole to tacrolimus-treated kidney transplant recipients: a prospective randomized study

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Abstract

Background. Since the introduction of calcineurin inhibitors, there has been a significant improvement in the results of solid organ transplantation, including graft and patient survival. However, high cost, chronic nephrotoxicity and other side effects stand as major challenges for long-term use of these drugs. The long-term safety and financial benefits of the combination ketoconazole–cyclosporine previously studied. However, data about the effect of the addition of ketoconazole addition to tacrolimus-treated patients are scarce. Therefore, this study was conducted to evaluate the safety and financial impact of that combination.

Methods. The subjects of this work included 70 live-donor stable kidney transplant recipients receiving tacrolimus. Their age ranged from 16 to 45 years. Among them, 54 were males and 16 were females. All of them were 6 months or more post-transplantation. Patients were randomly divided into two equal groups. Group I patients initially received ketoconazole 100 mg/day in addition to their usual treatment, while group II patients were considered a control. Patients were followed-up for 6 months.

Results. Concomitant ketoconazole–tacrolimus resulted in marked reduction of tacrolimus dose (by 58.7%) and cost (by 56.9%). It also resulted in significant improvement in graft function and fungal skin infection, in addition to a decrease of gastrointestinal episodes and hospitalization.

Conclusion. We conclude that ketoconazole–tacrolimus combination in kidney transplant recipients is safe, has outstanding impact on treatment costs and improves patient and graft outcome.

Keywords: ketoconazole; kidney transplantation; tacrolimus

Introduction

The development of immunosuppressant agents such as tacrolimus and cyclosporine has greatly contributed to improving the results of organ transplantation [1]. However, tacrolimus may induce side effects including nephrotoxicity, diabetes mellitus and gastrointestinal complications [2,3]. Furthermore, the high cost of tacrolimus therapy is an important disadvantage [1]. This financial burden is of major concern especially in developing countries.

Both tacrolimus and cyclosporine are metabolized in the liver through the hepatic cytochrome P450 system. In man, cytochrome P450 is also present in the upper gastrointestinal tract [4].

Drugs that inhibit the cytochrome P450 system will increase tacrolimus and cyclosporine levels. This may be of therapeutic benefit. For example, diltiazem makes a logical cyclosporine and tacrolimus-sparing agent because of the potential financial savings and therapeutic benefits [5].

Ketoconazole, an imidazole antifungal drug, was reported to interact with tacrolimus and cyclosporine through inhibition of cytochrome P450 microsomal enzymes in the liver, leading to inhibition of tacrolimus and cyclosporine metabolism and subsequently increasing their blood levels [4,6]. Additionally, ketoconazole increases tacrolimus and cyclosporine bioavailability through inhibition of their gut metabolism [7,8].

Long-term safety and financial benefits of the ketoconazole–cyclosporine combination were recently reported by Sobh et al. [9]. They stated that this combination resulted in a marked reduction of cyclosporine dose with a cost saving of ~70% and excellent long-term safety.
However, similar clinical trials concerning safety and financial benefits of the tacrolimus–ketoconazole combination after kidney transplantation are scarce. Thus, our work was conducted in order to study this interesting subject.

Subjects and methods

Patients

This prospective, randomized study included 70 live-donor kidney transplant recipients selected from the pool of kidney transplant patients in the Urology and Nephrology Center, Mansoura University, Egypt. Their age ranged from 16 to 45 years. Among them, 54 were males and 16 were females. Inclusion criteria required for recruitment into the study were: (i) immunosuppression protocol that includes tacrolimus, (ii) stable tacrolimus trough levels for at least 2 months, (iii) tacrolimus dose ≥4 mg/day, (iv) stable graft function with serum creatinine value <2.5 mg/dl, (v) 6 months or more post-transplantation, (vi) normal liver function tests, (vii) women included in the study were not pregnant and were using one method of contraception and (viii) patient consent.

Study design

After baseline evaluation, patients were randomly divided into two equal groups. Group I (ketoconazole group) patients received ketoconazole 100 mg/day in addition to their usual treatment while group II served as a control. In group I patients, information about ketoconazole was provided prior to its prescription and concomitant to its first administration, tacrolimus dose was reduced by 50%.

