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Correlation Between Dose and Level of Cyclosporine After Orthotopic Liver Transplantation

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It is generally accepted that, in actual clinical practice, the concentration of cyclosporine in blood is the principal determinant of the dosage to be prescribed for a given patient. However, many physicians, in describing immunosuppression policies, still refer to the dose of cyclosporine prescribed after transplantation. The present analysis was undertaken to determine the degree of correlation between the dose and level of cyclosporine in stable liver transplant recipients.

PATIENTS AND METHODS

The records of all adult patients who underwent orthotopic liver transplantation at the Presbyterian-University Hospital, Pittsburgh, between January and October 1987 were evaluated.

Immunosuppression Protocol

The techniques for orthotopic liver transplantation and immunosuppressive protocols utilized in these cases have been described in detail previously.[1,2] In particular, all patients were treated with a combination of cyclosporine and steroids. Cyclosporine (17.5 mg/kg) was administered orally preoperatively. During the operation Medrol 1g and cyclosporine (2 mg/kg) were given intravenously at the time of revascularization of the graft. Postoperatively, the patients received Medrol 200 mg, which was reduced by 40 mg daily until a maintenance dose of 20 mg daily was achieved, and cyclosporine 6 mg/kg intravenously in 3 divided doses. Oral cyclosporine (20 mg/kg) was introduced as soon as the patients had stabilized after the transplant procedure and resumed an oral diet. The dose of cyclosporine was adjusted to maintain a 12-hour cyclosporine whole blood trough level of approximately 1000 ng/mL.

Rejection episodes, in the presence of adequate cyclosporine levels, were treated with a solumedrol bolus. A re-cycle of the Medrol was used in the patients who failed to respond to the steroid bolus. Steroid resistant rejection episodes were treated with the monoclonal antibody OKT3.

Cyclosporine levels were determined on whole blood utilizing a radioimmunoassay kit obtained from Sandoz.

The whole blood cyclosporine level achieved and the dose of cyclosporine used for each patient at the time of the first outpatient visit were recorded. This time-point for analysis was chosen because patients are discharged from hospital only if graft function and whole blood cyclosporine levels are stable. Typically patients are discharged three to eight weeks after transplantation.

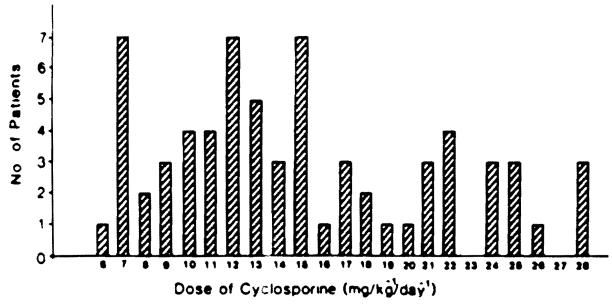

Fig 1. Dose of cyclosporine (mg/kg/day) used by the liver transplant recipients studied.

RESULTS

Thirty-one male and 44 female consecutive adult liver transplant recipients who survived for greater than 3 months with stable allograft function were included in the study. The mean age of the patients was 43.36 ± 1.33 years (mean ± SEM) and the ages ranged from 21 to 70 years.

The doses of cyclosporine used in these patients, as shown in Fig 1, ranged from 6 to 57 mg/kg/day and the median dose was 15 mg/kg/day. Thirteen transplant recipients (17.3%) received doses less than 12 mg/kg/day while 11 patients (14.7%) required doses greater than 22 mg/kg/day.

The concentrations of cyclosporine in the blood in these stable allograft recipients are shown in Fig 2. The median cyclosporine level was 1025 ng/mL with a range of 180 to 1925 ng/mL. The cyclosporine level in one patient was only 180 ng/mL. However, despite this inadequate cyclosporine level, this patient had normal bilirubin and transaminase levels. The remaining 74 liver recipients had cyclosporine levels greater than 500 ng/mL. Cyclosporine levels greater than 1600 ng/mL were found in seven patients (9.3%).

The ideal cyclosporine level in liver transplant recipients with normal hepatic function and without any evidence of cyclosporine toxicity, in our institution, should be between 700 and 1300 ng/mL. In this study 52 patients (69.3%) had cyclosporine levels within this range (Fig 3). The median dose of cyclosporine required to maintain ideal levels was 13 mg/kg/day with a range of 6 to 57 mg/kg/day. This dose of cyclosporine required to maintain ideal levels was less than 10 mg/kg/day in nine patients (17.3%) and was greater than 23 mg/kg/day in 11 patients.

DISCUSSION

Descriptions of the immunosuppression protocols used after organ transplantation typically refer to the dose of cyclospo-

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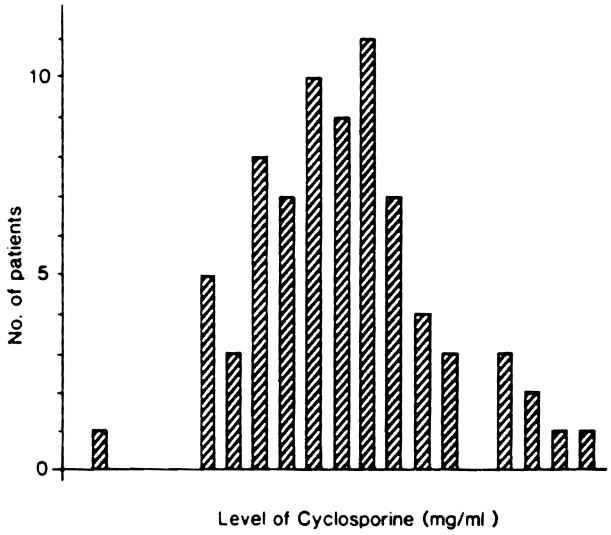

Fig 2. Concentration of cyclosporine in whole blood (ng/mL) in liver allograft recipients.

rine (on a per weight basis) given to patients. In actual clinical practice, however, the amount of cyclosporine given to patients is determined principally by the level of the drug in the blood. This analysis of the amount of cyclosporine administered to and the concentration of cyclosporine achieved in whole blood in 75 liver allograft recipients revealed that the majority of patients had levels of cyclosporine within the standard or universally accepted "therapeutic" range. A few patients with stable graft function had

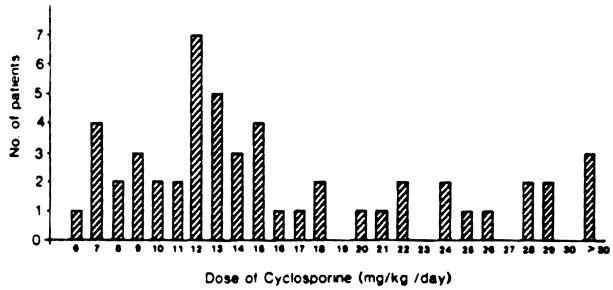

Fig 3. Dose of cyclosporine (mg/kg/day) required to achieve a cyclosporine level of 700-1300 ng/mL in liver transplant recipients.

levels which were outside the therapeutic range. The dose of cyclosporine required to maintain these levels varied widely in these patients.

Furthermore, this study demonstrated that the trough concentration of cyclosporine achieved in blood did not correlate with the dose of cyclosporine administered to stable transplant recipients. This study emphasizes the fact that immunosuppression protocols must include measurements of the level of cyclosporine achieved in blood and not simply the dose of the drug administered.

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