

NEPHROTOXICITY OF CYCLOSPORIN A IN LIVER AND KIDNEY TRANSPLANT PATIENTS

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Summary In six of twelve orthotopic liver recipients nephrotoxicity was noted after 13–22 days of treatment with 16.3 ± 2.9 (SEM) mg/kg per day of cyclosporin A (CyA). With a decrease in the daily CyA dose to 9.2 ± 2.3 (SEM) mg/kg kidney function returned to normal. No hepatic rejections occurred on this lowered CyA dose. In 4 out of 66 kidney recipients a switch from a CyA dose of 5.2–10.7 mg/kg daily to azathioprine was done 4–8 months after transplant because of unsatisfactory kidney function, suspected to be due to nephrotoxicity. In three patients, this resulted in an improved graft function. A fourth transplant was lost to an irreversible rejection 13 days later. Thus CyA is nephrotoxic but this toxicity is easily reversed, even after many months of treatment, and the ease with which this complication can be managed suggests that nephrotoxicity should not diminish the high expectations that transplant surgeons have for CyA.

Introduction

CYCLOSPORIN A (CyA), a metabolite from the fungi *Cylindrocarpum lucidum* and *Trichoderma polysporum*, was discovered by Dreyfuss et al.¹ Its immunosuppressive properties were first reported by Borel et al.² The earliest clinical studies of CyA on kidney transplant patients were reported in 1978, when the possibility of nephrotoxic side effects was raised.^{3,4} Calne et al.^{3,5} reported a putative acute nephrotoxic syndrome leading to anuria or oliguria in 11 out of 32 patients treated with CyA. They thought that this problem was ameliorated by inducing forced diuresis with fluids and mannitol. They recommended delaying the administration of the first dose of CyA until post-transplantation diuresis was established. In our own experience, this early kidney failure was usually caused by acute rejection rather than by nephrotoxicity of CyA and could be prevented or treated with steroids.^{6,7} Thus, we have started treatment with CyA preoperatively.

To clarify the question of CyA nephrotoxicity further, we have studied renal function in liver transplant recipients who were treated with this drug. In addition, observations relevant to nephrotoxicity were made in four kidney graft recipients whose therapy was changed from CyA to azathioprine 4–8 months after transplantation.

TABLE I—NEPHROTOXICITY* FROM CYCLOSPORIN A FOUND IN LIVER TRANSPLANT PATIENTS

Patient	Time of max. toxicity after transplant (days)	Max. serum creatinine ($\mu\text{mol/l}$)	CyA dose (mg/kg)	Non-toxic CyA dose (mg/kg)
1	22	221	13.0	11.0
4	22	548	17.5	8.2
5	17	248	17.5	14.0
6	13	424	17.5	7.2
7	15	221	17.5	8.7
9 (a)	13	813	20.0	7.5
9 (b)	41	274	11.0	7.5
Mean \pm SE	$17 \pm 3.8 \dagger$	393 ± 206	16.3 ± 2.9	9.2 ± 2.3

*Nephrotoxicity defined as a serum creatinine $>175 \mu\text{mol/l}$.

\dagger Excluding 9 (b).

Patients

After liver transplantation, twelve patients were treated with CyA and low doses of prednisone. All twelve were given one dose of CyA, 15–20 mg/kg, before operation and this daily dose was continued afterwards intramuscularly or orally. Before operation and afterwards renal function was monitored with daily serum creatinine (table 1) and blood urea nitrogen (BUN) determinations, plus one to two times weekly creatinine clearances. Postoperatively, renal scans were done with ^{131}I -hippuran and $^{99\text{m}}\text{Tc}$ -diethylenetriamine-pentaacetic acid (DTPA),⁸ and in six patients the results could be compared with similar preoperative studies. One patient died on the 19th postoperative day from a complete hepatic artery thrombosis plus a partial portal vein thrombosis. With one exception, the eleven surviving recipients now have normal liver function. The exceptional patient has chronic rejection with a bilirubin of 113 $\mu\text{mol/l}$, but he has not shown any signs of nephrotoxicity with a CyA dose of 9.5 mg/kg.

From December, 1979, to September, 1980, 66 patients given 67 cadaveric kidney transplantations have received CyA and prednisone.^{6,7} In 4 of those 66 patients the immunosuppression was changed after 4–8 months from CyA and prednisone to azathioprine and prednisone. The prednisone dose was kept constant. Indications and timing of the switch are listed in table II.

