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CYCLOSPORIN A HEPATOTOXICITY IN 66 RENAL ALLOGRAFT RECIPIENTS[1]

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Liver functional abnormalities were seen in 13 (19.7%) of 66 recipients of cadaveric renal homografts treated with cyclosporin A and prednisone. However, such presumed hepatotoxicity was a minor problem in the use of cyclosporin A. The complication was less frequent than that of nephrotoxicity, was as easily manageable with reductions in the cyclosporin A dosage, and generally did not cause clinical illness. In an occasional case, late hepatotoxicity can force a therapeutic change from cyclosporin A to azathioprine, but careful consideration should be given to the dangers of subsequent rejection.

When cyclosporin A (Cy A), an immunosuppressive agent discovered (*1, 2*) and produced by the Sandoz Corporation, was first being used in humans by Calne et al. in 1978 (*3*), hepatic dysfunction was noted in some of the patients, which has since been noted by others (*4, 5*). The purpose of this paper is to clinically analyze the incidence, the manageability, and the consequences of this side effect.

MATERIALS AND METHODS

Between December 22, 1979 and September 28, 1980, 66 patients received 67 cadaveric kidneys at the University of Colorado Health Sciences Center. Nine of the 66 recipients were given their second or third homograft. The renal function and the fate of the patients have recently been reported in detail elsewhere (*6*).

A total of 6 patients of the 66 were hepatitis B surface antigen (HBsAg)-positive preoperatively. One patient had cirrhosis of the liver prior to the renal transplantation. No liver biopsies were obtained in the 66 patients.

Immunosuppression. A dose (or doses) of 17.5 mg/kg/day of Cy A was given orally prior to surgery and usually maintained for 8 weeks postoperatively. Usually, the dose was then lowered to the 10 mg/kg/day range. This decrease was done earlier in the event of serious nephro- or hepatotoxicity.

Prednisone was given concomitantly with the Cy A in most patients. In all adults after the first 20 cases, 200 mg/day was given on the day of operation. The dose was tapered by 40 mg daily for 4 days. On day 5, the dose was reduced by 20 mg to reach the maintenance dose of 20 mg/day.

If rejection intervened, it was treated by an intravenous bolus of 1 g of methylprednisone or hydrocortisone and the oral prednisone was temporarily increased. Cyclosporin was not increased.

RESULTS

Thirteen patients had at least one episode of hepatotoxicity, defined as a rise in bilirubin over 2.0 mg/100 ml (34.2 mmol/liter). One of the 13 patients was HBsAg positive before transplantation.

Early toxicity. Eleven of these 13 patients (16.7% of the 66) showed signs of hepatotoxicity 2 weeks to 2 months after the transplant (Table 1). It occurred 4.9 ± 1.9 (SE) weeks postoperatively. The cyclosporin at the time was 17.7 ± 1.1 (SE) mg/kg/day, range 15.9 to 19.5 mg/kg/day. The peak total bilirubin averaged 3.9 ± 1.6 (SE) mg/100 ml (66.7 ± 27.4 (SE) μmol/liter). After Cy A was lowered to 10.6 ± 1.9 (SE) mg/kg/day, the bilirubin normalized (<1.5 mg/100 mg (<25.7 μmol/liter)) within a few days. None of the patients were ill.

Late toxicity. Late toxicity manifested itself in patients 1, 12, and 13 (Table 2). One of these patients had previously had early hepatotoxicity which receded with dose reduction. The late toxicity occurred at 13, 8, and 7 months after transplantation. The bilirubin ranged from 2.5 (42.8 μmol/liter) to 6.0 mg/100 ml (102.6 μmol/liter). The three patients were changed from Cy A and prednisone to azathioprine and prednisone. Patients 12 and 13 also had nephrotoxicity as an indication for this therapeutic change. Patient 1 had normal kidney function both before and after the change in immunosuppression. All patients had their liver functions return to normal within a few days after the adjustments in therapy were made. Their subsequent serum bilirubin levels ranged from 0.6 to 0.9 mg/100 ml (10.3 to 15.4 μmol/liter).

