

KETOCONAZOLE TO REDUCE THE NEED FOR CYCLOSPORINE AFTER CARDIAC TRANSPLANTATION

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Abstract Background. Because ketoconazole can markedly reduce the need for cyclosporine and because it also has antimicrobial properties, it may offer benefits in the treatment of patients after cardiac transplantation.

Methods. We randomly assigned 43 patients at the time of cardiac transplantation to receive ketoconazole (200 mg per day) (23 patients) or no ketoconazole (20 patients). The main end points were the dose of cyclosporine required and the incidence of cardiac rejection and infection.

Results. Ketoconazole reduced the dose of cyclosporine needed to maintain target levels by 62 percent at one week and by 80 percent at one year. The cost savings per patient (in U.S. dollars, inclusive of the cost of ketoconazole) was about \$5,200 in the first year and about \$3,920 in each subsequent year. The mean (\pm SD) rate of rejection in the first month was lower in the ketoconazole group than in the controls (4.2 ± 0.8 vs. 5.7 ± 1.0 episodes per 100 patient-days, $P<0.001$), and the av-

erage number of days to the first rejection was higher (30 ± 29 vs. 15 ± 8 , $P=0.03$). In the first year, 22 percent of the ketoconazole group required cytolytic therapy, as compared with 35 percent of the controls, and 9 percent of the ketoconazole group required total lymphoid irradiation, as compared with 15 percent of the controls ($P=0.07$). The incidence of infection was lower in ketoconazole-treated patients than in controls in the second month (1.4 ± 0.5 vs. 2.8 ± 0.7 episodes per 100 patient-days, $P<0.001$) and in the third month (0.8 ± 0.3 vs. 2.3 ± 0.6 episodes per 100 patient-days, $P<0.001$). Transient, asymptomatic cholestasis was observed in the ketoconazole group.

Conclusions. After cardiac transplantation, ketoconazole greatly reduced the need for cyclosporine, resulting in substantial cost savings. Ketoconazole also reduced the rates of rejection and infection, without persistent toxic effects. We now use ketoconazole routinely in cardiac-transplant recipients. (N Engl J Med 1995;333:628-33.)

THE interaction of ketoconazole with cyclosporine, resulting in the delayed metabolism of cyclosporine, and the potential for cyclosporine-induced nephrotoxic effects have been well described.^{1,2} The key to the safe administration of these two agents in combination is the appropriate adjustment of the dose of cyclosporine. The two drugs have been used safely together for periods as long as 47 months.³⁻⁶

The deliberate use of ketoconazole to reduce the need for cyclosporine is not new, but it is particularly relevant because of the high cost of cyclosporine. Butman et al. used ketoconazole in patients with heart transplants six months or later after transplantation and compared the results with those in historical controls.⁶ The requirement for cyclosporine was reduced by 88 percent. No toxic effects were seen in more than two years of follow-up. First et al. reported similar findings in a randomized study of renal-transplant recipients.⁵

Other theoretical advantages of ketoconazole include a reduction in the rate of infection because of the drug's broad antimicrobial effects. Also, a decrease in the level of low-density lipoprotein (LDL) cholesterol reduces the level of LDL-bound cyclosporine, leaving a higher level of free cyclosporine. A reduction in serum cholesterol levels could theoretically decrease any role that cholesterol might have in the development of coronary artery disease in transplants. Possible disadvantages include the known hepatotoxicity of ketoconazole (particularly since cyclosporine itself is mildly hepatotoxic) and the possible emergence of resistant strains of fungi and yeast.

In a randomized trial, we sought to determine pro-

spectively whether low-dose ketoconazole (200 mg daily) could be used safely from the time of transplantation and whether it would provide a clinically useful cyclosporine-sparing effect. We also evaluated the effect of ketoconazole on rates of rejection and infection.

