PART XX

CYCLOSPORIN A IN TRANSPLANTATION

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NEPHROTOXICITY AND PHARMACOKINETICS OF CYCLOSPORIN A IN RENAL TRANSPLANT RECIPIENTS

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Summary

The endogenous creatinine clearance has been studied in 57 renal transplant patients entered into a prospective randomized trial to compare Cyclosporin A (CyA) and azathioprine (Aza), both in combination with low dose prednisone. Initially 37 received Aza and 35 CyA. In the CyA group, 16 were randomly selected for conversion to Aza at three months after transplantation.

The pharmacokinetics of CyA were evaluated in 14 patients on days three and 15 after transplantation. The half-life of CyA showed considerable inter-individual variation; moreover in most cases drug accumulation was observed during treatment and this was associated with a significant prolongation of the half-life. At three months the mean endogenous creatinine clearance was significantly lower in the CyA treated group than in the Aza group whereas at six months the mean creatinine clearances for both the converted and non-converted CyA-treated patients did not differ significantly from that found for the Aza-treated group. Furthermore, the increment in creatinine clearance observed two weeks after conversion from CyA to Aza showed a linear relationship ($r = 0.9061$) with the CyA trough levels before discontinuation of the drug. This indicates that CyA treatment induces a dose-dependent, reversible nephrotoxic effect.

Introduction

The effectiveness of Cyclosporin A (CyA) as an immunosuppressive drug has been proven in both clinical and experimental transplantation [1,2]. The effect of the drug on the in vitro lymphocyte response [3] and the in vivo suppression of allo-antibody formation [2] is dose-dependent. No consensus about the dose-dependency of the nephrotoxic side effect of the drug, especially during chronic treatment, has been reached as yet [4–6]. If it is assumed that CyA has a relatively narrow therapeutic index, extensive knowledge of its pharmacokinetics vary widely among individuals, the results of one study of 15 patients suggesting that in two cases the pharmacokinetics even changed during chronic treatment [7].

The aim of this study was to examine CyA pharmacokinetics over a three-month treatment period and to determine whether trough levels provide an indication of the nephrotoxic effect of CyA.

Patients and methods

Seventy-two patients who received a cadaveric renal allograft were randomly assigned to CyA (n=35) or Aza (n=37) therapy. All of the 57 patients (29 on CyA and 28 on Aza) whose grafts had functioned for at least four months were included in the study. Three months after transplantation, 16 CyA-treated patients were randomly selected for conversion to Aza. CyA was given twice daily in a dose of 16mg/kg/day tapering to 10mg/kg/day over the course of three months; for the 13 patients who remained on CyA therapy the dose was tapered to 5mg/kg/day between three and six months after transplantation. In addition to CyA or Aza all patients received low doses of prednisone. CyA levels were determined twice a week in whole blood by radioimmunoassay (RIA) using the Kit supplied by Sandoz.

CyA pharmacokinetics were studied in 14 of the 35 CyA-treated patients as described previously [8]. Twelve-hour blood level studies were performed three and 15 days after transplantation to calculate the CyA elimination half-life ($t_{½}$), area under the curve (AUC) and total blood clearance ($Cl = \frac{Dose}{AUC}$). Paired observations on days three and 15 were statistically analysed with the paired Student's 't' test. In nine cases the terminal half-life after conversion to Aza was determined. For the total of 16 patients who were converted to Aza, endogenous creatinine clearances were calculated on the day before discontinuation of the CyA and two weeks after conversion. The increment in renal function was expressed as per cent increment in endogenous creatinine clearance. Twenty-three of the 35 CyA-treated and 17 of the 35 Aza-treated patients had a functioning graft and were followed for at least six months; 13 of these 23 CyA-treated patients were converted to Aza. Creatinine clearances of these patients calculated three and six months after transplantation were compared and statistically analysed with the unpaired Student's 't' test.

