Nephro-Urol Mon. 2011;3(4):296-300
Nephro-Urology Monthly
Journal home page: www.NUmonthly.com

Cyclosporine Through and 2 Hour Post Dose Monitoring and Its Contributing Factors among Pediatric Kidney Recipients

Fatemeh Beiraghdar [1], Zohreh Rostami [1*], Behzad Einollahi [1]

[1] Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, IR Iran

ARTICLE INFO

Article Type:
Original Article

Article history:
Received: 15 Jul 2011
Revised: 26 Jul 2011
Accepted: 13 Aug 2011

Keywords:
Cyclosporine
Pediatric
Kidney transplantation

ABSTRACT

Background: Cyclosporine (CsA) is one of the most frequently used anti-rejection drugs in organ transplant. Pediatric patients have different CsA pharmacokinetics than adults.
Objectives: The aim of this retrospective study was to evaluate the CsA blood levels monitoring in pediatric renal transplant recipients in a single-center setting, after the first year of transplantation.
Patients and Methods: We reviewed 236 pediatric kidney recipients (aged ≤ 18) years old who received a kidney for the first time with at least a minimum time of 1 year after transplantation between April 2008 and June 2010. Mean follow-up was at least 6 months.
Results: The male to female ratio was 1.3/1.0. Mean age of patients' were 14 ± 3 years. A negative relation was found between CsA levels (C0 and C2) with serum creatinine (r = -0.1, $P = 0.001$ and r = -0.1, $P = 0.01$, respectively). A significant correlation was found between C0 level and liver enzymes. Although increase in the donor age had a negative effect on C0 as well as C2 levels, significant value was only shown in C2 level (r = -0.5, $P = 0.1$ *vs.* r = -0.15, $P = 0.000$). C0 level was higher in male than female gender ($P = 0.000$) as well as in deceased donor source ($P = 0.000$). Serum creatinine level, serum alkaline phosphatase, liver enzymes affected C0 blood level; whereas, donor age and serum creatinine were the confounding variables on C2 level.
Conclusions: We conclude that C0 was affected by serum creatinine level, serum alkaline phosphates, liver enzymes; whereas, C2 level was influenced by donor age and serum creatinine.

Implication for health policy/practice/research/medical education:
The optimal maintenance dose of cyclosporine is an important issue because adequate blood level of cyclosporine is required to prevent renal allograft rejection and nephrotoxicity; therefore, targeting cyclosporine levels is an important issue in pediatric kidney transplants.

Please cite this paper as:
Beiraghdar F, Rostami Z, Einollahi B. Cyclosporine Through and 2 hour Post Dose Monitoring and Its Contributing Factors among Pediatric Kidney Recipients. *Nephro-Urol Mon*. 2011;**3**(4):296-300.

1. Background

The outcomes in renal transplant recipients depend on multiple factors. Among these factors, efficacy and safety of immunosuppressive drugs play essential role. Cyclosporine (CsA) is one of the most frequently used anti-rejection drugs in organ transplantation (1). Although CsA is widely used after renal transplantation over the long term, there is still no firm consensus on the best way to monitor CsA blood levels (2). A narrow therapeutic blood level of CsA has led to the monitoring of its blood concentration (3). It is routinely monitored by the level obtained just before the next dose known as trough level (C0) or two hours post dose level (C2). Despite

* *Corresponding author at:* Zohreh Rostami, Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, IR Iran. Tel/Fax: +98-2181262073.
E-mail: rostami@inju.ir

