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Adverse Effects of Cyclosporine Therapy in Renal Transplant Recipients

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Abstract: Cyclosporine is being used as an immunosuppressive agent in transplant recipients for more than fifteen years and has been reported to cause various toxic manifestations in such patients. A study was carried out on sixty indigenous renal transplant recipients on cyclosporine therapy to assess the drug toxicity. The patient population was divided into three groups depending upon the dose and blood cyclosporine levels. The parameters used to assess the toxicity included renal and liver functions tests, serum lipids levels, gum hyperplasia , hypertension and skin changes. A significant and gradual decrease in toxicity was recorded with an increase in post transplant period in patients of all groups ($P<0.001$). The results showed that cyclosporine can be used for long term in renal transplant recipients as an essential part of their management without evidences of progressive toxic nephropathy.

Key words: Cyclosporine, immunosuppression, kidney, transplantation

Introduction

The end stage renal disease progresses to death unless intercepted by transplantation. The commonest end stage renal disease in Asian population is chronic glomerulonephritis (Mitsuishi and Cecka, 1993). Renal transplantation has its own complications, the greatest being threat of rejection, which depends upon the coordinated activation of antigen presenting cells (Germain, 1993; Weiss and Littman, 1994) and can be correlated with the degree of MHC/HLA mismatching (Cecka and Terasaki, 1993). Successful renal transplantation has been made possible by better comprehension of the rejection response and judicious use of immunosuppressive drugs (Suthanthiran and Strom, 1994) including cyclosporine, azathioprine and corticosteroid.

Cephalosporine was first used in 1978 as immunosuppressant in human organ transplantation and since then has been approved for use in kidney, liver, heart, lung, pancreas and bone marrow transplants. Majority of renal transplant recipients (RTRs) tolerate long term cyclosporine therapy without evidence of progressive toxic nephropathy (Calne, 1987). The adverse effects of cyclosporine can be manifested as increased blood urea nitrogen, serum bilirubine and creatinine levels (Young *et al.*, 1995) with hyperchlorestelemia (Zdrojewski *et al.*, 1994).

Regular monitoring of cyclosporine levels in the blood of RTRs is mandatory to reduce the occurrence of toxicity. Much data on the cyclosporine toxicity has been published from other parts of the world, however, such informations are scarce from this region. The present study was therefore, initiated with the objectives to generate the baseline data and determine the cyclosporine toxicity in indigenous renal transplant recipients.

Materials and Methods

The study was conducted at Armed Forces Institute of Pathology (AFIP) during 1996-1997 and comprised of sixty randomly selected renal transplant recipients (46 male and 14 female). Each patient was examined in the outpatient department and relevant history, time since transplantation, HLA typing and plasma levels were noted. Eight ml of blood was collected and divided into two equal parts. The EDTA mixed blood was used for cyclosporine and haematological measurements while serum from rest of the blood was used for the renal functions and lipid profile. The cyclosporine levels were estimated using Abbot TDX automated system based on the fluorescent polarization immunoassay. The data was analyzed by using t-test and a value of $P \leq 0.05$ was taken as an indicator of significant difference.

Results

Sixty randomly selected RTRs were divided into three groups, based on the duration of transplantation and blood cyclosporine levels. Group A comprised of thirteen RTRs having blood cyclosporine levels above the recommended therapeutic range (355 ± 21 ng/ml). Group B comprised of thirty-four patients, all had cyclosporine levels within the therapeutic range (174 ± 10 ng/ml). The group C had thirteen patients with sub therapeutic levels of cyclosporine (102 ± 21 ng/ml). There were no significant differences in these groups based on the age, sex, donor source, primary disease or initial renal function tests. The post transplant periods of the patients were different for each group. Group A patients had the smallest time interval since transplantation i.e. 10.9 ± 0.9 months, whereas groups B and C both had 254 ± 0.5 months post transplant interval. Their clinical finding and laboratory test reports are shown in Table 1 and 2. Serum creatinine levels were within the normal range in all the groups, while serum urea levels were increased, the highest being in group B.

Serum cholesterol was within the normal range in all groups however, it was lowest for group C patients. Serum triglycerides were raised in group A (2.36 ± 0.28 mmol/L) and B (2.32 ± 0.19). Systolic blood pressure was highest in group A. The diastolic pressure showed an upward trend in group B and C. Gum hypertrophy and skin changes were most frequent in group A and a remarkable decrease in such lesions was noticed in group B and C patients. Serum uric acid levels were within the normal range, highest being in group B (Table 1).

Discussion

cyclosporine is a powerful immunosuppressive agent used as a mainstay in the management of renal transplantation (Miach, 1986; Ianhez *et al.*, 1991). The present study comprised of sixty RTRs, getting cyclosporine therapy as immunosuppressant for over six months. The effects of

Table 1: Comparison of various variables in patients grouped on the basis of cyclosporine levels (A: high; B: therapeutic range; C: sub-therapeutic range)

