Cyclosporin-A in the Treatment of Nephrotic Syndrome: The Importance of Monitoring C_0 (Trough) and C_2 (Two Hours After its Administration) Blood Levels

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Abstract: Cyclosporin-A (CsA) is often used in the treatment of nephrotic syndrome. The effectiveness of CsA and the value of C_2 blood levels in the treatment of nephrotic syndrome, due to various glomerular diseases, were studied. Forty-two nephrotic patients (M/F 21/21), with well-preserved renal function (creatinine clearance 87±20ml/min) were included in the study. The original diagnoses were minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), IgA nephropathy (IgAN), and lupus nephritis (LN). All patients were treated with prednisolone and CsA for 24 months. Cyclosporin-A C_0 and C_2 blood levels were determined at regular intervals. Remission of the nephrotic syndrome was observed in all patients with MCD, IgAN and LN, in 75% with FSGS and in 83% with MN. Relapses were observed in some patients with MCD (25%) and MN (36%). The C_0 levels were 93±15 ng/ml and the corresponding C_2 levels were 498±110 ng/ml. However, significantly lower (340±83 ng/ml) or higher (680±127 ng/ml) to the average C_2 levels were found in 6 patients (14%). No relation of C_0 and C_2 levels with the remission and relapse rate of the nephrotic syndrome and with renal function impairment was observed. Small doses of CsA with prednisolone are effective in the treatment of nephrotic syndrome. Although an individual variation of C_2 was observed for the same target C_0 levels, no relation of C_2 levels was found with the remission or relapse rate of the nephrotic syndrome.

Key Words: Cyclosporine, C_2 blood levels, glomerulonephritis, nephrotic syndrome.

INTRODUCTION

Cyclosporin-A (CsA) has been used for the treatment of idiopathic nephrotic syndrome in children and adults [1]. It has also been tried in patients with membranous nephropathy and nephrotic syndrome resistant to corticosteroids and cytotoxic drugs [2]. CsA has also been used in the treatment of lupus nephritis and other primary and secondary glomerular diseases [3]. The administration of CsA is frequently followed by remission of nephrotic syndrome, but relapses can occur with discontinuation of treatment [4]. A lower relapse rate has been reported with gradual tapering of the drug dose [3]. CsA is a potentially nephrotoxic drug, but its administration at low doses is not usually followed by classical histological lesions of nephrotoxicity [5].

Studies in kidney transplanted patients show, that trough blood levels (C_0) do not accurately reflect the individual's exposure to the drug [6]. There is increasing evidence that blood levels two hours after drug administration (C_2) represent the most sensitive marker for the extent and consistency of cyclosporin exposure, in an individual allograft recipient [7]. This has been attributed to pharmacokinetic and pharmacodynamic characteristics of CsA [8].

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Whether C_2 levels are related to the effectiveness of CsA in inducing remission of the nephrotic syndrome and preventing CsA nephrotoxicity is not known. In this study an estimation of the value of C_2 levels in the use of CsA for treatment of nephrotic patients, with various types of glomerulonephritis (GN), was attempted, by comparison of C_2 to trough (C_0) CsA levels.

PATIENTS AND METHODS

Forty-two patients (21 males and 21 females) aged 48±16 years old with nephrotic syndrome (urinary protein 8±4 g/24h), due to various GN and well-preserved renal function (creatinine clearance 87±20 ml/min), were included in the study. The mean blood pressure of patients at presentation was 140/85 mmHg. Diuretics, β-blockers and calcium channel blockers were used for the treatment of the arterial hypertension. The original diagnoses were minimal changes disease (MCD) (n=8), focal segmental glomerulosclerosis (FSGS) (n=4), membranous nephropathy (MN) (n=18), IgA nephropathy (IgAN) (n=6), and lupus nephritis (LN) (n=6).

Cyclosporin-A (3 mg/kgBW/day) and prednisolone (0.5 mg/kgBW/day) were given to all patients. The dose of CsA was adjusted according to trough blood levels (C_0 target levels: 100 ng/ml) for 18 months and then it was gradually reduced by 0.5 mg/kgBW/day per month for six months. The dose of prednisolone was also gradually reduced to 5 mg on alternate day and continued for the period of 24-month

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treatment. During these 24 months and for at least 12 months after CsA discontinuation, all patients were followed-up monthly. Body-weight, blood pressure, urinalysis, full-blood count and biochemical profile, 24h urinary protein and creatinine clearance were recorded at each visit.

Complete or partial remission of the nephrotic syndrome was considered if proteinuria reduced to <0.3 g/24h and between 0.3 and 3 g/24h respectively. No remission was considered if proteinuria was persistently above 3 g/24h. Relapse of the nephrotic syndrome was considered if edema and proteinuria >3 g/24h were reappeared in patients with remission. The relapses over the period of treatment and for 12 months after its withdrawal were recorded.

