

478

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^{99m}Tc-DTPA and ¹³¹I-Hippuran Findings in Liver Transplant Recipients Treated with Cyclosporin A¹

The effects of cyclosporin A (CyA), an immunosuppressive agent that is potentially nephrotoxic, on the kidneys of 9 liver transplant recipients were studied with serial ^{99m}Tc-DTPA and ¹³¹I-hippuran scans. In addition, renal function was determined by measuring serum creatinine levels during the second postoperative week in the 9 unselected CyA-treated patients and, retrospectively, in a control group of 29 liver transplant recipients who had not been treated with CyA and who were selected because they had survived for at least 3 months postoperatively. The early postoperative creatinine level was significantly greater in the CyA group. Eight of the 9 CyA patients showed imaging abnormalities in all preoperative and postoperative studies. Five of the 8 patients showed a pattern similar to that of acute tubular necrosis (relatively preserved perfusion) in at least one study. Lowering the dosage of CyA permitted the continuation of therapy, and all 9 patients are alive after 8 to 14 months.

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CYCLOSPORIN A (CyA) is a metabolite from the fungi *Cylindrocarpon lucidum* and *Trichoderma polysporum* that has been shown to have a strong immunosuppressive action in a wide variety of transplant situations with different animal models (1-9). CyA has been successfully used in humans who have received kidney, liver, pancreas, and bone marrow allografts (10-14). The drug has also produced good results in the treatment of chronic polyarthritis and psoriasis (15, 16).

The enormous potential of CyA in organ transplantation is illustrated by the experience of Calne *et al.* (17) and by our own experience (18). In both Calne's institution and ours, the projected one-year survival rate of primary cadaveric kidneys is 80% or better. In a recent series of liver recipients treated with CyA, the one-year survival rate for patient and graft is projected at 90% (19). However, these experiences with CyA have also shown that this drug must be used with care. The patient has to be observed for signs of hepatotoxicity and nephrotoxicity (10, 11, 13, 14).

The possibility of nephrotoxic side effects of CyA was first reported in 1978 (12), but the extent of the problem could not be defined in the context of renal transplantation. In a recent article we showed that 6 out of 12 liver transplant recipients experienced at least one episode of possible nephrotoxicity, but that the resultant functional disturbances were easily and quickly reversed by downward adjustments of CyA dose, with no resultant rejections (20).

The present study was undertaken in an effort to clarify the effect of CyA upon radionuclide examinations of the kidneys, without the confusing elements added by renal transplantation (*i.e.*, ischemic acute tubular necrosis and rejection).

MATERIALS AND METHODS

CyA Group

Nine patients³ received an orthotopic liver transplant between March and September 1980, and were treated with CyA and prednisone. The first dose of CyA, 15-20 mg/kg/day, was given 2 to 6 hours before the transplantation and continued for 8 weeks; the dose was then gradually reduced to about 10 mg/kg/day. The dose was decreased earlier if life-threatening infection occurred or if clinically overt nephrotoxicity developed (manifested by oliguria, azotemia, and elevation in the serum creatinine level). A low prednisone dose was also given to 8 of the patients. Intravenous steroids were administered as well as oral steroids for treatment of rejection (13, 14, 18).

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³ The study originally included 12 patients. Because of insufficient data, 3 patients are not included, although 2 of the 3 are still well.

TABLE I: Results of ^{99m}Tc-DTPA Renal Studies in Orthotopic Liver Transplant Recipients Treated with Cyclosporin A

