PHARMACOKINETICS AND DRUG DISPOSITION

The erythromycin breath test as a predictor of cyclosporine blood levels

The daily dose of cyclosporine required to attain a desired blood level can vary greatly among patients. Because elimination of cyclosporine depends on its metabolism in the liver by an enzyme (cytochrome P-450IIIA) that also demethylates erythromycin, we reasoned that the ability of patients to demethylate a test dose of erythromycin might be useful in estimating their appropriate daily doses of cyclosporine. Accordingly, the [^{14}C-*N*-methyl] erythromycin breath test was administered to 32 patients before they received 3.0, 5.0, or 7.5 mg/kg/day cyclosporine to treat psoriasis. We found that a simple mathematical equation incorporating just the $^{14}CO_2$ production, the age of the patient, and the daily dose of cyclosporine accounted for almost 80% (R^2 = 0.78) of the interpatient variability in cyclosporine blood levels we observed. Our data indicate that P-450IIIA activity largely accounts for the relationship between dose of cyclosporine and blood levels for an individual patient. We conclude that the erythromycin breath test may be a convenient guide for cyclosporine dosing. (CLIN PHARMACOL THER 1990;48:120-9.)

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Cyclosporine, an immunosuppressive drug widely used to prevent allograft rejection in transplant recipients, appears to be useful in the treatment of many common autoimmune diseases (reviewed by Bach[1]). More than 5000 patients are currently receiving cyclosporine for autoimmune diseases, which represents a small fraction of the persons that may benefit from this drug. Enthusiasm for the therapeutic effects of cyclosporine has been tempered, however, by the high incidence of side effects associated with cyclosporine treatment, particularly renal dysfunction and hypertension (reviewed by Myers).[2]

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In an attempt to limit toxicity while maximizing the therapeutic effects of cyclosporine, blood levels are usually closely monitored for at least several weeks after patients begin treatment with cyclosporine, and the daily dose is adjusted to achieve a trough blood level within a relatively narrow range.[3-7] This is often a tedious and costly process because the daily dose of cyclosporine required to achieve a target blood level can vary at least 10-fold among patients.[6] Thus an empirical initial dose of cyclosporine will produce either potentially subtherapeutic or potentially toxic blood levels in many patients. Furthermore, because cyclosporine has a relatively long elimination half-life in blood,[8] it may take many days or weeks to arrive at an appropriate cyclosporine dosing regimen for some patients. To better estimate individual dosing requirements, cyclosporine pharmacokinetics are routinely determined in each patient before cyclosporine therapy in some medical centers.[6,9] These studies take several days to perform and have not become a standard practice.

It has recently been discovered that the elimination of cyclosporine from the body depends on its metabolism in the liver by cytochrome P-450IIIA,[10,11] a phase 1 enzyme whose catalytic activity varies manyfold among patients.[12,13] Because P-450IIIA also catalyzes

the *N*-demethylation of erythromycin,[14] we reasoned that the ability of a patient to demethylate erythromycin might be useful in predicting an appropriate initial dosing regimen for cyclosporine. This was an especially attractive idea because studies in rats and in human patients indicate that hepatic erythromycin *N*-demethylase (P-450IIIA) activity can be measured as the production of breath $^{14}CO_2$ after intravenous injection of [^{14}C-*N*-methyl]erythromycin.[14] This test requires no special expertise or equipment to perform, and the results could be available in most institutions within hours.[14]

We therefore administered the breath test to 32 patients scheduled to receive cyclosporine to treat psoriasis. We found that, for most patients studied, the steady-state cyclosporine blood level could be accurately predicted by a simple equation incorporating the breath test result, the age of the patient, and the dose of cyclosporine received.

Table I. Descriptive measures of predictor variables used in modeling steady-state cyclosporine blood levels

Pretherapy variable	*Minimum*	*Maximum*	*Mean*	*SD*
Breath test*	1.39	4.56	2.51	0.75
Weight (kg)	64.0	116.0	85.8	13.4
Age (yr)	19	67	43.8	13.2
Body surface area (m^2)	1.55	2.40	2.01	0.20
HDL cholesterol (mmol/L)†	0.70	2.20	1.16	0.31
LDL cholesterol (mmol/L)†	2.23	5.41	3.58	0.74
Total cholesterol (mmol/L)†	3.98	7.16	5.51	0.88
Triglycerides (mmol/L)†	0.50	3.22	1.69	0.82

n = 32.
* % ^{14}C exhaled in 1 hour.
† Serum.

