

# Pharmacokinetics of Cyclosporine in Heart Transplant Recipients Receiving Metabolic Inhibitors

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**Background:** Inhibitors of cyclosporine metabolism are commonly co-administered with cyclosporine in transplant recipients. The aim of this study was to compare cyclosporine pharmacokinetics using the conventional formulation (Sandimmune) and after switching to the microemulsion (Neoral) formulation, in stable heart transplant recipients receiving various cyclosporine metabolic inhibitors.

**Methods:** Steady-state blood concentration–time profiles of Sandimmune were studied in 47 transplant recipients receiving either cyclosporine alone (Group A,  $n = 11$ ) or in combination with diltiazem (120 mg/day, Group B,  $n = 11$ ), ketoconazole (200 mg/day, Group C,  $n = 13$ ), or both ketoconazole and diltiazem (200 and 120 mg/day, respectively, Group D,  $n = 12$ ), and restudied 1 week after switching to Neoral.

**Results:** Neoral resulted in more rapid cyclosporine absorption as judged by the shorter absorption half-lives in all groups ( $p < 0.05$ ). The mean percentage increase in the values of area-under-the-concentration–time curve was 42% and 37.5% higher for Neoral compared with Sandimmune for Groups A and B, respectively, but only 5.4% higher for Group C and 9.5% higher for Group D. The mean morning trough concentration of cyclosporine was not significantly different after administration of Neoral compared with Sandimmune in any of the groups studied (179 vs 167  $\mu\text{g/liter}$  for Group A; 171 vs 147  $\mu\text{g/liter}$  for Group B; 189 vs 194  $\mu\text{g/liter}$  for Group C; and 181 vs 201  $\mu\text{g/liter}$  for Group D). Neoral did not alter serum concentrations of sodium, potassium, creatinine, and urea in any of the study groups.

**Conclusions:** The faster absorption and improved bioavailability of cyclosporine (around 40%) with Neoral compared with Sandimmune was not seen in patients receiving ketoconazole, where in fact cyclosporine bioavailability was already maximal. Mean morning trough levels of cyclosporine did not reflect the improvement in bioavailability seen in patients switching from Sandimmune to Neoral. Cyclosporine dose adjustment may be needed when switching from Sandimmune to Neoral for patients not receiving sparing agents or who receive diltiazem, but trough levels cannot necessarily be relied upon to determine the degree of adjustment needed. For patients

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on ketoconazole, the absorption profile is already optimized and no dosage alteration seems necessary. *J Heart Lung Transplant* 2001;20:431–438.

**A**dministration of the conventional formulation of cyclosporine is associated with extensive pharmacokinetic variability and a characteristically erratic absorption profile.<sup>1</sup> The microemulsified formulation of cyclosporine (Neoral), however, has been shown to reduce variability in bioavailability, resulting in higher peak concentrations and more reproducible area-under-the-concentration–time curves in healthy volunteers and transplant recipients.<sup>2</sup>

The calcium-channel blocking agent, diltiazem, is commonly used for its antihypertensive and anti-atherogenic effects, and the azole derivative, ketoconazole, is used for its antifungal properties in transplant recipients.<sup>3–7</sup> Both diltiazem<sup>5</sup> and ketoconazole<sup>6</sup> also reduce cyclosporine metabolism by inhibiting the cytochrome P450-3A4 isoenzymes<sup>8</sup> and/or the P-glycoprotein system<sup>9</sup> in both liver and intestinal mucosa. Despite the frequent use of diltiazem, and to a lesser extent ketoconazole, the pharmacokinetic characteristics of Neoral have not been characterized in transplant patients being given metabolic inhibitors.

The aim of the present study was to determine the pharmacokinetic characteristics of Neoral compared with conventional Sandimmune, in patients receiving diltiazem and/or ketoconazole concomitantly, and also to examine the need for cyclosporine dosage modification in these patients.