METHODS

The study was approved by the Ethics and Research Committee at our hospital. All the patients gave informed consent. Forty-three consecutive cardiac-transplant recipients over 18 years of age were randomly assigned in a prospective, nonblinded study to receive either ketoconazole (Nizoral, Janssen-Cilag) or no ketoconazole. Four additional patients were not randomized. Two of these were under 18 years of age, one received a donor heart known to have coronary artery disease, and one received a heart and a kidney simultaneously. Treatment with oral ketoconazole (200 mg daily) was started on day 2 after transplantation; the drug was taken two hours before therapy with histamine H₂ antagonists to avoid the possibility of reduced absorption as a result of taking the two agents together.⁷

We analyzed the following variables: the dosage and blood level of cyclosporine, hepatic and renal function, subfractions of serum lipoproteins, serum testosterone levels (men only), the incidence of cardiac rejection, the number of days to the first rejection, the requirement for cytolytic therapy, the use of total lymphoid irradiation, the use of plasmapheresis and photopheresis to treat resistant rejection, and rates of infection (overall, viral, bacterial, and fungal or yeast).

Treatment with Immunosuppressive Agents

The patients received four to six days of induction therapy with equine antithymocyte globulin (Atgam, Upjohn), with the dose titrated to maintain a CD2 cell count of about 100 per cubic millimeter. Maintenance antirejection therapy consisted of cyclosporine, azathioprine, and prednisolone. Cyclosporine was given preoperatively to patients whose serum creatinine levels were below 1.8 mg per deciliter (160 μ mol per liter) and whose hepatic aminotransferase levels were less than three times the normal value; this treatment was started within 48 hours after transplantation in the other patients. Azathioprine (1.5 to 2 mg per kilogram of body weight per day) was given from day 1. Prednisolone (1 mg per kilogram per day) was given in divided doses that were tapered to 0.18 mg per kilogram per day by day 14 and 0.10 mg per kilogram per day by 6 months. The

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total withdrawal of corticosteroid therapy was never attempted. The dosage of cyclosporine was correlated with cyclosporine levels in whole blood (TDx analyzer, Abbott).

All the patients received trimethoprim (160 mg) plus sulfamethoxazole (800 mg) two days per week for one year as prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis.⁸

Patients with endomyocardial-biopsy specimens that showed cardiac rejection of grade 2 or higher (according to the classification system of the International Society for Heart and Lung Transplantation) were treated with intravenous methylprednisolone (3 g given over a period of 3 consecutive days) if the rejection occurred within the first 28 days or with a 14-day tapering dose of oral prednisolone if the rejection occurred more than 28 days after transplantation.⁹ Hemodynamically important rejection and rejection that persisted despite two complete courses of corticosteroids were treated with OKT3 monoclonal antibody (muromonab-CD3) or antithymocyte globulin. Total lymphoid irradiation was used to treat patients who had received one course of cytolytic therapy and who had had four or more episodes of rejection in the first three months or five or more episodes in the first six months. Each biopsy specimen showing rejection was counted, even when it represented the continuation of a rejection noted in a previous specimen, in accordance with our usual method of reporting. Only infections requiring antimicrobial treatment were counted (oral herpes simplex infections were excluded).

To avoid confounding the interpretation of the results of the trial, no study patient was treated with diltiazem, verapamil, or felodipine. (These agents may also interact with cyclosporine.) When fungal or yeast infections developed that required treatment with itraconazole or fluconazole, ketoconazole therapy was suspended. Data on cyclosporine and creatinine levels during treatment with itraconazole or fluconazole have been omitted from the analysis, but data on infection and rejection during these periods are included.

In the first 22 patients, cyclosporine levels were measured with a polyclonal-antibody assay for the parent compound and its metabolites (TDx, Abbott). In subsequent patients the Abbott monoclonal-antibody assay for cyclosporine (the parent compound only) was used. The cyclosporine levels used as targets in the monoclonal assay were as follows: from the time of transplantation through month 2, 300 to 400 μg per liter; during month 3, 250 to 350 μg per liter; during months 4 through 6, 200 to 300 μg per liter; during months 7 through 12, 200 to 250 μg per liter; and beyond month 12, 120 to 180 μg per liter. Divided samples from each patient were assayed for a six-month period to permit an evaluation of the relation between the results of the polyclonal and monoclonal assays in each group.

