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Cyclosporine Pharmacokinetic Profiles in Liver, Heart, and Kidney Transplant Patients as Determined by High-Performance Liquid Chromatography

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CYCLOSPORINE PHARMACOKINETICS has been described in patients following kidney, liver, heart, and bone marrow transplantation.[1] Many of these studies have been performed using high-performance liquid chromatography (HPLC) because of its specificity for cyclosporine (Cs). Even using a specific assay, the results of these pharmacokinetic studies are difficult to interpret due to the complex natures of the drug and of transplant patients. Similar studies of comparative groups of subjects must be performed to permit the proper understanding of the effect of the disease state and the transplant operation on the disposition of Cs. This article, therefore, briefly reviews the HPLC assay of Cs, presents Cs kinetic profiles by HPLC on both nontransplant comparative groups and transplant patients, and discusses the interpretation of differences between transplant groups and comparative groups.

HPLC ASSAY

Several HPLC procedures are available to measure Cs in biological fluids and are summarized in Table 1. HPLC procedures require extensive sample extraction or a column-selective isolation technique. The latter procedure requires specialized instrumentation not commonly available in all laboratories. The extraction of Cs from biological fluids involves solid-liquid or liquid-liquid extraction methods. In the solid-liquid method, Cs is separated from endogenous substances using columns such as Baker cyano columns.[9,12] In the liquid-liquid extraction method, Cs is extracted with ether. In some procedures, further sample purification is carried out using haxane.[8]

The isolated Cs can be chromatographed using a C-18 or cyano column maintained at a temperature of 55 °C to 75 °C. The mobile phase generally consists of various combinations of acetonitrile, methanol, and water. Cs and CsD (internal standard) usually elute within 12 minutes. After liquid-liquid extraction procedures, late peaks (possibly phthalates) may occasionally lengthen the chromatography time to as long as 25 to 30 minutes. HPLC is specific for unchanged Cs and is sensitive to concentrations as low as 25 ng/mL using 1 mL of blood. HPLC is linear over the range of 25 to 4,000 ng/mL and is useful for the analysis of blood, bile, plasma, serum, urine, cerebrospinal fluid (CSF), and breast milk. The HPLC methodology is easily adapted to measure metabolites of Cs[14] and other immunosuppressive compounds specifically, and we now use an HPLC method for the determination of CsG using Cs as the internal standard.[15]

Cs monitoring and pharmacokinetic studies have been performed using whole blood, serum, and plasma. The concentrations of Cs in blood are approximately twice those measured in plasma, which reflects the extensive distribution of Cs into erythrocytes.[16,17] The relative distribution of Cs between blood cells and plasma depends on several factors, includ-

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Table 1. HPLC Assays to Quantitate Cyclosporine Biological Fluids

Sample	Preparation	Column/Conditions	Mode of Analysis	Mobile Phase (%)	Minimum Detection Limit (ng)
Serum[2]	S-L	μBondapak C-18*; 55 °C	Isocratic	M/W (95/5)	100
Plasma[3]	L-L	Ultrasphereoctyl†; 72 °C	Isocratic	A/W/M (47/20/33)	31
Blood and plasma[4]	L-L	μBondapak C-18*; 25 °C	Gradient	I/H (14/86 to 36/64) in 30 min	100
Plasma[5]	S-L	Zorbax TMS‡; 55 °C	Isocratic	A/W (60/40)	100
Plasma and urine[6]	L-L	Lichrosorb RP-8§; 72 °C	Gradient	A/W/M (20/60/20 to 75/5/20) in 26 min	25
Plasma and blood[7]	PP	Lichrosorb C-18§; 70 °C	Column switching	6 Solvent-switching scheme with step gradient	20
Plasma and blood[8]	L-L	Supelcosil LC-18‖; 75 °C	Isocratic	A/W (68.5/31.5)	25
Serum[9]	S-L	Ultrasphere ODS†; 70 °C	Gradient	A/W (35/65 to 5/15) at 15 min	50
Plasma and blood[10]	PP	Supelcosil LC-8‖; 75 °C	Column switching	A/W (55/45 switched to 75/25)	8 (plasma); 20 (blood)
Plasma, serum, and blood[11]	S-L	Zorbax Cyanopropyl‡; 58 °C	Isocratic	A/W (51/49)	10–15
Serum and blood[12]	S-L	Brown Lee RP-8¶; 70 °C	Isocratic	A/W (72/28)	<50
Plasma[13]	L-L	Lichrosorb RP-8§; 73 °C	Isocratic	M/W (83/17)	2

