The Prophylactic Use of Orthoclone OKT3 in Kidney and Heart Transplantation

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CYCLOSPORINE A (CsA) has improved considerably the results of organ transplantation. However, its nephrotoxic properties remain a problem, especially in the direct postoperative period, and this effect must be carefully balanced with its potent immunosuppressive property. The incidence of delayed renal function after kidney transplantation increased from 13.5% to 25.2% ($P < .05$) at our center after the introduction of CsA. We also observed a serious impairment of renal function after heart transplantation, reflected by a mean 148-μmol/L increase of serum creatinine to a mean peak level of 264 μmol/L (range, 104 to 628) in the first postoperative week. The association of CsA therapy with other potential assaults on kidney function, eg, long cold ischemia times in kidney transplantation and the use of diuretics, in combination with hemodynamic instability in heart transplantation, will certainly have contributed to these nephrologic problems.

In order to prevent the combination of various adverse effects on renal function after kidney transplantation, we recently studied the introduction of CsA on the sixth postoperative day during a seven-day prophylactic course of horse antilymphocyte serum (ALS) in combination with azathioprine (Aza) and low-dose steroids. Compared with a schedule where CsA was given from the day of operation, this immunosuppressive scheme resulted not only in a reduction of acute renal failure from 30.4% to 15.2%, but also in a reduction of acute rejection episodes from 47.8% to 23.9%.[1] We therefore prefer the sequential use of antilymphocyte antibodies and CsA in the early posttransplantation period.

Immunosuppression with monoclonal antibodies may have several advantages over the use of heterologous antilymphocyte preparations. Their specificity is strictly defined, and they can be produced consistently without the problems of batch-to-batch variation in specificity or affinity. Moreover, their in vitro production capacity can be more easily expanded than the in vivo production process of the classic antisera. Orthoclone OKT3 (Ortho Pharmaceutical Corp, Raritan, NJ) is an IgG2a murine monoclonal antibody that reacts with a 20,000-dalton protein associated with the human T cell antigen receptor. Interaction of OKT3 with its target protein blocks the function of T cells and intravenous (IV) injections of OKT3 are effective in reversing acute rejections of allografts and in preventing allograft rejection during the period of OKT3 administration.[2,3] However, its use is limited by the development of antimonoclonal sensitization, which may totally abrogate the therapeutic effect of OKT3, although in combination with conventional immunosuppression, this antibody response against OKT3 can be reduced.[4] We report our initial experience with a short course of prophylactic OKT3 in combination with Aza and low-dose steroids followed by CsA therapy with low-dose steroids in 17 kidney and heart transplant recipients.

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PATIENTS AND METHODS

Kidney Transplantation

OKT3 (5 mg/d) was administered from the day of transplantation immediately before surgery to ten transfused renal allograft recipients (ages 23 to 66 years [mean, 53]; peak lymphocytotoxic antibody level [LAL] 2% to 55% [mean, 10], current LAL 0% to 14% [mean, 10]). One patient received a second allograft with a repeated mismatch for HLA-A3. All other patients were primary transplant recipients. HLA match grade was 1.30 for HLA-A, 1.00 for HLA-B, and 1.20 for HLA-DR. Cross-matches with historical and current sera were negative. Before the first OKT3 dose, 50 mg methylprednisolone and 4 mg clemastine (an antihistaminic) were administered IV. Before subsequent doses, 25 mg methylprednisolone and 4 mg clemastine were administered. OKT3 was prescribed for six to 15 days (mean, 14) in combination with Aza (1.0 mg/kg/d) and 15 mg prednisone. Oral CsA therapy was introduced two days before the last dose of OKT3 and Aza was stopped simultaneously with OKT3. Rejection episodes were diagnosed on histological criteria only. Mean follow-up is 5 months.

Heart Transplantation

Twelve recipients of a first heart transplant with creatinine clearance of >30 mL/min were, in an ongoing study, randomly allocated to CsA therapy from the day of transplantation or to OKT3 given in a dosage of 5 mg/d for seven days starting six hours after transplantation, in combination with Aza (1.0 mg/kg/d) and low-dose steroids. Methylprednisolone (50 to 25 mg) and clemastine (4 mg) were given to prevent side effects. Oral CsA was introduced and Aza was stopped on the fifth postoperative day. All patients had received at least one pretransplantation blood transfusion. Cross-matches with historical and current sera were negative.