MATERIAL AND METHODS

Patients and treatment. Patients enrolled in this study were selected from 85 patients with recalcitrant psoriasis who were scheduled to receive varying doses of oral cyclosporine in an otherwise unrelated study. Both the psoriasis treatment and the breath test protocols had been approved by the institutional review board of the University of Michigan Medical Center (Ann Arbor, Mich.). Consent was obtained in writing from each patient after the nature and procedures of the study had been explained. The study population was in good general health, and the entrance criteria included renal function (BUN, creatinine, 24-hour creatinine clearance) and liver chemistries (bilirubin, aspartate aminotransferase, alanine aminotransferase, albumin, and alkaline phosphatase) that were within 15% of the normal range.

At the time of enrollment, each patient was assigned a consecutive number that had been randomly assigned to a specific treatment group before the start of the study. Patients received placebo (vehicle alone) or 3.0, 5.0, or 7.5 mg/kg cyclosporine daily without knowledge of their dosing assignments. All patients were instructed to take their medications as a single dose before noon each day. On the days of their clinic visits, all patients were instructed to take their doses after "trough" blood levels were obtained. Patients were not routinely questioned regarding medication compliance unless a blood level greater than 400 ng/ml was obtained. In that case, patients were contacted and questioned about compliance by phone.

Enrollment in our study was initially limited to 30 patients in accordance with regulations of the Food and Drug Administration concerning radiopharmaceuticals administered under an institutional Investigational New Drug (IND) designation. For this reason, an investigator (C.N.E.) who was unblinded to the treatments randomly selected patient numbers from each treatment group before the project began; the placebo and 3 mg/kg/day groups received fewer assignments. Before completion of the study, an individual IND was obtained for the erythromycin breath test. This enabled us to study each of the last seven patients enrolled in the psoriasis study, resulting in a total of 34 entered patients. The breath tests were performed and analyzed without knowledge of the daily cyclosporine dose that each patient was scheduled to receive. Data from one patient had to be discarded because of a laboratory error resulting in an uninterpretable initial breath test result. In another patient, all cyclosporine blood levels (a total of three) had to be discarded because of poor compliance. Characteristics and selected demographics of the 32 remaining patients are shown in Table I. Seven patients were women. Eight patients were receiving medications to control blood pressure; however, no changes in their regimens were made during the study interval. The remaining 24 patients did not receive systemic medications other than cyclosporine.

Laboratories. Trough cyclosporine blood levels were obtained in all patients after week 1 and week 2 of cyclosporine treatment and every 2 weeks thereafter. Additional blood levels were obtained in some patients when past values were greater than 400 ng/ml. Cyclosporine levels were determined in whole blood by HPLC.[15] Serum triglycerides, total cholesterol, and

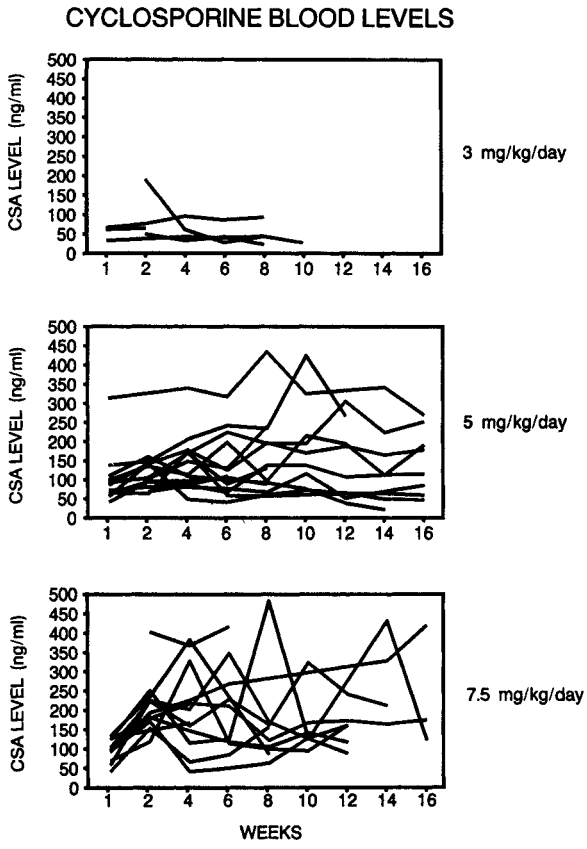

Fig. 1. Blood levels of cyclosporine observed in patients receiving each dose. Each *line* connects the cyclosporine blood levels for an individual patient.

high density lipoprotein (HDL) cholesterol levels were determined by commercial automated systems (METPATH). Low density lipoprotein (LDL) cholesterol levels were estimated as follows: Total cholesterol − (HDL + triglycerides/5).