## MATERIALS AND METHODS

### Patients and Study Design

Forty-seven stable heart transplant recipients were studied. Cyclosporine blood concentration–time data were collected, over dosing intervals at steady state, at times of 0, 0.5, 1, 2, 3, 5, 7, and 12 hours after both formulations, with cyclosporine having been taken at the same dosage for at least 1 week. Total concentration of cyclosporine in whole blood was determined using an enzyme multiplied immunoassay technique (EMIT 2000 Cyclosporine Specific Assay, Syva/Behring, Inc., San Jose, CA) performed at the Department of Chemical Pathology, St. Vincent's Hospital.

The study was approved by the research and ethics committee of St. Vincent's Hospital, Sydney, and each patient gave informed consent. Concentration–time data were obtained from each patient after administration of a morning dose of the con-

ventional formulation of cyclosporine (Sandimmune, Novartis Pharmaceuticals). Patients were switched to the microemulsified formulation of cyclosporine (Neoral, Novartis Pharmaceuticals) and the pharmacokinetic characteristics were assessed 7 days after the dosage form switch. Biochemical indices (serum creatinine, urea, sodium, and potassium) were also monitored at the same time as the pharmacokinetic studies. In addition, cyclosporine trough concentration and biochemical indices were measured in all patients 17 days after initiation of the microemulsified formulation. Cyclosporine dose was not altered between day 0 and day 17 of the study.

Patients were stratified into four groups depending on the long-term concomitant administration of drugs known to inhibit cyclosporine metabolism, as part of their routine pharmacotherapy. The first group (Group A, 11 patients) received no long-term cyclosporine metabolic inhibitors, while other patients received cyclosporine administered with a slow-release (SR) formulation of diltiazem (Group B,  $n = 11$ ; 120 mg/day), with ketoconazole (Group C,  $n = 13$ , 200 mg/day), or with a combination of diltiazem (SR) and ketoconazole (Group D,  $n = 12$ , ketoconazole 200 mg/day and diltiazem 120 mg/day) for at least 24 months.

### Data Analysis

Cyclosporine blood concentration–time data at steady state were analyzed by model-independent pharmacokinetic methods.<sup>10</sup> The following parameters were derived from the steady-state concentration–time profiles of cyclosporine: maximum whole blood concentration ( $C_{max}$ ); time to maximum whole-blood concentration ( $t_{max}$ ); and area-under-the-cyclosporine-concentration–time curve during a morning 12-hour dosing interval at steady state ( $AUC_{ss}$ ), which was calculated using the linear trapezoidal rule. The values of apparent clearance ( $Cl/F$ ) were derived by dividing cyclosporine dose by  $AUC_{ss}$ . The first order absorption rate constant ( $k_{abs}$ ) was calculated using a model-dependent approach by fitting a one-compartment pharmacokinetic method implemented in the P-PHARM pharmacokinetic software package (P-PHARM version 1.3, Simed, France). Absorption half-life ( $t_{1/2 abs}$ ) was derived as follows:  $0.693/k_{abs}$ .

**TABLE I** Demographic characteristics of patients

	Concomitant Drug Therapy			
	Group A: CsA (n = 11)	Group B: CsA + Diltiazem (n = 11)	Group C: CsA + Ketoconazole (n = 13)	Group D: CsA + Diltiazem + Ketoconazole (n = 12)
Gender (M/F)	8/3	10/1	9/5	10/2
Age (years)	54 ± 12	52 ± 8	52 ± 9	47 ± 12
Weight (kg)	78 ± 10	82 ± 13	89 ± 16	90 ± 21
Time posttransplant (months)	49 ± 19	61 ± 15	32 ± 15	28 ± 5

CsA, cyclosporine. Data expressed as mean ± SD.

**Statistical Analysis**

Descriptive statistics (including mean, standard deviation, and 95% confidence intervals), comparative statistical (paired or unpaired Student's *t*-test), and multiple linear regression analyses were performed using SPSS for WINDOWS (release 6.1, SPSS, Inc., Chicago, IL). All *p*-values were based on two-tailed tests and *p* < 0.05 was considered significant.

