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BRIEF REPORT

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Need for reduction of cyclosporin dosage in renal transplant patients with hypertriglyceridemia but not hypercholesterolemia

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Abstract Currently there is a paucity of data regarding the influence of high serum triglyceride levels on cyclosporin A (CyA) levels and dosing. We therefore undertook a retrospective study to determine the relationship of serum lipid levels to CyA levels and CyA dosages. Renal transplant patients at a 0.5-to-3-year post-transplant stage, with a stable CyA dosage, who were not on medications that affect CyA metabolism or renal function, were entered into the study. The CyA dosage was adjusted by clinicians to maintain whole blood. 12-h CyA trough levels between 200 and 250 ng/ml (monoclonal TDX method, which measures the parent compound). Forty-four patients qualified for the study. The data clearly indicated that high cholesterol levels (> 300 mg/dl and with normal triglyceride levels) did not influence the CyA levels or the dosages. Conversely, high triglyceride levels (> 500 mg/dl) significantly reduced the amount of CyA required. A decreased clearance of CyA in the presence of hypertriglyceridemia led to high CyA levels in some patients. Reducing the CyA dosage to achieve levels between 200 and 250 ng/ml improved renal allograft function and decreased other side effects attributed to CyA toxicity. These studies indicate that high triglyceride levels, but not high cholesterol levels, increase CyA levels, which can lead to CyA toxicity.

Key words CyA, hypertriglyceridemia, kidney transplantation · Hypertriglyceridemia, CyA, kidney transplantation · Hypercholesterolemia, CyA, kidney transplantation · Immunosuppression, CyA, kidney transplantation · Kidney transplantation, hypertriglyceridemia, CyA

Introduction

One of the major problems with the administration of cyclosporin A (CyA) has been the lack of standardized dosing. Due to the drug's complex and variable pharmacokinetics, it has been necessary to chronically measure the drug level in the blood of individual patients to assure a therapeutic dosage for each patient. This issue is also complicated; as Kasiske et al. [4] have reported, CyA itself has also been implicated in increasing serum lipid levels. This group also noted a reduction in rejection episodes in hyperlipidemia patients, which suggests that an enhanced drug effect may be attributable to the hyperlipidemic state. In contrast, Ingulli et al. [3] indicate that extremely high cholesterol levels in children with nephrotic syndrome are associated with low CyA levels and that dosages of CyA should be increased. Similarly, Bastani et al. [1] have reported reduced CyA nephrotoxicity in hypercholesterolemic recipients of cadaveric renal grafts. In both these studies, however, serum triglyceride levels were not available [1, 3].

Table 1 Influence of lipid levels on cyclosporin A dosage (± SE). Each data point is a mean of three separate measurements

* $P < 0.001$ when comparing group 4 with any one of the first three groups

	Group 1	Group 2	Group 3	Group 4
Number of patients	10	23	4	7
Cholesterol (mg/dl)	184 ± 2.4	237 ± 2.3	330 ± 3.5	300 ± 12
Triglyceride (mg/dl)	131 ± 8	195 ± 7	130 ± 7	571 ± 35
CyA dosage (mg/kg per day)	5.10 ± 0.28	5.26 ± 0.24	6.60 ± 0.18	2.61 ± 0.09*
CyA level (ng/ml)	220 ± 16	223 ± 10	216 ± 18	271 ± 21
Creatinine (mg/dl)	1.75 ± 0.06	1.77 ± 0.07	2.07 ± 0.19	2.10 ± 0.06
Mean weight (kg)	85.3	80.2	81.2	86.1
Weight (range)	69–101	73–101	76–94	71–103

As we have also encountered patients with grossly elevated lipid levels, we undertook a study to determine the relationship of serum lipid levels with CyA levels and CyA dosing. Our experience has suggested a relationship between elevated triglyceride levels and elevated CyA levels. We present data indicating that reducing CyA dosages to lower levels in these patients does not worsen renal allograft function.

Subjects and methods

We did a retrospective study on renal transplant patients, from 6 months to 3 years post-transplantation, with stable CyA dosages. These patients were not on medications that affect CyA metabolism or renal function. Requirements for entry into the study included a minimum age of 18 years, a minimum of three simultaneous measurements of weight, CyA dosage, 12-h CyA trough levels (monoclonal TDX method, which measures the parent compound), fasting cholesterol and triglyceride levels. Further, all measurements were made at a baseline CyA dosage that was constant for each patient and covered a period of at least 3 months. The CyA dosage was adjusted to achieve whole blood, 12-h trough levels that were predetermined to be optimal to prevent rejection of the allograft and also to avoid toxicity (i.e., 200–250 ng/ml).