Erythromycin breath test. Of the 32 patients studied, 30 received the erythromycin breath test within 3 weeks before starting cyclosporine treatment and two patients were tested approximately 16 weeks before receiving cyclosporine (these patients were initially randomized to receive placebo (vehicle) and were subsequently switched to 3 mg/kg/day). Each patient was retested after 1 and 4 weeks of treatment with cyclosporine. The breath test was administered during scheduled clinic visits, immediately after blood samples for cyclosporine were taken and before the patients took their daily dose of cyclosporine. Each patient was intravenously injected with 3 μCi (0.074 μmol) of [^{14}C-*N*-methyl]erythromycin (Du Pont New England Nuclear Research Products, Boston, Mass.) dissolved in 2.5 ml of 5% dextrose in water according to a previously published protocol.[14] At timed intervals during the next hour, the patient was asked to exhale through a tube, creating bubbles in a solution of 4 ml hyamine hydroxide (Sigma Chemical Co., St. Louis, Mo.) and ethanol (1:1) that contained a trace amount of thymolphthalein. Patients were instructed to blow bubbles until the blue color vanished, at which point 2 mmol CO_2 had been trapped. Twelve milliliters of Aquasol solution (New England Nuclear Research Products) was then added to each vial, and the specific content of carbon 14 was determined by scintillation counting. The percentage of administered carbon 14 exhaled per minute was calculated at each time point on the basis of an endogenous production of carbon dioxide of 5 mmol CO_2/m^2 body surface area[16] and was plotted as a function of time after injection. The resulting area under the curve estimates the percentage of injected carbon 14 exhaled in breath during the first hour after injection.[14]

Statistical analysis. For each patient, the mean of all cyclosporine blood levels obtained after the first week of therapy was determined. Because many patients required dosage adjustments before completion of the study, only blood levels obtained while they were receiving the original assigned dosages were considered (Fig. 1). The mean duration of treatment at the initial dose was 11 weeks. Three individual values were discarded from analysis in two patients because there was chart documentation that these patients had erroneously taken the cyclosporine dose on the morning of their clinic visit. Multiple regression analysis by the least-squares method[17] was used to construct models for predicting the mean cyclosporine levels from variables determined before therapy. Before the regression analysis, the mean blood levels of cyclosporine were converted to their logarithms (base 10) because this reduced the heterogeneity of variances between the dosage groups. A predictor variable was retained in the model if the associated two-tailed p value was less than or equal to the 0.05 level of significance. The analyses were performed with the use of MIDAS (Michigan Interactive Data Analysis System), a statistical software package developed by the Statistical Research Laboratory at the University of Michigan.

RESULTS

***Production of CO_2* from erythromycin and cyclosporine blood levels.** There was a severalfold range in the production of $^{14}CO_2$ from [^{14}C-*N*-methyl]erythromycin, determined before therapy in the 32 patients studied (Table I). This is comparable to the

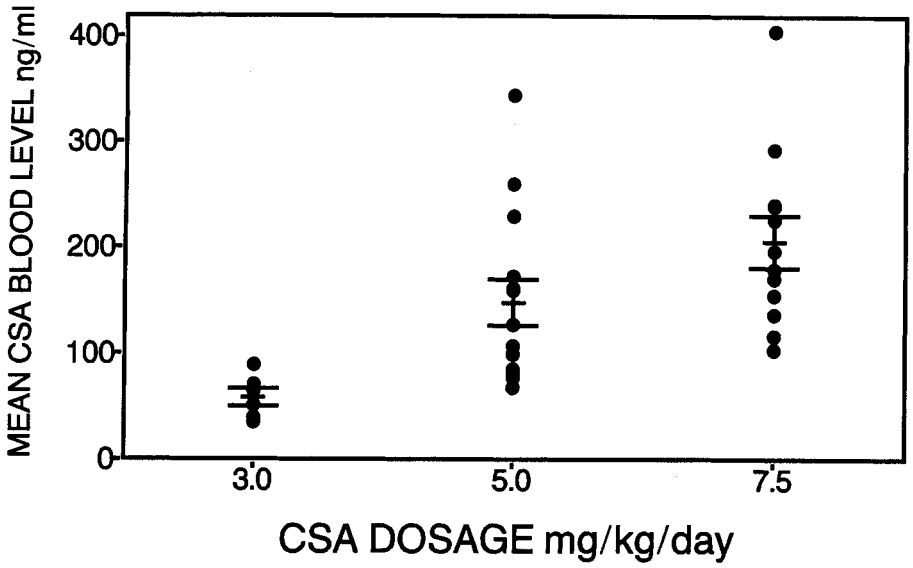

Fig. 2. Mean blood levels of cyclosporine observed at each dose. Each *point* represents the mean cyclosporine level of one patient. The *small horizontal bars* indicate the mean for each group; *wider bars* indicate 1 SEM.

range of values obtained in patients hospitalized with a variety of illnesses.[14] After the code was broken, it was determined that six patients had received 3.0 mg/kg/day cyclosporine, 14 patients had received 5.0 mg/kg/day cyclosporine, and 12 patients had received 7.5 mg/kg/day cyclosporine.

