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Cyclosporine drug monitoring with C0 and C2 concentrations in children with stable renal allograft function

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Abstract: Cyclosporin A (CsA) has a narrow therapeutic window and necessitates monitoring of blood concentration. We aimed to evaluate trough (C0) and second hour (C2) level after ingestion of drug monitoring in renal allograft recipients. In this retrospective study, 12 children eight boys and four girls; mean age at transplantation 14.6 ± 3.7 yr (ranges: 7.0–19.0), mean age post-transtplant 17.8 ± 4.9 yr (ranges: 9.0–24.0) who were transplanted >6 months were enrolled in this evaluation. Ten were recipients of a living related donor and two deceased donor grafts. While six children were receiving CsA, steroids and azathioprine, the other six received CsA, steroids and mycophenolate mofetil. Clinical course, blood pressure, renal and liver function tests were recorded. Mean C0 and C2 were 96.2 ± 59.5 and 504 ± 305.4 ng/mL respectively. Mean serum creatinine level was 1.2 ± 0.45 mg/dL and mean creatinine clearance (CrCl) was 89.2 ± 36.8 mL/min/1.73 m^2. There was a correlation between serum creatinine level, CsA dose and C2 levels,whereas,there was no correlation between age, blood pressure, CrCl and C2 levels. However, no correlation was found between C0 levels and any of the above parameters. In conclusion, our data suggest that C2 levels are correlated better with dose and serum creatinine level.

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CsA has been used as a primary drug in renal transplantation for over 20 yr. The therapeutic range of the drug is very narrow, pharmacokinetics have individual differences and which causes therapeutic difficulties. Dosage of the drug must be adjusted according to serum levels. Therefore, serum trough (C0) and C2 levels after ingestion of CsA have been used. Kelles et al. (1) reported that C2 levels were more highly correlated with the area under curve than the C0 levels in renal transplant recipients. Shapiro et al. (2) concluded that nephrotoxicity was reduced by C2 monitoring after liver transplantation. It is not clear which level should be used for monitoring of clinical response and drug toxicity. Especially in children, pharmacokinetics and pharmacodynamics of this drug display marked variations. Studies in adult patients with renal allografts have shown that C2 levels of the drug are more appropriate for clinical follow-up than trough levels, but the data are not clear in children (3–6). In this study, C0 and C2 levels, and their relationship to CsA dosage and renal function tests were evaluated retrospectively in children with stable renal allograft function.

Abbreviations: AUC, area under curve; AZA, azathioprine; CrCl, creatinine clearance; CsA, cyclosporin A; CV, coefficient of variation; MMF, mycophenolate mofetil.

Materials and methods

Patients with stable renal allograft function receiving at least 6 months CsA were evaluated retrospectively. Of the 12 patients, eight were male and four were female. Demographic features, blood pressure, C0 and C2 CsA levels, simultaneous serum creatinine levels, creatinine clearance in 24-h urine collection [calculated by the formula urine volume (mL) × urine creatinine (mg/dL) × 1.73/1440 × serum creatinine (mg/dL) × body surface area (m^2)], and liver

function tests were recorded. Additionally, protocols of treatment, complications of therapy, clinical course and cause of withdrawal of CsA if it was withdrawn were also recorded.

Furthermore, the patients were evaluated according to the immunosuppressive therapy protocol used. Of the 12 patients, six received a combination of AZA, CsA and prednisolone, six received MMF, CsA and prednisolone. These two groups were compared regarding their serum CsA levels.

CsA levels were measured at time 0 and 2 h after drug intake using a monoclonal fluorescence polarization immunoassay (FPIA, Tdx; Abbott Laboratories, Abbott Park, IL, USA). In 167 samples, both levels were measured on the same day, in 52 samples, only C2 levels were measured.

Data were presented as mean ± s.d. A p-value of < 0.05 was considered statistically significant. The paired *t*-test to compare the mean values of quantitative parameters, chi-square for qualitative variables and regression analysis to correlate quantitative parameters were used. The reproducibility of CsA concentration measurements in an individual was assessed by using the CV (CV% = s.d. of mean × 100/mean), using all values obtained during the follow-up period. The paired *t*-test was used to compare the CV%.