Patients were stratified into four groups – group 1 had normal fasting cholesterol (< 200 mg/dl) and normal triglycerides (< 250 mg/dl) levels; group 2 had moderately elevated cholesterol (210–275 mg/dl) and normal serum triglyceride levels; group 3 had severely elevated cholesterol (> 300 mg/dl) and normal triglyceride levels; and group 4 had elevated cholesterol and triglyceride levels. There was no statistical difference between age and hematocrit in these four groups.

We analyzed the results by multivariate analysis and we used serum cholesterol, triglyceride, and creatinine levels as independent variables. We used the CyA dosage as the dependent variable to determine the significance of the independent variables. A nonlinear regression equation model was calculated (log [CyA dosage] = 2.9 - 0.60 log [creatinine] – 0.20 log [triglyceride] + residual error). From this equation and the multivariate analysis, we calculated the regression coefficients for each significant variable and the r^2 value determining the influence of each significant independent variable upon the dependent variable. A "Q" plot of the equation showed reasonable linearity, and the regression coefficients (0.6 for creatinine and 0.2 for triglyceride) had P values less than 0.01. We calculated the r^2 values for creatinine and triglycerides determined from the multivariate analysis as 0.15 and 0.12, respectively. We used Student's t-test for the univariate analysis of the four groups, which we did by multiple comparisons of all possible pairing of the groups. For example, group 4 was compared independently with each of the other groups. The P value was determined for all three measurements of each of the variables involved.

Results

We were able to identify 44 patients who qualified for the study. The data are summarized in Table 1. The patients were divided into four groups based on their fasting cholesterol and triglyceride levels during the study period. All patients had standard serum laboratory measurements and their CyA levels were measured by the monoclonal TDX method, which detects only the parent compound.

The results in Table 1 show that the triglyceride ($P < 0.002$), but not the cholesterol ($P = 0.23$), level significantly influenced CyA dosing. The CyA dosages of group 1 and group 2 were not statistically different, but the differences between groups 2 and 4 were significant. The CyA trough levels were not statistically different among the four groups. The serum creatinine level in group 4 was not significantly different from that in the other groups, despite the fact that CyA dosages in group 4 were significantly lower than those of the other groups. The data comparison for groups 3 and 4 would suggest that the decreased CyA dosage in group 4 (to maintain therapeutic levels) was mostly an effect of increased triglyceride levels and was not due to severe hypercholesterolemia. Indeed, for the 27 hypercholesterolemic patients with normal triglyceride levels (i.e., groups 2 and 3), the dosages were not reduced. In fact, they were increased for some patients to maintain therapeutic CyA trough levels. These observations agree with those of previous studies [1, 3].

Figure 1 shows a graph of the triglyceride and CyA levels of one patient; the levels correlate well. This patient started mevacor around day 200 and began a low-fat diet. The patient discontinued mevacor around day 525, as a result of side effects, after which the triglyceride level increased. Figure 2 exemplifies the data for a 59-year-old obese (100 kg) diabetic patient whose CyA dosage was reduced from 3.5 mg/kg per day to 2.0 mg/kg per day to achieve therapeutic CyA levels, as he had presented with marked tremors, gum swelling and an increased serum creatinine level. Despite the re-

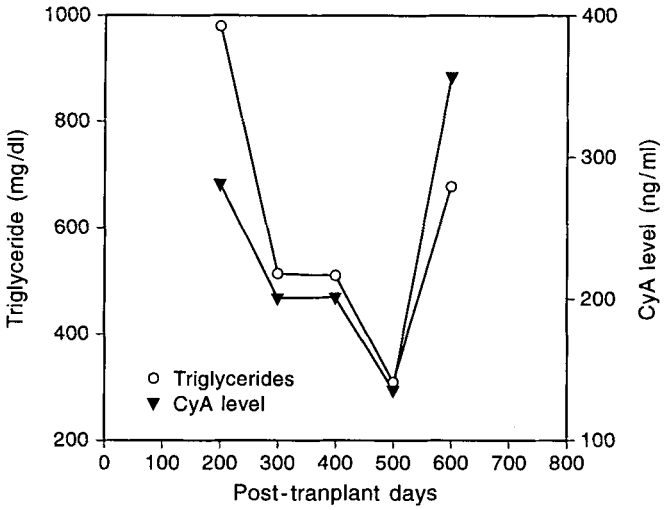

Fig. 1 Correlation of cyclosporin A *(CyA)* with triglyceride levels. This patient began taking mevacor and started a low-fat diet around day 200. Mevacor was discontinued around day 525. The CyA level was measured using the monoclonal TDX method

duced CyA dosage to a dosage generally considered inadequate to induce optimum immunosuppression, the patient's renal function did not deteriorate, but actually improved. We believe this to be a secondary effect of reducing the CyA toxicity in this patient by lowering the dosage. Figure 2 demonstrates that, while the elevated triglyceride levels remained stable, the CyA dosage, and the serum creatinine and CyA levels all decreased together in this patient. Conversely, as the triglyceride level decreased (after mevacor therapy), the CyA dosage had to be increased to maintain adequate levels. However, the serum creatinine level remained stable.