The seven patients allocated to OKT3 therapy had a mean age of 52 (range, 46 to 56) years, peak LAL 0% to 47% (mean, 5%), current LAL 0% to 47% (mean, 0%). HLA match grade was 0.86 for HLA-A, 0.57 for HLA-B, and 0.57 for HLA-DR. Diagnosis of rejection was based on routine histologic criteria according to Billingham.[5] Rejection treatment was given only in case of myocyte necrosis. Endomyocardial biopsies were performed weekly for the first 6 weeks. Mean follow up is 4.5 months.

OKT3 and Anti-OKT3 Assays

OKT3 and anti-OKT3 levels were determined by a specific enzyme-linked immunosorbent assay as described by Jaffers et al,[6] with slight modifications. Unconjugated and alkaline phosphatase-conjugated affinity purified antibodies (goat antimouse IgG, goat antimouse IgM, and goat antihuman IgG) were obtained from Southern Biological Associated Inc (Birmingham, Ala). OKT3 levels were calculated with a standard curve of purified OKT3 (Ortho-Cilag, Ltd, Schaffhausen, Switzerland). Anti-OKT3 levels were expressed as the ratio of color development (OD 405) of the test samples and the pretransplantation samples of the patient.

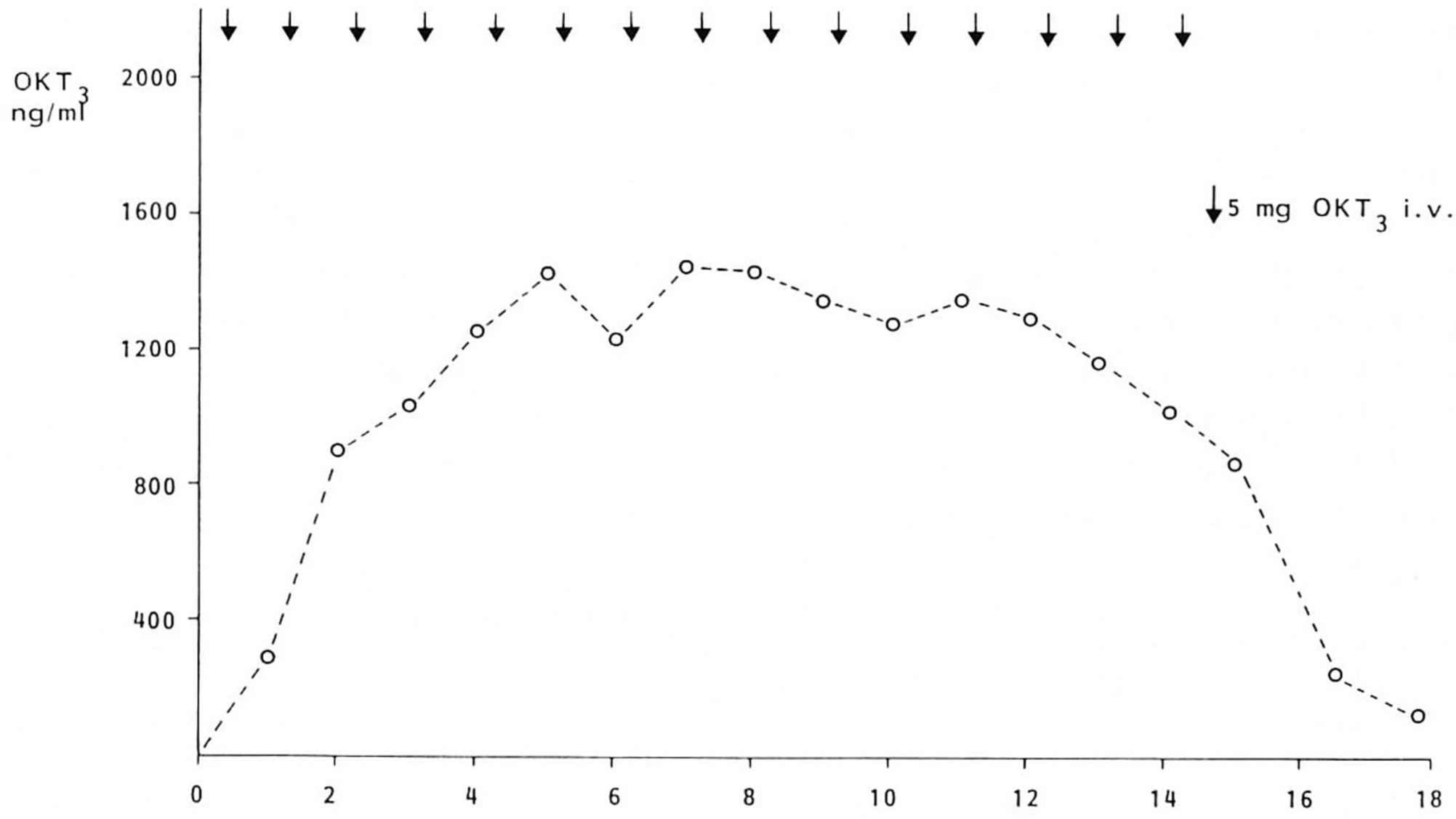

Fig. 1. Mean OKT3 levels in kidney transplant recipients.