improvement in therapeutic CsA monitoring in renal transplant recipients, it should be modulated to balance the risks of allograft rejection and CsA nephrotoxicity (4). To avoid side-effects, therefore, monitoring of CsA blood level is necessary to modify the individual doses of the drug (5). The optimal maintenance dose of CsA is an important issue because adequate blood level of CsA is required to prevent renal allograft rejection; therefore, targeting CsA levels to prevent acute rejection is an important issue. CsA pharmacokinetics has inter- and intra-individual variability and pediatric recipients require larger dose than adults due to variation in biological maturation status (3). Contributing factors in pediatric patients is the variation of CsA bioavailability through intestinal length, metabolism in gut, type of organ transplant and transplant duration (6). Although, systemic clearance is relatively higher in the children, there is no difference in volume of distribution of CsA between pediatric and adult transplant recipients (6, 7). On the other hand, it is identified that the C2 blood level is the most sensitive marker for the area under the curve of drug and it has been planned as a more convenient method for pharmacokinetic monitoring than usual C0 assay (8, 9). In Pharmacokinetic studies, C0 blood level has demonstrated a poor correlation with both CsA exposure and the development of acute rejection and nephrotoxicity (5). The limited data are available in literature on CsA therapeutic monitoring in pediatric renal transplant recipients (10-12). Therefore, we conducted a retrospective study to evaluate the CsA blood levels monitoring in Iranian pediatric renal transplant recipients in a single-center setting after the first year post-transplantation.

2. Objectives

A retrospective study was carried out to detect the correlation between cyclosporine (CsA) levels and renal allograft function and to determine which CsA level indexes were more reliable for CsA monitoring in Iranian children between April 2008 and June 2010.

Table 1. Demographic Data of Pediatric Renal Transplant Recipients (n = 236)

Variables	**Values**
Gender of recipient, No. %	
Male	135 (57)
Female	101 (43)
Gender of donor, No. %	
Male	152 (79)
Female	40 (21)
Donor sources, No. %	
Living related donor	25 (11)
Living unrelated donor	190 (85)
Deceased	9 (4)
Age of recipient, y, Mean ± SD	14 ± 3.7
Age of donor, y, Mean ± SD	27 ± 6.4
Trough level of CsA [a], ng/mL, Mean ± SD	118 ± 65
2-hour post dose of CsA, ng/mL, Mean ± SD	471 ± 148
Serum creatinine, mg/dL, Mean ± SD	1.89 ± 1.47
Blood urea, mg/dL, Mean ± SD	56.6 ± 36.6
Fasting blood sugar, mg/dL, Mean ± SD	90.8 ± 19.6
Hb [a], g/dL, Mean ± SD	11.9 ± 2.0
AST [a], IU/L [a], Mean ± SD	22.2 ± 25.9
ALT [a], IU/L, Mean ± SD	27.2 ± 53.7
ALP [a], IU/L, Mean ± SD	311.5 ± 222.6
HDL [a] cholesterol, mg/dL, Mean ± SD	47.0 ± 13.2
LDL [a] cholesterol, mg/dL, Mean ± SD	94.1 ± 36.7
Uric acid, mg/dL, Mean ± SD	6.6 ± 1.9

[a] Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CsA, cyclosporine; Hb, hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein

Table 2. Univariate Analysis: Correlation between CsA Levels and Other Variables

Variables	**CsA [a] Trough level, *P* value (r)**	**CsA 2 h Post-Dose level, *P* value (r)**
Age		
Recipient	0.4 (-0.2)	0.8 (-0.009)
Donor	0.1 (-0.05)	0.000 (-0.15)
Serum creatinine	0.001 (-0.1)	0.01 (-0.1)
FBS [a]	0.2 (-0.05)	0.9 (-0.002)
LDL [a] cholesterol	0.4 (0.1)	0.5 (0.05)
HDL [a] cholesterol	0.3 (-0.06)	0.4 (-0.07)
AST [a]	0.03 (0.09)	0.06 (-0.1)
ALT [a]	0.002 (0.1)	0.2 (0.07)
ALP [a]	0.2 (0.05)	0.06 (0.1)

[a] Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CsA, cyclosporine; Hb, hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein

3. Patients and Methods

3.1. Patients

We enrolled 236 pediatric kidney recipients aged ≤ 18 years old who received a kidney for the first time with at least a minimum time of 1 year after transplantation (5.9 ± 3.3 years). One thousand and sixty-nine blood samples were obtained in a single laboratory for measurements of serum creatinine (SCr), CsA through level (C0) and 2-hour post-dose level of CsA (C2).

