ACUTE REJECTION AND MASSIVE CYCLOSPORINE REQUIREMENTS IN HEART TRANSPLANT RECIPIENTS TREATED WITH RIFAMPIN

Rifampin has been shown to enhance the antifungal effect of amphotericin B (1, 2). Two heart transplant recipients immunosuppressed with cyclosporine and prednisone contracted pulmonary aspergillosis. In vitro studies indicated a synergistic effect of rifampin in combination with amphotericin B against the infecting strains of Aspergillus fumigatus. Previous reports, however, have documented that rifampin induces accelerated liver metabolism of prednisone, presumably due to enhancement of liver microsomal enzymes (3), and, in addition, alters the pharmacokinetic disposition of cyclosporine (4), possibly by a similar mechanism. These effects would be expected to increase the requirements for cyclosporine to maintain stable serum levels—and, possibly, to precipitate acute graft rejection episodes; this expectation was confirmed in the cases described below.

Case Reports

Case No. 1. A 22-year-old woman with the diagnosis of idiopathic cardiomyopathy underwent cardiac transplantation complicated by acute rejection on postoperative days 8 and 21. These were treated successfully with high-dose methylprednisolone and antithymocyte globulin of rabbit origin. Maintenance immunosuppression consisted of cyclosporine and prednisone. On postoperative day 28 pulmonary infection with A fumigatus was diagnosed by transthoracic aspiration of a pulmonary nodule. Treatment with amphotericin B was initiated and gradually increased up to 42 mg/kg/day. Temporary discontinuation of amphotericin B for five days was required because of thrombocytopenia. Thereafter, amphotericin B was reinstated without further declines in platelet counts. On postoperative day 77 a small nodule was noted in the s.c. tissue of the midposterior thoracic region, and this proved to contain A fumigatus upon excisional biopsy. No other extrapulmonary lesions were noted at that time by physical examination or computed tomographic scanning of the thorax and abdomen.

Because of the dismal prognosis of disseminated Aspergillus infection, rifampin (600 mg/day) was added to the amphotericin on postoperative day 83, based on in vitro studies that indicated a synergistic effect of the two drugs, although up to 100 μg/ml of rifampin alone was incapable of inhibiting the Aspergillus isolates. Without rifampin, the minimal inhibitory concentration (MIC) for amphotericin B was 2.0 μg/ml. In the presence of 6.25, 12.5, or 100 μg/ml of rifampin, the MIC for amphotericin B was progressively reduced to 1.5 and 0.25 μg/ml respectively. On postoperative day 88 a new s.c. nodule was excised in the posterior cervical region and this also contained A fumigatus. The regimen for administration of amphotericin B was changed to continuous infusion at a total dose of 1.2–1.4 mg/kg/day, beginning on postoperative day 92. This dosage schedule was well tolerated.

Within eleven days of initiation of treatment with rifampin, however, serum cyclosporine levels (radioimmune assay) decreased from 478 ng/ml to less than 31 ng/ml and severe acute graft rejection ensued, requiring repeat treatment with methylprednisolone and antithymocyte globulin. The dose of cyclosporine was increased in a stepwise fashion (Fig. 1) and cyclosporine levels reached a plateau over the next two and one-half weeks before decreasing precipitously a second time, without any change in cyclosporine dosage. This second decline in cyclosporine levels necessitated rapid escalation of the dosage to greater than 30 mg/kg/day in order to obtain serum levels within the targeted range of 100–300 ng/ml. On postoperative day 115, at the site of a previous bone marrow biopsy from the left iliac crest, a new abscess containing Aspergillus developed. Synergy data identical to those previously described were also demonstrated with this Aspergillus isolate.

On postoperative day 127 the patient developed marked arterial hypotension secondary to severe left ventricular failure as documented by echocardiography, which demonstrated a marked decrease in left ventricular contractile function. Cardiac biopsy was performed on an urgent basis, and it demonstrated mild acute rejection. The patient was treated again with methylprednisolone, but also required continuous inotropic support. Cardiac arrest occurred on the following day and resuscitation was not successful. Postmortem examination revealed severe acute rejection characterized by an interstitial mononuclear cellular infiltrate, interstitial edema, and focal hemorrhage. The lungs contained a moderate number of granulomas, most of which were surrounded by dense connective tissue, and some of these contained persistent fungal forms.

