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RESEARCH PAPER

Association of Calculated Area under the Curve or Cyclosporine C_0 and C_2 Level Monitoring in Pediatric Renal Transplant Patients

Kaan Savas Gulleroglu[1], Esra Baskin[1], Aydincan Akdur[2], Gokhan Moray[2] and Mehmet Haberal[2]*

[1]*Pediatric Nephrology, Baskent University, Ankara, Turkey*

[2]*General Surgery, Baskent University, Ankara, Turkey*

***Corresponding author:** *Kaan Savas Gulleroglu, Associated Professor, Department of Pediatric Nephrology, Baskent University, Şehit Temel Kuğuluoğlu Caddesi, No: 24, Bahçelievler, Çankaya, Ankara, 06490, Turkey, Tel: 903122234936*

Abstract

Aim: Cyclosporine A (CsA) is highly variable pharmacokinetically and has a narrow therapeutic window; the serum level of patients treated with CsA must be monitored carefully. We investigated the trough and second-hour serum levels of CsA, the calculated area under the curve (AUC), and their association of those factors with chronic allograft dysfunction in pediatric patients.

Methods: Fifteen renal allograft recipients (8 boys and 7 girls; mean age, 15.2 ± 3.5 years) who were undergoing treatment with cyclosporine were included in the study. The patients were divided into 2 groups according to the serum creatinine level and the presence of proteinuria: The "stable" group (n = 10, serum creatinine level < 1. 5 mg/dL, no proteinuria) and the "chronic allograft dysfunction (CAD)" group (n = 5, serum creatinine level > 1.5, and/or daily protein excretion > 4 mg/m^2/h). Trough (C_0) and second-hour (C_2) cyclosporine serum levels were measured, and AUC values was calculated according to the formula (AUC = 990 + 10.74 × C_0 + 2.28 × C_2).

Results: The mean duration of post transplant follow-up was 25 ± 23 months (range, 8-72 months). The mean cyclosporine dose was 4.8 ± 1.4 mg/kg/d. The mean C_0, C_2, and calculated AUC values were 91.5 ± 62.1 ng/mL, 561.2 ± 241.5 ng/mL, and 3380 ± 996 ng.h/mL, respectively. Patients in the stable group had a history of fewer acute rejection episodes than did patients with CAD ($P < 0.05$). Calculated AUC values in the patients with CAD were significantly higher than in the stable patients. C_0 and C_2 levels did not correlate with CAD.

Conclusion: In the monitoring of cyclosporine dosing for the follow-up of CAD, calculated AUC values may be a better parameter than levels of C_0 or C_2 alone.

Keywords

Cyclosporine, Trough levels, Calculated area under the curve

Introduction

Since the 1980s, cyclosporine (CsA) has been the major immunosuppressive agent used for the prevention and treatment of allograft rejection [1]. It is also a widely used drug for treatments of nephrotic syndromes, rheumatologic disorders and cancers. CsA is a highly lipophilic molecule that displays important variations in absorption; those variations result in highly variable pharmacokinetics [2]. Dosing of CsA is also complicated by the narrow therapeutic window that allows adequate T-cell immunosuppression with a minimum risk of adverse events such as hypertension or renal dysfunction [3]. For that reason, the serum levels of patients treated with CsA must be monitored closely.

The satisfactory immunosuppressive effects of CsA correlate with drug exposure, which is indicated by the calculated area under the curve (AUC). However, calculated AUC measurement is not practical in patients treated with CsA as maintenance therapy after renal transplantation [4,5]. The utility of serum cyclosporine second hour levels for adequate drug dose determination during the first year has been well characterized, but there are few data on its utility on maintenance therapy [6]. In this study, we investigated the trough

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levels and second-hour serum levels of CsA, the calculated AUC values, and the association of those factors with chronic allograft dysfunction (CAD) in pediatric renal allograft recipients.

Materials and Methods

The patient population consisted of 15 renal allograft recipients (8 boys and 7 girls; mean age, 15.2 ± 3.5 years) who were undergoing treatment with various dosages of CsA, mycophenolate mofetil (1200 mg/m^2/d), and prednisolone (0.25 mg/kg/d). CsA was started within the first 12 hours after transplantation with a dose between 4 - 6 mg/kg/day given orally, twice daily. Cyclosporine dosage was adjusted related to serum concentrations during follow-up. Cyclosporine intake was recommended before meal.

The age and sex of each patient, the cause of chronic renal failure, the post transplant follow-up duration, and the number of acute allograft rejection episodes, the dose of CsA, the cold ischemia time, and the patient's HLA status were recorded. Testing, including complete blood count and other biochemical analyses, were performed on a blood sample obtained from each patient. Daily protein excretion in urine was determined by 24-hour urine collection. Trough (C_0) and second-hour (C_2) cyclosporine serum levels were measured by fluorescence polarization immunoassay (AxSYM System, Cyclosporine, Cat No: 34-3164/R8, Abbott, IL, USA). Through serum level samples were obtained before morning dose of CsA and second-hour serum level samples were obtained two hours after morning dose. The AUC value was calculated according to the formula (AUC = 990 + 10.74 × C_0 + 2.28 × C_2) [3].

