Evaluation of Renal Function in Transplant Patients on Tacrolimus Therapy

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Glomerular filtration rate (GFR), as measured by 24-hour creatinine clearance and clearance of iothalamate, and effective renal plasma flow (ERPF), as measured by the clearance of para-aminohippuric acid (PAH), were evaluated at 2 weeks, 1 month, and 3 months after transplantation in 8 renal transplant patients and at 1 month and 1 year after transplantation in 9 liver transplant patients receiving tacrolimus (Prograf®) therapy. In renal transplant patients, there was a significant increase in GFR after transplantation. There was no change in GFR at 1 and 3 months as compared to 2 weeks after transplantation, while ERPF (ml/min/1.73 m^2) was lower ($p < 0.05$) at 3 months (212 ± 42) compared to 1 month (306 ± 118) after transplantation. In liver transplant patients, GFR and ERPF were below normal despite normal serum creatinine concentrations, but there was no difference in GFR or ERPF at 1 month and 1 year after transplantation. Although below normal, renal function was well preserved in transplant patients while receiving chronic tacrolimus therapy over the study period. Dosage alterations of renally eliminated drugs may be required for drugs with a narrow therapeutic index.

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Organ transplantation is an accepted therapeutic option for patients with an end-stage organ disease. After transplantation, patients often receive multiple drug therapy that includes immunosuppressive agents, antibiotics, antifungal agents, antiviral agents, and antihypertensive agents. Many of these drugs are excreted primarily through the kidney, and the functional status of the kidney in transplant patients is very important in determining the kinetics and dynamics of renally excreted drugs. In transplant patients, renal function may be compromised by factors such as ischemia/reperfusion injury to the kidney during or after surgery and because of the use of nephrotoxic agents.

Tacrolimus and cyclosporine are currently the two primary immunosuppressive drugs used to prevent organ rejection. Tacrolimus (Prograf ®, Fujisawa, Chicago), a relatively new immunosuppressive drug, was isolated from the fungus *Streptomyces tsukubaensis* in 1984,[1] and clinical trials were initiated in 1989 by Starzl and coworkers.[2] The 1-year patient and graft survival under tacrolimus immunosuppression are 88% and 82% after liver transplantation,[3] and 95%[4] to 96%[5] and 89%[4] to 91.2%,[5] respectively, after renal transplantation. Despite the significant improvement in patient and organ survival, a major side effect of tacrolimus therapy is nephrotoxicity. Clinically, nephrotoxicity induced by tacrolimus is often inferred based on an increase in serum creatinine or blood urea nitrogen (BUN) or, occasionally, by a reduction in creatinine clearance or histological changes in the kidney.[6,7] These parameters, however, do not provide an accurate estimate of the functional capacity of the kidney. Limited information is available on the quantitative aspects of kidney function in transplant patients treated with tacrolimus. The objectives of this study were to as-

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sess renal function quantitatively in kidney and liver transplant patients receiving tacrolimus as their primary immunosuppressive therapy and to characterize the time course of changes in renal function following transplantation.

MATERIAL AND METHODS

The protocol for this study was approved by the institutional review board, and the study was conducted at the General Clinical Research Center at the University of Pittsburgh. Patients were randomly selected, and recruited for the study with the approval of their primary physician if they met the inclusion and the exclusion criteria. The study protocol was explained to the patients, and informed consent was obtained from each participant.

Study Population

The demographics and characteristics of the patients enrolled in this study are shown in Tables I and II. Eight renal transplant patients (4 male, 4 female) and 9 liver transplant patients (7 male, 2 female) were recruited for the study. Male and female transplant patients, between the ages of 18 and 60 years, with no secondary organ involvement were included in this study. The typical dosing regimen for tacrolimus in these patients was 0.2 to 0.3 mg/kg/day in two divided doses. Liver transplant patients were required to have a serum creatinine of less than 1.5 mg/dl at the time of recruitment, and the renal transplant patients were required to have primary renal allograft function. Patients were excluded if they were pregnant, had a hematocrit of less than 25%, or were allergic to iodine or hippurate. At the time of the study, all the patients were receiving tacrolimus as their primary immunosuppressive therapy and were not on any other concurrent medication that would either be nephrotoxic or induce or inhibit hepatic drug-metabolizing enzymes.