Cost

The cost of cyclosporine was calculated as follows. The total number of milligrams of cyclosporine used per patient in years 1 and 2 was calculated from the dosages in milligrams per kilogram per day at days 7 and 14 and months 1, 2, 3, 4, 5, 6, 9, and 12, assuming that the dosage remained fixed between two time points. This method tends to overestimate cyclosporine use marginally in the first three months, but thereafter the calculated dosage corresponds with our schedule of alterations in the clinical dosage. The mean weight of the recipients in the study (72 kg) was used in the calculation. During the trial, the cost of cyclosporine was 5.5 cents (U.S.) per milligram.

Statistical Analysis

Rates of cardiac rejection (i.e., episodes of grade 2 or higher that were treated) and rates of treated infection were compared by a linearized rate-comparison test. Numbers of events were compared by the chi-square test, differences between Cutler-Ederer curves of actuarial survival by the Cox-Mantel test, and means (\pm SD) by the two-tailed t-test. All reported P values are two-tailed.¹⁰

RESULTS

Demographic Variables

Twenty-three patients were randomly assigned to the ketoconazole group, and 20 patients to the control

group. The clinical characteristics of the two groups were similar (Table 1).

Cyclosporine Dosage

The cyclosporine-sparing effect of ketoconazole was apparent immediately. In the ketoconazole group, the dosage of cyclosporine needed to maintain the target cyclosporine level was reduced by 62 percent at day 7, by 68 percent at day 28, by 74 percent at month 6, and by 80 percent at month 12 (Fig. 1).

Among the 43 patients, cyclosporine levels were measured with the polyclonal assay in 22 (15 men and 7 women) and with the monoclonal assay in 21 (15 men and 6 women). The mean difference in cyclosporine level between the ketoconazole group and the controls was not significant with either assay. The correlation coefficient between the levels measured by the polyclonal assay and those measured by the monoclonal assay in the control group was 0.52. In the ketoconazole group, these levels were very closely correlated ($r=0.95$), in keeping with the expectation that the cyclosporine measured in patients receiving ketoconazole consists predominantly of the parent compound rather than the parent compound plus its metabolites.

Actuarial Survival

Actuarial survival at one year was 96 percent in the ketoconazole group and 88 percent in the control group ($P=0.08$). There was one death in the ketoconazole group (from gram-negative septicemia), and there were

Table 1. Demographic Characteristics and Use of Medications after Transplantation in the Two Study Groups.*

VARIABLE	KETOCONAZOLE GROUP (N = 23)	CONTROL GROUP (N = 20)
Sex (M/F)	16/7	14/6
Mean age (yr)	46 \pm 14	47 \pm 13
Type of cardiomyopathy (no. of patients)		
Ischemic	8	11
Idiopathic dilated	9	6
Peripartum	2	2
Valvular	3	0
Hypertrophic	1	1
Months of follow-up in study	25 \pm 4	25 \pm 4
Nonstudy medications (% of patients)		
Angiotensin-converting-enzyme inhibitors	87	80
Beta-blockers	26	5
Simvastatin	4	5
Nifedipine	13	20
Prazosin	13	0
Hydralazine	20	10
Furosemide	17	20
Omeprazole	13	5
Antithymocyte globulin (mg)	2.7 \pm 0.6	2.7 \pm 0.6
Prednisolone (mg/kg/day)		
Day 7	0.51 \pm 0.04	0.52 \pm 0.10
Mo 1	0.26 \pm 0.10	0.22 \pm 0.02
Mo 3	0.20 \pm 0.02	0.20 \pm 0.02
Mo 12	0.17 \pm 0.02	0.16 \pm 0.02
Azathioprine (mg/kg/day)		
Day 7	2.1 \pm 0.2	2.0 \pm 0.3
Mo 1	1.8 \pm 0.2	1.7 \pm 0.2
Mo 3	1.5 \pm 0.5	1.7 \pm 0.2
Mo 12	1.6 \pm 0.3	1.6 \pm 0.3

*Plus-minus values are means \pm SD. No comparisons were statistically significant.

two in the control group (from acute rejection and a cerebrovascular accident).