Abbreviations: S-L, solid-liquid extraction; L-L, liquid-liquid extraction; PP, Protein Precipitation; M, methanol; W, water; A, acetonitrile; I, isopropanol; H, Heptane. *Waters, Milford, MA; †Altex Division, Beckman Instruments Inc, San Ramon, CA; ‡DuPont, Wilmington, DE; §EM Industries Inc, Hawthorne, NY; ‖Supelco Inc, Bellefonte, PA; ¶Brownlee, Santa Clara, CA.

ing the temperature of separation of plasma from erythrocytes, the patient's hematocrit, the drug concentration, and the lipoprotein content and composition in patient plasma. Plasma samples separated at room temperature have up to 50% lower Cs concentrations than samples separated at 37 °C.[18–20] The temperature-dependent concentration of Cs in plasma is due to altered red blood cell and lipoprotein uptake of Cs at different temperatures. The optimal temperature for separation of plasma from blood for obtaining physiologically meaningful pharmacokinetic parameter estimates is 37 °C in order to simulate in vivo Cs distribution in blood. Since the temperature-dependent Cs distribution is reversible, samples stored at <37 °C can be reequilibrated at 37 °C for plasma separation. This approach should be used for pharmacokinetic studies but may be impractical for routine clinical monitoring. Since the concentration of Cs in plasma is lower than that in the blood, there tends to be a greater variability in Cs estimations in plasma as compared with whole blood.[21]

Pharmacokinetic parameters that are based on the absolute quantity of Cs in the specimen, such as clearance and volume of distribution, may therefore vary depending whether blood or plasma or serum was used.

Nontransplant Patient Studies

Cyclosporine has been administered to several groups of patients who have not undergone solid organ or bone marrow transplantation. These studies provide a valuable comparative group for interpreting changes in the pharmacokinetic profiles in transplant patients. Table 2 lists the half-life ($t_{1/2}$), the total body clearance (CL), the steady state volume

Table 2. HPLC Cyclosporine Kinetic Parameters in Nontransplant Studies

Patient Population	Number of Subjects	Biological Fluid	Study Dosing Interval (h)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vd (L/kg)	F (%)
Healthy volunteers[22]	5	Blood	48	6.2 (4.7–9.5)	3.9 (2.9–5.5)	1.3 (±0.3)	
Patients with renal failure[23]	4	Blood	48	15.8 (±8.4)	5.9 (±1.4)	3.5 (±2.7)	
Uremic patients[24]	21	Blood	48	12.2 (6.4–26.9)	5.1† (±1.4)	8.6 (±5.1)	38 (±17)
Patients with liver failure*	8	Blood	48	20.4 (10.8–48)	2.8 (1.9–4.8)	3.9 (±1.8)	11.9
Patients with liver disease[25]	9	Serum	20	8.7 (±3.3)	30.4 (±15.5)	13.8 (±11.2)	
Pediatric patients with congestive heart failure[26]	5	Blood	24	7.5 (±2.1)	1.9 (±0.3)	0.9 (±0.2)	24.4 (n = 1)

*Unpublished observations.

†Assuming 70 kg body weight.

of distribution (Vd), and the fraction of an oral dose that was absorbed (F) for Cs in nontransplant patients. This information should expand considerably over the next few years as the use of Cs in autoimmune disease broadens.

Transplant Patient Studies

Table 3 summarizes the studies performed utilizing HPLC in transplant patient groups. Most of the studies have used whole blood Cs concentrations; but those using serum have performed the separation of blood and serum at room temperature.

DISCUSSION

An examination of Tables 2 and 3 point out some important differences between transplant patients and either healthy volunteers or patients with renal, liver, or cardiac disease.