Patients were grouped according to their serum creatinine level and the presence of proteinuria as "stable" (n = 10, serum creatinine level < 1.5 mg/dL, and daily protein excretion < 4 mg/m^2/h) or CAD (n = 5, serum creatinine level > 1.5 mg/dL, and/or daily protein excretion > 4 mg/m^2/h). Another drug different from stable group was not administered in CAD group during sampling time. Last treatment for rejection episode in CAD group was at least 1 month ago before sampling time. The Mann-Whitney *U* and the chi-square test were used to compare the patient groups. Pearson correlation was used to determine the correlations. A value for *P* less than 0.5 was considered significant. Local ethical committee approval and voluntary informed consent were obtained. The authors confirm that there are no known conflicts of interest associated with this publication.

Results

The mean post transplant follow-up duration was 25 ± 23 months (range, 8-72 months). The mean cyclosporine dose was 4.8 ± 1.4 mg/kg/d. The mean C_0, C_2, and calculated AUC levels were 91.5 ± 62.1 ng/mL, 561.2 ± 241.5 ng/mL, and 3380 ± 996 ng.h/mL, respectively (Table 1). Body mass index of patients in stable group was between 85th and 95th percentiles (overweight) for seven patients and was above 95th percentile (obese) for three patients. Body mass index of patients in CAD group was between 85th and 95th percentiles for 2 patients and was above 95th percentile for three patients.

Table 1: Demographic profile of patients and results of laboratory testing.

	N = 15
Age (y)	15.2 ± 3.5
Sex (male/female)	8/7
Post transplant duration (mo)	25 ± 23
Primary disease	
Urologic	6
Chronic glomerulonephritis	6
Tubulointerstitial nephritis	1
Nephronophythisis	1
Unknown	1
Cyclosporine dosage (mg/kg/d)	4.8 ± 1.4
Renal function (n)	
Stable patients	10
Patients with CAD	5
C_0 (ng/mL)	91.5 ± 62.1
C_2 (ng/mL)	561 ± 241
AUC (ng.h/mL)	3380 ± 996

CAD: Chronic Allograft Dysfunction; C_0: Serum Cyclosporine Trough Level; C_2: serum Cyclosporine Second-Hour Level; AUC: Area under the Curve

Table 2: Pharmacokinetic profile of subjects and cyclosporine dose.

	Stable Patients (n = 10)	Patients with CAD (n = 5)
Cyclosporine dosage (mg/kg/d)	4.6 ± 1.9	4.4 ± 2.5
C_0 (ng/mL)	73.5 ± 61.4	132.5 ± 54.8
C_2 (ng/mL)	501.1 ± 242.4	692.1 ± 118.2
AUC (ng.h/mL)*	2868 ± 1058	4380 ± 542
Acute rejection attacks (n)*	2/10	4/5
Glomerular filtration rate (mL/min/1.73 m^2)	84 ± 29	76 ± 51
Posttransplant duration (mo)	20.4 ± 22.8	34.1 ± 21.5

*$P < 0.05$

The stable group had a history of less acute allograft rejection than did the patients with CAD (2 of 10 patients versus 4 of 5 patients, respectively, $P < 0.05$). Calculated AUC values in patients with CAD were significantly higher than those in stable patients (4380 ± 542 ng.h/mL and 2868 ± 1058 ng.h/mL, respectively, $P < 0.05$). A significant relationship was noted between the calculated AUC levels and CAD ($r = 0.58$, $P < .05$). C_0 and C_2 levels did not correlate with CAD (Table 2).

The age of the subjects, the primary disease, the drug absorption profile, cold ischemia time, and HLA status were similar between the groups. We could not demonstrate any significant correlation between body mass index and C_0 and C_2 levels and AUC values. Amlodipine was used by 3 patients in stable group and 4 patients in CAD group due to hypertension.

Discussion

The introduction of CSA was a major advance in the prevention and treatment of allograft rejection. Because CsA, the drug of first choice in transplantation surgery, is characterized by a low therapeutic index and variable absorption, close monitoring of patients undergoing treatment with that drug is required to optimize dosing. Because of the interpatient and intrapatient variability of the pharmacokinetics of CsA, frequent dosage modifications of trough levels can result in increased toxicity or insufficient immunosuppression.