Results

Clinical features and laboratory findings of the patients were shown in Table 1. None of the patients had acute rejection. We found that C2 levels were positively correlated with serum creatinine levels and dose of CsA ($p = 0.006$, $r = 0.23$ and $p < 0.01$, $r = 0.20$ respectively; Figs 1 and 2). There was no significant correlation between dose of CsA and creatinine clearance, age, blood pressure ($p > 0.05$). There was no correlation between C0 levels and any parameter.

However comparing immunosuppressive treatment regimens, C0 and C2 levels, were higher in the group receiving MMF than the group receiving AZA ($p = 0.002$ and $p < 0.001$ respectively; Table 2). Therefore, we reduced the dose of CsA in the MMF given group. Regarding the CsA dose serum creatinine levels and creatinine clearance, there was no significant difference between the groups ($p > 0.05$).

Table 1. Clinical and laboratory features of the patients with renal allograft recipients

Features	Ranges	Mean ± s.d.
Age of transplantation (yr)	7–19	14.6 ± 3.7
Follow-up duration (month)	9–117	44.8 ± 38.8
C0 levels (ng/mL)	21–156	96.2 ± 59.5
C2 levels (ng/mL)	102–992	504 ± 305.4
Serum creatinine (mg/dL)	0.12–1.6	1.2 ± 0.45
Creatinine clearance (mL/min/1.73 m^2)	58–192	89.2 ± 36.8

C0, trough level of cyclosporine; C2, second hour level of cyclosporine after ingestion.

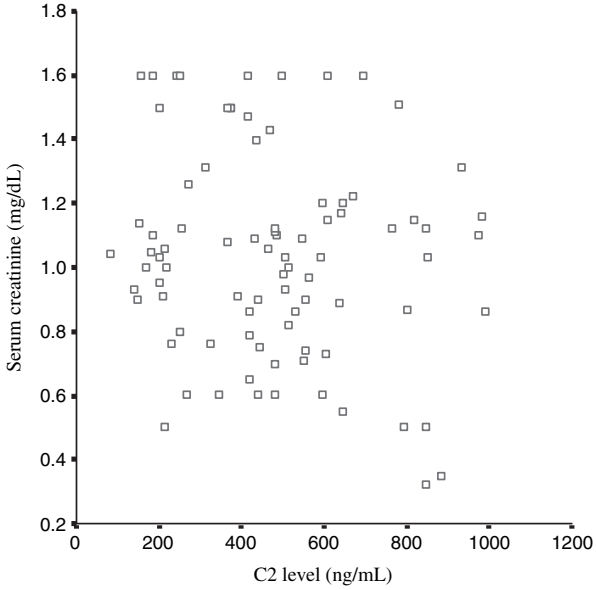

Fig. 1. The correlation of C2 level with serum creatinine level in renal transplant recipients ($p = 0.006$, $r = 0.23$).

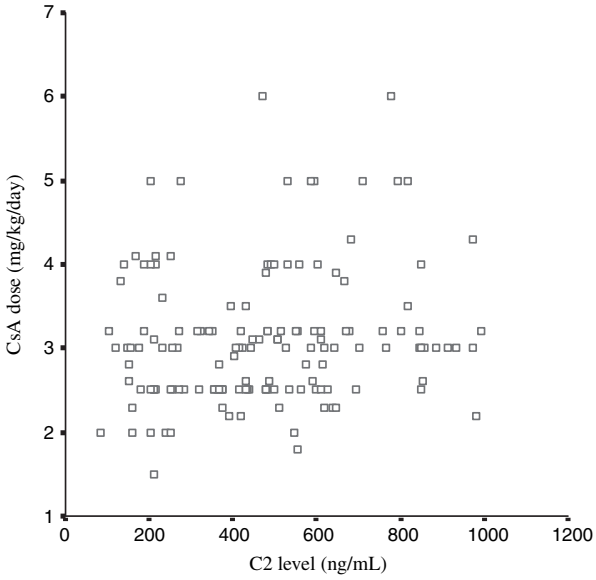

Fig. 2. The correlation of C2 level with cyclosporin A (CsA) dose in renal transplant recipients ($p < 0.01$, $r = 0.20$).