Results

Significant renal function abnormalities were noted on seven occasions in six of the twelve liver transplant recipients. The deteriorations occurred suddenly with sharp rises in the serum creatinine and BUN after 13–22 days of CyA treatment. A drop in urine output and weight gain was also noted. The CyA dose at the time ranged between 11 and 20 (mean 16.3) mg/kg (table 1). The renal scans showed normal blood flow, with decreased clearance, a finding described in kidney transplants as consistent with acute tubular necrosis (ATN).⁸

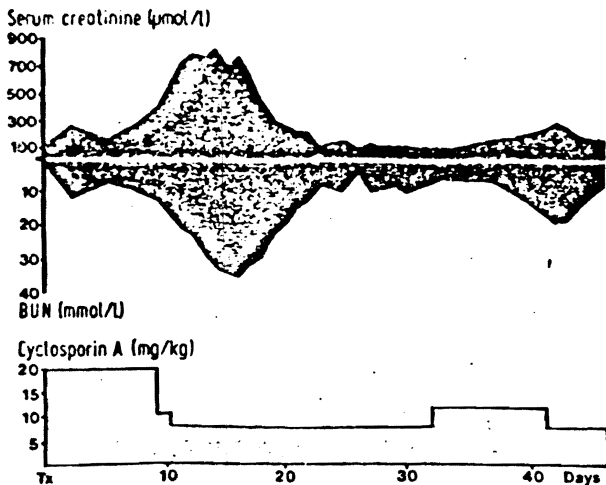
After decreasing the CyA dose, the foregoing changes in renal function promptly disappeared. The narrow margin between an acceptable situation and clinically overt

TABLE II—NEPHROTOXICITY IN RENAL TRANSPLANTED PATIENTS FROM CYCLOSPORIN A RECORDED AS KIDNEY FUNCTION JUST BEFORE DISCONTINUING CYCLOSPORIN A

Patient	Time of change to azathioprine after transplant (mo)	Serum-creatinine on CyA ($\mu\text{mol/l}$)	CyA dose (mg/kg)	Serum creatinine on azathioprine ($\mu\text{mol/l}$) [*]	Indications for change of immunosuppression
3	8	274	10.7	133	Suspected nephrotoxicity plus hepatotoxicity (bilirubin $50 \mu\text{mol/l}$) \ddagger
9	6	318	7.0	159	Suspected nephrotoxicity
12	4	407	7.0	230	Suspected nephrotoxicity
21	5	318	5.2	Kidney loss	Suspected nephrotoxicity

*Kidney function for patients on azathioprine recorded when the function had reached a steady state. Steroid treatment remained unchanged during this period (prednisone 10–20 mg/day).

\ddagger Patient 3 had a normal liver function within 2 weeks.



Kidney function in liver recipient no. 9.

CyA dose of 20 mg/kg daily resulted in a severe episode of uraemia. Patient not dialysed. After reduction in CyA dose, kidney function returned to normal. Later increase in CyA from 7.5 to 11.0 mg/kg daily caused second deterioration in kidney function; function again normal after CyA dose adjustment.

nephrotoxicity is exemplified by liver patient 9. Early pronounced nephrotoxicity was relieved by reducing CyA from 20.0 to 7.5 mg/kg per day. Later, an increase in the CyA from 7.5 to 11.0 mg/kg resulted in a second example of nephrotoxicity (see figure). A third episode was observed one month after the time shown in the figure when the dose of 11 mg/kg was temporarily reinstated. The non-toxic CyA dose has been found to range from 7.4 to 14.0 (mean 9.2) mg/kg in patients with liver grafts. None of these patients have shown any signs of acute hepatic rejection.

SI CONVERSION

Creatinine: 1 $\mu\text{mol/l}$ = 0.011 mg/dl
 Bilirubin: 1 $\mu\text{mol/l}$ = 0.059 mg/dl
 Urea nitrogen: 1 mmol/l = 1.4 mg/dl

Just before changing from CyA to azathioprine, all 4 of the renal transplant patients had good renal blood flow on scans which were interpreted as consistent with ATN. After the switch, renal function improved within 1-3 weeks in three recipients with halving of the average serum creatinine concentrations. Two of these three recipients had a normal renal function after the transplant. It took 5-7 months on a stable CyA dose of 7 to 10.7 mg/kg for the nephrotoxicity to reveal itself. The fourth patient experienced graft rejection within 13 days of changing to azathioprine.