The blood levels of cyclosporine for all but one patient increased between week 1 and week 2 of cyclosporine therapy; however, there was no clear upward or downward trend in blood levels after 2 weeks of therapy (Fig. 1). To minimize random variations in blood levels, the mean of all blood level measurements obtained after week 1 was determined for each patient and used in subsequent analyses. There was significant variability in the mean blood levels among individuals receiving the identical dose of cyclosporine, and the distribution of values within each group did not appear to be normal (Fig. 2). Nevertheless, there was an inverse correlation between the production of CO_2 from erythromycin and the mean blood levels of cyclosporine in the patients in each treatment group (Fig. 3): for those receiving 3 mg/kg/day, $r = -0.83$; 5 mg/kg/day, $r = -0.61$; and 7.5 mg/kg/day, $n = -0.70$. The correlation was statistically significant at each dose level ($p < 0.05$). Logarithmic transformation of the mean cyclosporine levels reduced the heterogeneity of variances between the groups and increased the symmetry within each group (data not shown) and also improved the correlations with the breath test results: $r = 0.88$ for 3 mg/kg/day; $r = 0.64$ for 5 mg/kg/day; and $n = 0.70$ for 7.5 mg/kg/day. The strong correlations indicate that differences in erythromycin demethylase (P-450IIIA) activity largely accounted for interpatient variation in cyclosporine blood levels at each dose.

Construction of a predictive model. We next investigated whether the results of the erythromycin breath test could be incorporated into a mathematical model capable of predicting, for each individual, the cyclosporine blood levels we observed. We also wanted to determine if other patient characteristics and widely available blood chemistries (Table I) might add to the predictive capacity of the model. The demographic variables listed in Table I were included in our analysis because some studies have suggested that they may influence cyclosporine pharmacokinetics.[18-20] The influence of plasma lipid fractions was also assessed because cyclosporine appears to exist in blood largely bound to lipoproteins and uptake of cyclosporine by the liver may depend in part on lipoprotein receptors.[21] We simultaneously analyzed the data from all 32 patients using a stepwise, multiple regression method. The logarithm of the mean cyclosporine level was taken as the dependent variable, and cyclosporine dosage, patient gender, weight, body surface area, age, and pretherapy values for the erythromycin breath test result, serum HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides were taken as independent, or predictor, vari-