Case No. 2. A 33-year-old man developed acute graft rejection seven days after cardiac retransplantation performed because of constrictive pericarditis that developed after the primary procedure. Serial graft biopsy showed reversal of rejection after treatment with methylprednisolone and antithymocyte globulin. On postoperative day 34 pulmonary aspergillosis was diagnosed by needle aspiration of one of four pulmonary lesions. Treatment consisted of i.v. amphotericin B at a dose of 0.6 mg/kg/day. The total cumulative dose over the subsequent 67 days amounted to 3 g rifampin, 600 mg/day, was also given during the first 56 days of treatment (Fig. 2). Cyclosporine and prednisone were administered on a twice-daily dosage schedule for maintenance immunosuppression. Although no further rejection episodes occurred over the 131-day period of hospitaliza-

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2Abbreviation used in this article: MIC, minimal inhibitory concentration.

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![Figure 1](#): Clinical course of case No. 1 posttransplantation, showing creatinine clearance, creatinine and BUN, as well as cyclosporine dose and serum cyclosporine levels.
tion, cyclosporine dose requirements increased from 8.5 mg/kg/day to a maximum of 28.5 mg/kg/day in order to maintain therapeutic serum levels (Fig. 2). Three days prior to discontinuation of the amphotericin B and rifampin, the cyclosporine dosage was abruptly decreased to 8.5 mg/kg/day in anticipation of rebound toward higher levels because of withdrawal of rifampin. The serum creatinine level increased from 1.5 mg/dL and peaked at 2.3 mg/dL. Levels of blood urea nitrogen showed similar changes, and serum creatinine clearance measurements remained depressed at approximately 24 ml/min. over the next several days. By discharge on postoperative day 131, values for serum creatinine, blood urea nitrogen, and creatinine clearance showed trends toward pretransplant levels and the serum cyclosporine value was stable within a therapeutic range at a dose of 8.5 mg/kg/day. No further rejection episodes occurred.

The use of rifampin, in addition to amphotericin B, to treat *Aspergillus* infections in two heart transplant patients immunosuppressed with cyclosporine and prednisone resulted in marked decreases in serum cyclosporine levels within 11 days of initiation of rifampin, despite previous studies documenting increased serum concentrations of cyclosporine in the presence of amphotericin B (5). This necessitated increases in cyclosporine dosage by as much as fourfold in both patients. In the first patient, acute rejection occurred eleven days after beginning rifampin and never resolved completely upon serial biopsy. It is likely that low serum cyclosporine levels contributed to the persistence of the rejection process and eventual death. The possibility of amphotericin B cardiotoxicity, however, cannot be entirely excluded. In one other published report, two asyloptic episodes followed amphotericin B infusion in a 76-year-old comatose patient with disseminated *Candida albicans* infection (6). Although a temporal relationship was demonstrated for the two asyloptic episodes, a causal relationship was not and, furthermore, additional episodes of asylope occurred at times when amphotericin was not being administered. In our second patient the dose of cyclosporine and the serum levels obtained were substantially higher than in the first case, and rejection did not occur.

Although formal pharmacokinetic studies of cyclosporine and prednisone metabolism were not obtained in our patients, previous studies of prednisolone clearances have documented a marked increase in hepatic metabolism under the influence of rifampin, presumably due to enhanced liver microsomal enzymes (3). The temporal relationships between rifampin administration and decreased cyclosporine levels in our patients strongly suggest cause and effect. Within 11 days of the onset of rifampin administration, in both patients, a 2-3-fold increase in cyclosporine requirement occurred. Further, after 6 weeks of therapy in both patients, a second decline in cyclosporine levels occurred; and, in both cases, despite a marked increase in cyclosporine dosage, cyclosporine levels remained subtherapeutic. The mechanism by which rifampin may result in decreases of cyclosporine serum levels is not known at present, but it is reasonable to attribute a mechanism similar to that demonstrated for prednisolone. Changes in absorption or different means of excretion cannot be excluded. In summary, we suggest that extremely close surveillance of serum cyclosporine levels be maintained in transplant recipients requiring treatment with rifampin to ensure continuously efficacious immunosuppression.

DENNIS L. MODRY, MD
EDWARD B. STINSON
PHILIP E. OVER
STUART W. JAMESON
JOHN C. BALDWIN
NORMAN E. SHUMWAY
Department of Cardiovascular Surgery
Stanford University Medical Center
Stanford, California 94305

REFERENCES

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*Address correspondence to: Dr. D. L. Modry, Division of Thoracic and Cardiovascular Surgery, University of Alberta, Canada T6G 2B7.