Discussion

This investigation attempts to correlate the influence of lipids on CyA dosing and also on CyA blood levels. These data suggest that cholesterol is not as important in this relationship as triglycerides. Our data suggest that higher CyA levels can be expected with higher triglyceride levels. Our observation of several patients indicates that clinical toxicity in the form of tremors, nervousness, increased creatinine levels, and other symptoms are associated with high CyA levels in hypertriglyceridemic patients. Reducing the CyA dosages for the hypertriglyceridemic patients to maintain therapeutic CyA trough levels decreased toxicity and did not worsen renal allograft function (Table 1, Fig. 2).

It is well known that CyA is distributed primarily in the lipophilic portions of the blood (roughly 50 % in red blood cells, 35 %–40 % in lipoprotein moieties, and the remainder in white blood cells, with a very small fraction outside these compartments). It appears that an increase in the CyA level might correspond to a greater concentration of triglycerides and vice versa, which would in turn dictate the reduction of the dosage to achieve therapeutic levels. Pharmacokinetic studies of uremic patients would agree with the present concept [5]. Lindholm et al. [5], using multivariate analysis, have clearly shown that high triglyceride levels, but not high cholesterol levels, are associated with high CyA levels in serum, and this may be due, in part, to decreased clearance. The data in Table 1 and Fig. 2 provide suggestive evidence to support the concept of a decreased clearance of CyA in the presence of hypertriglyceridemia. A reduced CyA dosage/kg body weight correlated inversely with the level of triglycerides but not with the level of cholesterol. Conversely, changes in the cholesterol level in themselves do not appear to affect CyA levels, except by any indirect association they may

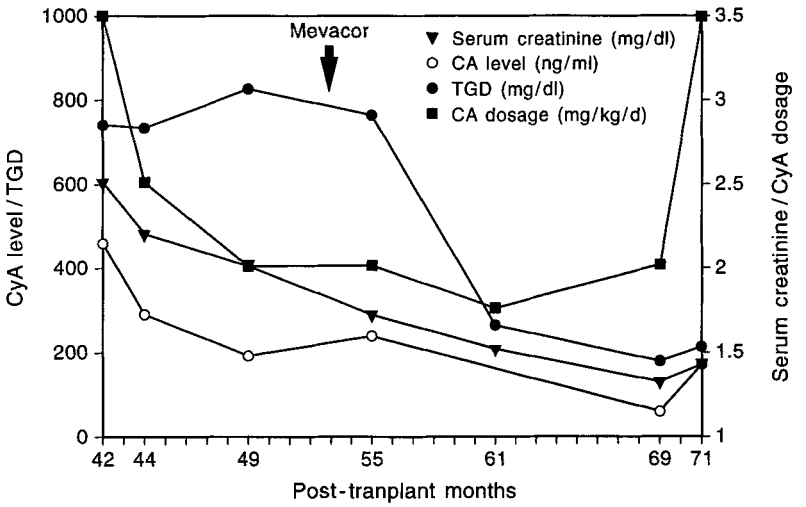

Fig. 2 Influence of triglyceride *(TGD)* levels on CyA dosing and renal function. This patient presented with symptoms of CyA toxicity. CyA levels were high, necessitating a reduction in dosage. Patient was started on mevacor to lower the TGD levels. Note that CyA dosage had to be increased to maintain the desired CyA levels once serum TGD decreased to normal levels

have with an increased triglyceride level. Previous investigations have clearly demonstrated that hypercholesterolemia does not increase CyA toxicity and, in fact, one may have to increase the dosage of CyA to maintain therapeutic levels. Our data support these previous studies [1, 3].

Other investigators have data demonstrating that obese individuals have a decreased CyA clearance and a reduced volume of distribution. This requires a lower CyA dosage than for a patient with normal weight; i.e., when the dosage is calculated in milligrams of CyA per kilogram body weight [2]. The lower dosage of CyA in the group 4 patient (Table 1) cannot be explained on the basis of obesity as there was no difference in weights among the groups.

Nemunaitus et al. [6] reported a correlation between raised serum triglyceride levels and unusually high CyA levels (> 1000 ng/ml) in bone marrow transplant recipients. These high CyA levels were not associated with nephrotoxicity. These authors caution against reducing the CyA dosage for these hyperlipidemic patients, as lower serum CyA levels may increase the risk of graft-versus-host disease. Our data for renal transplant recipients conflict with those of Nemunaitus et al. Reducing the CyA dosage did not worsen renal allograft function but, instead, reduced nephrotoxicity (Table 1, Fig. 2). In our studies, we used an assay system that predominantly measures the parent compound, while in the bone marrow recipients, a radioimmunoassay (which measures the parent compound and its metabolites) was used. However, the type of assay system used cannot entirely explain these conflicting observations, and clearly more studies are required to resolve this complex issue.

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