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The Clearance of Cyclosporine by Hemodialysis

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Abstract: The pharmacokinetics of cyclosporine were studied in five liver transplant patients when they were on and off hemodialysis. There was no significant difference in the blood clearance of cyclosporine between these two periods. Less than 1 per cent of the dose of cyclosporine was recovered in the dialysate. The mean dialysis clearance was less than 1 ml/min. This represents less than 1 per cent of the total blood clearance of cyclosporine. Dosage alterations of cyclosporine during or after hemodialysis do not appear to be necessary.

CYCLOSPORINE is a cyclic undecapeptide of fungal origin with significant immunosuppressant activity.¹ Cyclosporine and prednisone are the primary immunosuppressive agents used in the recipients of transplanted kidneys, livers, hearts, heart-lungs, and bone marrow.²⁻⁵ Kidney transplant recipients may require temporary hemodialysis due to acute tubular necrosis which occurs in 12 to 40 per cent of these patients.^{6,7} At our institution, approximately 10 per cent of liver transplant recipients require hemodialysis due to surgical complications or drug-induced toxicity. Hemodialysis is known to increase the clearance of certain drugs.⁸ This study was undertaken to determine the extent to which cyclosporine is removed by hemodialysis and to predict whether cyclosporine dose supplements are necessary for patients after dialysis. This information is of importance since it is generally felt that the success of an organ transplant is closely related to optimal early immunosuppression.

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Methods

Five adult recipients of transplanted livers were studied. All patients required hemodialysis to manage postoperative renal failure. Patients were dialyzed with a Gambro 17 dialyzer (Gambro Inc., Newport News, Va.) (surface area 1.02 m², membrane thickness 17 μ) for 4 hours. All patients received cyclosporine (Sandoz Pharmaceuticals, East Hanover, N.J.) by intravenous infusion over 1 to 1.5 hours. The cyclosporine doses ranged from 100 to 200 mg administered at 8-hour intervals. Hourly venous blood samples were obtained during the dosing interval prior to dialysis and during the next dosing interval in which the patient was dialyzed. Blood samples were stored at -20°C until analysis.

Dialysate (Eri-Lyte 8336; Erika Inc., Rock Leigh, N.J.) was collected from four of the patients and analyzed for cyclosporine. Aliquots (100 to 300 ml) of dialysate were lyophilized to 10 to 15 ml prior to extraction using a freeze dryer (Virtis Company, Inc., Gardiner, N.Y.). Blood and dialysate were extracted using the procedure of Sawchuck and Cartier.⁹ Samples were analyzed by high-pressure liquid chromatography us-

TABLE I
Cyclosporine Clearance Off and On Dialysis

Patient no.	Clearance off dialysis (ml/min)	Clearance on dialysis (ml/min)
2	483	337
3	536	385
4	506	518
5	324	353
Mean ± S.D.	463 ± 95	398 ± 82*

* $P > 0.10$ by paired t -test.

ing a 25-cm, 5 μ , C₁₈ column (Supelco, Bellefonte, Penn.) heated to 70°C and by ultraviolet detection (Model 441, Waters Assoc., Milford, Mass.) at 214 nm. Standards were prepared in blank blood and dialysate, and the internal standard was cyclosporin D (Sandoz Pharmaceuticals, Basel, Switzerland). The mobile phase was acetonitrile: water (68.5:31.5) delivered at 1.8 ml/min. Under these conditions, the retention time was 9.8 minutes for cyclosporine and 12.8 minutes for cyclosporin D.

The total body clearance of cyclosporine was calculated on and off dialysis by

$$\text{clearance} = \frac{\text{dose}}{\text{AUC}(0-\tau)} \quad (1)$$

where $\text{AUC}(0-\tau)$ is the area under the blood concentration-time curve over the dosing interval τ studied.

The dialysis clearance was calculated from

$$\text{dialysis clearance} = \frac{R}{\text{AUC}(0-t)} \quad (2)$$

where R is the total amount of solute recovered in the dialysate and $\text{AUC}(0-t)$ is the area under the blood concentration-time curve over the period of dialysis (t).