Cardiac Rejection

In the ketoconazole group, the rate of cardiac rejection was significantly lower than among the controls in the first month, and there was a significantly longer interval before the first and third rejections (Table 2 and Fig. 2). These differences between study groups could not be explained by differences in the dosages of antithymocyte globulin, prednisolone, or azathioprine (Table 1).

The patients receiving ketoconazole had lower requirements for cytolytic therapy and total lymphoid irradiation than the controls. Twenty-two percent of the patients in the ketoconazole group required OKT3, as compared with 35 percent of the controls ($P=0.08$). Three control patients required cytolytic therapy on two occasions, but no patients receiving ketoconazole needed such therapy twice. Lymphoid irradiation was needed in only 9 percent of the ketoconazole group, as compared with 15 percent of the control group. The combined need for cytolytic therapy or lymphoid irradiation averaged 0.30 event per patient for patients receiving ketoconazole as compared with 0.60 event per patient for the controls ($P=0.10$).

Infection

The overall rate of infection was significantly lower in the second and third months in the ketoconazole

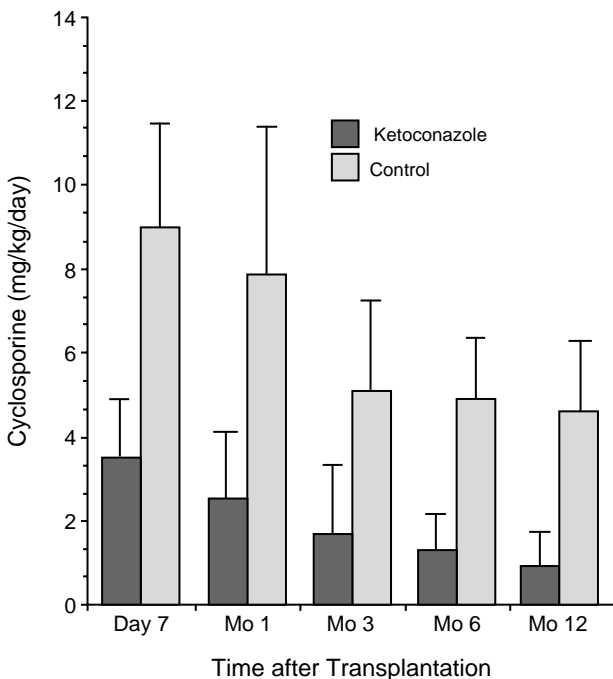


Figure 1. Mean (\pm SD) Dosages of Cyclosporine in the Two Study Groups.

When the ketoconazole group was compared with the control group, the dosage of cyclosporine required to maintain the target level was reduced by 62 percent at day 7, by 68 percent at month 1, by 67 percent at month 3, by 74 percent at month 6, and by 80 percent at month 12 ($P<0.001$ for the difference between groups at each point).

Table 2. Time to First Rejection, Rates of Rejection and Infection, and Measurements of Renal and Hepatic Function.