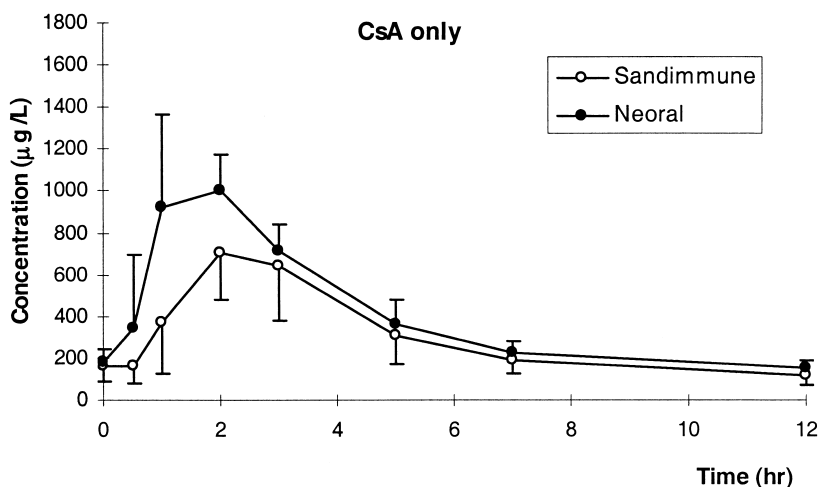
**RESULTS**

Demographic characteristics of patients in the various groups are shown in Table I. Patients' gender, age, and weight were not significantly different among the four study groups. In addition, cyclosporine daily dosage was kept constant in all patients during the Neoral and Sandimmune arms of the pharmacokinetics study. The mean group cyclosporine blood concentration–time plots over a morning

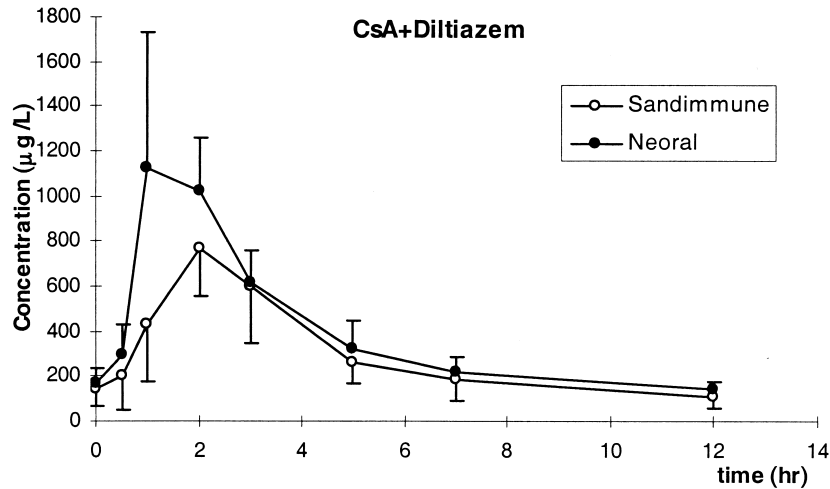
dosing interval at steady state for patients receiving the two cyclosporine formulations are shown in Figure 1A–1D.

Table II provides a summary of pharmacokinetic parameters, including mean cyclosporine daily dose, AUC<sub>ss</sub>, C<sub>max</sub>, t<sub>max</sub>, and absorption half-life. The AUC<sub>ss</sub> was significantly greater after administration of Neoral in patients who were not receiving metabolic inhibitors (Group A) or receiving diltiazem alone (Group B). However, the AUC<sub>ss</sub> was not significantly higher after Neoral in patients receiving either ketoconazole alone (Group C) or receiving ketoconazole in combination with diltiazem (Group D) (Table II).

Administration of Neoral resulted in a significant increase in maximum steady-state concentration in all groups with the exception of those receiving ketoconazole only (Group C). The time to maxi-



**FIGURE 1A** Mean steady-state concentration–time profile of cyclosporine in heart transplant recipients receiving no metabolic inhibitors (11 patients) after administration of cyclosporine as conventional (Sandimmune) and microemulsion (Neoral) formulations. Error bars show standard deviation.