Cyclosporin-A was determined in whole blood samples on a TDx Analyzer (Abbott Laboratories, Illinois, USA). The assay utilizes fluorescence polarization immunoassay (FPIA) technology. In every patient two blood samples were drawn for the determination of CsA levels: a) at zero time (C_0) before the receipt of the drug and b) two hours later (C_2).

The results were expressed as means ± SD. Student's t-test for paired data and chi-squared test as well as linear regression analysis were used for statistical analysis. A p value <0.05 was considered to be significant.

RESULTS

Complete remission of the nephrotic syndrome, after treatment with prednisolone and CsA, was observed in 8 (100%) patients with MCD, in 1 with FSGS (25%), in 7 with MN (39%), in 3 with IgAN (50%) and in 2 patients with LN (33%). Two patients with FSGS (50%), 8 with MN (44%), 3 with IgAN (50%) and 4 with LN (77%) showed partial remission. Persistent nephrotic syndrome was observed in 1 patient with FSGS (25%) and in 4 with MN (22%). Relapses of the nephrotic syndrome after discontinuation of treatment occurred in 2 out of 8 patients with MCD, in 5 out of 14 (36%) patients with MN who showed partial or complete remission with treatment and in 1 out of 6 (17%) patients with IgAN. The remission and relapse rate of the nephrotic syndrome in all patients are shown in Table **1**.

No serious side effects related to prednisolone and CsA administration were observed. Cushingoid features and hirshuitism that were evident in five patients disappeared after lowering the prednisolone and CsA doses.

Renal Function During Follow-Up

A stable renal function was observed in 37 out of 42 patients (88%) during the treatment period of 24 months as no significant difference was observed between the creatinine clearance in the beginning and at the end of follow-up (Clcr 88±20 *vs*. 82±14 ml/min, p=NS). Deterioration of renal function (Clcr from 76±15 to 35±12 ml/min, p<0.05) was observed in 5 out of 42 patients (12%). No difference in the blood pressure control was evident between patients with stable or deteriorating renal function. Two of these patients had persistent nephrotic syndrome and 3 had frequent relapses. The original diagnoses were FSGS (n=1), IgA nephropathy (n=1), and membranous nephropathy (n=3).

Comparison Between C_0 and C_2 Blood Levels in CsA Treated Patients with Nephrotic Syndrome

During the treatment with CsA, the C_0 levels remained within the target (93±15 ng/ml) and the corresponding C_2 levels were 498±110 ng/ml (Fig. **1**). However, significantly lower or higher to the average C_2 levels were found in 6 patients (14%). Low C_2 (340±83 ng/ml) was found in 3 (7%) and high C_2 levels (680±127 ng/ml) in the other 3 (7%) patients with C_0 within the target levels. The original diagnoses of these patients were MCD, FSGS, MN and LN.

Complete or partial remission of the nephrotic syndrome with treatment was observed in all patients with low C_2 and in 2 of 3 with high C_2 levels whereas persistent nephrotic syndrome was observed in 1 of these patients. A stable renal function (Clcr: 83 ml/min) during the follow-up period was evident in all patients with high C_2 levels. No correlation of C_0 and C_2 levels with the remission or relapse rate of the nephrotic syndrome was observed.

DISCUSSION

In this study, the effectiveness of CsA and the value of C_2 levels in the remission and relapse rate of nephrotic syndrome, due to various types of GN, were estimated. It was shown that a regimen of small doses of CsA and prednisolone is effective in inducing remission in most patients. Although an individual variation of C_2 levels was observed in patients with C_0 within the target levels, no

Table (1). Remission and Relapse Rate of Nephrotic Syndrome in CsA Treated Patients with Various GN [# of Patients (%)]

Nephrotic syndrome	MCD (n=8)	FSGS (n=4)	MN (n=18)	IgAN (n=6)	LN (n=6)
Complete remission	8(100)	1(25)	7(39)	3(50)	2(33)
Partial remission	—	2(50)	8(44)	3(50)	4(77)
No remission	—	1(25)	3(17)	—	—
Relapse	2(25)	—	5/15(33)	1(17)	—

MCD: minimal changes disease, FSGS: focal segmental glomerulosclerosis,

MN: membranous nephropathy, IgAN: IgA nephropathy, LN: lupus nephritis.