Table 3. HPLC Cyclosporine Kinetic Parameters in Transplant Patient Studies

Patient Population	Number of Subjects	Biological Fluid	Study Dosing Interval (h)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vd (L/kg)	F (%)
Renal transplant patients[24]	11	Blood	48		4.6 (±1.3)	9.2 (±3.2)	41 (±15)
Bone marrow transplant serum bilirubin <1.2 mg/dL[27]	10	Serum	12	6.7 (±1.6)	12.8 (±1.6)	4.3 (±0.9)	
Bone marrow transplant serum bilirubin <2.0 mg/dL[27]	11	Serum	12	12.7 (±6.1)	9.8 (±2.1)	3.5 (±1.1)	
Adult renal transplant patients[28]	41	Blood	24	10.7 (4.3–53.4)	5.7 (0.6–23.9)	4.5 (±3.6)	28 (±21)
Pediatric renal transplant patients[29]	7	Blood	12–24	7.3 (6.1–16.6)	11.8 (9.8–15.5)	4.7 (±1.5)	31 (±10)
Adult liver transplant patients[30]	6	Blood	12		5.5 (4.9–7.6)		27 (8–60)
Pediatric liver transplant patients[31]	26	Blood	8		8.4 (1.9–13.9)		<5–19
Heart transplant patients[32]	4	Blood	12	6.4 (5.2–9.3)	4.0 (2.1–5.3)	1.3 (±0.2)	35 (±11)

These differences will be discussed in relation to the absorption, distribution, and metabolism of Cs in each group.

The absorption of Cs is variable, slow, and incomplete.[28,33] Peak concentrations in blood or plasma are observed one to eight hours after oral dosing, and the absorption half-life ranges from 0.6 to 2.3 hours.[33,34]Considerable variation has been observed in the peak concentrations of Cs in blood or plasma in recipients of kidneys, hearts, and allogenic bone marrow grafts following oral therapy.[28,35,36] Following the ingestion of Cs, 600 mg, the peak serum HPLC concentration varied from 240 to 1,250 ng/mL in six medical patients.[34] Renal transplant patients receiving 17.5 mg/kg with breakfast had peak whole blood HPLC concentrations of 862 to 3,431 ng/mL.[37]

Marked variability in the extent of Cs absorption has been observed in patients after organ transplantation. In adult kidney transplant patients, the absolute bioavailability ranged from <5% to 89% with a mean of 28%.[28] The bioavailability of Cs in children following renal transplantation is 31%,[29] and following cardiac transplantation in adults, it is 35%.[32] Adult liver transplant recipients have a mean bioavailability of 27% with a range of 8% to 60%.[30] Pediatric liver transplant patients absorb <5% to 19% of an orally administered dose of Cs in the immediate postoperative period.[31]

Orally administered Cs is poorly absorbed in the presence of intestinal disease.[38,39] In bone marrow transplant patients, intestinal dysfunction may be mediated by chemoradiation enteritis secondary to the conditioning regimen for marrow transplantation, acute graft-*v*-host disease of the intestine, or *Candida* enteritis. Patients with greater than 500 mL of diarrhea in 72 hours have a significantly lower area under the Cs serum concentration curve *v* the time curve (AUC), indicating impaired drug absorption.[39] Impaired Cs absorption has also been noted in pediatric liver transplant patients with diarrhea.[31] In these patients, intravenous (IV) Cs should be administered to provide adequate immunosuppression.

Coadministration of Cs with food may alter Cs bioavailability. A preliminary report[36] suggested that food delayed and impaired the absorption of Cs. We recently studied the effect of food on the absorption of Cs in renal transplant patients.[28] A significant increase in the C_{max}, C_{min}, and AUC following Cs administration with food was observed compared with the fasted state. Additional studies are required to confirm this increase in the absorption of Cs with food following other transplant procedures (eg, liver transplantation, where no gallbladder is present) and to determine the effect of dietary composition on the absorption of Cs.

The absorption of fat and fat-soluble material is impaired in patients with liver disease. Because Cs is fat soluble, its bioavailability is very low (12%) in patients with severe liver disease,[40] as seen in Table 2. In the study by Venkataramanan et al,[40] patients with a total serum bilirubin of <10 mg/100 mL absorbed more than 5% of the administered drug, while the patients with a total serum bilirubin of >10 mg/100 mL absorbed less than 5%. Surgically induced cholestasis in dogs resulted in a decrease in Cs bioavailability from 23.5 ± 9.7% before surgery to 7.4 ± 3.7% 1 week after surgery (unpublished observation). The poor bioavailability of Cs in patients with liver disease and in liver transplant patients during the immediate postoperative period may be related to the lack of sufficient bile and bile salts for Cs absorption.