Results

The mean values of the pharmacokinetic data, as calculated from 12-hour blood level studies on days three and 15, are listed in Table I for 14 patients on CyA therapy. Twelve-hour studies could not be performed on day three in three cases and on day 15 in two cases. The 12-hour curve obtained for two patients on day three showed more than one absorption peak which hampered calculation of the elimination half-life. The large standard deviations of the calculated pharmacokinetic parameters indicate large inter-individual variations. Furthermore, the half-life of CyA was significantly longer with much higher CyA levels on day 15 than on day three. This is in accordance with a significantly reduced total blood clearance (Cl) on day 15. The terminal half-lives calculated for nine patients after discontinuation of CyA varied from 24–93 hours with a mean of 40 hours.

TABLE I. Pharmacokinetic parameters (mean±SD) three and 15 days after transplantation in 14 patients treated with CyA

	n	day 3	n	day 15	p
T½ (hr)	9	6.3±3.2	12	9.0±4.4	<0.05
Cl (1/hr)	11	46±17	12	28±10	<0.01
CyA levels (μg/L)	14	653±358	14	1166±511	<0.01

Evaluation of the 16 patients converted to Aza shows that a linear relationship exists between the CyA trough level before conversion and the per cent increment in creatinine clearance two weeks after conversion (Figure 1). All patients had stable renal function before conversion and did not receive anti-rejection therapy within two weeks after conversion. In Figure 2 the mean creatinine clearances are shown for the CyA and Aza-treated patients with a functioning graft at six months. At three months, the mean creatinine clearance for the CyA-treated group was significantly lower than that found for the Aza-treated group (38±2.1 and 53±4.1ml/min (mean±SEM), respectively; $p<0.001$); at six months the creatinine clearances found for patients converted to Aza and those still on CyA therapy were not significantly different from that of the Aza-treated patients. The mean increment in renal function for the group of patients who continued on CyA therapy was, however, less than that found for those who were converted to Aza at three months (40±2.9 to 48±2.5ml/min

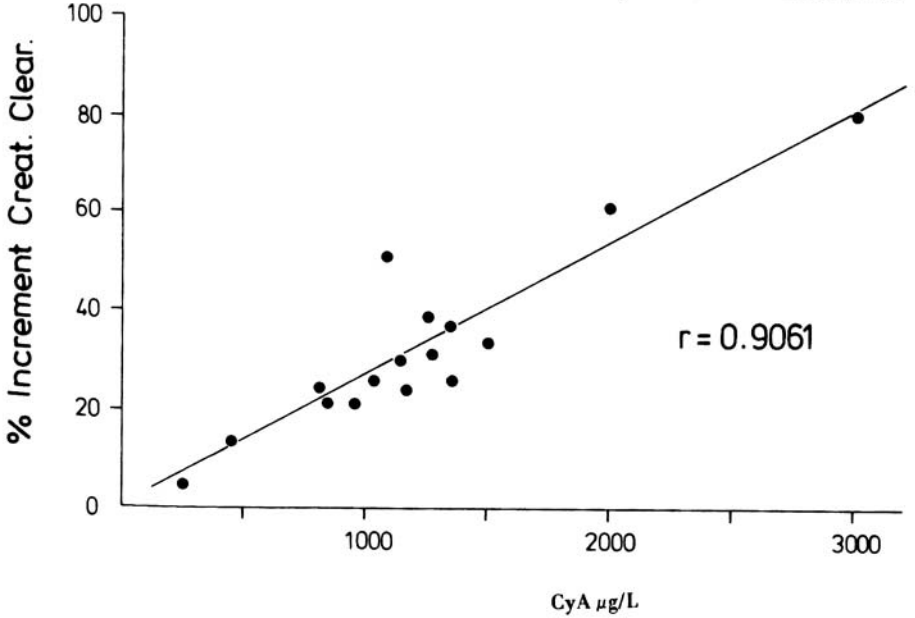

Figure 1. Relationship between the CyA trough level before conversion and the per cent increment in creatinine clearance two weeks after conversion in 16 transplant recipients