Other liver function tests. In the 13 patients whose total bilirubin increased, nonconjugated bilirubin was responsible for 50% of the rise. The changes in other liver values were nonspecific. SGOT and SGPT stayed within normal limits in one-half of the patients and in the other half of the numbers rose to three times normal. Alkaline phosphatase stayed normal or just over the normal limit. Seven of the 13 patients were on other potentially liver-toxic drugs (six on cimetidine and three on isoniazid). These drugs were not changed during the toxic episodes.

DISCUSSION

The two most serious side effects of cyclosporin are nephrotoxicity and hepatotoxicity. We have previously analyzed the nephrotoxicity in liver transplant patients (*7*). Although the incidence of nephrotoxicity at Cy A dose levels of 17 mg/kg/day was 50%, this complication could easily be managed and proved to be highly reversible with dose reduction.

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TABLE 1. Early Cy A hepatotoxicity in cadaveric renal transplants

Patient	Time of postoperative hepatotoxicity (weeks)	Before dose adjustment		After dose adjustment	
		Total bilirubin (mg/100 ml (μmol/liter))	Cy A dose (mg/kg/day)	Total bilirubin (mg/100 ml (μmol/liter))	Cy A dose (mg/kg/day)
1	8	2.1 (35.9)	19.3	1.3 (22.2)	10.0
2	5	2.5 (42.8)	17.5	1.2 (20.5)	9.0
3	4	6.6 (112.9)	18.5	1.0 (17.1)	14.0
4	5	5.5 (94.1)	16.9	1.9 (32.5)	7.9
5	4	4.5 (77.0)	17.5	1.1 (18.8)	13.9
6	8	4.0 (68.4)	19.5	1.0 (17.1)	8.9
7	3	6.3 (107.7)	16.6	1.4 (23.9)	9.2
8	5	2.9 (49.6)	17.5	0.6 (10.3)	11.5
9	7	2.3 (39.3)	19.0	1.1 (18.8)	10.6
10	2	2.2 (37.6)	17.5	1.5 (25.7)	10.0
11	3	3.8 (65.0)	15.9	0.7 (12.0)	11.3
Mean ± SE	4.9 ± 1.9	3.9 ± 1.6 (66.7 ± 27.4)	17.7 ± 1.1	1.2 ± 0.3 (20.5 ± 5.1)	10.6 ± 1.9

TABLE 2. Late Cy A hepatotoxicity in cadaveric renal transplants

Patient	Time of postoperative hepatotoxicity (months)	Total bilirubin (mg/100 ml (μmol/liter))	Cy A dose (mg/kg/day)	Total bilirubin after change from Cy A to azathioprine (mg/100 ml (μmol/liter))
1	13	6.0 (102.6)	5.0	0.6 (10.3)
12	8	2.9 (49.6)	8.9	0.9 (15.4)
13	7	2.5 (42.8)	7.0	0.9 (15.4)

In this study, a 16.7% incidence of hepatotoxicity occurred within 2 months after transplantation. As with the nephrotoxicity, the hepatotoxicity receded rapidly with dose reduction.

In three patients with late hepatotoxicity, the dose was already so low that it was not thought to be safe to reduce it further. Subsequent experience has shown this anxiety to be unfounded. Doses of 7 to 8.9 mg/kg/day as in patients 12 and 13 have been shown to be immunosuppressive as well as safe (*6*). The exact lower limits of acceptability are not clear. If late serious hepatotoxic side effects occur on daily doses as low as 5 mg/kg/day, a change from Cy A to azathioprine may be in order.

At the time of this study, serum levels of Cy A could not be obtained in the North American continent. Whether the phenomenon of late occurring toxicity in the use of Cy A is attributable to changes in the absorption, in metabolism, or in tissue accumulation of the drug needs to be resolved in future studies which should include plasma levels.

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