Discussion

The opportunity to measure renal function in twelve liver transplant recipients permits conclusions to be drawn about the nephrotoxicity of CyA without the confusion inherent with such studies on kidney transplant patients. The good liver function which was achieved in eleven of these patients precludes the hepatorenal syndrome as a factor. Six patients exhibited nephrotoxicity in doses of 11.0-20.0 mg/kg daily. The complication responded to dose reduction and was completely reversible.

The evidence of nephrotoxicity is almost as convincing in the four renal recipients who were changed from CyA to azathioprine. Here, nephrotoxicity apparently occurred in doses as low as 5.2 mg/kg daily. The risk of such a therapeutic change under these circumstances was shown by the prompt rejection of one of the four kidneys despite substitution of

azathioprine for CyA. In the exceptional case, just as in the other three, the renal scans before the drug switch had shown the combination of good perfusion plus impaired clearance, which we have associated with nephrotoxicity rather than rejection.⁶

Although nephrotoxicity was thus a feature of CyA therapy after both liver and kidney transplantation, the usefulness of the drug was little affected. Dose adjustments were easy to make and were not followed by rejection in most instances. In our view, CyA remains a major advance in clinical immunosuppression.

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Preliminary Communication

INHIBITION OF PENTAGASTRIN-STIMULATED AND OVERNIGHT GASTRIC SECRETION BY LM24056, A NEW PHENOTHIAZINE-DERIVED ANTISECRETORY DRUG

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Summary LM24056, a tricyclic drug, weakly inhibited pentagastrin-stimulated gastric secretion but was a powerful inhibitor of nocturnal gastric secretion in 5 healthy volunteers. In 23 patients with duodenal ulcer, LM24056 at doses of 100, 200, and 300 mg inhibited overnight acid output by 31%, 70%, and 81%, and overnight pepsin secretion by 15%, 50%, and 69%, respectively. In view of its gastric inhibitory effects, LM24056 warrants clinical evaluation in the treatment of peptic ulcer disease.

INTRODUCTION

LM24056 is a phenothiazine (fig. 1) (Pharmuka, Gennevilliers, France) which has been shown in animal studies to inhibit the gastric secretory response to pentagastrin, 2-deoxyglucose, carbachol, and food, but not the response to histamine. The drug protects rats against experimental gastric ulceration induced by indomethacin and phenylbutazone. We have studied the effects of LM24056 on pentagastrin-stimulated and overnight gastric secretion in man in order to determine whether the drug has therapeutic potential for the treatment of peptic ulceration.

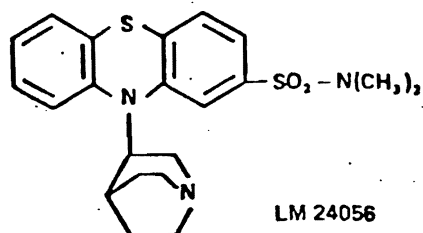


Fig. 1—Structural formula of N,N-dimethyl sulphamoyl-2-(quinuclidinyl-3)-10-phenothiazine (LM24056).

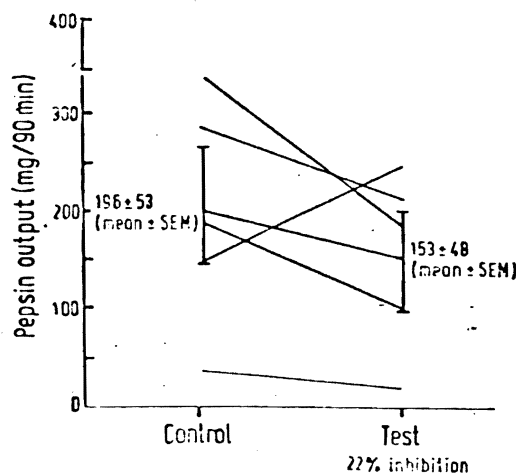
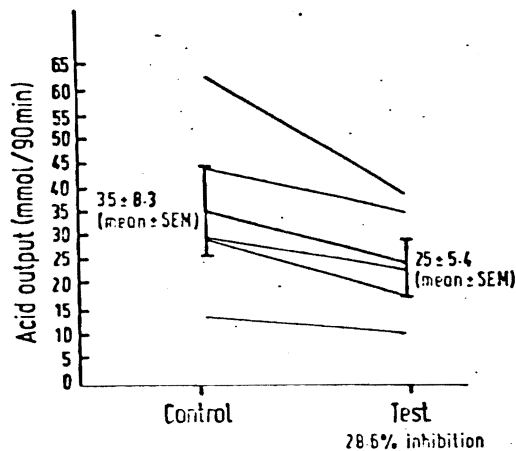


Fig. 2—Effect of LM24056 (200 mg) on pentagastrin-stimulated gastric secretion.

