1275

Pharmacokinetics of Cyclosporine and Nephrotoxicity in Orthotopic Liver Transplant Patients Rescued With FK 506

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CYCLOSPORINE (CyA) has been used extensively in organ transplantation, but its use is limited by its nephrotoxicity.[1] FK 506 is a novel immunosuppressive drug that synergizes with CyA in in vitro and in animal studies.[2,3] Combination therapy of FK 506 and CyA appears to be effective in clinical trials. However, preliminary animal studies have shown FK 506 to also be nephrotoxic.[4] In initial clinical trials, combined use of CyA and FK 506 resulted in severe renal dysfunction.[5] The mechanistic basis for this observation is not completely understood. The aim of the present study is: (1) to evaluate the kinetics of CyA before and during FK 506 therapy in orthotopic liver transplant (OLTx) patients, in order to determine the presence of any pharmacokinetic drug interaction; (2) to determine the changes in serum creatinine during the study period; and (3) to monitor terminal disposition half-life of CyA after the drug is discontinued in patients receiving FK 506 therapy.

STUDY DESIGN

The first seven consecutive OLTs who were on CyA for 23 days to 7 years (median 3 years), and were switched to FK 506, were selected for this study. There were four males and three females, ranging in age from 19 to 45 years, and in body weight from 49 to 100 kg. Intravenous (IV) CyA kinetic studies were performed one day prior to FK 506 therapy (day 0); after 2 days of IV FK 506 therapy (0.15 mg/kg per day) (n = 7), and after 7 days of FK 506 treatment (0.15 mg/kg per day IV for 3 days and 0.3 mg/kg per day PO for 4 days) (n = 4). Three patients discontinued CyA before 7 days of FK 506 therapy. On the study day, CyA was administered as a short IV infusion over 1.5 to 3 hours, and multiple blood samples were collected over 24 hours. Whole blood CyA concentrations were measured by HPLC, and various pharmacokinetic parameters were calculated according to standard methods.[6]

In another 22 patients who were converted from CyA to FK 506, CyA blood concentrations were measured daily for 7 to 10 days (whole blood TDx) after discontinuation of CyA therapy. Terminal disposition rate constant (λ) was calculated from linear regression analysis of log blood concentration versus time data, and the half-life was calculated as $0.693/\lambda$.

Analysis of variance was used to determine the significance of any differences in various pharmacokinetic parameters of CyA measured at different time periods using a P value of .05.

RESULTS

The blood CyA concentration versus time profile in one patient on days 0, 2, and 7 is shown in Fig 1. Various pharmacokinetic parameters of CyA, during the three different study periods (days 0, 2, and 7 of FK 506 treatment), are shown in Table 1 for each patient. The mean (±SD) half-life of CyA was 9.9 (±3.4) hours before FK 506 treatment, 10.4 (±3.1) after 2 days of FK 506 treatment, and 9.0 (±3.1) after 7 days of FK 506 treatment. Similarly, the clearance of CyA was 5.6 (±3.3) mL/min per kilogram on day 0, 6.5 (±3.3) on day 2, and 6.8 (±7.5) on day 7 (Table 2). None of the pharmacokinetic parameters were significantly different between the three study periods. FK 506 trough plasma concentrations on days 2 and 7 are shown in Tables 2 and 3. FK 506 concentrations were 2.9 (±2.2) ng/mL on day 2, and 2.0 (±1.4) ng/mL on day 7.

The mean serum creatinine prior to FK 506 treatment was 1.6 (±0.7), which increased to a value of 3.0 (±1.3) after 7 days of FK 506 treatment in the presence of CyA. The renal function improved once CyA was discontinued,

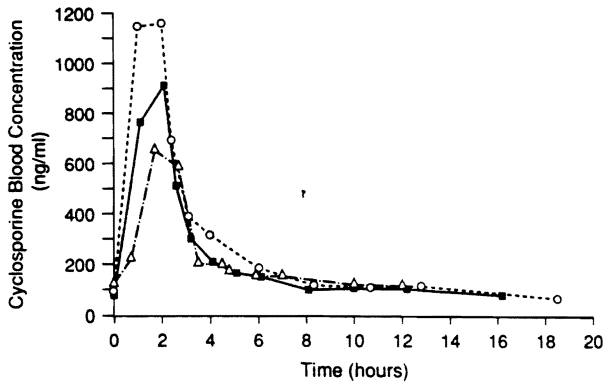

Fig 1. Whole blood CyA concentration versus time curve in one patient on day 0 (■) (CyA dose of 80 mg); day 2 (△) CyA dose of 64 mg; and day 7 (○) (CyA dose of 80 mg) after FK 506 treatment.

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Table 1. Pharamcokinetic Parameters of CyA

Patients	Half Life (hours)			Clearance (mL/min per kilogram)			Volume of Distribution (L/kg)		
	Day 0	Day 2	Day 7	Day 0	Day 2	Day 7	Day 0	Day 2	Day 7
R.F.	9.3	12.8	—	—	—	—	—	—	—
L.W.	14.6	13.0	—	6.1	7.8	—	5.4	5.0	—
D.J.	10.4	10.8	13.6	8.5	8.0	17.8	—	3.3	14.2
M.B.	8.5	11.2	7.0	4.1	2.9	1.5	2.1	1.7	0.7
W.D.	4.3	5.6	17.0	0.9	4.8	4.8	0.4	1.4	3.1
D.W.	13.3	13.0	9.7	3.8	4.0	3.1	2.6	3.1	1.3
H.W.	9.6	6.7	—	9.9	11.7	—	4.9	3.8	—

with a mean serum creatinine of 2.1 (± 0.9) (Table 2). These differences are statistically significant ($P = .045$).