| Patient No. | Preoperative Renal Study | Postoperative Renal Studies | | Clinical Data at Time of Postoperative Study | | |
|-------------|-------------------------------|-----------------------------|-------------------------------|----------------------------------------------|------------------------------------|-----------------------------------------|
| | | Days Postop | Findings* | Cyclosporin A Dose (mg/kg/day) | Serum Creatinine Level (mg/100 ml) | Total Serum Bilirubin Level (mg/100 ml) |
| 1 | — | 23 | Abnormal without dissociation | 11.3 | 2.7 | 1.9 |
| 2 | — | 22 | Abnormal with dissociation | 10.8 | 1.3 | 6.8 |
| 3 | — | 12 | Abnormal without dissociation | 11.4 | 1.0 | 3.9 |
| 4 | — | 8 | Abnormal without dissociation | 15.7 | 1.2 | 5.8 |
| | | 25 | Abnormal with dissociation | 9.4 | 6.2 | 1.2 |
| 5 | Abnormal without dissociation | 22 | Abnormal without dissociation | 10.6 | 2.6 | 5.7 |
| 6 | Normal | 14 | Abnormal with dissociation | 14.8 | 4.2 | 6.5 |
| | | 35 | Abnormal with dissociation | 7.1 | 1.2 | 4.1 |
| | | 158 | Abnormal with dissociation | 7.4 | 2.9 | 1.5 |
| 7 | Abnormal with dissociation | 17 | Abnormal with dissociation | 10.5 | 2.5 | 4.0 |
| 8 | Normal | 154 | Normal | 7.6 | 0.7 | 1.0 |
| 9 | Normal | 17 | Abnormal with dissociation | 20.0 | 8.6 | 2.2 |
| | | 26 | Abnormal with dissociation | 7.5 | 1.5 | 1.2 |
| | | 37 | Abnormal with dissociation | 7.7 | 1.8 | 1.3 |

* "Dissociation" indicates 2 or more grading points between perfusion and clearance with relatively preserved perfusion in ^{99m}Tc-DTPA renal study.

Control Group

The last 29 liver transplant recipients who were treated with azathioprine and prednisone (with or without antilymphocytic globulin) and who survived for more than 3 months were studied retrospectively to determine their renal function as reflected in serum creatinine levels. They underwent transplantation between September 1976 and February 1980. During this period the 3-month mortality after liver transplantation was 41% (14). Renal dysfunction usually developed at some time in patients who eventually died. Thus, the selection of successful cases with conventional immunosuppressive therapy created a potential major bias in a comparison with CyA, since the 3-month mortality in the 12 patients treated with CyA was only 8.3%.

Laboratory Values

Serum creatinine and total bilirubin levels were measured serially, including preoperatively, in both the CyA and control groups. They were compared using the t-test.

Imaging Protocol and Grading System

Five of the 9 patients underwent a baseline renal imaging study prior to CyA treatment and liver transplanta-

tion. In all 9 patients postoperative radionuclide imaging was done from 8 to 154 days after transplantation, usually at the time when functional renal abnormalities developed.

The renal imaging study consisted of both a ^{99m}Tc-DTPA and a ¹³¹I-hippuran study. No computer processing was done. During a single viewing session all studies were evaluated by one of us (W.C.K.) without knowledge of the patient's renal or liver function, or of the time of transplantation. In the ^{99m}Tc-DTPA studies, the following parameters were evaluated: perfusion, clearance, and parenchymal transit time. In the ¹³¹I-hippuran studies, clearance and parenchymal transit time were prolonged. Each parameter was graded 1 to 5, with 1 representing normal and 5 severe abnormality. Studies with poor bolus injections were excluded. A significant dissociation between perfusion and clearance was determined to be present when the 2 parameters were graded 2 or more points apart. The grading system has been described in detail (21).

RESULTS

Laboratory Values

Preoperatively, only one patient (in the control group) had an abnormal serum creatinine level. Postoperatively, none of the control patients showed

