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Effect of cyclosporin on lung diffusing capacity in renal transplant patients

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Abstract A prospective lung function study pre- and postrenal transplantation was performed on 21 patients in order to evaluate whether cyclosporin decreased the lung diffusing capacity due to lung toxicity. Initial inclusion criteria were absence of respiratory symptoms and normal findings in both chest X-ray and pulmonary function tests. Participants had to be non-smokers. We determined spirometry including lung volumes, arterial blood gases, carbon monoxide diffusing capacity by the single breath method (D_LCO_{SB}), and rate of CO uptake per unit of lung volume (KCO) before and 3, 6, and 12 months after transplantation. Immunosuppression consisted of prednisone and cyclosporin, maintaining total blood levels between 100 and 250 ng/ml. Spirometric and blood gases data remained within reference levels during the follow-up. Hemoglobin (Hb) pretransplant concentrations remained low, returning to their normal levels post-transplantation. Pretransplant D_LCO_{SB} levels were slightly decreased but fell within the therapeutic range after correction for Hb concentration, unlike the mean KCO levels which remained slightly diminished despite their correction. In post-transplant controls, the values obtained for both D_LCO_{SB} and KCO were significantly higher at the different post-transplant intervals ($P < 0.005$) than pretransplantation but only when compared without Hb correction. No significant differences for D_LCO_{SB} were found when corrected values were compared, and an improvement in the KCO appeared to be significant at 12 months posttransplantation. Based on these findings, we feel that when serum levels are within the therapeutic range, cyclosporin fails to alter the respiratory function or the pulmonary diffusing capacity of the lung.

Key words Cyclosporin, lung diffusion · Renal transplantation, lung diffusion · Lung diffusion, cyclosporin

Introduction

Cyclosporin is a strong immunosuppressive drug that is used in organ transplantation to prevent rejection. Some authors have reported its toxicity [1]. Previous studies have suggested that cyclosporin, in patients undergoing a heart transplantation, decreases the lung diffusing capacity due to lung toxicity [5, 12]. However, further research is needed to confirm this.

In order to assess likely pulmonary toxicity of cyclosporin, 21 patients with chronic renal failure who were also renal transplant candidates were prospectively studied. Lung function tests were performed at different intervals pre- and post-transplantation and included a forced spirometry with assessments of lung

Table 1 Pulmonary function tests pre- and postrenal transplantation. Values represent percentage of the predicted value ($\bar{x} \pm SD$). [(*FVC* forced vital capacity, FEV_1 forced expiratory volume, *TLC* total lung capacity, P_{aO_2} oxygen arterial pressure (torr), P_{aCO_2} carbon dioxide arterial pressure (torr)]

	FVC (%)	FEV_1 (%)	TLC (%)	P_{aO_2}	P_{aCO_2}
Pre	109 ± 17	113 ± 20	113 ± 15	93.6 ± 2.8	40.3 ± 3.1
3rd month	106 ± 11	112 ± 15	108 ± 11	92.8 ± 2.7	43.7 ± 2.7
6th month	109 ± 13	115 ± 17	109 ± 12	93.0 ± 2.2	43.8 ± 2.8
12th month	107 ± 10	111 ± 11	109 ± 11	93.7 ± 2.5	43.7 ± 2.4

Table 2 Lung diffusing capacity and carbon monoxide uptake pre- and postrenal transplantation. Values represent percentage of the predicted value ($\bar{x} \pm SD$). Normal immunosuppression level 100–250 ng/ml. (D_LCO_{SB}) lung diffusing capacity, *KCO* rate of CO uptake per unit of lung volume, *cor* value corrected for hemoglobin *(Hb)* concentration)

	D_LCO_{SB} (%)	D_LCO_{SB}cor (%)	KCO (%)	KCOcor (%)	Cyclosporin	Hb
Pre	78 ± 17	100 ± 17	64 ± 15	79 ± 16		8.2 ± 1.6
3rd month	107 ± 19*	110 ± 13 (NS)	87 ± 16*	82 ± 6 (NS)	235 ± 101	12.7 ± 1.0
6th month	102 ± 15*	105 ± 18 (NS)	92 ± 18*	83 ± 9 (NS)	196 ± 62	12.9 ± 1.0
12th month	107 ± 25*	111 ± 23 (NS)	94 ± 22*	97 ± 16**	187 ± 40	13.0 ± 1.4

* $P < 0.005$ and ** $P < 0.05$ compared to pretransplant value

volumes, arterial blood gases, and lung diffusing capacity.

Materials and methods

Patients

Twenty-one patients (16 males and 5 females) with a mean age of 37 years (SD ± 11 years) were undergoing hemodialysis due to terminal renal failure. All patients were candidates for renal transplantation. Initial inclusion criteria were: absence of respiratory symptoms, normal chest X-ray and forced spirometry, and pulmonary volumes and arterial blood gases within reference values [11, 14, 17]. Participants in the study had to be nonsmokers. Patients who did not meet these requirements were excluded. All patients later underwent transplantation.

Determinations

Lung function studies were performed with a Collins DSII Plus device. The determinations made included: forced vital capacity, forced expiratory volume in the first second (FEV1), total lung capacity (TLC), carbon monoxide diffusing capacity by the single breath method (D_LCO_{SB}), and rate of CO uptake per unit of lung volume (KCO) following Cotes' recommendations [7] and considering apnea time according to Ogilvie et al.'s technique [15]. Both D_LCO_{SB} and KCO were corrected according to hemoglobin (Hb) levels [10] because of the chronic anemia these patients usually have before transplantation [9]. Reference values were consistent with those of Roca et al. [18]. Arterial blood gases were determined using a blood gas analyzer ABL-300 (Radiometer).