Study Protocol

The study was performed at approximately 2 weeks, 1 month, and 3 months after renal transplantation and approximately 1 month and 1 year after liver transplantation. These days were chosen so as to coincide with the patient's routine clinical visits. On the day of the study, the subjects were asked to eat a light breakfast consisting of apple/orange juice, muffins, toast, or cereal with their morning medications and were asked to refrain from taking any caffeine-containing products. Patients were asked to take their morning dose of tacrolimus, and the study was started within 2 to 3 hours thereafter. All subjects were fasted for approximately 2 to 3 hours prior to starting the study and for at

Table I Renal Transplant Patients: Demographics and Characteristics

	Renal Transplant
Age (years)	
Mean ± *SD* (*n* = 8)	45 ± 9
Range	28-55
Gender	4 male, 4 female
Race	4 black, 4 white
Donor age (years)	
Mean ± *SD* (*n* = 7)	36 ± 16
Range	18-58
Weight (kg)	
Two weeks (mean ± *SD*)	74.2 ± 12.1
One month (mean ± *SD*)	74.0 ± 10.9
Three months (mean ± *SD*)	78.4 ± 11.9
Indications for transplantation (*n*)	
Hypertension	3
Reflux nephropathy	1
Wegener's granulomatosis	1
Polycystic kidney disease	2
Diabetes, hypertension	1

Table II Liver Transplant Patients: Demographics and Characteristics

	Liver Transplant
Age (years)	
Mean ± *SD*	48 ± 6
Range	39-58
Gender	7 male, 2 female
Race	9 white
Weight (kg)	
One month (mean ± *SD*)	74.6 ± 15.0
One year (mean ± *SD*)	84.7 ± 18.8
Indications for transplant (*n*)	
Chronic hepatitis B	1
Hepatitis C	1
Autoimmune hepatitis	1
Alcoholic hepatic disease	1
Primary sclerosing cholangitis	1
Cirrhosis	3
Alpha-1 antitrypsin deficiency	1

least 3 hours after initiation of the administration of the renal function markers. Exceptions were made for diabetic patients, who were given crackers and juice as necessary during the study.

Each subject was asked to collect urine for 24 hours, approximately 24 to 36 hours prior to the start of the study. On the morning of the study, a blood sample was withdrawn, and the subject was asked to void before starting the infusion of the renal markers. Diuresis was initiated by consumption of 200 ml of water orally prior to starting the study and every half hour thereafter. A priming dose of 217 mg iothalamate and 3 mg/kg para-aminohippuric acid (PAH) was given intravenously over 5 minutes. This was followed by a continuous infusion of iothalamate and PAH for 2.5 hours to achieve target steady-state concentrations of 30 μg/ml and 15 μg/ml, respectively. Blood samples were withdrawn at 1, 1.5, 2, and 2.5 hours after initiation of infusion, and timed urine sample were collected at half-hour intervals.

Laboratory Analysis

Iothalamate and PAH were analyzed in plasma and urine by high-performance liquid chromatography (HPLC). Two hundred μl of plasma and urine samples were mixed with 100 μl of para-amino benzoic acid in water (50 μg/ml or 100 μg/ml) as the internal standard and subjected to protein precipitation with 100 μl of perchloric acid. The samples were vortexed and then centrifuged for 10 minutes at 3000 rpm. The supernatant was injected onto a reverse-phase HPLC column. The mobile phase for PAH consisted of disodium citrate, hydrochloric acid, and di-n-butylamine adjusted to a pH of 2.5. For iothalamate, 35 ml of acetonitrile were added to 965 ml of the mobile phase described above. The flow rate was 1 ml/min, and the UV detector was set at 254 nm. The standard curve was linear in the concentration range of 7.5 μg/ml to 100 μg/ml for both markers in plasma and urine. The interassay and intra-assay coefficients of variation for PAH and iothalamate were less than 6.3% and less than 6.5%, respectively, in the urine and less than 3.5% and 8.3%, respectively, in the plasma.