RESULTS

Pyrexia (37.7 to 40.4°C; mean 38.4°C) was seen in all ten kidney transplant recipients after the first OKT3 dose. This was accompanied by chills (N = 5), bronchospasm (N = 2), and hypotension (N = 2). Minor temperature rises without other concomitant symptoms were noted after the second OKT3 dose. Thereafter, no fever was observed. One patient had diarrhea on days 3 and 4 of the OKT3 treatment. Heart-transplant recipients had far fewer side effects. Only mild temperature rises up to 38.7°C were observed after the first two doses.

OKT3 levels in both kidney and heart transplant recipients showed large interindividual variation. After the first dose, 24-hour trough levels of 300 ng/mL (range, 200 to 620) were reached. Mean OKT3 trough levels slowly increased to a plateau of 1,300 ng/mL (range, 400 to 2,200) at day 4. After cessation of therapy, OKT3 levels rapidly decreased and became undetectable two to four days after the last injection (Figs 1 and 2).

Significant anti-OKT3 activity was found in three heart transplant recipients from day 6 after transplantation (Fig 3). In another heart transplant patient, anti-OKT3 became positive at day 12 after surgery. All four patients remained anti-OKT3-positive during follow-up. In none of the kidney transplant recipients was anti-OKT3 activity detected during or after treatment.

In Table 1 the perioperative serum creatinine levels are shown for the heart transplant recipients (mean range). In the OKT3-treated patients, a decrease from 148 μmol/L to 87 μmol/L was found, while in the patients on CsA, mean serum creatinine increased from 105 μmol/L to 168 μmol/L and dropped again to 92 μmol/L in the 2-week follow-up. This transient impairment of renal function was less notable than in the historical control patients who had a mean 148 μmol/L increase of serum creatinine to a mean peak level of 264 μmol/L.

None of the kidney transplant recipients showed signs of rejection during the mean follow-up of 5 months. Five heart transplant recipients with a mean follow-up of 6 months remained free of rejection for a mean period of 10 weeks. In these patients, the first rejection