METHODS

Five healthy volunteers underwent two tests in random order on separate days. In each test, after an overnight fast, the duodenum was intubated and a vented nasogastric tube was positioned for aspiration of gastric contents. Basal gastric secretions were collected in 15 min samples for 1 h, after which pentagastrin was administered by constant intravenous infusion at a dose of $2 \mu\text{g kg}^{-1} \text{h}^{-1}$. Pentagastrin-stimulated gastric juice was collected in 15 min samples for 90 min. Throughout the test 155 mmol/l sodium chloride was infused down the duodenal tube at 3 ml/min. At the start of the basal collection either LM24056 200 mg (as crushed tablets) in 10 ml of physiological saline solution, or 10 ml of saline solution alone, was instilled during 2 min down the duodenal tube.

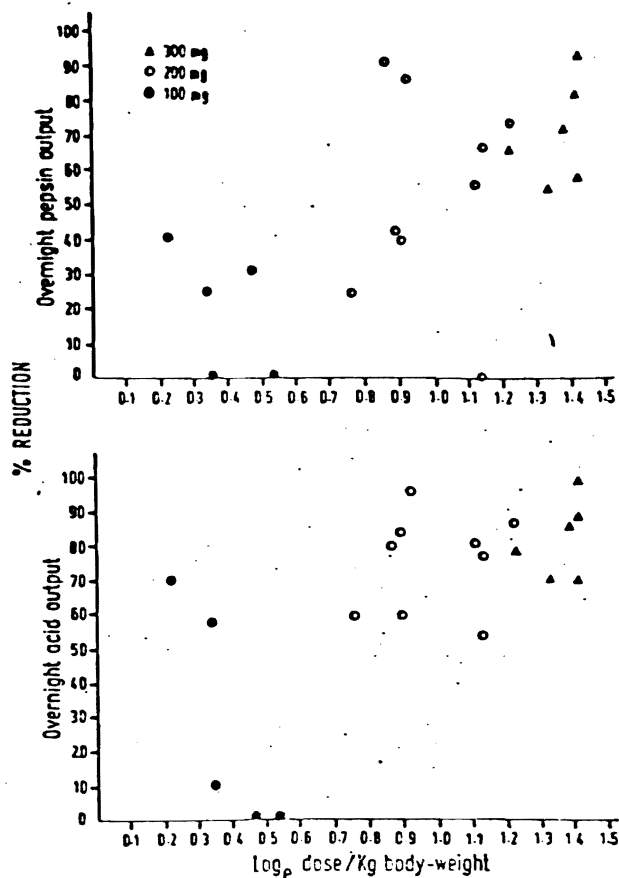


Fig. 3—Relation between dose of LM24056 and degree of inhibition of gastric secretion.

The volume of gastric juice aspirated during each 15 min period was recorded and a sample was assayed for pH, acid concentration, and peptic activity.

23 patients (18 with active duodenal ulcers and 5 volunteers who were known to have high acid outputs) had gastric juice collections on two separate nights. They had a light tea at 6 P.M. and gastric juice was collected from 9 P.M. till 9 A.M. the next morning. On one of the nights LM24056 was taken orally at 7 P.M. 6 subjects received LM24056 100 mg, 11 received 200 mg, and 6 received 300 mg. Gastric juice was collected in hourly samples, the volume was recorded and a sample assayed for pH, acid concentration, and peptic activity. pH was measured by means of an automatic titrator (Radiometer). Acid concentration was determined by titration to pH 7.0 with sodium hydroxide. Pepsin was assayed by the method of Berstad.¹

RESULTS

Response to Pentagastrin

LM24056 (200 mg) administered intraduodenally inhibited mean acid output during the 90 min of pentagastrin stimulation by 29% and pepsin output by 22% (fig. 2). Reduction in acid output was attributable to a reduction in the rate (volume) of secretion, which fell by a mean of 34%. The concentrations of acid and pepsin did not change significantly.

Overnight Gastric Secretion

All doses of LM24056 reduced overnight acid and pepsin output in a dose-dependent manner (fig. 3). With 100 mg the decrease was attributable to a reduction solely in the rate of secretion. However, with 200 mg and 300 mg (see accom-