The significance of the difference between the total body clearance of cyclosporine on and off dialysis was analyzed by a paired t -test.

Results

The standard curve for the estimation of cyclosporine was linear over a concentration range of 50 to 2000 ng/ml. The coefficient of variation of the analytical method was 3.95 per cent at 600 ng/ml ($N = 10$). No

TABLE II
Dialysis Clearance of Cyclosporine

Patient no.	Dose of iv cyclosporine (mg)	Dialysate volume (liters)	Amount of cyclosporine in dialysate (μ g)	Dialysis clearance (ml/min)
1	150	48	31.8	1.068
2	150	37	11.1	0.072
3	140	38	5.1	0.021
4	200	54	19.7	0.057
Mean ± S.D.			16.9 ± 11.6	0.305 ± 0.509

TABLE III
Arterial and Venous Cyclosporine
Blood Concentrations

Sample no.	Cyclosporine concentration (ng/ml)*	
	Arterial	Venous
1	259	259
2	432	491
3	353	213
4	2143	2203
5	1343	1231
6	736	991
7	610	552

* $P > 0.10$ by paired t -test.

significant difference was observed in the blood concentration-time curves of patients on or off dialysis. The total body clearance of cyclosporine while on dialysis was not significantly different ($P > 0.10$) from the clearance off dialysis (Table I). Two of the four patients studied had a decrease in total body clearance during the dosing interval on dialysis. Patient 1 was not included in this comparison since blood samples were obtained from this patient only before, after, and at the midpoint of dialysis.

Very little cyclosporine was recovered from the dialysate of the patients studied (mean $16.9 \mu\text{g}$). The mean dialysis clearance was determined to be 0.305 ± 0.509 ml/min (Table II).

In one patient (No. 3), arterial and venous blood samples were obtained during two dialysis periods (total of seven samples) and analyzed for cyclosporine to determine if a difference might be observed. There was no statistical difference ($P > 0.10$) between arterial and venous concentrations of cyclosporine when analyzed by a paired t -test (Table III).

Discussion

The present studies were carried out at steady state over one dosing interval. The relatively smaller dosing interval (8 hours) with reference to the half-life of the drug

($t_{1/2} = 6.4$ to 27 hours)¹⁰ precluded calculation of pharmacokinetic parameters other than the clearance of the drug.

The total body clearance of cyclosporine for patients being dialyzed did not differ significantly ($P > 0.10$) from the clearance when the patients were not being dialyzed. The lower clearance of cyclosporine in two patients during dialysis may be due to diurnal variations in clearance that have been observed in several of our patients studied (unpublished observations). The clearance of cyclosporine appears to be lower during the day (patients were dialyzed during the day) compared to at night.

The mean dialysis clearance was 0.305 ml/min for all patients studied. Excluding patient 1, whose dialysis clearance was considerably higher than the other three patients studied, the mean dialysis clearance was 0.050 ± 0.026 ml/min. Patient 1 had a much higher dialysis clearance than the other patients studied. Her dose was similar to the other patients, and all doses were given by the intravenous route. The actual reasons for such a difference in the dialysis clearance is not known. However, the difference observed in the dialysis clearance in this patient does not alter the conclusion that dialysis clearance represents less than 1 per cent of the total body clearance.

Cyclosporine is not significantly removed from the body by hemodialysis. The results are explained by the fact that cyclosporine is only minimally eliminated by the kidneys, has a high molecular weight (1202), is highly lipid soluble, is significantly bound to plasma lipoproteins, and has a large volume of distribution.¹¹⁻¹³ These factors are all known to influence the dialyzability of drugs.^{14,15} No difference was observed between the concentration of cyclosporine in arterial and venous blood samples. This indicates that very little cyclosporine passed through the dialyzer membrane.

Substantial differences in dialysis clearance have been observed among different dialyzers.⁸ Only one dialyzer type was used

in our study, but little difference would be expected in the dialysis clearance of cyclosporine among dialyzers. The process of hemodialysis does not significantly affect the total body clearance of cyclosporine, and dosage alteration of cyclosporine during or after hemodialysis is not necessary.

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