In an additional 22 patients, the daily CyA concentrations were measured by TDx after discontinuation of the last dose of CyA. In this group of patients, the half-life of CyA was more prolonged than what had been reported for CyA in transplant patients. The half-life was 31.5 to 67.2 hours when serum bilirubin was 0.4 to 1.1 mg/dL, and 38.4 to 206.7 hours when the serum bilirubin was 2.3 to 50.9 mg/dL.

DISCUSSION

Significant nephrotoxicity has been reported in patients receiving FK 506 and CyA.[5] In the present study, we evaluated the presence of any pharmacokinetic interaction between FK 506 and CyA. Pharmacokinetics of CyA was studied over a dosing interval of 24 hours. The half-life of CyA in the present kinetic study, before and during FK 506 treatment, is unchanged. These values are similar to the half-lives reported in the literature based on 24-hour kinetic studies.[7,8] It is clear from this study that FK 506 does not alter any of the pharmacokinetic parameters of CyA, indicating that there is no pharmacokinetic interaction between these two drugs.

After termination of CyA treatment, the half-life was approximately 3 days in patients with serum bilirubin of less than 1.2 mg/dL, and was nearly 9 days in patients with high serum bilirubin (2 to 50 mg/dL). Anecdotal reports indicate persistence of CyA in patients long after discontinuation of CyA therapy.[9] It is possible that complete withdrawal of CyA therapy after chronic CyA dosing results in slow release of the drug from peripheral tissue compartments to the vascular compartment. In the presence of hepatic dysfunction, the clearance of CyA is likely to be further decreased, and hence, the half-life is prolonged. Therefore, the observed long half-life of CyA in patients switched from CyA to FK 506 may not be mediated by FK 506. Indirect evidence for this is available from in vitro studies, where FK 506 inhibits the cytochrome P-450 system responsible for CyA metabolism only at higher concentrations.[10] At concentrations of FK 506 corresponding to that observed clinically (Tables 2 and 3), FK 506 does not appear to be an inhibitor of CyA metabolism. However, it was not possible to determine the effect of FK 506 on the elimination of CyA metabolites in this study. FK 506 may inhibit further metabolism or biliary excretion of CyA metabolites, and thereby prolong the half-life estimated based on TDx concentrations. Further studies in animals are necessary to completely characterize this interaction. Independent of the mechanism of the FK 506 and CyA interaction, it is our practice at the present time not to use this combination clinically, because of the significant impairment in renal function.

In conclusion, there appears to be no pharmacokinetic drug interaction between CyA and FK 506, when the parent CyA is measured by HPLC. Since the terminal half-life of CyA could be as long as 9 days in some patients with poor liver function, combined use of CyA and FK 506 will result in renal impairment due to additive or synergistic nephrotoxicity. The observed synergistic advantages of CyA and FK 506 in vitro and in animal models cannot be extended to clinical practice because of the nephrotoxic effects of these drugs.

Table 2. Mean CyA Pharmacokinetic Results and Kidney Function

Day	Clearance (mL/min per kilogram [SD])	Half Life (hours [SD])	Volume of Distribution (1/kg [SD])	FK 506 Plasma Concentration (ng/mL [SD])	Serum Creatinine (mg/dL [SD])
0	5.6 ± 3.3	9.9 ± 3.4	3.1 ± 2.1	0	1.6 ± 0.7
2	6.5 ± 3.3	10.4 ± 3.1	3.1 ± 1.3	2.9 ± 2.2	—
7	6.8 ± 7.5	9.3 ± 3.1	4.8 ± 6.3	2.0 ± 1.4	3.0 ± 1.3
21–30	—	—	—	—	2.1 ± 0.9
P value	.86	.89	.70	.69	.045
Significance	NS	NS	NS	NS	S

Table 3. FK 506 Plasma Concentrations (ng/mL)

Patient	Day 0	Day 2†	Day 7‡
R.F.*	—	0.4	0.4*
L.W.*	—	0.3	0.5
D.S.	—	5.0	3.0
M.B.	—	5.2	1.9
W.D.	—	1.6	3.9
D.W.	—	5.1	3.1
H.W.	—	3.0	1.4
Mean (SD)		2.9 (2.2)	2.0 (1.4)

*Plasma separated at room temperature.
†Twenty-four–hour through after 0.15 mg/kg IV FK 506.
‡Twelve-hour through after 0.15 mg/kg PO FK 506.

REFERENCES

1. Iwatsuki S, Esquivel C, Klintmalm G, et al: Transplant Proc 17(suppl 1):791, 1985

2. Zeevi A, Duquesnoy R, Eiras G, et al: Transplant Proc 19:40, 1987

3. Todo S, Demetrius A, Ueda Y, et al: Transplant Proc 19:57, 1987

4. Nalesnik M, Lai HS, Murase N, et al: Transplant Proc 22:87, 1990

5. McCauley J, Fung J, Jain A, et al: Transplant Proc 22:17, 1990

6. Gibaldi M, Perrier D: Pharmacokinetics. New York, Marcel Dekker, 1985

7. Ptachcinski RJ, Venkataramanan R, Burckart G: Clin Pharmacokinetics 11:107, 1986

8. Venkataramanan R, Habucky K, Ptachinski RJ, et al: Clin Pharmacokin 16:134, 1989

9. Jain A, Elias E, Gunson B, et al: Transplant Proc 20(suppl 2):516, 1988

10. Omar G, Shah A, Thompson AW, et al: Transplant Proc 23:934, 1991