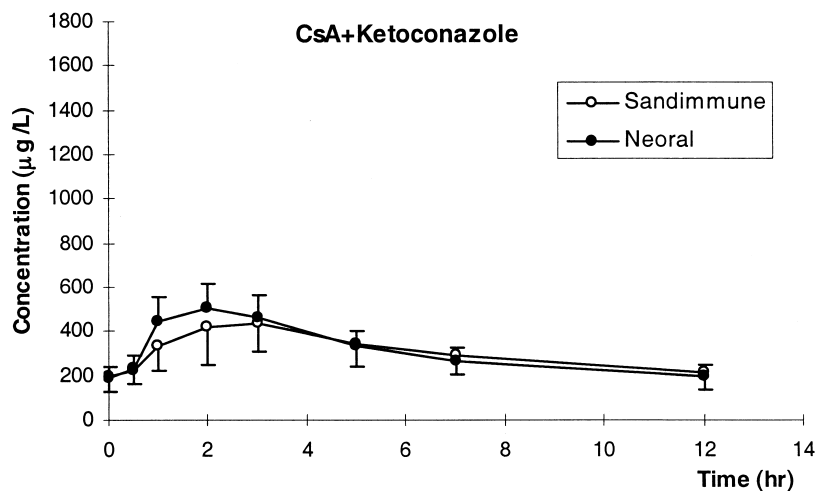


**FIGURE 1B** Mean steady-state concentration–time profile of cyclosporine in heart transplant recipients receiving no metabolic inhibitors (11 patients) after administration of cyclosporine as conventional (Sandimmune) and microemulsion (Neoral) formulations. Error bars show standard deviation.

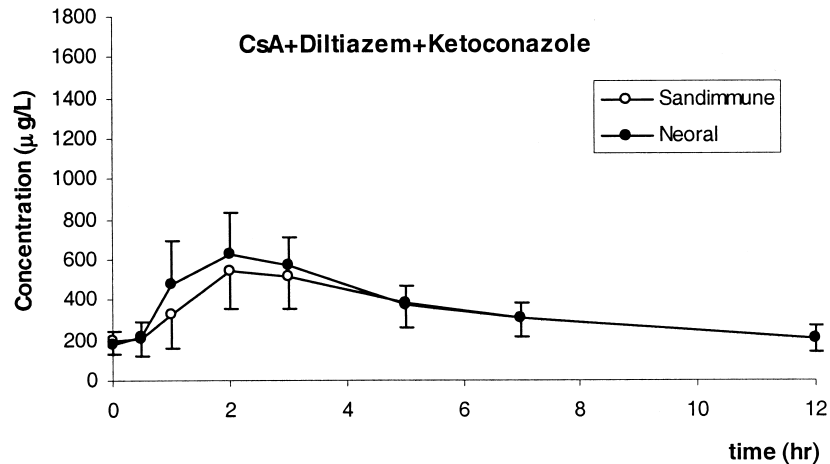
mum concentration ( $t_{max}$ ) was significantly shorter for patients given Neoral (vs Sandimmune) in all groups. The exception was for patients in Group D who received cyclosporine concomitantly with ketoconazole and diltiazem (Table II). The absorption half-life ( $t_{1/2\text{ abs}}$ ) of cyclosporine was significantly shorter ( $p < 0.05$ ) for patients receiving cyclosporine microemulsion, irrespective of the type of concomitant medications (Table II).

Apparent clearance of cyclosporine was significantly lower in Neoral formulation only for Groups A and B (Table III).

The variability in morning ( $C_{ss,0}$ ) and afternoon ( $C_{ss,12}$ ) trough concentrations of cyclosporine, expressed as coefficient of variation (CV%), was less pronounced after administration of microemulsion in all groups (mean CV% of  $C_{ss,0}$  was 42% for Sandimmune vs 33% for Neoral [ $p < 0.05$ ], and for  $C_{ss,12}$  was



**FIGURE 1C** Mean steady-state concentration–time profile of cyclosporine in heart transplant recipients receiving no metabolic inhibitors (13 patients) after administration of cyclosporine as conventional (Sandimmune) and microemulsion (Neoral) formulations. Error bars show standard deviation.