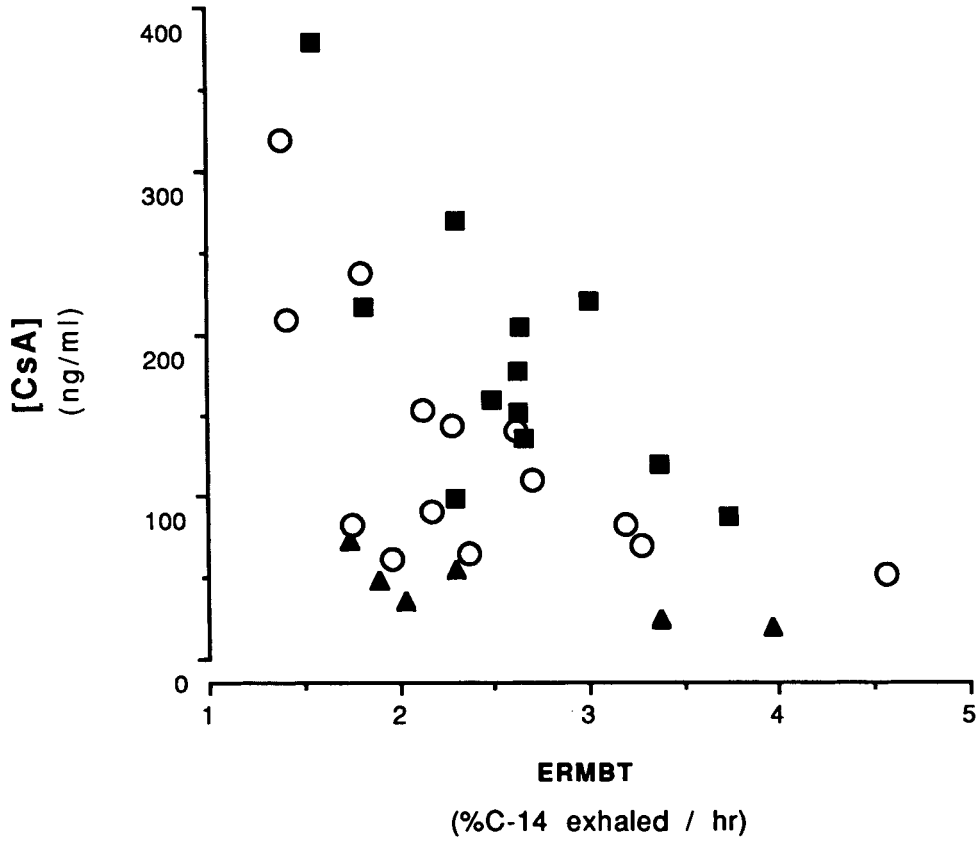

Fig. 3. Correlation between the erythromycin breath test result and mean cyclosporine blood levels. Each *point* represents the mean cyclosporine blood level and the erythromycin breath test result (ERMBT) obtained in a single patient. Symbols denote the dosages of cyclosporine each patient received: *triangles*, 3.0 mg/kg/day; *circles*, 5.0 mg/kg/day; *squares*, 7.5 mg/kg/day.

ables. This statistical approach examines all predictor variables simultaneously and, in the initial regression step, selects the single variable with the highest correlation with the logarithms of the blood levels of cyclosporine. A mathematical equation, or "model," is then generated that best estimates the log cyclosporine blood level as a function of the selected variable. At each subsequent regression step, the partial correlations *(R)* of unselected variables are calculated on the basis of the model that includes the variable(s) already incorporated. The most predictive variable is then incorporated into the model if its predictive value is statistically significant ($p < 0.05$). The predictive accuracy of the model created at each step is assessed by the coefficient of multiple determinations, or R^2.[17]

As shown in Table II, dose was the predictive variable selected in the first regression step. Dose was positively correlated with log cyclosporine blood level as expected ($R = 0.68$). However, the model incorporating dose alone accounted for less than one half of the interpatient variability observed ($R^2 = 0.47$).

After differences in assigned dosages of cyclosporine were taken into account, the erythromycin breath test result had the highest predictive value of the remaining variables (Table II, step 2). Variables that were also significantly predictive ($p < 0.05$) were patient age, weight, and HDL cholesterol (Table II, step 2). Negative correlations were observed with LDL cholesterol and total cholesterol, but these did not attain statistical significance. The breath test result was therefore selected in the second regression and the model containing dose and the breath test result accounted for 72% of the interpatient variability observed ($R^2 = 0.72$) (Table II, step 2).

Patient age was the only variable that remained predictive after dose and the breath test result were incorported into the model (Table II, step 3). Body weight no longer contributed to the predictive capacity of the

Table II. Summary of the stepwise selection procedure used in creating a multiple regression model capable of predicting the logarithm of the observed mean cyclosporine blood level

Step	*Variable**	*R†*	*p Value*	*Cumulative R^2‡*
1	*Dosage*	*0.68*	*<0.00005*	*0.47*
2	*Breath test*	*−0.68*	*<0.00005*	*0.72*
	Age	0.486	0.0056	
	Weight	0.38	0.034	
	HDL cholesterol	−0.38	0.034	
	Triglycerides	0.24	0.20	
	Total cholesterol	−0.18	0.31	
	LDL cholesterol	−0.19	0.31	
	Body surface area	0.18	0.33	
	Gender	−0.049	0.79	
3	*Age*	*0.48*	*0.0074*	*0.78*
	Triglycerides	0.19	0.31	
	Gender	−0.18	0.34	
	Weight	0.13	0.50	
	Body surface area	0.065	0.73	
	LDL cholesterol	−0.044	0.82	
	HDL cholesterol	0.039	0.84	
	Total cholesterol	−0.037	0.85	

*Variables are listed at each regression step in rank order of predictive capacity. The variable in italics was selected to be incorporated into the model at that step.
†Partial correlation coefficient.
‡Coefficient of multiple determinations reflecting the predictive capacity of the model after incorporation of the variable selected at that step.

model; this was because there was a significant negative correlation between body weight and the breath test result ($r = -0.44$, $p = 0.01$). The predictive capacity of the model was also not improved at this step by incorporating HDL cholesterol because it correlated with the breath test result ($r = 0.62$, $p < 0.001$). Patient age was therefore incorporated in the third regression step, which resulted in a slight improvement in the predictive capacity of the model ($R^2 = 0.78$; Table II, step 3). The model was not significantly improved by additional regressions incorporating the other variables (data not shown). The following mathematical equation (Table III) was derived from our analysis:

log (cyclosporine blood level, ng/ml) =
1.7 + 0.099(dose, mg/kg/day) −
0.157(breath test, %^{14}C) + 0.0055(age,years)

A comparison of the cyclosporine blood levels predicted by this model and those actually observed in each of our patients is shown in Fig. 4. The observed blood levels were within 50 ng/ml of that predicted by our model in 26 of the 32 patients (81%).