VARIABLE	KETOCONAZOLE GROUP	CONTROL GROUP	P VALUE
	<i>mean \pmSD</i>		
Time to cardiac rejection — days			
First episode	30 \pm 29	15 \pm 8	0.03
Third episode	90 \pm 76	52 \pm 25	0.05
Episodes of rejection — no./100 patient-days*			
Mo 1	4.2 \pm 0.8 (667)	5.7 \pm 1.0 (600)	<0.001
Mo 2	2.9 \pm 0.7 (660)	3.1 \pm 0.7 (576)	0.10
Mo 3	2.6 \pm 0.6 (660)	2.8 \pm 0.7 (570)	0.10
Mo 4–6	0.8 \pm 0.2 (2002)	0.6 \pm 0.2 (1729)	0.06
Mo 7–9	0.3 \pm 0.1 (2002)	0.1 \pm 0.1 (1691)	0.10
Mo 10–12	0 \pm 0	0.1 \pm 0.1	
Bacterial, viral, and fungal infections — no./100 patient-days*			
Mo 1	1.2 \pm 0.4 (667)	1.2 \pm 0.4 (600)	0.10
Mo 2	1.4 \pm 0.5 (660)	2.8 \pm 0.7 (576)	<0.001
Mo 3	0.8 \pm 0.3 (660)	2.3 \pm 0.6 (570)	<0.001
Mo 4–6	0.7 \pm 0.2 (2002)	0.5 \pm 0.2 (1729)	0.02
Mo 7–9	0.3 \pm 0.1 (2002)	0.1 \pm 0.1 (1691)	0.10
Mo 10–12	0.1 \pm 0.1	0 \pm 0	
Serum creatinine — μ mol/liter†			
Mo 1	120 \pm 30	110 \pm 40	0.10
Mo 3	120 \pm 20	110 \pm 20	0.04
Mo 6	130 \pm 30	120 \pm 30	0.10
Mo 12	120 \pm 20	110 \pm 10	0.04
Creatinine clearance — ml/min‡			
Mo 3	1.00 \pm 0.21	1.21 \pm 0.44	0.10
Mo 12	1.22 \pm 0.40	1.20 \pm 0.16	0.10
γ -Glutamyltransferase — units/liter			
Mo 1	213 \pm 148	101 \pm 55	0.003
Mo 3	263 \pm 409	54 \pm 38	0.03
Mo 6	85 \pm 95	36 \pm 18	0.04
Mo 12	52 \pm 83	30 \pm 13	0.10
Serum alkaline phosphatase — units/liter			
Mo 1	87 \pm 45	86 \pm 37	0.10
Mo 3	90 \pm 47	65 \pm 25	0.04
Mo 6	69 \pm 29	72 \pm 24	0.10
Mo 12	71 \pm 31	84 \pm 31	0.10

*The numbers in parentheses are the number of patient-days at risk.

†To convert values for serum creatinine to milligrams per deciliter, divide by 88.4.

‡To convert values for creatinine clearance to milliliters per second, multiply by 0.01667.

group than in the control group because of a reduction in the number of bacterial, viral, and fungal infections (Table 2 and Fig. 3). Only 9 percent of the ketoconazole group had fungal infections (two patients had pulmonary aspergillosis), as compared with 40 percent of the control group (three had pulmonary aspergillosis, four had esophageal candidiasis, and one had cryptococcal meningitis; $P=0.04$).

Renal and Hepatic Function

The mean serum creatinine level was marginally higher in the ketoconazole group than in the controls at months 3 and 12, but it remained in the normal range (Table 2). Urinary creatinine clearance did not differ significantly between the two groups.

Serum bilirubin and alanine aminotransferase levels usually remained within the normal range. γ -Glutamyltransferase levels, however, rose progressively in both groups, but significantly more so in the ketoconazole group, peaking at month 3. This increase was inde-

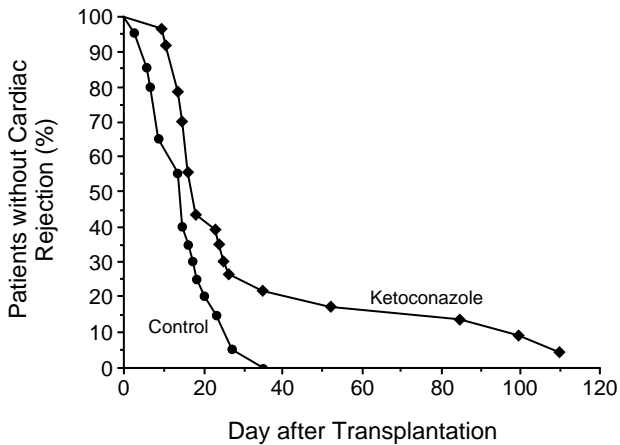


Figure 2. Life-Table Analysis Showing the Occurrence of First Episodes of Cardiac Rejection.

Rejection occurred significantly less often and significantly later in the ketoconazole group than in the control group ($P=0.04$).