**FIGURE 1D** Mean steady-state concentration–time profile of cyclosporine in heart transplant recipients receiving no metabolic inhibitors (12 patients) after administration of cyclosporine as conventional (Sandimmune) and microemulsion (Neoral) formulations. Error bars show standard deviation.

39% for Sandimmune vs 26% for Neoral ( $p < 0.01$ ). The values for morning trough ( $C_{ss,0}$ ) concentration of cyclosporine, however, were not significantly higher

for the Neoral formulation in any of the groups studied. This indicates that the observed increase in exposure to cyclosporine for Groups A and B was not

**TABLE II** Cyclosporine dose, area-under-the-concentration–time curve at steady state ( $AUC_{SS}$ ), maximum concentration ( $C_{max}$ ), time to reach maximum concentration ( $t_{max}$ ), and absorption half-lives ( $t_{1/2\text{ abs}}$ ) for cyclosporine administered as the conventional (Sandimmune) or microemulsified (Neoral) formulation

	Concomitantly Administered Drugs			
	Group A: Csa (n = 11)	Group B: Csa + Diltiazem (n = 11)	Group C: Csa + Ketoconazole (n = 13)	Group D: Csa + Diltiazem + Ketoconazole (n = 12)
CsA dose (mg/kg per day)	3.90 ± 1.03	2.98 ± 0.64	0.79 ± 0.27	0.90 ± 0.54
AUC (µg hour/liter)				
Sandimmune	3655 ± 1120*	3605 ± 1079*	3601 ± 933	4070 ± 1099
Neoral	4911 ± 935	4747 ± 923	3703 ± 772	4369 ± 993
$C_{max}$ (µg/liter)				
Sandimmune	827 ± 204**	816 ± 183**	480 ± 164****	574 ± 192**
Neoral	1147 ± 307	1288 ± 415	532 ± 93	652 ± 204
$\Delta C_{max}$ (%)	+43%	+59%	+17%	+15%
$t_{max}$ (hours)				
Sandimmune	2.27 ± 0.47***	2.09 ± 0.54*	2.61 ± 0.96*	2.58 ± 0.90****
Neoral	1.55 ± 0.52	1.45 ± 0.69	2.00 ± 0.57	2.33 ± 0.49
$\Delta t_{max}$ (%)	-32%	-26%	-18%	-2%
$t_{1/2\text{ abs}}$ (hours)				
Sandimmune	2.72 ± 1.45***	1.44 ± 1.16*	1.65 ± 1.22**	1.81 ± 1.09*
Neoral	0.51 ± 0.28	0.58 ± 0.62	0.67 ± 0.34	1.07 ± 0.57

The  $p$ -values refer to statistical differences between Sandimmune and Neoral dosage forms. Data expressed as mean ± SD. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ; \*\*\*\*not significant.

**TABLE III** Values of cyclosporine apparent clearance (liters/hour) for Sandimmune and Neoral for various subgroups of patients

	Concomitant Therapy	n	Apparent Clearance (liters/hour)	
			Sandimmune	Neoral
Group A	None	11	46.7 ± 21.1	31.8 ± 9.5*
Group B	Diltiazem	11	36.7 ± 14.1	26.8 ± 9.0*
Group C	Ketoconazole	13	9.7 ± 4.3	9.1 ± 3.8
Group D	Ketoconazole + diltiazem	12	10.1 ± 6.4	9.1 ± 4.9

Values expressed as mean ± SD.

\*Significantly lower than Sandimmune, at  $p < 0.05$ .

necessarily reflected by the morning trough concentration of cyclosporine, the commonly used index of cyclosporine dosing (Table IV).

The serum concentration of sodium, potassium, urea, and creatinine did not differ significantly between the Sandimmune and Neoral study days nor at 17 days after the switch of dosage form (Table V). Administration of Neoral did not result in deterioration in renal function despite the increased overall exposure to cyclosporine.