Patients were prospectively followed up for 6 months in the outpatient clinic once weekly for 1 month, every other week for 2 months and every month thereafter. At each visit, clinical, laboratory and radiological assessment was performed. Thorough clinical evaluation was done with emphasis on blood pressure, fungal skin infection and drug tolerance. Hypertension was generally defined as blood pressure >140/90 mmHg or maintenance on anti-hypertensive medications. Laboratory evaluation included monitoring of graft function by serum creatinine, creatinine clearance, urine analysis and 24 h urinary proteins, liver function tests, serum electrolytes, cholesterol, uric acid, prothrombin concentration and tacrolimus whole blood trough level (MEA II; Abbott Imx analyser). In patients who experienced unexplained graft dysfunction, graft biopsy was performed. The target tacrolimus whole blood trough level was 3–7 ng/mL. The tacrolimus dose was adjusted according to the drug level. The ketoconazole dose in the ketoconazole group was reduced to 50 mg/day in patients who experienced high levels of tacrolimus despite reduction of the tacrolimus dose to 1 mg/12 h.

Statistical analysis

Continuous values were expressed as means±standard deviation and compared by t-test (paired for comparison within the same group and unpaired for comparison between the two groups). Non-homogeneous data were expressed as median/range and compared by a Mann–Whitney test. Numeric data were compared using a chi-square test between the two groups.

Results

At the start of the study, both groups were comparable with regard to their baseline characteristics (Table 1) except for prevalence of fungal skin infection and initial doses of tacrolimus, which were significantly higher in the ketoconazole group (P=0.02 and 0.007, respectively). At the start of the study, one patient in the ketoconazole group was having nephrotic range proteinuria (8 g/day) due to recurrence of original kidney disease in the graft (MPGN).

Administration of ketoconazole to group I patients resulted in a marked reduction of tacrolimus dose, so that it became significantly lower than that of the control group. This difference persisted throughout the duration of the study (Figure 1) and was of high statistical significance (P<0.001).

The maximal percentage reduction of the tacrolimus dose in the ketoconazole group was 58.7% and occurred at the end of the study. On the other hand, in the control group, the maximal percentage reduction

| Table 1. Baseline characteristics of patients in both groups at the start of the study |
|-----------------|-----------------|-----------------|
| **Ketoconazole group (n=35)** | **Control group (n=35)** | **P** |
| **Age (years)** | 28.14±12.14 | 27.69±9.34 | 0.86 |
| **Sex (male/female)** | 26/9 | 28/7 | 0.57 |
| **Weight (kg)** | 70.26±20.59 | 71.17±15.72 | 0.84 |
| **Months of transplantation** | 39.58±19.89 | 47.79±37.39 | 0.26 |
| **Original kidney disease** | | | |
| Unknown | 14 (40%) | 9 (25.7%) | |
| Glomerular | 10 (28.6%) | 9 (25.7%) | 0.47 |
| Tubulointerstitial | 9 (25.7%) | 13 (37.2%) | |
| ESRD | 2 (5.7%) | 4 (11.4%) | |
| Hypertension | 23/35 (65.7%) | 21/35 (60%) | 0.81 |
| Post-transplant DM | 6/35 (17.1%) | 2/35 (5.7%) | 0.26 |
| Fungal infection | 9/35 (25.7%) | 2/35 (5.7%) | 0.02 |
| **Initial dose of FK (mg/day)** | 6.46±2.24 | 5.11±1.75 | 0.007 |
| **Immunosuppression** | | | |
| Steroid+FK | 5 (14.3%) | 2 (5.7%) | |
| Steroid+FK+Aza | 8 (22.9%) | 14 (40%) | 0.21 |
| Steroid+FK+MMF | 22 (62.9%) | 19 (54.3%) | |
| Serum creatinine (mg/dl) | 1.74±0.43 | 1.52±0.46 | 0.45 |
| Fasting blood glucose (mg/dl) | 93±27.78 | 90±18.94 | 0.53 |
| Serum bilirubin (mg/dl) | 0.55±0.25 | 0.59±0.20 | 0.49 |
| Serum albumin (g/dl) | 3.94±0.34 | 3.81±0.35 | 0.13 |
| ALT (IU/l) | 21.31±10.18 | 21.14±6.87 | 0.94 |
| AST (IU/l) | 19.20±5.91 | 20.29±6.51 | 0.47 |
| Serum cholesterol (mg/dl) | 162.34±37.65 | 154.26±37.65 | 0.37 |
| FK level (ng/ml) | 6.87±1.59 | 6.42±1.44 | 0.22 |
| Haemoglobin (g/dl) | 12.17±2.33 | 12.55±1.80 | 0.44 |
| Prothrombin concentration (%) | 87.97±6.34 | 87.74±5.62 | 0.87 |
| 24h urinary protein (g/day) (median/range) | 0.5/0.1–8 | 0.45/0.06–2.1 | 0.48 |
of the tacrolimus dose was only 9.32% and was also achieved at the end of the study.

Tacrolimus trough levels were comparable in both groups throughout the study (Figure 1). During the first month of the study, ketoconazole-treated patients were monitored weekly for their tacrolimus trough level. All levels were within the therapeutic window, except for three patients whose tacrolimus level at the first week ranged from 10 to 11 ng/ml.