Variables	Group A vs Group B		Group A vs Group C		Group B vs Group C	
	t-value	*p-value*	*t-value*	*p-value*	*t-value*	*p-value*
Cyclosporine levels (ng/ml)	6.49	0.001*	7.61	0.001*	3.19	0.001*
Post-transplantation period (month)	3.70	0.001*	2.38	0.03*	0.02	0.98
Cyclosporine dose (mg/kg)	4.08	0.001*	2.99	0.01*	0.34	0.73
Serum creatinine (mmol/l)	4.11	0.001*	1.02	0.32	1.80	0.08
Uric acid (mmol/l)	0.08	0.43	0.03	0.98	0.87	0.39
Serum Urea (mmol/l)	0.90	0.34	0.44	0.67	0.23	0.82
Total cholesterol (mmol/l)	1.07	0.29	1.75	0.09	2.95	0.01*
Triglyceride (mmol/l)	0.12	0.91	1.44	0.16	1.58	0.12
Diastolic B.P. (mmHg)	0.54	0.59	0.98	0.34	0.55	0.58
Systolic B.P. (mmHg)	0.01	0.99	1.40	0.17	1.73	0.09
Haemoglobin (g/dl)	0.13	0.90	1.19	0.24	1.18	0.24
Total serum protein (g/l)	0.38	0.70	0.06	0.96	0.37	0.71

Table 2: Mean ± SEM of various variables in patients grouped on the basis of cyclosporine levels (A: high; B: therapeutic range; C: sub-therapeutic range)

Variables	Group A (n = 13) Mean ± SEM	Group B (n = 34) Mean ± SEM	Group C (n = 13) Mean ± SEM
Cyclosporine levels (ng/ml)	354.45 ± 26.1	174.06 ± 9.51	102.02 ± 20.48
Post-transplantation period (month)	10.92 ± 0.98	24.44 ± 3.52	24.31 ± 5.53
Cyclosporine dose (mg/kg)	4.03 ± 0.29	2.68 ± 0.16	2.53 ± 0.41
Serum creatinine (mmol/l)	149.46 ± 14.4	278.91 ± 28.01	192.23 ± 39.25
Uric acid (mmol/l)	398.92 ± 32.07	429.8 ± 21.85	397.69 ± 29.96
Serum Urea (mmol/l)	7.95 ± 1.35	9.61 ± 1.07	9.06 ± 2.15
Total cholesterol (mmol/l)	5.28 ± 0.26	5.66 ± 0.24	4.66 ± 0.24
Triglyceride (mmol/l)	2.36 ± 0.28	2.32 ± 0.19	1.81 ± 0.26
Diastolic B.P. (mmHg)	46.54 ± 4.54	93.53 ± 3.26	90.77 ± 3.79
Systolic B.P. (mmHg)	146.54 ± 6.92	146.47 ± 5.1	135.38 ± 3.9
Haemoglobin (g/dl)	12.91 ± 0.55	12.82 ± 0.43	11.83 ± 0.72
Total serum protein (g/l)	71.62 ± 1.61	70.91 ± 0.92	71.77 ± 2.13

ceplosporine including kidney functions, lipid profile, hypertension, changes on skin and gums were recorded. The derangement of these is most commonly reported in patients on cyclosporine therapy. We also correlated such findings with the dosage and length of post transplant period and agree with the reports of Hricik *et al.* (1991) and Burke *et al.* (1994). The blood concentration ranges of cyclosporine recommended for patients receiving solid organ transplants are 200-800 ng/ml initially, to be maintained at a level of 200-400 ng/ml (Kahan, 1989). The studied population was divided into 3 groups depending on their blood cyclosporine concentrations and duration since transplantation. Many causes of renal failure including hypertension (45%), insulin dependent diabetes mellitus (18.3%), drug toxicity (7%), nephrolithiasis (5%) and streptococcal related disease (3.3%), have been reported (Lin *at al.*, 1989).

Most of the patients (up to 80%) included in the study were on vigorous antihypertensive therapy, which is very essential in patients with chronic renal failure to slow the progression of renal impairment (Merion, 1984). Groups A and B having sub-therapeutic and therapeutic range of cyclosporine respectively, had better renal function profiles (Table 1). Several reports have suggested that higher cyclosporine levels are associated with better renal functions, which have to be balanced against the toxicity of the drug (Salomon *et al.*, 1991; Roth *et al.*, 1991; Basadonna *et al.*, 1993).

Hyperuricemia is a reported complication of cyclosporine therapy, which is caused by reduced urate clearance. Serum urate levels were raised in all the three groups (Table 1) as has already been reported by Lin *et al.* (1989).

Current study fails to confirm the changes in lipid profile. Previous studies showed low triglyceride and high cholesterol levels in patients on cyclosporine therapy (Hricik *et al.*, 1991). We noticed a decrease in both of these parameters this can be explained on the basis of differences in dietary patterns.

The skin accumulates cyclosporine avidly, accounting for cutaneous manifestations (Limu and Hastsman, 1987). All the patients showed skin changes including coarsening, acne, and hyperkeratosis which decreased with reduced drug concentration in blood. The cutaneous changes persisted for a minimum of six months after transplantation. Hirsutism was another side effect, which does not endanger life but is associated with significant non-compliance (Reznik *et al.*, 1987).

The dose dependant gingival hypertrophy was observed in all the RTRs, which was commonest in group A and least common in group C. It appears within the first six months of commencement of therapy (Seymour *et al.*, 1987) and is characterized by increased thickness of oral epithelium, increased collagen and matrix deposition (Wondimu *et al.*, 1995). In the present study, severe toxicity induced by cyclosporine therapy was not noticed as has also been reported previously ((Hricik *et al.*, 1991). This may partly be due to the use of new micro emulsion preparation that facilitates dose adjustment and absorption.

We conclude that majority of renal transplant recipients tolerate long-term cyclosporine therapy without evidence of progressive toxic nephropathy and strongly substantiate the views of Burk *et al.* (1994) and Calne (1987) that it can safely be continued for 5 years in such patients to achieve desired results.

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