Effect of Chronic Therapy on Absorption and Disposition of Cyclosporine

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CYCLOSPORINE (CyA) has contributed significantly to the improved success of heart, liver, and kidney transplantation. Several factors such as disease state, coadministered drugs, and time elapsed since the transplant surgery influence the dosing regimen of CyA.[1] During the immediate postoperative time period therapeutic blood CyA concentrations can be achieved with doses of 15 to 20 mg/kg/d, whereas several months after transplantation doses of 3 to 5 mg/kg/d result in similar blood CyA concentrations.[2,3] The overall goal of our study was to determine the factors responsible for the decreased dosage requirement of CyA with time. The specific objective of this experiment was to determine the effect of chronic pretreatment with olive oil or CyA on the pharmacokinetics of CyA after single-dose oral administration.

MATERIALS AND METHODS

Four male beagle dogs weighing between 12 and 15 kg were used in this study. The animals received oral CyA (300 mg) on three separate occasions after an overnight fast. Initially, the dogs received CyA without any pretreatment (control period). On the next occasion CyA was administered to the same group of dogs after chronic (ten days) oral treatment with 3 mL olive oil per day. On the last occasion, CyA was administered a day after chronic (ten days) treatment with 300 mg oral CyA per day. During each study day, multiple blood samples were drawn just before and at various times after CyA administration and analyzed for unchanged CyA by a high-pressure liquid chromatographic method.[4]

The terminal disposition rate constant (λ_z) was calculated by linear regression analysis of the log terminal blood concentration–v-time data. The area under the blood concentration–v-time curve (AUC) was calculated by the trapezoidal method. The principal of reversed superposition was used to calculate the actual AUC after CyA administration in the CyA pretreatment phase.[5] The analysis of variance was used to determine the significance of any differences in the parameters calculated. A P value of $<.05$ was consider to be significant.

RESULTS

The mean (±SD) peak blood CyA concentration (c_{max}) in the control period was 1,416 (±364) ng/mL (Table 1). The mean c_{max} values of CyA observed after olive oil treatment and after CyA treatment were not significantly different from the control values. There were also no significant differences in the time to achieve peak blood concentrations (t_{max}) during the three study periods (Table 2).

The mean (±SD) λ_z of CyA was 0.0839/h (±0.0002), which corresponded to a harmonic mean half-life of 8.3 hours during the first phase. The half-life was significantly ($P <$ .05) prolonged to 14.8 and 22 hours after olive oil or CyA treatment, respectively (Table 3).

The mean (±SD) AUC was 10,166 (±2,857) ng/mL/h during the control period. The mean AUC after olive oil pretreatment (17,498 ng/ml/h) and after CyA pretreatment (13,048 ng/ml/h) was significantly

Table 1. Peak CyA Blood Concentrations After Various Pretreatments

	Blood Concentration (ng/mL)		
Dog No.	Control	Olive Oil Pretreatment	Cyclosporine Pretreatment
1	1,244	1,072	1,629
2	1,763	1,337	1,599
3	1,668	1,204	1,927
4	987	1,388	1,480
Mean	1,416	1,250	1,659
±SD	±364	±141	±190

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Table 2. Time to Achieve Peak CyA Blood Concentrations

	Time (h)		
Dog No.	Control	Olive Oil Treatment	Cyclosporine Treatment
1	1.5	1.4	1.4
2	1.6	1.1	1.5
3	1.0	2.3	1.5
4	1.1	1.6	1.5
Mean ±SD	1.3 ±0.3	1.6 ±0.5	1.5 ±0.0

Table 3. CyA Half-Life After Various Pretreatments

	Half-life (h)		
Dog No.	Control	Olive Oil Pretreatment	Cyclosporine Pretreatment
1	8.2	14.9	20.5
2	8.4	12.8	21.5
3	8.3	16.9	24.8
4	8.1	15.2	21.8
Harmonic mean	8.3	14.8	22.0

($P < .05$) higher than the AUC after the control period.

DISCUSSION

In the present study we have documented that chronic administration of olive oil or chronic treatment with CyA results in higher blood CyA concentrations in dogs receiving a single oral dose of CyA as compared with a control period. Higher blood CyA concentration may be the result of alterations in CyA absorption, distribution, or metabolism.

Olive oil increases the oral absorption of heparin in rats by increasing bile production or by inducing changes in the permeability of intestinal microcirculation.[6] A similar phenomenon may result in increased CyA absorption and therefore increased CyA AUC after olive oil or CyA pretreatments. However, the lack of significant differences in the c_{max} and t_{max} tends to suggest minimal or no change in the absorption of CyA after pretreatments. These results are contrary to the previous observations made in kidney transplant patients.[7]

On the other hand, we observed a significant increase in CyA half-life after olive oil or CyA pretreatment. Both olive oil and CyA may therefore alter CyA disposition. In vitro studies using rat liver homogenates indicate that CyA is a potent inhibitor of drug metabolism.[8] In vivo studies in rabbits have demonstrated impairment in *N*-demethylation of aminopyrine after chronic CyA treatment.[9] Therefore, changes in the disposition of CyA after chronic olive oil or CyA administration appear to be primarily responsible for the observed results. However, intravenous and oral CyA pharmacokinetic studies in dogs after chronic CyA administration are necessary to determine the exact mechanism responsible for the altered CyA pharmacokinetics.

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