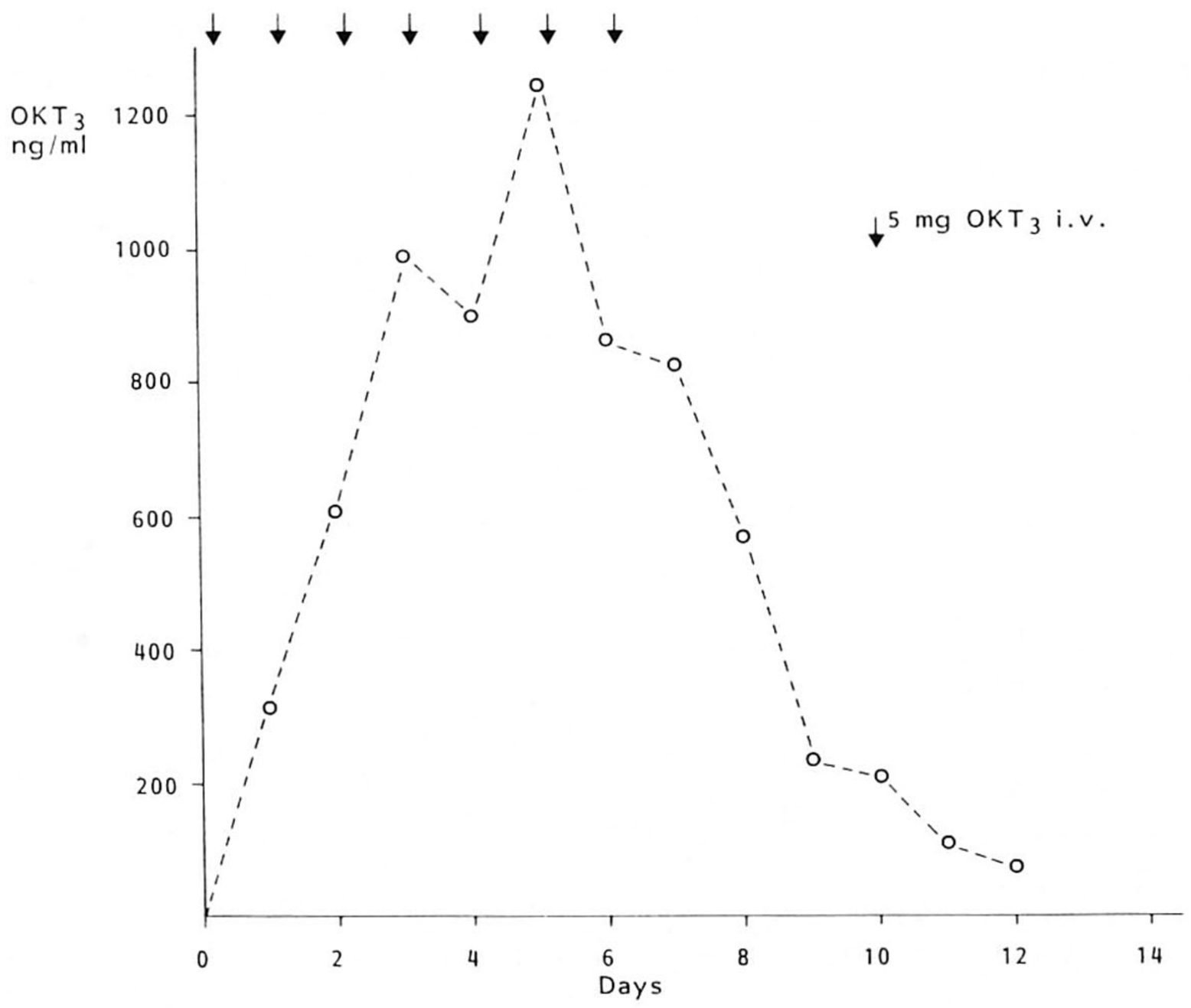

Fig. 2. Mean OKT3 levels in heart transplant recipients.

