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Brief Communication

Diurnal Variation in Cyclosporine Kinetics

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Cyclosporine (CyA) is now considered a primary immunosuppressant used to prevent organ rejection in liver, kidney, and heart transplant patients (1–3). It has been recommended that the blood level of CyA be monitored in these patients to minimize the possibility of rejection due to low CyA blood concentrations or potential toxicity due to high CyA concentrations (4,5). This is based on the observation of marked variations in the trough CyA blood levels between and within patients. Such variations in blood levels are the result of pronounced differences in the pharmacokinetic parameters, such as clearance and bioavailability (6–8). We report on one factor, diurnal variation, that may contribute to the observed variability in the pharmacokinetics of CyA in transplant patients.

CyA pharmacokinetics were studied during two or three different dosing intervals (8 h) in two patients who underwent orthotopic liver transplantation at the University of Pittsburgh. The same maintenance dose of CyA (patient 1, 140 mg; patient 2, 150 mg) was administered over 1 h as an intravenous infusion in the morning and at night. Hourly blood samples were drawn and analyzed for cyclosporine following modifications of a high pressure liquid chromatographic assay (9). Kinetic parameters were calculated according to standard techniques (10).

The biochemical profiles on different study periods in a given patient were similar.

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Table 1 summarizes the pharmacokinetic parameters obtained. The 8-h trough levels (C_{min}) obtained following drug administration at night were lower than the trough levels obtained following drug administration during the day. The apparent blood CyA clearance was higher following drug administration at night as compared with the clearance obtained following daytime drug administration in both subjects. Patient 2 was studied on a third occasion (day 5 postoperatively), during the day, and was found to clear the drug in a pattern similar to that observed previously. Other pharmacokinetic parameters, such as the elimination rate constant and volume of distribution, could not be calculated because of the short dosing interval employed in treating these patients.

In both the subjects studied, the clearance of CyA was higher during the night as compared with the clearance during the day. This phenomenon cannot be attributed to any variation in the analytical methodology, as our analytical procedure is highly reproducible. The coefficient of variation at 600 ng/ml is 3.4% (n = 6). The intrapatient variability in CyA kinetics cannot account for the observed differences in CyA kinetics, as demonstrated by the data obtained from Patient 2. During the study period, the patients did not receive any drugs known to induce or inhibit drug-metabolizing enzymes. The presence of circadian rhythms in various biological systems has long been recognized. Recently, diurnal variations in the pharmacokinetics of theophylline (11), valproic acid (12), prednisolone (13), and ethanol (14) have been reported. The actual mechanism(s) responsible for the observed diurnal variation in CyA kinetics is

TABLE 1. *Pharmacokinetics of cyclosporine in liver transplant patients*

Subject	Day post-transplant	Time of study	Dose (mg)	C_{min} (ng/ml)	CyA clearance (ml/min)	CyA clearance (ml/min/kg)
1	21	2 p.m.–10 p.m.	140	519	385	5.13
	18	10 p.m.–6 a.m.	140	301	536	7.14
2	3	10 a.m.–6 p.m.	150	391	337	4.32
	3	8 p.m.–4 a.m.	150	328	479	6.20
	5	9 a.m.–5 p.m.	150	453	369	4.82

CyA, cyclosporine.

not clear at this point. It may be related either to (a) circadian variations in the activities of one or more hepatic drug-metabolizing enzymes, as CyA is metabolized to a significant extent by the liver in humans (15) or to (b) possible diurnal changes in plasma lipoprotein profiles, as CyA is primarily transported by lipoproteins. Regardless of the mechanism involved in the diurnal variation observed in the kinetics of CyA, it is essential to standardize the time of blood sampling for accurate CyA blood level monitoring.

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