Similarly, the absorption of Cs is poor in liver transplant patients with external bile drainage via a T-tube. A significant increase in the trough blood concentration follows T-tube clamping.[41] Following clamping or removal of the T-tube, the rate and extent of absorption appears to increase as indicated by faster and higher peak blood concentrations.[42] Comparative bioavailability studies in the same liver transplant patients with and without external bile drainage indicate a mean increase of 422% in the dose-normalized AUC

following T-tube clamping (unpublished observation). This observation cannot be attributed to enterohepatic recycling of Cs since <1% of a dose of Cs is excreted in the bile as unchanged drug.[43] Increased bile flow into the gut following T-tube clamping is most likely responsible for the improved Cs absorption. Whenever external bile diversion is instituted or discontinued, adjustments in Cs dosage must be made.

The oral administration of bile salts may be beneficial in patients with Cs malabsorption. In a preliminary study in six cirrhotic patients, the administration of 750 mg of chenodeoxycholic acid increased Cs oral absorption in four patients, did not affect absorption in one patient, and decreased Cs absorption in one patient (unpublished observation). Additional research into the solubilization of Cs in the gut and its absorption will be necessary to optimally use pharmacologic facilitation of absorption.

While improving absorption with increased bile flow is expected in liver transplant patients, improved absorption may also occur in renal transplant patients over the course of therapy. In kidney transplant patients, three- to fivefold increases in oral bioavailability over time have also been noted.[44] In one study, the mean bioavailability was 24.2 ± 18.1% during the first 2 weeks after kidney transplantation and increased to 50.2 ± 7.9% at 6 to 12 months after transplantation.[45] The exact nature of this improvement in absorption is not known.

Limited numbers of studies of Cs absorption have been performed in cardiac transplant recipients, but no major problem has been noted with their drug absorption. The most significant pharmacokinetic variant that is shared by the cardiac transplant patients, children with severe heart disease prior to transplantation, and healthy volunteers is their small volume of distribution in comparison with other transplant patients. The volumes of distribution of 1.3, 0.9, and 1.3 L/kg for the heart transplant,[32] heart disease,[26] and volunteer studies,[22] respectively, are three- to fivefold smaller than in renal and liver transplant patients.[28,30] This reduced volume of distribution will produce higher blood concentrations for any administered dose for the heart transplant recipient than for other transplant patients and may put the heart transplant recipient at increased risk of Cs toxicity. While hematocrit may partially explain these changes in distributional volume, other factors are most likely involved since the hematocrit varied from 29.8 to 63.6 in our pretransplant congestive heart failure study,[26] with little variation in the volume of distribution.

The plasma protein binding of Cs appears to be highly variable among different patients and among different animal species. The unbound fraction of Cs in plasma from transplant patients at 37°C ranges from 0.04 to 0.17 and is significantly different than the unbound fraction in normal blood (unpublished observation). The unbound fractions of Cs in dogs, humans, rats, and rabbits are 0.07, 0.15, 0.19, and 0.33, respectively (unpublished observation). These values appear to be related to the quantity of lipoproteins in the different species tested.

Based on blood clearance estimates obtained by HPLC, Cs can be classified as a low to intermediate clearance drug. Both its clearance and elimination half-life are highly variable among patients and are influenced by the type of transplant, age, disease state, and concurrent drug therapy.

The elimination of Cs is influenced by the age of the patient. Pediatric patients appear to clear the drug more rapidly than adults on a body weight basis. The harmonic mean clearance of Cs in a study involving 26 pediatric liver transplant patients was 8.4 mL/min/kg (range 1.9 to 13.9 mL/min/kg), which is higher than the clearance of Cs in adult liver transplant patients.[31] Pediatric kidney transplant recipients reportedly have a significantly higher harmonic mean clearance of Cs (11.8 mL/min/kg; range, 9.8 to 15.5 mL/min/kg) compared with adult renal transplant patients (5.7 mL/min/kg).[29] Kahan et

al[45] reported a higher Cs clearance from serum using radioimmunoassay (RIA) in patients less than 45 years of age compared with patients older than 45 years. The higher clearance in the pediatric population appears to be the result of more rapid removal of Cs from the body. Therefore, children may require more frequent and larger doses of Cs per kilogram of body weight to achieve blood concentrations of the drug similar to those observed in adults. The kinetics of Cs have not been completely studied in the geriatric population. Impairment in renal function with age should not contribute to any changes in Cs elimination.