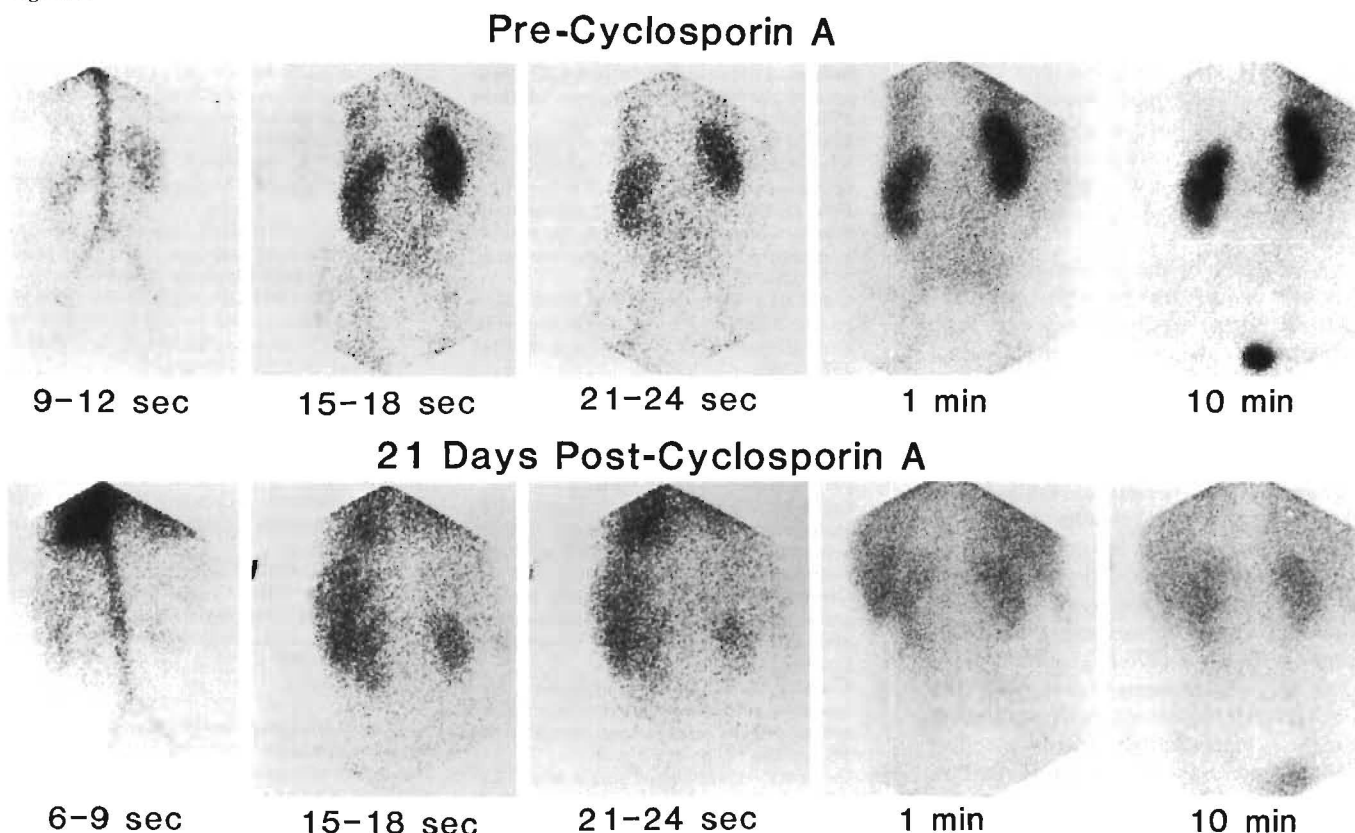
an increased serum creatinine level more than 7 days after the transplantation; 3 patients had transient episodes of serum creatinine level elevations of 2.1, 4.3, and 2.7 mg/100 ml at 2, 3, and 3 days, respectively. For the control group, the maximum serum creatinine levels in the second postoperative week ranged from 0.4 to 1.3 mg/100 ml (0.87 mg/100 ml ± 0.24 S.D.). In the CyA-treated group the serum creatinine levels ranged from 0.8 to 9.2 mg/100 ml (3.31 mg/100 ml ± 2.47 S.D.) during the second postoperative week. Five of the 9 patients had abnormal serum creatinine levels (>1.5 mg/100 ml). Renal function during the second postoperative week, as judged from the serum creatinine levels, differed significantly between the two groups (*p* < 0.01).

The postoperative liver function, as measured by total serum bilirubin levels, did not differ between the control group and the CyA-treated group. The total serum bilirubin level for the CyA-treated group was 3.7 mg/100 ml ± 2.1 S.D., and for the azathioprine-treated group it was 4.7 mg/100 ml ± 4.2 S.D. in the second postoperative week.