These determinations were made before transplantation and 3, 6 and 12 months later. Since the date of transplantation could not be known beforehand, the assessments were repeated every 6 months and always the day before dialysis.

Immunosuppression

Immunosuppression after transplantation consisted of prednisone (initial dosage 30 mg/day, later decreasing progressively to 15 mg/day in the 3rd month and to 10 mg/day after the 6th month) and cyclosporin [initial dosage 7 mg/kg per day, adjusted to total blood levels within the 100–250 ng/ml range and obtained by specific monoclonal RIA (Cyclo-trac, Incstar)]. During the first 2 months, azathioprine was administered at an initial dosage of 1.5 mg per day, decreasing progressively until total suppression at day 60 post-transplantation [16]. No other xenobiotics with known potentially toxic effects on the lungs were administered.

Statistics

Statistical differences were tested by a one-way analysis of variance and Bonferroni's *t*-test.

Results

Table 1 shows the results of lung function tests, arterial blood gases, Hb, and serum cyclosporin levels pre- and post-transplantation. Spirometric and blood gases data remained within reference levels during the follow-up; no post-transplant variations were found. Hemoglobin pretransplant concentrations remained low, returning to their normal levels after transplantation. Body weight changes of 1.5 kg were observed before and after transplantation. Pretransplant D_LCO_{SB} levels (Table 2) were slightly decreased but fell within the normal therapeutic range after correction for Hb (D_LCO_{SB}cor %); this was not the case with the mean KCO levels, which remained slightly reduced despite their correction (KCO cor %). In post-transplant controls, the values obtained for both D_LCO_{SB} and KCO were signif-

icantly higher at the different post-transplant intervals ($P < 0.005$) than pretransplantation but only when compared without Hb correction. No significant differences were found when the corrected values were compared, except for the KCOcor % at 12 months post-transplantation ($P < 0.05$).

Mean cyclosporin values in months 3, 6, and 12 posttransplantation are shown in Table 2. All were within the normal range (100–250 ng/ml).

The renal graft was functional during the time studied with no complications or intercurrent processes.

Discussion

Transplantation requires strong immunosuppressive therapy in order to prevent organ rejection. Although some immunosuppressive drugs have been shown to have toxic effects on the lung, the effect of cyclosporin has scarcely been studied and some data are controversial [1, 3, 5, 19, 21].

We have studied patients with previously normal lung function and assessed the posttransplant respiratory function alteration which, in the absence of other pathology, could only be due to cyclosporin.

In patients with chronic renal failure, a decrease in pulmonary volume has been reported [4], as well as a reduction in D_LCO_{SB}. Either could result from the presence of subclinical lung edema or interstitial fibrosis secondary to chronic lung edema [5], persisting even after transplantation [4].

In patients undergoing heart transplantation [5], a decrease in D_LCO_{SB}cor and KCOcor is thought to be due to cyclosporin toxicity affecting the lung. In bone marrow transplant recipients, some authors have reported interstitial pneumonitis attributable to cyclosporin [8] or to the association of cyclosporin and radiotherapy [13], while others have found no significant changes [3, 6, 21]. In the present study, we did not find any changes either. The different results from various studies may be due to several factors. First, there may be baseline lung function alterations before transplantation, especially in heart transplants [5]. Thus, ruling out other causes does not necessarily imply that these diffusing alterations are due to cyclosporin. To avoid this problem, we studied patients with normal lung function. Second, a certain degree of subclinical lung edema may occur after a heart transplantation. It may be very difficult to detect and may lead to diminished lung diffusing capacity. Third, the dose of the immunosuppressive agent used to prevent rejection in other studies may in some cases, have been much higher than that given in ours [2, 13]. Blood levels in the different studies are difficult to compare because some authors evaluated total blood levels [5, 20] while others assessed serum values [2, 6]. Furthermore, on some occasions, other drugs or therapeutic techniques, such as radiotherapy, were used, leading to lung toxicity as in bone marrow transplantation [8, 13]. Finally, several of these factors may have come into play in the same patients.

Patients with terminal chronic renal failure usually have a chronic anemia, mainly related to their erythropoietin deficit [10]. Thus, the pretransplant D_LCO_{SB} and KCO determinations are below normal levels and have to be corrected for the patient's Hb concentration [9]. Following successful renal transplantation, Hb concentration usually returns to normal spontaneously. In our study, D_LCO_{SB} and KCO levels before and after transplantation were significantly different, with KCO posttransplantation higher when it was not corrected for Hb. Even when it was corrected, the values obtained after renal transplantation were within the normal range for D_LCO_{SB} and slightly decreased for KCO. Surprisingly, in both cases, there appears to be a trend, with both increasing as a function of time following transplantation.

The frequent monitoring of cyclosporin blood levels is necessary to maintain the therapeutic dose, which must be adjusted according to blood and serum levels due to the drug's variable absorption and metabolism. Previous studies have already reported that a daily dosage of 7–8 mg/kg per day is enough to prevent kidney rejection, resulting in a lower rate of side effects on the kidney itself [6, 20]. Our patients maintained serum cyclosporin levels in months 3, 6, and 12 posttransplant that were within the therapeutic range. In the controls, a great variation was observed during the 3rd month that showed slightly higher levels; however, this did not appear to influence D_LCO_{SB} or KCO.

Based on these findings, we feel that cyclosporin, given at the usual dosage and with serum levels within the therapeutic range, fails to alter the respiratory function or the pulmonary diffusing capacity of the lung.

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