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were calculated as the renal clearance of iothalamate and PAH corrected to body surface area, respectively. The renal clearance was calculated as the amount excreted in urine/AUC for each collection interval. The average of the renal clearances over the collection intervals of 60 to 90 minutes, 90 to 120 minutes, and 120 to 150 minutes was calculated for each subject.

Statistical Analysis

Results were reported as mean ± standard deviation (*SD*). The data for renal transplant patients were analyzed by using repeated-measures ANOVA (Figures 1, 2 [discussed below]). A paired *t*-test was used for analysis of data from liver transplant patients (Figures 3, 4 [discussed below]). A repeated-measures ANOVA was used for testing statistical significance for the estimated creatinine clearance in Figure 3. An unpaired *t*-test was used for comparison of GFR and ERPF between renal and liver transplant patients in Figure 5. The statistical package used was SAS, version 6.12. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Renal Transplant Patients

Seven cadaveric and 1 living related renal allograft recipients completed the study at 2 weeks and 1 month. The living related recipient did not complete the study at 3 months when she was diagnosed to have acute rejection. The data given below are for all 8 patients at 2 weeks and 1 month and for 7 patients at 3 months. The pretransplant serum creatinine concentrations of 7.3 ± 3.6 mg/dl improved to 1.4 ± 0.3 within 2 weeks after transplantation in these patients. Serum creatinine remained stable and within the normal range during the entire 3-month study period after transplantation (Table III). The estimated creatinine clearance by the Cockcroft and Gault method increased from 10.3 ± 3.7 ml/min to 54 ± 8.8 ml/min at 2 weeks after transplantation and remained stable thereafter (54 ± 12.1 at month 1 and 51 ± 7.3 at month 3). The GFR as measured by 24-hour creatinine clearance and iothalamate clearance did not change over the 3-month time period (Figure 1). However, ERPF as measured by PAH clearance at 3 months was similar to values at 2 weeks but was lower ($p < 0.05$) compared to the values at 1 month (Figure 2). Filtration fraction (GFR/ERPF) remained constant over 3 months. The fractional excretion of sodium (FeNa%) that is reflective of tubular function was unchanged over time (Table III). Poor correlations were observed when estimated creatinine clearance was correlated with 24-hour creatinine clearance ($r^2 = 0.1$, $p = 0.1$) and iothalamate clearance ($r^2 = 0.31$, $p = 0.007$). In addition, the 24-hour creatinine clearance showed a poor correlation with iothalamate clearance ($r^2 = 0.19$, $p = 0.04$). Renal function as evaluated by 24-hour creatinine clearance, iothalamate clearance, and PAH clearance was below normal at all the time points studied.

Table III Renal Transplant Patients: Biochemical Parameters and Tacrolimus Therapy

Parameters	Values
Serum creatinine, mg/dl	
Pretransplant	7.3 ± 3.6
Two weeks	1.4 ± 0.3[a]
One month	1.4 ± 0.3[a]
Three months	1.5 ± 0.3[a]
BUN, mg/dl	
Two weeks	29 ± 8.1
One month	27.5 ± 5.2
Three months	24.4 ± 3.6
Filtration fraction	
Two weeks	0.28 ± 0.1
One month	0.25 ± 0.07
Three months	0.29 ± 0.05
FeNa%	
Two weeks	1.8 ± 0.4
One month	1.8 ± 0.9
Three months	1.5 ± 0.6
Tacrolimus dose, mg/kg/day	
Two weeks	0.3 ± 0.1
One month	0.3 ± 0.1
Three months	0.2 ± 0.1
Tacrolimus dose, mg/day	
Two weeks	24 ± 8.4
One month	21.3 ± 9.0
Three months	16 ± 8.4[b]
FKWB concentrations, ng/ml	
Two weeks	20.2 ± 4.6
One month	19.5 ± 9.1
Three months	17.0 ± 4.6