Imaging Studies

Of the 5 preoperative studies, 3 were normal and 2 were abnormal (TABLE I). One abnormal study showed

Figure 1



Two ^{99m}Tc -DTPA studies, pretransplantation and posttransplantation, are shown. The first study is normal (Grade 1 perfusion, clearance, and parenchymal transit time). The second study, after 21 days of cyclosporin A immunosuppressive therapy, shows a mild-to-moderate decrease in perfusion (Grade 2) and a severe decrease in clearance (Grade 4).

dissociation between perfusion and clearance with relatively preserved perfusion, and one was abnormal without dissociation. "Abnormal without dissociation" was defined as a parallel decrease in both parenchymal transit time and clearance.

Fourteen postoperative renal studies were done in the 9 patients treated with CyA (TABLE I). One was normal, 4 were abnormal without dissociation, and 9 showed dissociation with relatively preserved perfusion (Fig. 1). Two of the patients with abnormal postoperative studies had had normal imaging studies prior to transplantation.

The findings in the ^{131}I -hippuran studies were qualitatively similar to the findings in the ^{99m}Tc -DTPA studies, particularly with respect to clearance. For this reason, and because dissociation between perfusion and clearance can only be demonstrated with ^{99m}Tc -DTPA, the ^{131}I -hippuran findings are not included in TABLE I.

Radionuclide studies of the kidneys were not performed in the retrospective control patients who were treated

with conventional immunosuppressive drugs.

DISCUSSION

The limitations of this study are evident. Preoperative renal scans were obtained in only 5 of the 9 patients, and in 2 of them they were markedly abnormal before CyA therapy was instituted. An additional patient who was not included because postoperative imaging studies were not obtained also had pre-existing excretion abnormalities with good perfusion. Thus, the existence of pre-existing renal abnormalities could be as high as 50%. Furthermore, all of the 9 patients had long and difficult operations with many blood transfusions (maximum 20 liters) and variable bouts of intraoperative hypotension. Finally, the results in the unselected CyA group had to be compared with the results in the selected group of patients with favorable courses under conventional immunosuppression, none of whom had un-

dergone radionuclide renal scanning before or after surgery.

Whatever primary role pre-existent renal disease played, it was important to suspect the additional role of CyA in nephrotoxicity and to adjust the CyA dose downward accordingly. It has already been suggested that dissociation between perfusion and excretion in renal transplant recipients is a characteristic drug-mediated manifestation (13). In the liver transplant recipients who all had an initial period of seemingly normal renal function within five days, there were no safe alternative explanations for secondary increases in creatinine and blood urea nitrogen levels. Imperfect postoperative liver function could have been contributory, but this was also true in the retrospective control patients.

What has emerged from these studies and, far less commonly, from observations in kidney graft recipients (13) is an injury pattern possibly associated with or aggravated by CyA. It has been impossible to differentiate this pattern of well-preserved perfu-

sion with disproportionately impaired excretion from that of acute tubular necrosis (13). This is a signal for dose reduction, not discontinuance, of this valuable drug. A parallel fall in perfusion and excretion was seen at some time in the kidneys of 4 of the liver recipients, and may represent a less specific variant of CyA nephrotoxicity.

Awareness of the potential nephrotoxicity of CyA has been the most important factor in its proper use. In a previous study of many of the same recipients (20), the rapid reversal of nephrotoxicity following dose reduction was documented. The importance of patient management has been underscored by the eventual results in the 9 patients in the present study. All have remained on reduced doses of CyA and all 9 are still alive from 8 to 14 months later. Kidney graft recipients have also undergone long-term treatment with CyA (17, 18), with the appropriate precautions that can often be delineated accurately with serial radionuclide scanning. Doubtless, the same principles will be important in managing the recipients of other organs such as the heart and pancreas. If precautions in its use are taken, it seems likely that CyA will have a more important impact on transplantation than any other development in nearly two decades.

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