## DISCUSSION

Administration of Neoral is known to increase cyclosporine bioavailability and produce a more consistent absorption profile than the conventional formulation.<sup>1,2</sup> Despite this increase in cyclosporine exposure, however, it has been shown that neither immunosuppressive efficacy nor side-effects differ significantly between the two formulations in recipients of heart or lung transplantations.<sup>11,12</sup>

Ketoconazole and diltiazem are frequently co-administered with cyclosporine either for their ther-

apeutic effects or to reduce the cost of cyclosporine treatment.<sup>3,7</sup> Most pharmacokinetic investigations of the concomitant use of ketoconazole or diltiazem with cyclosporine, however, have been carried out using the nonmicroemulsified formulation of cyclosporine. Because many patients have now been switched to Neoral, it is essential to reinvestigate the pharmacokinetic parameters to ensure that the patients on cyclosporine-sparing agents are not being exposed to dangerously high concentrations of cyclosporine. This study is the first to report on the pharmacokinetics of the microemulsified cyclosporine formulation in heart transplant recipients receiving long-term ketoconazole or diltiazem or a combination of both.

The present study also provides insight into the possible site of metabolism for cyclosporine after oral administration by examining the interaction of diltiazem and ketoconazole with cyclosporine. Cyclosporine is metabolized in the liver and gastrointestinal tract by an isoenzyme of the cytochrome P450-3A family.<sup>13</sup> Metabolism involves mainly hydroxylation, demethylation, and cycliza-

**TABLE IV** Trough concentrations of Sandimmune and Neoral at the beginning ( $C_{SS,0}$ ) and end ( $C_{SS,12}$ ) of dosing interval and at 17 days after start of Neoral treatment

	Concomitant Drug Therapy			
	Group A: None (n = 11)	Group B: Diltiazem (n = 11)	Group C: Ketoconazole (n = 13)	Group D: Diltiazem + Ketoconazole (n = 12)
$C_{SS,0}$ (µg/liter) Sandimmune	167 ± 77	147 ± 79	194 ± 72	201 ± 68
$C_{SS,0}$ (µg/liter) Neoral	179 ± 64**	171 ± 61**	189 ± 54**	181 ± 62**
$C_{SS,12}$ (µg/liter) Sandimmune	117 ± 43	112 ± 56	211 ± 82	207 ± 69
$C_{SS,12}$ (µg/liter) Neoral	153 ± 39*	142 ± 39*	198 ± 52**	211 ± 57**
$C_{SS,0}$ at day 17 (µg/liter) Neoral	174 ± 51	161 ± 35	190 ± 84	210 ± 62

Values expressed as mean ± SD.

\* $p < 0.02$  Neoral vs Sandimmune; \*\*not significantly different.

**TABLE V** Serum biochemical determination

Dosage Forms	Sodium (mmol/liter)	Potassium (mmol/liter)	Urea (mmol/liter)	Creatinine (mmol/liter)
Sandimmune	142.0 ± 2.4	4.17 ± 0.43	11.46 ± 4.35	0.14 ± 0.04
After 1 week on Neoral	140.5 ± 2.2	4.12 ± 0.44	10.80 ± 3.79	0.13 ± 0.04
After 17 days on Neoral	141.4 ± 2.2	4.36 ± 0.57	10.97 ± 4.11	0.14 ± 0.03

Values expressed as mean ± SD.

tion of different amino acids while the cyclic structure of the cyclosporine molecule remains intact.<sup>14</sup> Kolars and colleagues showed that the wall of the small intestine may be the primary site of cyclosporine metabolism.<sup>15</sup> These investigators administered cyclosporine into the small bowel of two liver transplant recipients and observed that metabolites of cyclosporine could be detected in portal venous blood.<sup>15</sup> This finding has been confirmed by other *in vitro* and *in vivo* investigations.<sup>16,17</sup>

More recently, Lown and colleagues<sup>18</sup> characterized the relationship between the extent of cyclosporine bioavailability and the quantity of P-glycoprotein and CYP3A4 expression in the intestine. The erythromycin breath test, a measure of hepatic CYP3A4 activity, was also measured. They found that the intestinal P-glycoprotein content varied almost 8-fold,<sup>18</sup> accounting for 40% of the interpatient variation in cyclosporine bioavailability not explained by the variation in hepatic CYP3A4 expression. The increase in the bioavailability of cyclosporine as a result of Neoral formulation can therefore be attributed to a significantly faster rate of absorption, which may result in the partial saturation of either CYP3A4 or P-glycoprotein systems in the gut mucosa.