Data are mean ± standard deviation. BUN, blood urea nitrogen; FeNa%, fractional excretion of sodium; FKWB concentrations, whole-blood concentrations of tacrolimus.

a. $p < 0.05$ as compared to pretransplant.

b. $p < 0.05$ as compared to 2 weeks and 1 month.

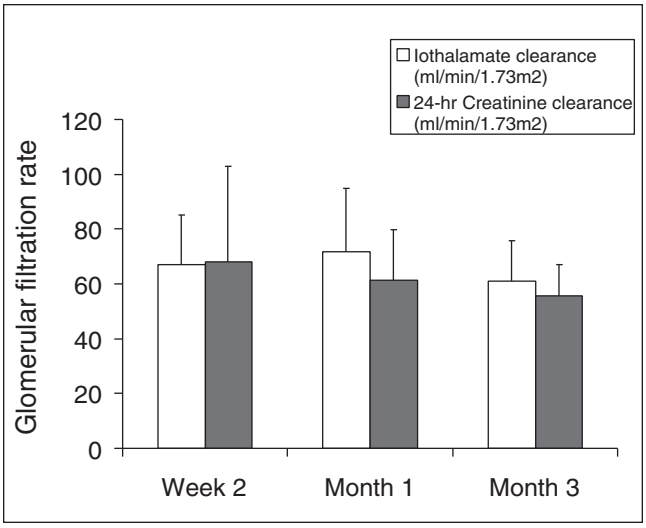

Figure 1. Glomerular filtration rate (GFR) as measured by 24-hour creatinine clearance and iothalamate clearance in renal transplant patients. Results are expressed as mean ± SD. GFR was evaluated by 24-hour creatinine clearance (dark bars) and iothalamate clearance (open bars) at 2 weeks, 1 month, and 3 months after renal transplantation.

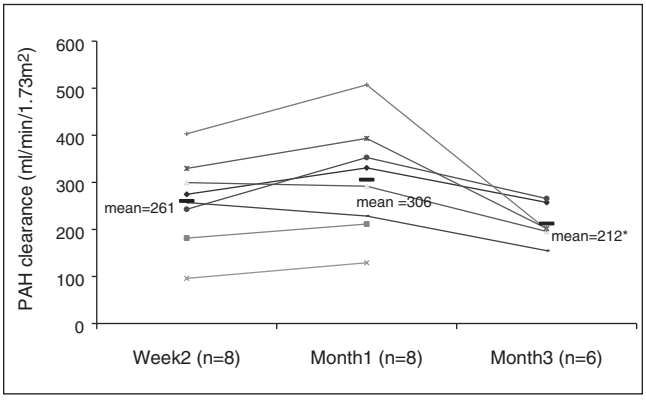

*Figure 2. Scatter plot of effective renal plasma flow (ERPF) as measured by p-aminohippurate (PAH) clearance in renal transplant patients. ERPF was measured at 2 weeks, 1 month, and 3 months after renal transplantation. *p < 0.05 versus 1 month.*

The dose of tacrolimus was lower ($p < 0.05$) at 3 months as compared to 2 weeks and 1 month. The whole-blood trough concentrations of tacrolimus showed a tendency to decrease with time, but this did not achieve statistical significance (Table III). No significant correlation was obtained when whole-blood concentrations of tacrolimus or the dose of tacrolimus were correlated with 24-hour creatinine clearance, the clearance of iothalamate, or the clearance of PAH.