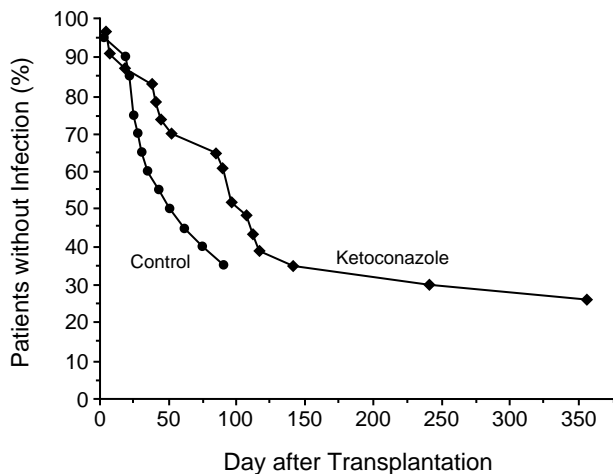


Figure 3. Life-Table Analysis Showing the Occurrence of First Episodes of Infection Requiring Treatment.

Bacterial, viral, and fungal infections occurred significantly less often in the ketoconazole group than in the control group ($P=0.04$).

pendent of the cyclosporine levels measured, and it occurred despite a dramatic reduction in the cyclosporine dosage. γ -Glutamyltransferase levels returned to normal by 12 months after transplantation, however, without the cessation of ketoconazole therapy. A small but significant elevation was also found in serum alkaline phosphatase at months 3 and 6 (Table 2).

No differences between the two groups were seen in serum levels of cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, or triglycerides; serum levels of testosterone (in men); or blood pressure or the number of antihypertensive agents required.

Side Effects

The only side effects attributable to ketoconazole therapy were transient visual flashes in two patients, which resolved spontaneously with no need to stop the therapy. There were two withdrawals. A 34-year-old

woman was withdrawn from ketoconazole treatment when she presented in the fifth month of pregnancy, having conceived 12 months after transplantation. The baby was born by cesarean section at 36 weeks and was developing normally at the age of 18 months at the time of this writing. The second withdrawal was that of a 64-year-old woman in whom a retroperitoneal lymphoma developed 18 months after transplantation. Treatment with cyclosporine and thus with ketoconazole was ended.

Cost

The economic effect of ketoconazole therapy was a reduction in the cost of cyclosporine during the first year from \$6,640 to \$1,130 per patient. When the cost of the ketoconazole (\$340) was included, the net savings in the first year was about \$5,200 per patient. In subsequent years, the expenditure for cyclosporine was reduced from \$5,200 to \$950 — a net savings of about \$3,920 per patient per year. In a unit performing 40 heart transplantations per year, this translates into a savings of approximately \$576,000 over a two-year period.

DISCUSSION

The use of ketoconazole after cardiac transplantation resulted in a lower requirement for cyclosporine, lower costs, and reduced rates of rejection and infection. The idea of exploiting the interaction between ketoconazole and cyclosporine is not new, but it has become even more relevant as economic considerations have increasingly restrained medical practice. The mechanism of the interaction is not clear but is thought to be due to strong binding of ketoconazole to the microsomal monooxygenase cytochrome P-450 enzyme system, which inhibits the metabolism of cyclosporine. Ketoconazole is known to inhibit the metabolism of methohexital and acenocoumarol in rats.¹¹ The inhibition of cyclosporine metabolism by ketoconazole has been demonstrated in dogs and rats, and a related agent, itraconazole, acts similarly in humans, with a reduction in the requisite dose of cyclosporine.^{12,13} Other proposed mechanisms of the ketoconazole–cyclosporine interaction include altered absorption of cyclosporine, competition for excretion, change in the volume of distribution of cyclosporine, and altered protein binding.^{2,14-16}

Diltiazem also blocks the metabolism of cyclosporine by cytochrome oxidase. In a prospective, randomized trial of diltiazem in patients with cardiac transplants, we found a 33 percent reduction in the cost of cyclosporine in the first year and a 39 percent reduction in the second year.¹⁷ There was also a significant reduction in systemic blood pressure during the period from 3 to 18 months after transplantation and significant improvement in renal function.¹⁷ Furthermore, diltiazem attenuated the development of hypercholesterolemia. A report by Schroeder et al. indicating reduced development of coronary artery disease in heart transplants is a further reason to include diltiazem in the medical regimen after transplantation.¹⁸

Ketoconazole differs from diltiazem in that its cyclo-

sporine-sparing effect begins rapidly. With diltiazem, the effect is not seen until days 4 to 7. The dose of cyclosporine should be reduced as early as one day after the start of ketoconazole therapy.¹ One practical issue is that cyclosporine doses are so small that patients receiving ketoconazole must take cyclosporine in solution to allow adequate flexibility of dosing.

