ELSEVIER

Correlation Between C_2 and AUC_{0-4} in Renal Transplant Patients Treated With Diltiazem

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ABSTRACT

Background. The area-under-the-curve (AUC) of cyclosporine (CsA) reflects exposure to the drug, but this monitoring strategy is time-consuming and not cost-effective. Recently, it has been suggested that the concentration at 2 hours after dosing (C_2) shows the best correlation with AUC. The C_2 has been replacing the trough measurement (C_0) to monitor CsA therapy, but in patients receiving diltiazem there is not much information about this issue. We investigated the correlations between C_2 and C_0 with absorption AUC over the first 4 hours (AUC_{0-4}) in renal stable transplant patients receiving CsA therapy with or without diltiazem.

Patients and methods. Ten patients (five men) of ages 23 to 68 years and 6 to 84 months after transplantation, were randomly assigned to an 8-week initial period of either diltiazem washout or controlled treatment with diltiazem. Time-concentration curves of cyclosporine were performed at the end of this period using a specific RIA measurement of blood samples. Thereafter, a crossover of the groups was performed and after another 8 weeks, a second curve was obtained. Drugs that change the pharmacokinetics of cyclosporine or diltiazem were not allowed.

Results. The cyclosporine daily dose was lower with diltiazem (173 ± 4 mg vs 213 ± 4 mg, $P = .002$), but despite a dose reduction of only 19% ± 1.5%, there was a trend to a larger AUC/dose (28 ± 5 ng · h/mL · mg vs 17 ± 2 ng · h/mL · mg, $P = .1$) and a trend to an increased C_2 when treatment included diltiazem (1035 ± 156 ng/mL vs 652 ± 126 ng/mL, P = NS). Moreover, we confirmed that C_2 showed the best correlation with AUC_{0-4}, ($r = 0.7$, $P = .04$), a correlation that improved with diltiazem ($r = 0.9$, $P < .002$).

Conclusion. C_2 is the point that correlates best with AUC_{0-4} with or without diltiazem. C_2 in the presence of diltiazem was associated with a stronger, more significant correlation with AUC_{0-4}.

THE AREA UNDER the 12-hour time-concentration curve (AUC_{0-12}) of cyclosporine (CsA) microemulsion (Neoral, Novartis), and the one obtained over the first 4 hours—an abbreviated curve (AUC_{0-4})—reflect drug exposure and predict toxicity and graft outcome.[1] However, this monitoring strategy is expensive and time-consuming.

Recently, it has been suggested that the CsA concentration at 2 hours postdose (C_2) correlates better with the AUC than any other single point. On the other hand, the predose concentration (C_0), or the trough level, correlates poorly with AUC.[2,3] Limited information is available about these correlations among patients using diltiazem, a drug frequently prescribed to influence CsA pharmacokinetics.[4] The aim of this study was to examine the correlations between C_2 and C_0 with AUC_{0-4} among renal transplant patients under treatment with diltiazem.

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PATIENTS AND METHODS

After obtaining written informed consent, 10 stable renal transplant patients who were more than 6 months after transplantation and were receiving CsA, azathioprine, and prednisone as well as diltiazem (90 mg twice a day) were enrolled in the study. These patients were randomly assigned to an 8-week period of continued therapy with diltiazem (five patients), or to a washout period removing DTZ from the treatment (five patients). At the end of this first period, the time-concentration curves of CsA during the first 4 hours following a dose of CsA were performed in all the patients, whether or not they were receiving diltiazem. CsA concentrations were measured on whole blood using a specific RIA (CYCLO-TracSP, Incstar, Stillwater, Minn, USA). Thereafter, the groups underwent a crossover followed by either diltiazem washout or reinstituted treatment with DTZ. At the end of the second period, the time-concentration curves were repeated.

During the whole study period, any drug that might alter CsA or diltiazem pharmacokinetics was avoided.

A commercial statistical package (GraphPad InStat, version 3.01 for Windows 95/NT, San Diego, Calif, USA) was used to perform the nonparametric Wilcoxon matched-pair test that evaluated differences between periods of treatment and Spearman's correlation to evaluate association between variables. Values were expressed as means ± SEM; P values $< .05$ were considered significant.

RESULTS

Of the 10 patients included in this study, five were men. The overall mean age was 41.9 years (range: 23 to 68) and the time posttransplant 45 months (range: 6 to 84).

The CsA concentrations (ng/mL) at different points in the curve and the AUC_{0-4} (ng · h/mL) are shown in Fig 1. The differences between treatments are illustrated in Table 1. The prescription of diltiazem was associated with a reduction in Neoral dosage by 19% ± 1.5%. A trend toward higher C_2 and AUC_{0-4} levels was observed among patients receiving DTZ treatment, despite a significant dose reduction; however, these differences did not reach statistical significance. The AUC_{0-4}/dose with diltiazem was 1.7-fold higher, but the difference was not significant ($P = .13$; see Table 1).

Correlations between C_0 and C_2 with the AUC_{0-4} were (1) CsA without diltiazem: C_2 versus AUC_{0-4} ($r = 0.7$, $P = .04$); C_0 versus AUC_{0-4} ($r = -0.04$, $P = .92$) versus (2) CsA + diltiazem: C_2 versus AUC_{0-4} ($r = .9$, $P = .002$), C_0 versus AUC_{0-4} ($r = 0.8$, $P = .004$). There were no significant changes in the levels of serum creatinine, blood urea nitrogen, serum potassium, or serum uric acid observed during the study. Likewise no significant changes in blood pressure values or adverse events were detected.