3.2. Data Collection

Demographic variables and other biochemical measurements were gender of recipient and donor, age of recipient and donor, donor sources (living and deceased), blood urea, lipid profile, fasting blood sugar (FBS), liver enzyme tests, uric acid and hemoglobin (Hb). All recipients were followed for at least 6 months.

The study was approved by local Institutional Ethics Committee.

3.3. Protocol of Treatment and Follow Up

Maintenance immunosuppressant in all recipients was primarily based on CsA. Majority of patients also received mycophenolate mofetil (MMF) and prednisolone, except those who withdrew these drugs due to their side effects or individuals undertaken in tapering of steroid protocol. Antithymocyte globulin (ATG) was routinely administered in highly sensitized patients. All patients beyond one year of transplantation were clinically examined every 1-2 months and a blood sample was taken for routine laboratory test, C0 and C2 blood levels as well as dose was adjusted as necessary. We considered target therapeutic ranges for C0 level as 100–250 ng/mL and C2 level as 600-800 ng/ml. CsA blood levels were determined from whole blood using the Cobas Mira-Plus analyzer (Roche).

3.4. Statistical Analysis

Data were statistically analyzed using SPSS for Windows version 17.0; and the quantitative results were presented as mean SD, while qualitative variables were expressed by number and percentage. The Kolmogorov-Simirnov test showed that C0 and C2 levels were not distributed normally; thus, Spearman's correlation analysis was used to determine the correlations between C0 and C2 concentrations with numeric variables. Comparisons of variables such as C0, C2 and SCr between male and female recipients were performed using the Mann-Whitney U-test, whereas comparisons of data among different donor sources (LRD, LURD and deceased) were done using Kruskal-Wallis test. Linear logistic regression was also applied to examine the relationship between C0 and C2 level with SCr, age of recipients and donors, liver enzymes, lipid profile, FBS, UA and Hb. A result was considered significant when the p value was less than 0.05.

4. Results

4.1. Demographic Data

We included 236 pediatric renal transplant recipients (PRTRs) with mean age of 14 ± 3 years. All of them received for the first time allograft kidney transplantation. The male to female ratio was 1.3/1.0. Living unrelated kidney donation was more popular in our PRTRs (85%). The donors were predominantly young and male gender was dominant (79%). *Table 1* summarizes all the laboratory data of patients.

4.2. Univariate Analysis

Univariate correlations between C0 and C2 levels with other variables are shown in *Table 2*. A negative relation was found between CsA levels (C0 and C2) with serum creatinine (r = -0.1, P = 0.001 and r = -0.1, P = 0.01, respectively). In contrast to C0 level which had a significant correlation with liver enzymes (ASL & ALT), no relation was observed with C2 level. Although growing the donor age had a negative effect on C0 as well as C2 levels, significant value was only shown in C2 level (r = -0.5, P = 0.1 *vs.* r = -0.15, P = 0.000) *(Table 2)*. C0 level was higher in male than female gender (P = 0.000) as well as in deceased donor source (P = 0.000); this significant difference was also observed for C2 level in donor source (P = 0.004), but not among the two genders (P = 0.3) *(Table 3)*. The mean serum creatinine in deceased kidney transplants was lower than living donor kidney recipients with no statistically significant values (P = 0.5) *(Table 3)*. The serum concentration of creatinine was higher in boys when compared to girls (P = 0.000).