Ketoconazole is a synthetic imidazole agent with fungistatic action, altering the structure of the fungal cell membrane and increasing cell permeability. It inhibits steroid synthesis by inhibiting carbon-14 demethylation of sterol intermediates and temporarily reducing serum testosterone levels, such that oligospermia and reduced libido are seen with doses of 800 mg per day and above. After doses of 200 mg per day for two weeks, there is a significant decrease in testosterone levels and an increase in the 17 α -hydroxyprogesterone concentration.¹⁹

The principal antimicrobial action of ketoconazole is against fungi, but there is also *in vivo* activity against *Staphylococcus epidermidis*, nocardia, candida, herpes simplex virus types 1 and 2, microsporium, trichophyton, and *Malassezia furfur*.²⁰ The reduction in the rate of infection in the first three months of this trial may reflect a reduced need for immunosuppression due to reduced rejection in the first month. The reduction in bacterial, viral, and fungal infections is due to the broad antimicrobial effects of ketoconazole. Forty percent of the control group had clinically important fungal or yeast infections requiring systemic therapy, as compared with only 9 percent of the ketoconazole group. This reduction in fungal infections with ketoconazole is consistent with published data. A retrospective review of 27 reports indicated that fungal infections can be prevented by prophylactic therapy in immunocompromised patients.²¹ Colonization with ketoconazole-resistant candida is a theoretical problem that we have not observed to date.

Dose-related side effects of ketoconazole include vomiting, flatulence, diarrhea, gynecomastia, pruritus, and reduced serum cholesterol levels. These side effects were not seen at the low dosages we used. Transient increases in hepatic aminotransferases, cholestasis, and mixed hepatotoxic effects (reversible within months of drug cessation) have also been associated with ketoconazole. Asymptomatic cholestasis did occur, but it resolved completely by 12 months after transplantation without the cessation of ketoconazole therapy.

The reason for the reduction in the rejection rate (despite similar doses of azathioprine, prednisolone, and antithymocyte globulin) in the first month is unclear, but reduced metabolism of corticosteroids may be responsible. Ketoconazole increases levels of methylprednisolone and prednisolone, and the area under the plasma-concentration-time curve doubles after six days at a dosage of 200 mg per day.²² We were aware of this interaction when we set up the trial. However, there is also *in vitro* evidence that ketoconazole binds to glucocorticoid receptors (functioning as an antagonist), and hence we elected not to reduce

the doses of corticosteroids despite the treatment with ketoconazole.

In a review of the costs of renal transplantation in 1988, Evans and Manninen commented that the cost of immunosuppressive agents is a major policy issue in organ transplantation.²³ The effect of the drug on rejection and survival notwithstanding, cyclosporine-sparing agents provide one practical way to contain costs.

The net savings on cyclosporine in year 1 (including the cost of ketoconazole) was about \$5,200 per patient, and in subsequent years about \$3,920. This does not take into account the advantage of reduced rates of infection and rejection and the reduced need for expensive cytolytic agents. In a unit performing 40 heart transplantations per year, the savings over a two-year period would be approximately \$576,000.

Low-dose ketoconazole can be safely used as a cyclosporine-sparing agent from the time of transplantation, resulting in a substantial reduction in the cyclosporine dosage after 12 months. Additional benefits include a reduced rate of rejection in the first month, a delay in the first episode of rejection, and reduced requirements for cytolytic agents. Rates of bacterial, fungal, and viral infection are also reduced, perhaps through the reduced rejection rate or by a specific antimicrobial effect. These last two very encouraging observations require confirmation in future trials. The toxic effects of ketoconazole are limited to transient cholestasis, which normalizes without the need to discontinue the treatment. As a result of this study, we now use ketoconazole to treat all recipients of cardiac transplants.

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