Since Cs is primarily eliminated by hepatic metabolism, its clearance is impaired in patients with liver disease. In eight patients with biopsy-proven cirrhosis, the harmonic mean clearance of Cs was 2.8 mL/min/kg (Table 2), which is approximately half the clearance value observed in kidney and liver transplant patients. The harmonic mean half-life of Cs in these patients was prolonged to 20.4 (range, 10.8 to 48.0) hours. Because of the marked influence of liver disease on Cs kinetics, blood concentration monitoring is essential in patients with severe liver dysfunction.

Cs clearance is impaired in patients with congestive heart failure, presumably due to alterations in hepatic blood flow and hepatic function. Follow-up studies on patients after heart transplantation have shown an increase in drug clearance rate from pre- to posttransplantation (2.1 to 3.9 and 2.0 to 7.2 mL/min/kg in two patients).[26] Heart transplant recipients will have changing rates of Cs clearance until they can stabilize their cardiac output and hepatic function.

Renal excretion is a minor pathway of elimination for Cs in humans and animals.[35] Less than 1% of an administered dose is excreted unchanged in the urine. Approximately 6% of an administered dose of radioactive Cs is excreted in the urine in 96 hours.[35] Therefore, changes in renal function alone should not alter Cs clearance. Additional support comes from the clearance rates in the two studies presented in Table 2 in pretransplant renal failure patients.[23,24]

A diurnal variation in the kinetics of Cs may occur in transplant patients. Eight patients (five male, three female) were studied approximately 2 weeks following cadaveric renal transplantation to examine variations within a day (unpublished observation). On the day of the study after an overnight fast, each patient received an identical standard meal at 7:00 AM and 7:00 PM. At 8:00 AM and 8:00 PM, each patient received their normal dose of Cs (mean 11.9 ± 6.3 mg/kg/dose) mixed with 240 mL of chocolate milk. Blood samples were obtained in heparinized tubes every two hours for the 24-hour study period. Whole blood samples were analyzed by HPLC and RIA. The mean (±SD) area under the blood concentration time curve following the morning dose of cyclosporine was 9,455 (±2,934) ng · h/mL, which was significantly higher ($P < 0.01$) than the AUC following the evening dose of Cs (7,604 ± 2,544). The peak concentration of Cs following the morning dose was 1,278 (±422) ng/mL compared with the peak of 920 (±413) following the evening dose ($P < 0.01$). There was no difference in the time to peak concentration (4.3 *v* 4.8 hours), Cs trough concentration (266 *v* 264 ng/mL), or elimination half-life (5.4 *v* 5.0 hours) between the morning and evening doses of Cs. Diurnal variations in the pharmacokinetics of Cs in patients following cadaveric renal transplantation probably do occur in a manner similar to previous observations in liver transplant patients.[2]

Several pharmacologic agents affect the clearance of Cs, and drug interactions are discussed elsewhere in this supplement. The most important inducers of Cs metabolism and elimination are phenytoin,[14,36] phenobarbital,[46] and rifampin.[47] These agents can lower blood Cs concentrations and are associated with rejection episodes in transplant patients. The most potent inhibitors of Cs metabolism are ketoconazole[48,49] and erythromycin.[50] As opposed to the slow onset of the metabolism

inducers, ketoconazole and erythromycin can rapidly increase Cs blood concentrations, resulting in an increased risk of nephrotoxicity. The reported interaction of high-dose methylprednisolone with Cs is questionable since no change in Cs clearance by HPLC can be detected during this steroid therapy.[51]

SUMMARY

Cs pharmacokinetic profiles using HPLC have aided in predicting necessary dosage alterations for specific groups of transplant patients. Additional information has been gained by HPLC profiles in nontransplant subjects who are healthy or have a stable disease state. The clinician now knows that liver disease not only impairs Cs elimination but may also have a pronounced effect upon drug absorption. While the cardiac failure patient may have reversible inhibition of Cs clearance, other factors may affect the distribution of the drug to lower dosage requirements. Impaired renal function is not an impediment to Cs elimination, but malabsorption similar to that observed in liver and bone marrow transplant patients may still occasionally complicate therapy.

Pharmacokinetic information on Cs must be integrated into the complex care plan of a transplant patient to optimally utilize and monitor this pharmacologic agent.

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