At the end of the study, percentage reduction of tacrolimus cost in the ketoconazole group (after addition of ketoconazole cost) was 56.9%, while it was only 8.4% in the control group. The difference between the two groups was highly significant ($P < 0.001$). Calculated from the cost at the end of the study, the yearly tacrolimus cost saving per patient in the ketoconazole group was $3173.66 compared with $370.29 in the control group.

Total days of hospitalization were significantly lower in the ketoconazole group throughout the study period (16 vs 38 days; $P = 0.01$). The commonest cause of hospitalization in both groups during the study was gastrointestinal episodes (vomiting and/or diarrhoea) followed by graft impairment episodes. Both aetiologies were significantly lower in the ketoconazole group ($P = 0.02$ and 0.005, respectively).

Initial serum creatinine at the start of the study was insignificantly higher in the ketoconazole group (mean $= 1.74$ mg/dl) compared with the control group (mean $= 1.52$ mg/dl). Subsequently, serum creatinine values remained comparable in both groups throughout the study (Figure 2). However, within the ketoconazole group, serum creatinine values on all follow-up occasions became lower than their initial serum creatinine value. This difference was highly significant ($P < 0.001$) at the first, fourth and sixth months, significant ($P = 0.01$) at the second month, but did not rank to significance at the third and fifth months ($P = 0.36$ and 0.46, respectively). In contrast, serial serum creatinine values in the control group were higher than initial serum creatinine and this difference was highly significant ($P < 0.001$) at the first month and significant thereafter ($P < 0.05$) except for the fifth month ($P = 0.08$).

Throughout the study, only one patient in the ketoconazole group experienced an acute rejection episode compared with five patients (one episode for each) in the control group.

Fasting blood sugar was comparable in both groups throughout the whole follow-up period. The number of patients with post-transplant diabetes mellitus remained the same throughout the study. Additionally, these patients remained comparable regarding type and dose of anti-diabetic agents.

Serum bilirubin, ALT and AST were comparable in both groups throughout the study. Serum albumin levels were comparable in both groups at the start and during the first 4 months of the study. However, their levels (g/dl) became significantly higher in the ketoconazole group compared with the control group at the fifth month ($4.06 \pm 0.33$ vs $3.83 \pm 0.34$, $P = 0.01$) and at the sixth month ($4.02 \pm 0.33$ vs $3.76 \pm 0.36$, $P = 0.002$).

Twenty-four hour urinary protein, serum cholesterol, haemoglobin, hematocrit and prothrombin concentration values were comparable in both groups throughout the study.

The incidence of hypertension in the ketoconazole group decreased from 65.7% before to 57.14% at the end of the study and remained constant (60%) in the control group. However, this apparent difference between the two groups did not rank to statistical significance.

At the study end, the prevalence of fungal skin infection in the form of tinea pedis, tinea versicolor and tinea circinata was significantly higher in the ketoconazole group (nine patients; 25.7%) than in the control group (two patients; 5.7%) ($P = 0.02$). Fungal skin infection in the control group patients was treated with topical anti-fungal creams and terbinafine (systemic anti-fungal agent that has no interaction with tacrolimus). At the third month of follow-up, the number of patients with fungal skin infection in the ketoconazole group dramatically decreased to only two patients (2.8%), similar to that in the control group. At the end of the study, there was complete recovery in the ketoconazole group, while one case in the control group was still resistant to therapy.
In group I, the dose of ketoconazole was reduced to 50 mg/day in four patients; one at the second month of the study and three at the last follow-up.

In general, ketoconazole-treated patients showed good tolerance to the drug. None of ketoconazole’s side effects was noticed and none of the patients stopped the drug at any time during the study.

Discussion

In this study, the major effect of ketoconazole was the dramatic decrease of tacrolimus dose. Percentage reduction of tacrolimus dose among ketoconazole patients in the first month of the study (50.9%) concurs with the proposed half dose reduction at the start of the study and thus explains stable tacrolimus trough levels during the first month among most of our patients (only three patients showed mild elevation of tacrolimus blood levels). Throughout the study, the percentage reduction of tacrolimus dose gradually increased to reach its maximum level (58.7%) in the last month; possibly due to a time-related increase in the ketoconazole–tacrolimus pharmacokinetic interaction. However, percentage reduction of the dose at the last follow-up was not markedly different from the proposed dose reduction at the initiation of the study. Accordingly, frequent monitoring of tacrolimus blood levels may not be especially necessary after the first month of starting the ketoconazole–tacrolimus combination. Thus, the additional cost and complexity of patient management could be avoided.