Table 3. Comparisons of CsA Levels and Renal Graft Function in Both Genders and All Donor Sources

Gender	Mean ± SD	*P* value	Donor source	Mean ± SD	*P* value
Trough Level of CsA [a]					
Male	138 ± 90	0.000	Living related donor	122 ± 66	0.000
Female	109 ± 60		Living unrelated donor	122 ± 77	
			Deceased	203 ± 139	
2 h Post-Dose CsA Level					
Male	488 ± 186	0.3	Living related donor	537 ± 212	0.004
			Living unrelated donor	471 ± 149	
Female	479 ± 130		Deceased	594 ± 125	
Serum Creatinine					
Male	1.5 ± 0.9	0.000	Living related donor	1.4 ± 0.7	0.5
Female	1.4 ± 1.0		Living unrelated donor	1.5 ± 1.0	
			Deceased	1.3 ± 0.4	

[a] Abbreviation: CsA; Cyclosporine

Table 4. Linear Regression Between C0 and C2 with Other Variables

Variables	C0 [a], *P* value	C2 [b], *P* value
Age		
Recipient	0.2	0.4
Donor	0.2	0.08
Serum creatinine	0.002	0.03
Alkaline phosphate	0.000	0.5
FBS [c]	0.6	0.3
HDL [c] cholesterol	0.4	0.4
LDL [c] cholesterol	0.9	0.9
AST [c]	0.001	0.06
ALT [c]	0.000	0.1
Uric Acid	0.9	0.8
Hb [c]	0.07	0.7

[a] Dependent Variable, Trough level of CsA
[b] Dependent Variable, 2 h post-dose CsA level
[c] Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FBS, Fasting blood sugar; Hb, Hemoglobin; HDL, Low density lipoprotein; LDL, High density lipoprotein

4.3. Multivariate Linear Regression Analysis

The results of linear regression are summarized in *Table 4.* Accordingly, serum creatinine level, serum alkaline phosphatase, AST and ALT contributed to C0 blood level; whereas, donor age and serum creatinine were the confounding variables on C2 level.

5. Discussion

We found a negative correlation between blood levels of CsA (C0 and C2) and serum creatinine. Marcen *et al.* showed a negative correlation between only C0 level and renal allograft function (13). Although Citterio *et al.* showed an association between C2 and clinically detectable chronic allograft nephropathy in 79 renal transplant recipients, there was no significant correlation between C2 and serum creatinine. On the other hand, Cole et al reported no correlation between C2 and serum creatinine (14). We showed a good relation between liver function tests, specifically ALT, and C0 blood level. Andrew et al found some liver dysfunction after CsA therapy in transplant patients; however, there was no relation between CsA blood levels and liver function tests (15). We also demonstrated a negative correlation between age of donors and C2 blood level. Although C0 level was higher in boys compared to girls in the current study, there is least or no sex related differences in hepatic or intestinal CYP3A activity for CsA metabolism (16). Other factors that could explain sex related pharmacokinetic differences included lower hepatic blood flow, lower body weight, higher percentage of body fat affecting volume of distribution, and higher glomerular filtration rate in male than in female (17).

Consistent with previous studies, there was no significant correlation between hemoglobin, uric acid, fasting blood glucose, plasma cholesterol and C0 and C2 blood levels by multivariate linear regression analysis. Marcen *et al.* showed no correlation between C2 level and hyperuricemia, diabetes mellitus and hypercholesterolemia (18). Abdelrahman et al reported that hyperuricemia is related to prolonged exposure to CsA rather than to its dose or blood concentration (19). Deceased donor had higher levels of C0 and C2 in comparison to living donors; it may be due to receiving higher dosage of CsA for prevention of rejection in deceased kidney transplants. We followed renal function of patients with serum creatinine, while evaluation with kidney biopsy and GFR estimation can be more accurate. The second limitation of the present study is its retrospective nature. We found that C0 was affected by serum creatinine level, serum alkaline phosphatas, AST and ALT; whereas, C2 level was influenced by the donor age and serum creatinine level.

Financial support

This study was funded by Nephrology and Urology Research Center, Baqiayatallah University of Medical Sciences.

Conflict of interest

None declared.

Acknowledgments

We would like to express our thanks to Dr. Heidari for English revision of our paper.

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