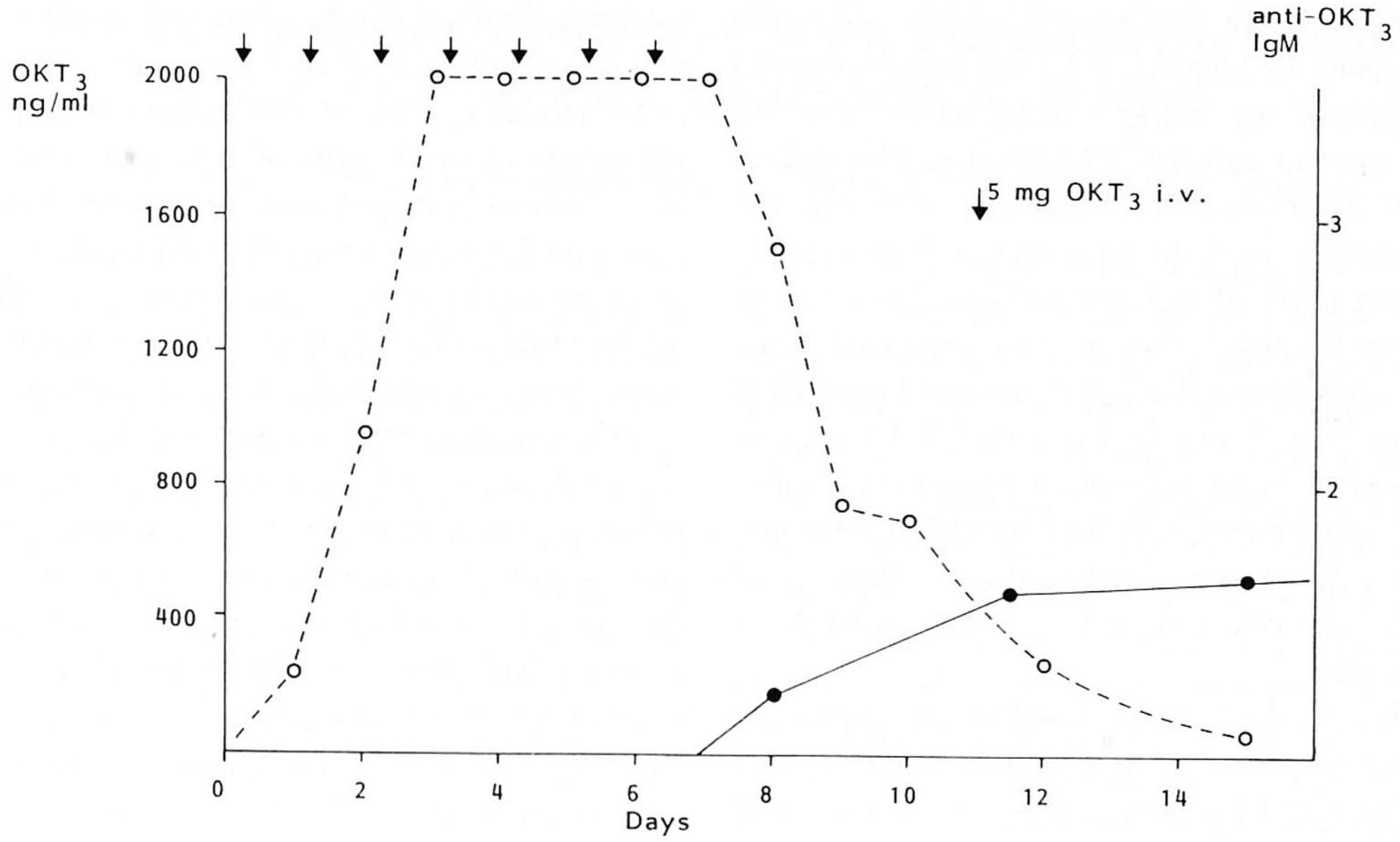

Fig. 3. OKT3 (○) and anti-OKT3 (●) levels in a heart transplant recipient.

was diagnosed at 5, 8, 10, and 10 weeks, respectively, while one patient with a follow-up of 6 months had no rejection.

DISCUSSION

Side effects of OKT3 were anticipated but were more severe than expected in the kidney transplant recipients. This may be due to the fact that the first injection was given just before transplantation and in a number of patients before the start of anesthesia. In the heart transplant recipients, who received their first injection of OKT3 after surgery while still on ventilation, only minor side effects were observed. In these patients, renal function improved during the first postoperative week, in contrast to the cardiac patients, who were treated with CsA from the first day on. The absence of nephrologic problems during this period made patient handling far less complicated.

Serum OKT3 levels varied widely among individuals, probably because a fixed dosage of 5 mg was used in all our patients, while body weight ranged from 50 to 90 kg. We found a slow daily increase of 24-hour OKT3 trough levels, which resulted in a plateau phase from day 4 onward. As none of our patients rejected during OKT3 treatment, these OKT3 levels of 400 to 2,200 ng/mL seem sufficient to prevent rejection.

Anti-OKT3 was found in heart transplant but not in kidney transplant recipients, although both patient groups received the same additional immunosuppression in the first postoperative week. Anti-OKT3 was even

Table 1. Serum Creatinine Before and After Heart Transplantation

	Serum Creatinine Levels (μmol/L) and Means		
	Preoperative	First Week	Second and Third Week
OKT3	148 (81-214)	87 (66-228)	101 (79-111)
CsA	105 (78-133)	168 (136-485)	92 (64-189)
CsA, historical	117 (69-293)	264 (104-628)	96 (40-166)

detected within that period, which makes the difference in length of Aza therapy between the groups an unlikely explanation for the difference in anti-OKT3 response. This differential antimonoclonal response between the two groups may be due to the immunosuppressed state of the uremic renal transplant candidates who also showed impaired antibody responses after influenza and hepatitis B vaccination.[7,8] The higher anti-OKT3 responsiveness of heart transplant recipients implies that higher dosages of Aza should be administered after heart transplantation than after kidney transplantation to prevent anti-OKT3 formation.

OKT3 prophylaxis resulted in adequate immunosuppression in all patients. Even when administered for seven days, as we did after heart transplantation, cessation of therapy was not accompanied by escape rejection episodes. In fact, none of our kidney transplant recipients showed signs of rejection, and the heart transplant patients remained free of rejection for a mean period of 10 weeks. None of these patients rejected in the first month while, at that time, 37% of our historical heart transplant controls had signs of rejection.

We conclude that a short OKT3 prophylaxis followed by CsA therapy is a safe and effective immunosuppressive schedule. Side effects can be minimized by giving the first dose of OKT3 postoperatively. The difference in anti-OKT3 production between kidney and heart transplant recipients could be diminished by the use of higher Aza dosages in cardiac patients.

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