Liver Transplant Patients

All 9 liver transplant patients recruited were evaluated at 1 month and 1 year after transplantation. At all time points, the serum creatinine was within the normal range. However, serum creatinine was significantly higher ($p < 0.05$) at 1 month and 1 year compared to pretransplant values (Table IV). The estimated creatinine clearance was significantly reduced at both 1 month and 1 year as compared to pretransplant values. Renal function as evaluated by estimated creatinine clearance (Cockcroft and Gault equation), 24-hour creatinine clearance, iothalamate clearance,

Table IV Liver Transplant Patients: Biochemical Parameters and Tacrolimus Therapy

Parameters	Values
Serum creatinine, mg/dl	
Pretransplant	1.0 ± 0.3
One month	1.2 ± 0.2[a]
One year	1.3 ± 0.2[a]
BUN, mg/dl	
One month	23.1 ± 8.6
One year	23.6 ± 11.1
Filtration fraction	
One month	0.24 ± 0.06
One year	0.21 ± 0.04
FeNa%	
One month	1.17 ± 0.5
One year	0.9 ± 0.3
Tacrolimus dose, mg/kg/day	
One month	0.2 ± 0.1
One year	0.1 ± 0.0
Tacrolimus dose, mg/day	
One month	15.5 ± 5.1[b]
One year	9.3 ± 3.3
FKWB concentrations, ng/ml	
One month	14 ± 4.0
One year	10.7 ± 3.5

Data are means ± standard deviations. BUN, blood urea nitrogen; FeNa%, fractional excretion of sodium; FKWB concentrations, whole-blood concentrations of tacrolimus.
a. $p < 0.05$ as compared to pretransplant.
b. $p < 0.05$ as compared to 1 year.

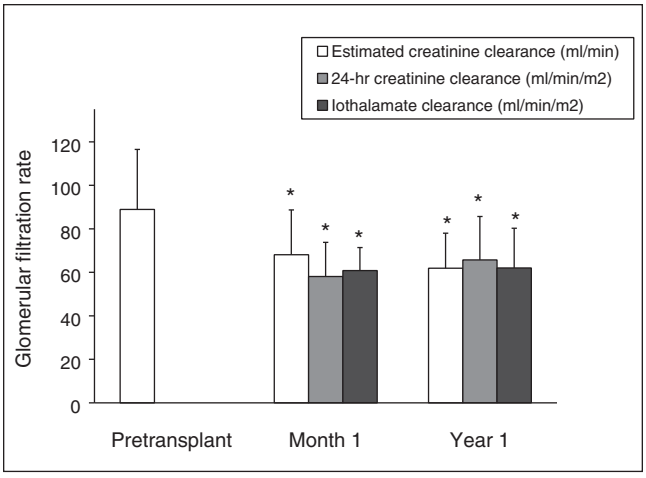

*Figure 3. Glomerular filtration rate (GFR) as measured by estimated creatinine clearance, 24-hour creatinine clearance, and iothalamate clearance. GFR was evaluated by estimated creatinine clearance (ml/min, hollow bars) based on serum creatinine (Cockcroft and Gault equation), 24-hour creatinine clearance (ml/min/m^2, gray bars), and iothalamate clearance (ml/min/m^2, dark bars). *p < 0.05 versus pretransplant.*

and PAH clearance were below normal (Figures 3, 4). There was no difference in any of these parameters over 1 year. The filtration fraction and the FeNa% did not change over 1 year (Table IV). As with renal transplant patients, poor correlation was observed between estimated creatinine clearance and 24-hour creatinine clearance ($r^2 = 0.2$, $p = 0.05$) or iothalamate clearance ($r^2 = 0.45$, $p = 0.002$) and between 24-hour creatinine clearance and iothalamate clearance ($r^2 = 0.25$, $p = 0.04$).