Breath test results at week 1 and 4. After 1 week of therapy with cyclosporine, there was a 20% decrease in the mean breath test value, from 2.64% to 2.11%, when all patients were considered. This decrease was statistically significant ($p < 0.0001$ as determined by a paired t test) and the percent decrease in the breath test result correlated with the cyclosporine blood level determined at week 1 ($r = 0.42, p = 0.05$). The mean breath test value did not change significantly between weeks 1 and 4 of treatment (2.11% and 2.13%, respectively).

Table III. Parameters of the final model*

Variable	*Coefficient*	*SEM*	*p Value*
Constant	1.700	0.130	<0.00005
Dose (mg/kg/day)	0.099	0.0145	<0.00005
Pretherapy breath test (% ^{14}C exhaled in 1 hr)	−0.157	0.032	<0.00005
Age (yr)	0.0055	0.0019	<0.0074

*Log (cyclosporine) = 1.7 + 0.099(dose) − 0.157(breath test) + 0.0055(age)

We next asked whether our model was valid for breath test results obtained while patients were receiving cyclosporine. We therefore repeated our multiple regression analysis, substituting the breath test values obtained after each patient had received cyclosporine for 4 weeks (data not shown). The resulting equation was almost identical to the equation obtained with the pretherapy breath test results (Table III):

log (cyclosporine blood level, ng/ml) =
1.64 + 0.093(dose,mg/kg/day −
0.137(breath test, %^{14}C) + 0.0054(age,years)

The predictive accuracy of this equation ($R^2 = 0.75$) was also comparable to the predictive accuracy of the model that was based on the initial breath test results.

DISCUSSION

Our data indicates that liver erythromycin *N*-demethylase (P-450IIIA) activity largely accounts for the relationship between the dose of cyclosporine and the blood levels for an individual patient. After differences in dose of cyclosporine were considered, the breath test result was the most predictive of the variables we examined (Table II, step 2). Indeed, our model incorporating just dosage and the breath test result accounted for 72% of the interpatient variability in the logarithms of the cyclosporine blood levels we observed (Table II, step 2). We also noted a significant positive correlation between the logarithms of the cyclosporine blood levels and patient weight, and this has been reported by others.[19] Our finding that the logarithms of the cyclosporine blood levels correlated with HDL cholesterol has not been previously reported, to our