In the present study, the cyclosporine absorption half-life was significantly shorter after administration of Neoral in all four groups, but the extent of absorption did not increase in patients taking concomitant ketoconazole or a combination of ketoconazole and diltiazem. The clinical significance of this is that the concomitant use of ketoconazole with cyclosporine had already resulted in maximal cyclosporine absorption and no further increase was possible by switching to Neoral. Ketoconazole is a potent inhibitor of CYP3A4 activity.<sup>19,20</sup> It has been shown *in vitro* that 0.26 μmol/liter of ketoconazole inhibits cyclosporine metabolism by 50% (IC<sub>50</sub>). In comparison, the IC<sub>50</sub> value for fluconazole was found to be 87.5 μmol/liter.<sup>20</sup> In a comprehensive pharma-

cokinetic study, Gomez and colleagues demonstrated that ketoconazole reduced apparent clearance of oral cyclosporine by 4.9-fold, whereas reduction in the clearance of intravenous cyclosporine was only 1.8-fold.<sup>8</sup> These investigators concluded that the observed magnitude of increase in cyclosporine bioavailability by the oral, but not intravenous, route is explained by the fact that ketoconazole inhibits metabolism of cyclosporine in the gastrointestinal mucosa by complete blockage of prehepatic metabolism, allowing optimal absorption.<sup>8</sup> The effects of ketoconazole on cyclosporine metabolism may be due in part to the inhibition of the intestinal P-glycoprotein system,<sup>18</sup> because ketoconazole is also known to be a potent inhibitor of this system.<sup>9</sup>

Diltiazem is metabolized by CYP3A4 and is a competitive inhibitor of cyclosporine metabolism, but the exact site(s) of this interaction is unknown.<sup>5</sup> The increase in the rate of cyclosporine absorption after administration as microemulsion results in a shorter residence time in gastrointestinal mucosa. It can also be speculated that the greater absorption rate may induce partial saturation of CYP3A4 or the P-glycoprotein system, resulting in a higher cyclosporine bioavailability. There is no increase in cyclosporine bioavailability with ketoconazole, which is consistent with complete prehepatic blockade of cyclosporine metabolism. Diltiazem, however, unlike ketoconazole, appears to have no effect on prehepatic metabolism of cyclosporine, because the magnitude of increase in bioavailability of cyclosporine following microemulsion administration was similar to that in patients not receiving metabolic inhibitors.

From a clinical standpoint, total exposure to cyclosporine was increased, as characterized by higher the C<sub>max</sub>, t<sub>max</sub>, and AUC<sub>ss</sub>, when the microemulsion dose form was used. However, the morning trough concentration of cyclosporine did not reflect the increase in total exposure to cyclosporine as detected by more detailed pharmaco-

kinetic determinations. Other monitoring approaches, including measurement of cyclosporine concentrations at 2 hours postdose, may provide a more meaningful index for Neoral dosage adjustment than the morning trough concentration of cyclosporine.<sup>21,22</sup>

On the basis of the present findings in stable heart transplant recipients, to achieve comparable total exposure to cyclosporine, an approximately 40% reduction in daily dose may be possible when switching to the Neoral formulation. No dosage adjustment is necessary, however, for patients receiving long-term ketoconazole as part of their posttransplant maintenance pharmacotherapy, because absorption is already maximal. In conclusion, in every group studied, administration of cyclosporine in its microemulsified form increased the rate of cyclosporine absorption. This formulation, however, did not increase cyclosporine bioavailability in patients given either ketoconazole or a combination of ketoconazole and diltiazem, in whom absorption already appeared to be optimized.

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