The dose of tacrolimus was significantly ($p < 0.05$) higher at 1 month than at 1 year. The whole-blood concentrations of tacrolimus were not significantly different but showed a trend to decrease at 1 year (Table IV). No correlation was observed between whole-blood concentrations of tacrolimus and 24-hour creatinine clearance or iothalamate clearance or PAH clearance. Similar results were seen when the three functional parameters (24-hour creatinine clearance, iothalamate clearance, and PAH clearance) were correlated with tacrolimus dose at 1 month and 1 year.

Renal and Liver Transplant Patients

A comparison of GFR and ERPF as measured by iothalamate and PAH clearance demonstrated that the values were similar at 1 month between the two patient populations (Figure 5).

DISCUSSION

In organ transplant patients, renal function may be influenced by intraoperative conditions, hemodynamic changes, and the use of nephrotoxic drugs. In addition, prolonged preservation time, reperfusion injury, and rejection will also affect renal function in renal transplant patients. Transplant patients are often on chronic therapy with tacrolimus or cyclosporine and are at risk for developing renal impairment. Initial observations suggested tacrolimus to be less nephrotoxic when compared with cyclosporine and with a lower incidence of rejection and hypertension.[8,9] However, with additional studies, tacrolimus was reported to be as nephrotoxic as cyclosporine.[5,7] Limited quantitative information is available on the functional capacity of the kidney after transplantation. The objective of the current study was to characterize the time course of changes in kidney function following transplantation using exogenous markers and to understand the functional status of the kidney in transplant patients on chronic tacrolimus therapy. Renal transplant patients

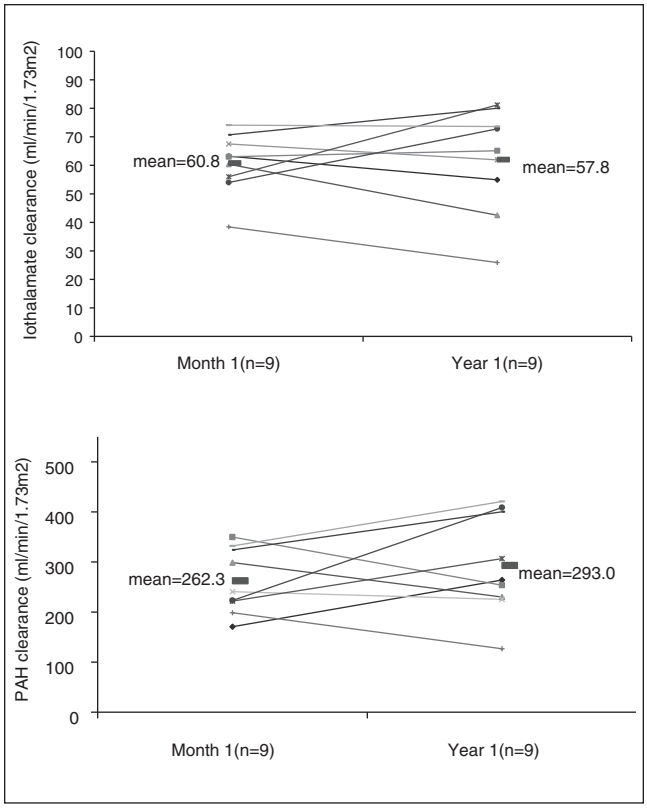

Figure 4. Scatter plot of glomerular filtration rate (GFR) as measured by iothalamate clearance in liver transplant patients (top panel). GFR was evaluated at 1 month and 1 year after liver transplantation. Scatter plot of effective renal plasma flow (ERPF) as measured by p-aminohippurate (PAH) clearance in liver transplant patients (bottom panel). ERPF was evaluated at 1 month and 1 year after liver transplantation.