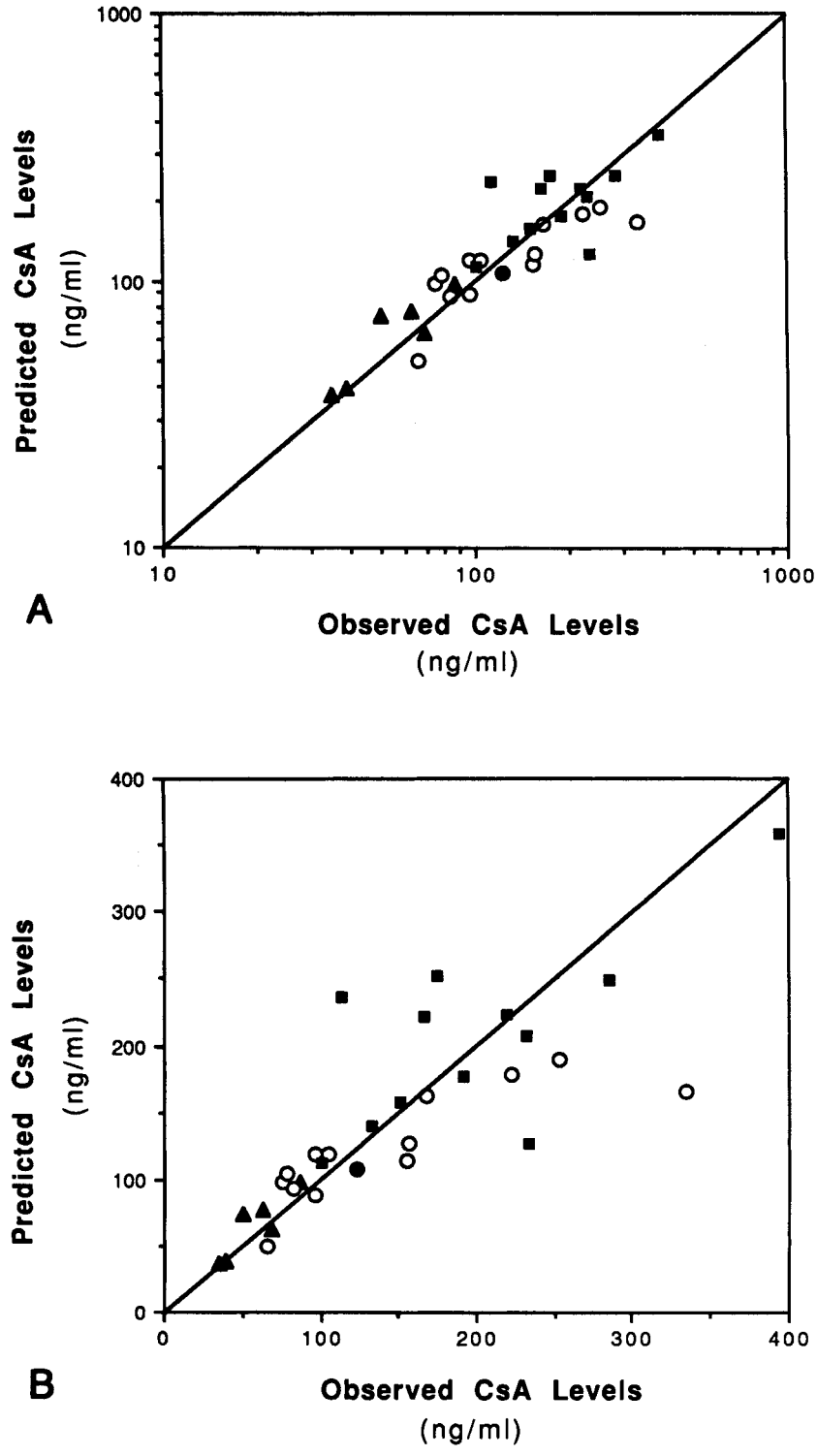

Fig. 4. Comparison of predicted and observed levels of cyclosporine. For each patient, the predicted cyclosporine blood level was derived by the mathematical model (Table III) and compared with the mean cyclosporine blood level actually observed. **A,** Logarithmic plot (R^2 = 0.78). **B,** Linear plot (R^2 = 0.68). *Symbols* denote the dosages each patient received: *triangles,* 3.0 mg/kg/day; *circles,* 5.0 mg/kg/day; *squares,* 7.5 mg/kg/day.

knowledge. We found, however, that the predictive capacities of weight and HDL cholesterol were lost after incorporating the breath test results into our model (Table II, step 3). This was because there was a significant negative correlation between patient weight and the breath test result and a significant positive correlation between HDL cholesterol and the breath test result. In a given individual, therefore, the logarithm of the cyclosporine blood levels were partially predicted by body weight and HDL cholesterol because these parameters partially predicted P-450IIIA activity. Of the remaining variables, only patient age was a significant predictor, and the positive correlation that we found was consistent with other reports that suggested that elderly patients require less cyclosporine.[20] Unlike patient weight and HDL cholesterol, the predictive capacity of patient age was not lost after incorporation of the breath test results into the model (Table II, step 3). This indicates that the influence of patient age on cyclosporine blood levels was independent of P-450IIIA activity, and we have not observed a consistent effect of aging on liver P-450IIIA activity in the more than 140 patients examined to date (Watkins PB, unpublished observations, March 1990).

We have previously reported that the erythromycin breath test results are significantly higher in women than in men,[14] and this has been confirmed in the more than 140 patients who have received the breath test to date (Watkins PB, unpublished observations, March 1990). The clearance of cyclosporine has also been reported to be more rapid in women than in men.[18] Gender had no predictive value in our model, however, and this presumably reflects the relatively small number of women studied. In aggregate, our data suggests that women may require less cyclosporine than men to attain target blood levels.

We also found that the breath test values of the patients decreased an average of 20% after they started therapy with cyclosporine, and that the decrease observed in each individual correlated with the cyclosporine blood level determined at the time the breath test was performed. This was an expected finding because both cyclosporine and the test dose of erythromycin should compete for in vivo binding to, and metabolism by, liver P-450IIIA. The 20% mean decrease in breath test results was modest compared with the severalfold interpatient variation in this parameter; this is why the model generated by the multiple regression analysis was almost identical whether we used the results from the pretherapy or week 4 breath test. The fact that the breath test values of the patients did not significantly change between week 1 and week 4 of therapy suggests that liver P-450IIIA is not induced or inhibited by prolonged treatment with cyclosporine. This probably explains why the model based on just the initial breath test value appeared to have predictive value during the duration of our study.