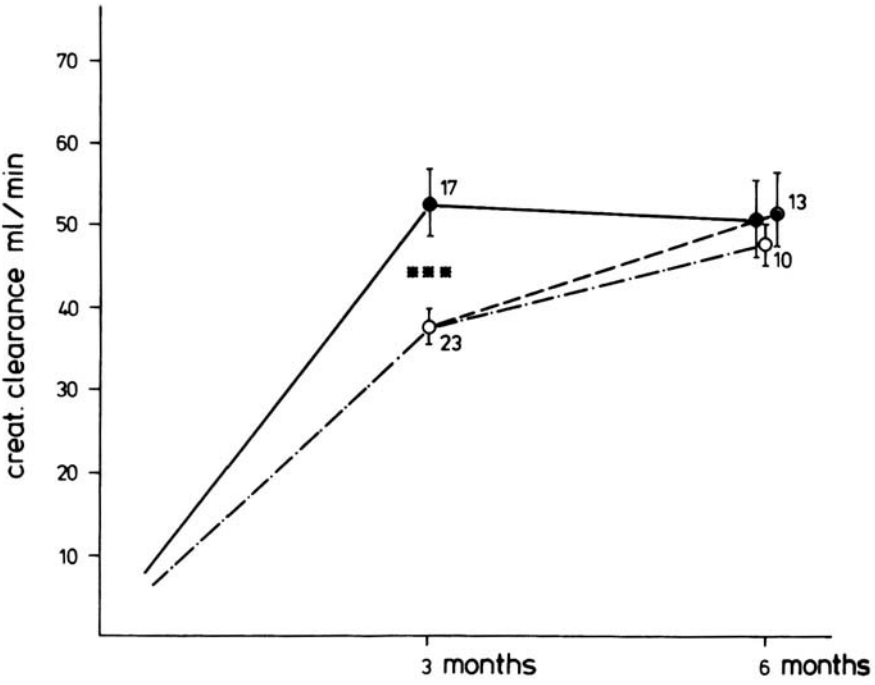

Figure 2. Creatinine clearances (mean±SEM) in patients treated with Aza (n=17, ●), CyA (n=23, 0) and CyA with conversion to Aza three months after transplantation (n=13, ◍). ***p<0.001

and 35±2.5 to 52±4.4ml/min, respectively). The increment in renal function in the first group was probably due to a decrease in CyA blood levels (1033±98μg/L and 601μg/L, respectively, three and six months after transplantation; $p<0.001$).

Discussion

The results of this study confirm the wide inter-individual variation in CyA pharmacokinetics observed by others [7]. The apparent decrease in blood clearance and the prolongation of the half-life suggest a decreased rate of drug elimination during the course of treatment. Since CyA is metabolized extensively in the liver and excreted into bile [9], the decreased elimination could be due to a saturable elimination process. Another explanation could be that one or more metabolites are formed that inhibit the hepatic enzymes involved in the elimination of the drug. It is also conceivable that there is in fact not an accumulation of unchanged CyA but instead an overestimation of the CyA concentration since the RIA method also measures some metabolites [10]. If the high CyA blood levels obtained with the RIA method are indeed partly attributable to metabolites then these metabolites apparently exhibit nephrotoxic effects since we observed a linear relationship between the CyA trough level and the increase in renal function after conversion. A dose-response relationship for the nephrotoxic effect of CyA was further suggested by the observation that renal function improved in patients who remained on CyA therapy: In this group the dosage

was reduced, resulting in significantly lower CyA blood levels six months after transplantation. Reversibility of the nephrotoxic side effect of CyA after three months of treatment has also been reported by others [5] but these authors found no correlation between improvement in renal function, expressed as serum creatinine, and CyA trough levels as measured in serum rather than whole blood [6]. In heart transplant patients who received CyA for 12 months, the nephrotoxic effect was irreversible and did not correlate with CyA trough levels in plasma [4].

In conclusion, our study shows that measuring CyA levels in whole blood by RIA is of practical importance for dose adjustments and for assessment of the nephrotoxic effect of the drug.

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