None of the patients had worsening liver function tests. Blood glucose levels and lipid profile were stabile. Two patients had transient hypertension. They did not require antihypertensive therapy. Of the six patients who had CsA withdrawn because of severe complications, five were changed to tacrolimus and one to sirolimus. Of the six patients, three were in the MMF and three were in the AZA group. These complications were gingival hyperplasia (in three patients), hypertricosis (in two patients), and

Table 2. Laboratory features of renal allograft recipients receiving MMF and AZA

Features	MMF group (n:6)	AZA group (n:6)	p-values
Serum creatinine (n:219; mg/dL)	1.18 ± 0.55	1.24 ± 0.45	NS
Creatinine clearance (n:119; mL/min/1.73 m^2)	95.7 ± 38.4	90.3 ± 33.8	NS
C0 levels (n:167; ng/mL)	120.7 ± 66.9	88.9 ± 54.6	0.002
C2 levels (n:219; ng/mL)	691.6 ± 336.1	430.8 ± 259.1	<0.001
CsA dose (n:219; mg/kg body weight)	3.27 ± 0.87*	3.22 ± 0.94	NS

NS, non-significant; MMF, mycophenolate mofetil; AZA, azathioprine; C0, trough level of cyclosporin; C2, second hour level of cyclosporin after ingestion; CsA, Cyclosporin A.
*Before reducing CsA dosage in MMF group

CsA nephrotoxicity proven by renal biopsy (in two patients). The side effects subsequently resolved.

The CV of C0 was 45.2% and of C2 was 45.9% ($p > 0.05$).

Discussion

CsA serum levels show wide variety causing difficulties in drug monitoring. AUC is a sensitive predictor of acute and chronic allograft rejection (3), but it is not feasible and not cost-effective. Therefore, C0 or C2 drug levels are used. In most studies, correlation between CsA dose and C0, and C2 levels have been reported to be widely variable. It has not been established which level is to be used for follow-up monitoring (3–5, 7–10).

Some studies have observed that C2 levels correlate better than C0 levels with the AUC in patients with kidney, heart and liver transplants (7–9). Wong et al (5) investigated the influence of C2 monitoring on post-transplantation clinical events such as rejection, CsA nephrotoxicity in 44 renal transplant patients in Asia. They found that the use of C2 monitoring correlated with lower incidence of acute rejection. Chueh et al. (10) compared C0 and C2 levels for drug monitoring in stable renal allograft recipient. C2 levels and CsA dose variability were lower than C0 levels. They concluded that it is feasible to change therapeutic CsA monitoring from C0 levels to C2 levels in stable renal transplant recipients.

Pharmacokinetic studies of CsA are different in children; absorption may be late and clearance may be delayed (11). In children, as gastrointestinal absorptive area is greater than adults, peak level is reached rapidly. Additionally, children have a high rate of metabolism of CsA therefore the drug is eliminated rapidly (12, 13). Kavukcu et al. (6) examined C2 levels in 17 adolescent renal transplant recipients in late post-transplant period and found that correlation of C2 levels with CsA dose was weaker than in the adult population. In our study, we noted that C2 levels correlated with CsA dose, but there was no difference between the CV of C0 and C2. The number of the patients is very small to reach a definite conclusion.

Because CsA is nephrotoxic agent, to minimize nephrotoxicity in maintenance immunosuppressive treatment regimen, CsA dose can be reduced with the addition of MMF. Grinyo et al. (14) compared patients receiving standard dose CsA and low-dose CsA plus MMF. They found that the level of clinical immunosuppression similar in the two groups. These findings suggest that MMF could be synergistic with the pharmacodynamic effect of low dose CsA. In our study, we also found CsA levels were higher in the CsA plus MMF group than in CsA plus AZA group; however, Pape et al. (15) studied in C2 levels in 33 children who received CsA alone and 15 children treated with additionally MMF, and found that C2 levels were lower in the MMF group.

As a result, we may suggest that CsA dosage should be adjusted according to serum C2 levels in children, as C2 levels are correlated better with CsA dose and serum creatinine levels. However, when the MMF and CsA combination is given, we recommend that CsA dose can be reduced.

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