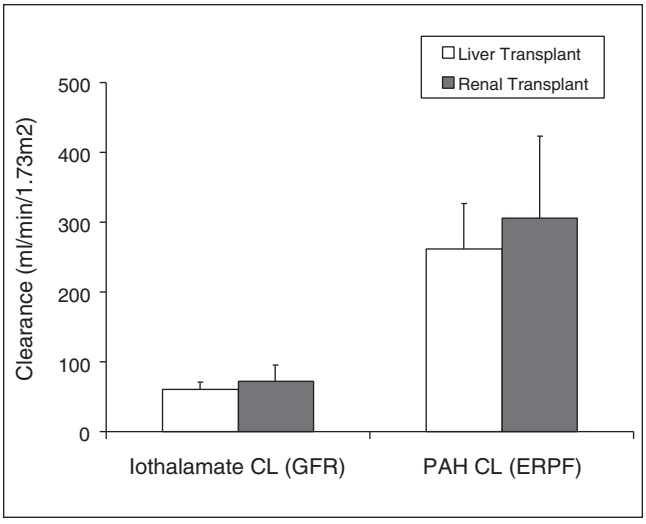

Figure 5. Mean renal hemodynamics (glomerular filtration rate [GFR] and effective renal plasma flow [ERPF]) at 1 month after renal and liver transplantation. GFR and ERPF were evaluated by iothalamate and p-aminohippurate clearance, respectively, in the renal (dark bars, n = *8) and liver transplant patients (hollow bars,* n = *9), respectively.*

were studied at 2 weeks, 1 month, and 3 months after transplantation, which allowed us to evaluate the recovery of renal function after renal transplantation and the effect of tacrolimus therapy on a newly transplanted kidney. Liver transplant patients were evaluated for the effects of acute and chronic tacrolimus therapy at 1 month and 1 year, respectively.

Serum creatinine is commonly used as an index of renal function in patients. In the current study, serum creatinine returned to normal or near-normal values within 2 weeks after renal transplantation. In liver transplant patients, the serum creatinine increased 1 month after transplantation but was well within the normal range throughout the study. Serum creatinine has been reported to be an insensitive indicator of kidney function in patients with kidney disease or after renal transplantation and also to provide no information about tubular function in these patients.[10,11] Previous studies in our laboratory have shown markedly lower clearance of cefotaxime and ceftizoxime (two drugs primarily excreted by the kidney) in liver transplant patients, despite normal serum creatinine concentrations.[12] Similarly, the half-lives of gentamicin and vancomycin were prolonged in liver transplant patients beyond what would be expected based on serum creatinine concentrations.[13] Therefore, in the present study, renal function was evaluated by creatinine clearance as estimated using the Cockcroft and Gault equation, as measured directly by collecting a 24-hour urine sample and by determining the clearance of two exogenous markers.

Very few studies have measured the functional aspects of the kidney in renal transplant patients. To our knowledge, this is the first report in which serial evaluation of renal function has been conducted with exogenous markers in kidney transplant patients on tacrolimus therapy. The estimated creatinine clearance significantly improved after renal transplantation. Glomerular filtration rate as measured by estimated creatinine clearance (Cockcroft and Gault method), 24-hour creatinine clearance, and iothalamate clearance was lower in kidney transplant patients as compared to normal subjects but remained stable over 3 months compared to baseline values at 2 weeks. The compromised renal function in the renal transplant patients is similar to the observation of Rostaing and coworkers,[14] who reported decreased renal hemody-

namics at 3 months after transplantation in patients on tacrolimus therapy. In comparison to subjects who have undergone unilateral nephrectomy, however, the renal hemodynamic values were only marginally lower in kidney transplant patients. It is well documented that after uninephrectomy, the remaining kidney hypertrophies to compensate for the loss of renal function.[15,16] Studies in subjects after uninephrectomy or in living related kidney transplant donors have shown that within the first few weeks after nephrectomy, GFR and renal plasma flow in the remnant kidney increase by approximately 40%. The GFR and ERPF then lie between 65% and 70% of prenephrectomy values in these subjects.[16-18]