Several factors probably account for the 22% variability in cyclosporine blood levels not accounted for by our model. First, it is likely that imperfect compliance went undetected in at least some patients in our study because compliance with the dosing regimen was checked only in patients whose blood levels exceeded 400 ng/ml. This is a likely explanation for wide intrapatient variation in cyclosporine blood levels that was especially evident in the patients receiving 7.5 mg/kg/day of the drug (Fig. 1). Second, studies in rats have suggested that the breath test can detect small changes in P-450IIIA catalytic activity only when pharmacologic doses of erythromycin are administered along with the radiolabeled compound.[14] The use of trace doses of erythromycin in our study may therefore have resulted in some inaccuracy in determining P-450IIIA activity. Finally, interpatient differences in gut absorption of cyclosporine are likely to have existed in our population.[22,23] Indeed, the very high predictive capacity of our model appears to contradict evidence that suggests that cyclosporine blood levels largely reflect the extent of absorption of the drug.[8,9,20] However, interpatient differences in the bioavailability of cyclosporine may be accounted for, in part, by the erythromycin breath test result. This is because P-450IIIA is present in human jejunal mucosa[24] where metabolism of cyclosporine by the enzyme might appear as incomplete oral absorption in a pharmacokinetic study. If the catalytic activity of intestinal P-450IIIA mirrors that of the liver in a given individual, both would be reflected in the breath test result. We have recently proved that cyclosporine is metabolized by intestinal P-450IIIA in rats,[25] and similar studies are now underway in human tissue.

Our data strongly suggest that the erythromycin breath test will provide useful information in individualizing at least the initial dosing of cyclosporine. Only three patients had differences between predicted and observed blood levels of more than 100 ng/ml (Fig. 4, *B*). Two of these patients were men receiving 7.5 mg/kg/day cyclosporine, and compliance was suspect in each of these subjects. One had two blood levels discarded because of documented improper dosing, and the other was the patient shown in Fig. 1 whose consecutive blood levels repeatedly varied in excess of 350 ng/ml. The remaining patient was a man receiving 5 mg/kg/day cyclosporine, and he appeared to be compliant. He had the highest mean cyclosporine blood levels in this treatment group (Fig. 1), and he had the

lowest breath test result of any patient studied (1.39% of administered ^{14}C exhaled per minute). Thus, although our model did not work well for this patient, his very low breath test results supports our hypothesis that interpatient differences in P-450IIIA activity largely explain the heterogeneous dosing requirements characteristic of the drug.

It is important to note that the actual mathematical model generated by our data may not be useful in other patient populations for several reasons. First, the patients we studied were receiving a relatively narrow range of daily doses of cyclosporine and the equation may therefore not apply to patients receiving other doses. For example, a 60-year-old man with an average breath test result of 2.5% (Table I) is predicted by our model (Table III) to have a cyclosporine blood level of 46 ng/ml when he is not even receiving the drug (dose = 0). Second, the patients we studied were generally healthy and psoriasis has no known effects on hepatic, intestinal, or renal handling of drugs. In contrast, the majority of patients currently receiving cyclosporine are organ transplant recipients who often have varying degrees of liver, intestinal, or renal dysfunction. Moreover, organ transplant recipients usually receive varying doses of steroids that are known inducers of P-450IIIA.[14,26] It therefore seems unlikely that a single breath test result will remain predictive over time in these patients. Finally, different methods for measuring parent cyclosporine[6] are used at different institutions, and the results are not always standardized.

Our study illustrates the potential clinical usefulness of tests capable of measuring the activity of individual liver cytochromes P-450. It has recently been appreciated that inherited defects are common in at least some hepatic cytochromes P-450 and that "poor metabolizers" may require reduced daily doses of some medications.[27] The situation is more complex with P-450IIIA where there appears to be a broad unimodal distribution of enzyme activity in the population, and a distinct subpopulation with a poor metabolizer phenotype has not been identified.[28] Our study is novel in that it represents the first attempt to use a measurement of a cytochrome P-450 activity (the erythromycin breath test) in a mathematical model that may be useful in estimating appropriate dosing for the majority of patients receiving a drug. As noninvasive assays of other cytochromes P-450 become available, we predict that they may also serve as useful guides in the dosing of many other drugs.

In summary, our data suggest that at a given daily dose of cyclosporine, an individual's trough blood level of the drug can be predicted by use of just two parameters: the erythromycin breath test result and the age of the patient. It should now be possible to adapt the breath test to use the nonradioactive isotope carbon 13.[29] Future studies will determine whether the erythromycin breath test also predicts blood levels of other drugs now known to be extensively metabolized by P-450IIIA, including nifedipine[12] and sex hormones.[12,30]

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