The financial benefit of tacrolimus dose reduction in the ketoconazole-treated group was outstanding. The yearly tacrolimus cost saving for the whole ketoconazole group (35 patients) was $11,077.98. Expanding the kidney transplantation programme in our developing country is hindered by financial problems, especially due to costly newer immunosuppressive medications such as tacrolimus. Concomitant use of ketoconazole in such patients will result in a marked reduction of tacrolimus dose and cost by ~60%. Furthermore, it may help the use of this medication in non-transplant indications such as in patients with idiopathic nephrotic syndrome [10] in whom cost stands as a major barrier.

Marked reduction in frequency of gastrointestinal and graft impairment episodes necessitating hospitalization among the ketoconazole group, with possible added cost saving and better patient quality of life, may be due to a marked reduction of tacrolimus dose. The tendency of transplant patients towards stability after the early post-transplant period is a possible contributing factor as there was a shorter, despite statistically insignificant, mean post-transplant period in the ketoconazole group. Additionally, other immunosuppressive agents may have a role in increased incidence of gastrointestinal episodes. More than half of patients in both groups were maintained on MMF. As diarrhoea is a possible, however not a very typical, adverse event in patients treated with tacrolimus, many of the gastrointestinal problems might be due to MMF treatment.

The higher incidence of post-transplant diabetes mellitus among the ketoconazole group patients, though statistically insignificant, may be due to a significantly higher initial dose of tacrolimus in that group. However, it is known that the trough level rather than the dose of tacrolimus is linked to higher incidence of diabetes mellitus [3], which may explain our subsequent observation that, despite a marked reduction of tacrolimus dose in the ketoconazole group throughout the study, the prevalence of diabetes mellitus remained the same. On the other hand, another finding in the ketoconazole group was the decreased prevalence of hypertension among its patients throughout the study; a finding that may be explained by the significant reduction in the serum creatinine and/or tacrolimus dose at the end of the study.

The interesting observation of improved graft function in the ketoconazole group may be explained by a marked reduction of tacrolimus dose in this group. Tacrolimus nephrotoxicity may be merely functional with deterioration of graft function, despite the normal range of tacrolimus levels. Improvement in graft function may occur with reduction of tacrolimus dose [11]. On the other hand, lowering of graft function in the control group may be attributed to more than one factor, including drug nephrotoxicity or more gastrointestinal and acute rejection episodes.

Although statistically insignificant, the lower incidence of acute rejection episodes in the ketoconazole group may be explained by its inhibitory effect on glucocorticoid metabolism [12]. It may also be explained by the possible effect of ketoconazole on phagocytic, lymphocytic and natural-killer cell response [13]. Long-term follow-up may support this observation.

Although ketoconazole is known to be hepatotoxic [14], this side effect was not observed in any of our ketoconazole group patients. Ketoconazole-associated hepatotoxicity may be idiosyncratic in nature [15]. This observation may also be attributed to the small dose of ketoconazole used (50–100 mg/day) and/or the marked reduction in tacrolimus dose which has a potential hepatotoxicity [16].

Our study documents the efficacy of ketoconazole in preventing and treating fungal skin infection in kidney transplant recipients. These results provide an added benefit for ketoconazole use in kidney transplant recipients in whom fungal skin infections are not uncommon [17], especially in communities with lowered socio-economic and hygiene standards.

In general, ketoconazole-treated patients showed good tolerance to the drug. None of ketoconazole’s side effects was noticed and none of the patients stopped the drug at any time during the study. Similarly, Buttman et al. [18] did not report side effects of ketoconazole when concomitantly used with cyclosporine in heart transplant recipients. Conversely, First et al. [19] reported discontinuation of ketoconazole therapy in four out of 43 kidney transplant recipients when used concomitantly with cyclosporine, mainly...
Ketoconazole-tacrolimus in kidney transplantation
due to gastrointestinal intolerance and sexual dysfunc-
tion. This difference in ketoconazole tolerance may
be due to different dose regimens, number of patients
and/or genetic factors. All patients in our study were
compliant to treatment with ketoconazole. It seems
that our previous experience with ketoconazole in
the field of kidney transplantation [9] allowed for better
physician experience and patient compliance.

In conclusion, concomitant ketoconazole–tacrolimus
administration in kidney transplant recipients is safe
and results in outstanding dose reduction. Moreover,
it results in significant improvement of graft function,
fungal skin infection as well as significant reduction in
the frequency of gastrointestinal episodes and patient
hospitalization. The great financial benefit of this
combination will allow wider use of tacrolimus in
transplantation as well as in other immune-mediated
diseases. However, long-term follow-up is recom-
ended to firmly document the safety and the possible
beneficial effects of this combination.

Conflict of interest statement. None declared.

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