In liver transplant patients on tacrolimus therapy, McCauley and coworkers[6] have reported a parallel decline in GFR and ERPF. A 9% and 42% reduction in GFR and ERPF, compared with expected values in normal subjects as measured by the single injection of radioactive iothalamate and orthoiodo-hippurate, has also been reported in liver transplant patients.[19] Canzanello and coworkers[20] observed a decrease in GFR and ERPF as measured by iothalamate and PAH clearance at 1 month after liver transplantation. There is limited information available on serial evaluation of GFR and ERPF in liver transplant patients. The lower GFR that was observed in the present study is in accordance with previous clinical studies, where GFR as evaluated by urinary iothalamate and indium diethylenetriamine penta-acetic acid (DTPA) measurements was diminished at 1 month and 1 year after liver transplantation.[7,21]

Both GFR and ERPF were similar in the renal and liver transplant patient populations at 1 month after transplantation. The kidney transplant donors were selected for kidney donation only when they had good renal function. The expectation was that better renal function would be observed in liver transplant patients who were screened for preexisting renal impairment (as measured by serum creatinine and estimated creatinine clearance) and who have two functioning kidneys as compared to the renal transplant patients with one functioning (transplanted) kidney. However, the liver transplant patients were relatively older (48 ± 6 years) than the kidney transplant donors (36 ± 16 years), which may be one of the factors that could account for the similar renal function that was observed in the two patient populations. As liver and renal transplant patients were not receiving any other concurrent nephrotoxic drug therapy at the time of the study, other factors, such as mild preexisting hepatorenal syndrome that was not detectable with routine clinical measures/biopsy examination or hypoperfusion or excessive damage to the kidneys during or after liver surgery, are possibilities that could have contributed to the observed results.

It was not possible to distinguish between decreased blood flow and decreased tubular secretion as the cause of lower clearance of PAH. Afferent arteriolar constriction may have been responsible for the observed decrease in renal hemodynamics in both patient populations.[22] This is supported by the unchanged filtration fraction in both renal and liver transplant patients. Afferent vasoconstriction has been documented with cyclosporine-induced nephrotoxicity and is thought to occur with tacrolimus-induced nephrotoxicity also.

Tacrolimus is a drug with a narrow therapeutic index, and therapeutic drug monitoring is essential to ensure maximum graft survival and minimal toxicity.[23,24] Initial studies in which tacrolimus was measured in plasma reported both good[25] and poor correlations[26] with tacrolimus toxicity. Subsequently, whole blood has been used as the matrix of choice, and positive correlations have been reported between tacrolimus blood concentrations and toxicity in liver and renal transplant patients.[27,28] In both of these studies, a large number of patients were studied, and the trough tacrolimus blood concentrations over a 7-day period before the onset of adverse effects were correlated with toxicity. In our study, there was a poor correlation between the functional hemodynamics and the dose or the whole-blood concentrations of tacrolimus on the day of the study, presumably due to smaller sample size and study design.

In conclusion, renal and liver transplant patients have a reduced GFR and ERPF as measured by exogenous markers. The functional parameters were lower than normal in both patient populations despite normal serum creatinine concentrations. When renal function was compared to patients who have undergone unilateral nephrectomy, renal function in the tacrolimus-treated renal transplant patients appeared to be preserved. In comparison to the initial postoperative baseline values, renal hemodynamics remained stable despite chronic tacrolimus therapy. Judicious monitoring of tacrolimus blood concentrations and adjustments in tacrolimus dose may play a role in preventing severe deterioration in renal function in transplant patients. Whether preservation of functional hemodynamics plays a role in preventing chronic toxicity in the long term due to tacrolimus therapy is an area that warrants further investigation. In general, in transplant patients with tacrolimus therapy, dosing regimen changes are needed only for renally eliminated drugs that have a narrow therapeutic index.

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