DISCUSSION

It has recently been suggested that C_2 is the point in the time-concentration curve of CsA that best correlates with AUC, while C_0 correlates poorly with it. On the other hand, information on patients cotreated with diltiazem scarce.[2,3] In light of our previous findings about the effects of diltiazem on CsA pharmacokinetics,[4] we were interested in evaluating these correlations in patients under diltiazem therapy.

In our center, we routinely combine diltiazem with CsA, azathioprine, and prednisone. In addition to its CsA-sparing effect, diltiazem has shown a good antihypertensive

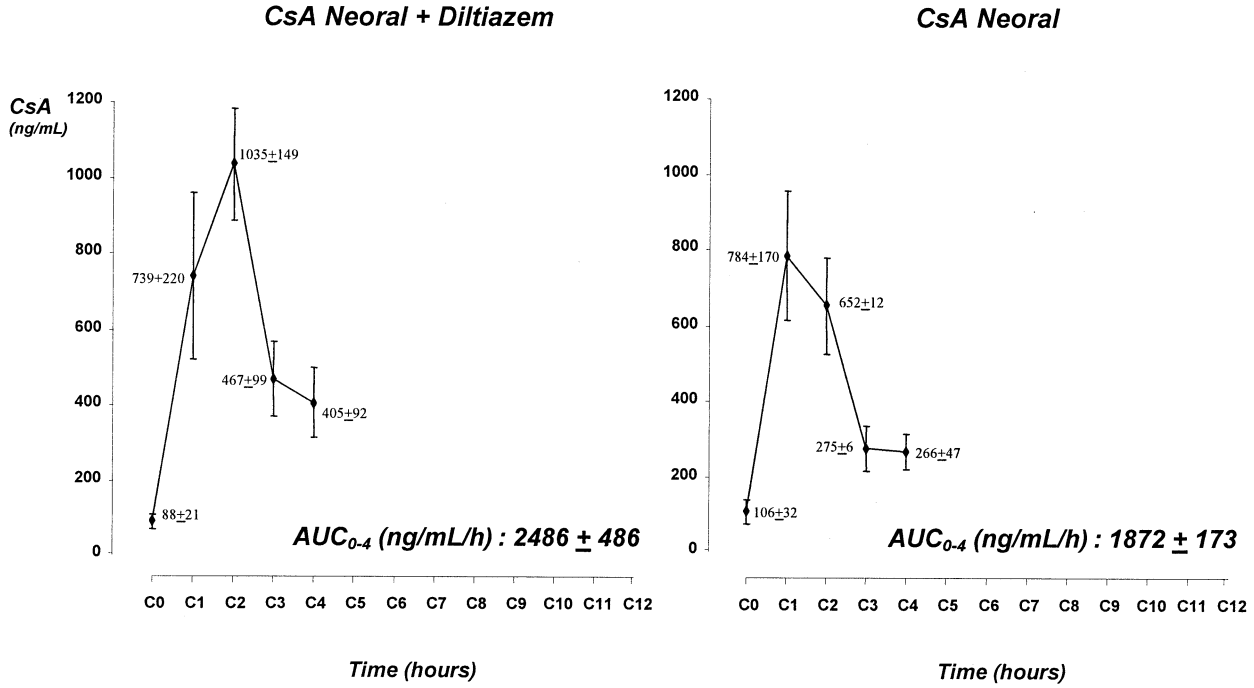

Fig 1. AUC_{0-4} curves in patients with and without diltiazem therapy.

Table 1. Doses, Blood Levels, and AUC in Patients With and Without DTZ Therapy

	CsA Neoral	CsA Neoral + diltiazem	*P*
CsA dose (mg)	113 ± 4	93 ± 4	.008
C_0 (ng/mL)	107 ± 32	88 ± 22	.56
C_2 (ng/mL)	652 ± 126	1035 ± 156	.28
AUC_{0-4} (ng · h/mL)	1872 ± 173	2486 ± 486	.28
AUC_{0-4} (ng · h/mL)/ dose (mg)	17 ± 2	28 ± 5	.13

action. Recently its use has been associated with lower rates of mortality and early graft loss.[5] Also, we have confirmed that patients cotreated with diltiazem showed better graft survival at 4 years post–renal transplantation.

The findings of this study are consistent with our previous observations.[4] We observed a similar trend toward an increased AUC and AUC/dose when stable renal transplant patients are cotreated with diltiazem despite a significant reduction (19%) in the daily CsA dose. These findings may be explained because DTZ is a well-known inhibitor of metabolism of CsA both in the liver and more importantly in the small bowel.[4,6–8] When we studied the extended AUC_{0-12} for parent drug and for its metabolites among patients cotreated with diltiazem, we observed a significant increase in both the parent drug AUC and the metabolites AUC, a finding that is not solely explained by inhibition of CsA metabolism exclusively in the liver.[4] Thus, the inhibition of CsA metabolism in the small bowel may increase drug bioavailability and have an impact on its pharmacokinetics.

Although the number of patients included in this study was small, we confirmed that C_2 is the point in the curve that shows the best correlation with the AUC whether patients are treated with or without diltiazem. Moreover, as a new finding, we observed that patients receiving diltiazem show a stronger and more significant correlation. The explanation for the improved correlation of C_2 with AUC when we added diltiazem is beyond the scope of this study, but we hypothesize that the improved bioavailability of CsA results in more predictable drug absorption. These findings and their mechanisms should be analyzed in a larger study.

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