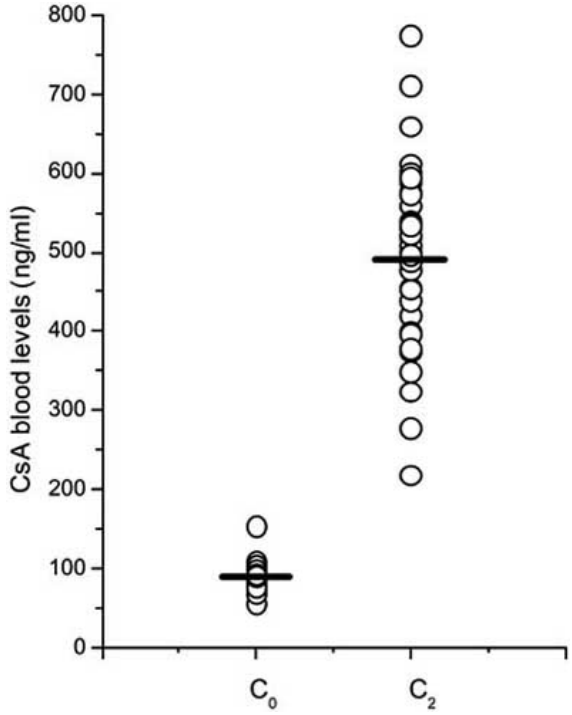

Fig. (1). Cyclosporin-A trough blood levels (C_0) and corresponding blood levels two hours after its administration (C_2), in patients (n=42) with nephrotic syndrome.

correlation of C_2 levels with the remission or relapse rate of nephrotic syndrome was recognized in CsA treated patients. Cyclosporin-A is a potentially nephrotoxic drug and its use is relatively hazardous in a dosage greater than 5.5 mg/kgBW/ day [5]. In this study a lower dose of CsA (3 mg/kgBW/day) was used in a combination with corticosteroids. Partial or complete remission of the nephrotic syndrome was observed in most patients (Table **1**). These results suggest that CsA induces remission of nephrotic syndrome even when used in low dosage regimens. Serious side effects or signs of severe nephrotoxicity were not observed, probably due to the low CsA doses. However, deterioration of renal function was observed in 5 patients (12%). Although these patients were treated by the same therapeutic regimen, they had either persistent nephrotic syndrome or frequent relapses. These findings suggest that deterioration of renal function was related to the persistence of nephrotic syndrome and to the natural history of the disease (FSGS, IgAN, MN) rather than to CsA toxicity.

Studies in kidney transplanted patients show that blood levels two hours after administration of CsA (C_2) represent more effectively and accurately the extent and consistency of cyclosporin exposure in an individual transplant recipient compared to trough levels (C_0) [7]. In addition, a link between the pharmacokinetics of CsA and clinical outcomes in transplant recipients has been identified [7]. Such data on the value of C_2 levels in CsA treated nephrotic patients, is not available. In this study, the determination of C_2 levels in patients with standard target trough levels (C_0) showed that 14% of the patients had either higher or lower to the expected C_2 levels. However, no relation of C_2 levels with remission and relapse rate of the nephrotic syndrome and with renal function impairment was identified and no additive information to the C_0 levels was obtained. A possible reason for this lack of correlation is that target C_0 levels in transplanted patients, are higher (200 ng/ml) than these in nephrotic patients (100 ng/ml). Small increases of CsA dosage evoke more extend changes in C_2 values than in C_0. The spread of C_2 values is greater when C_0 increases as in the case of transplanted patients and the risk of extreme C_2 values (either high or low) is higher. On the contrary, in low dosage of CsA as in the case of nephrotic syndrome, the decline from the average expected C_2 levels (Fig. **1**) and the risk for nephrotoxicity are lower.

It is well known that cytotoxic drugs used to treat nephrotic syndrome are followed by serious side effects (bone marrow toxicity, infections, gonadal dysfunction and malignancy). CsA is an alternative treatment to those regimens, but it is potentially nephrotoxic. Although typical histological lesions of cyclosporin nephrotoxicity have not been observed with doses lower than 5.5 mg/kgBW/day, we recently reported more severe glomerular sclerosis and interstitial fibrosis in repeat biopsies of some patients with membranous nephropathy and remission of nephrotic syndrome after treatment with a lower dose of CsA (3 mg/kgBW/day) and corticosteroids for 2 years (9). Thus, the estimation of optimum CsA dose in an individual basis is very important. Whether the regular determination of C_2 levels in CsA treated patients with GN is of value, remains to be clarified with studies including larger number of treated patients and repeat renal biopsies.

In conclusion, the results of this study provide evidence that small doses of CsA with prednisolone are effective in the treatment of nephrotic syndrome due to various GN. The response of nephrotic syndrome to CsA is rather related to the type of GN than to the drug dosage. The regular monitoring of C_2 blood levels instead of C_0 does not provide any additional benefit in determining the optimal CsA dose, for treatment of nephrotic syndrome.

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