The AUC-based monitoring of CsA dosing helps to optimize therapeutic drug monitoring and provides the most accurate determination of the serum level of CsA for "ideal immunosuppression," which includes the absence of adverse effects and the preservation of renal function [1,4,5]. However, conventional methods of measuring the AUC value require multiple analyses of the serum level of CsA during the 12-hour dosing interval, which is impractical and expensive especially for patients receiving maintenance treatment [1,3]. Fortunately, the estimated AUC value that is based on a limited number of blood analyses has been shown to be strongly correlated with the full analysis of AUC [7]. In the literature, several therapeutic time points have been suggested for use in the prediction of AUC values in patients undergoing treatment with CsA [3,7]. Sampling times within the first 4 hours of drug treatment with an interval of 2 hours between 2 points have been shown to be accurate [3,8,9]. In most institutions, including ours, trough and C_2 levels are frequently used to monitor CsA serum levels in the follow-up of patients who have undergone renal transplantation. It has been recently noted that when C_0 and C_2 are evaluated separately, C_0 levels correlate poorly with AUC values, although C_2 levels correlate satisfactorily with those values [10]. However, the formula that is based on both C_0 and C_2 levels has been shown to be an accurate method of estimating AUC values [10,11]. We thus used that formula to calculate AUC values according to 2 time points, an approach that required no additional cost other than that of routine workup.

Hypertension related to the stimulation of renal sodium chloride co-transporter may be a side effect of CsA [12]. Amlodipine is one of the widely used drugs for treatment. It was reported that calcium channel blockers such as verapamil, diltiazem or nicardipine can affect CsA serum level, but amlodipine has more harmless effects on CsA serum level [13]. We have not any need of dosage adjustment of CsA in 7 of 15 of our patients who received amlodipine.

Timing between meal and CsA intake and meal composition may influence drug absorption and serum level. It is difficult to determine these effects in vivo for each food. Recent studies mentioned that the largest influence of food realizes during the first few hours and especially lipid consumption may affect CsA serum level [14,15]. For these reasons we recommended our patients to intake their drug before meal.

It was demonstrated that body weight and body fat distribution is important for CsA blood levels and graft outcomes [16]. We could not show any effect of body weight on CsA serum levels. All patients of our study group were overweight or obese. We have not any patients group in normal body weight ranges. Our discordant finding about body weight with recent studies may be related with our study group.

Research has shown that calculated AUC values correlate with clinical events that occur during the post transplant period better than with single pharmacokinetic parameters. Many studies demonstrate that C_2 monitoring enables good tailoring of immunosuppressive therapy in the early post transplant period [17,18]. However, target serum levels for maintenance therapy have not been well established. Recently, Hu and colleagues [4] demonstrated that C_2 and C_0 levels did not differ in patients who exhibited a serum creatinine level > 1.5 mg/dL and < 1.5 mg/dL 1 year after having undergone renal transplantation. Those authors concluded that C_2 levels did not correlate with the long-term outcome of renal function. In this study, the relation between C_2 levels and long-term outcome of renal function was evaluated but the importance of calculated AUC in CAD has not been examined. In our study we found that the mean calculated AUC value was significantly higher in patients with CAD. On the other hand, Weber and colleagues [1] examined the levels of C_0 and C_2 and the calculated AUC values 3 weeks and 3 and 6 months after renal transplantation and the association of those values with the number of acute rejection episodes. Those investigators found that patients with lower calculated AUC levels 3 weeks after renal transplantation had a higher rate of acute rejection episodes than did those with higher calculated AUC values. C_0 and C_2

levels did not differ between patients with or without acute rejection during the early post transplant period. In another study Vavic and colleagues found that C_2 was a good predictor of acute graft rejection, while C_0 failed to point to the patients with the insufficient drug concentration [8]. Also Chang and colleagues demonstrated that C_2 monitoring has shown great promise as a comparatively safe and effective method to optimize outcomes among patients receiving CsA [19]. However, Einecke and colleagues recently showed that C_2 monitoring is limited as a predictor for the risk of rejection or CsA toxicity [20]. Narula and colleagues could not define a correlation between CsA trough levels and episodes of acute rejection [21]. In all these studies the relationship between CsA and calculated AUC with acute rejection was investigated. But chronic allograft dysfunction has not been evaluated.

The results of our study demonstrated that the mean calculated AUC value was higher in patients with CAD than in stable patients at a mean follow-up of 24 months after renal transplantation, perhaps because of the decreased elimination of CsA in patients with decreased renal function. However, C_0 and C_2 levels were not different between stable patients and those with CAD. Thus, because AUC levels are important in selecting treatment that prevents insufficient immunosuppression during the early post transplant period, those values are also helpful in decreasing the overexposure to CsA in long-term follow-up.

We conclude that calculated AUC values may be a better parameter in the monitoring of cyclosporine dosing for the follow-up of chronic allograft dysfunction than are C_0 and C_2 levels alone.

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