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Predicting patients' exposure to cyclosporin

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Abstract The introduction of a new formulation of cyclosporin, Neoral, has reduced pharmacokinetic variability and it may be possible to simplify area-under-curve (AUC) measurements using a limited sampling strategy. We have examined the timing of blood samples necessary to obtain accurate AUC predictions for cyclosporin using limited data from stable renal transplant patients dosed twice daily with Neoral. Best subset regression of blood concentration profile data obtained from ten patients at steady state indicated that two samples, timed at 2 and 8 h post-dose, accounted for 97 % of the variance in AUC. The accuracy of this prediction was tested using profile data collected in a further 36 patients on three occasions separated by 4 and 44 weeks. Using the regression, $AUC = 1.96 \times [2\ h] + 11.5 \times [8\ h] + 355.2$, the mean (95 % CI) prediction errors of the three occasions were 1.7 % (– 2.1–5.4 %), 3.3 % (– 2.6–9.2 %) and 0.4 % (– 3.4–4.2 %). Data are presented that suggest AUC monitoring with a single blood sample could be feasible in a clinical setting.

Key words Cyclosporin AUC · Therapeutic drug monitoring · Blood concentration

Introduction

Pre-dose or trough blood cyclosporin concentration is routinely monitored and the result used to alter patients' drug dosing. However, patients with identical pre-dose blood concentrations may have very different systemic exposure to the drug as measured by area under the cyclosporin blood concentration curve (AUC). For this reason it has been suggested that controlling cyclosporin drug dose and therapy would be better achieved by measuring individual patients' AUC rather than trough concentration [7]. Although AUC monitoring is undertaken in some centres, most believe that the variability in cyclosporin pharmacokinetics, together with the increased cost and complexity, make AUC monitoring impractical in a routine clinical setting.

It has been known for some time that two or three blood samples can be use to determine accurately a patient's AUC [4]. However, because of the variability in cyclosporin absorption following Sandimmun administration, the required blood samples must be drawn at very specific times and this makes the practical implementation of abbreviated or limited sampling AUC difficult [1, 4]. The introduction of a new formulation of cyclosporin, Neoral, has improved the drug's absorption and reduced the within- and between-variability in patients' pharmacokinetics [2, 3]. Since the drug's pharmacokinetics are more predictable following Neoral administration, it is probable that AUC could be estimated using a wider range of sampling times than has been possible for Sandimmun. Therefore, it may be possible to simplify AUC measurement using a limited sampling strategy which is more flexible and clinically practical than those previously suggested for Sandimmun. This paper describes such a strategy.

Materials and methods

Patients

During the clinical testing of Neoral, cyclosporin blood concentration profiles were measured in a group of 46 stable renal transplant patients at 8, 12 and 52 weeks after conversion from Sandimmun. On each occasion, blood was taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10 and 12 h after drug administration. The samples were taken into tubes containing EDTA anticoagulant and blood cyclosporin concentration was measured using a specific radioimmunoassay.

Statistical procedures

The AUC of each profile was calculated using the linear trapezoidal method.

The patients were arbitrarily split into two groups. The first consisted of the initial ten patients while the remaining 36 were allocated to the second group. The data from the first group of patients were used to determine the relationship between AUC and blood concentration using multiple linear regression. AUC was taken as the dependent variable and the independent variables were the blood concentrations grouped by time. Stepwise linear regression was used to determine the combination of time points that were most highly correlated with AUC. Predictive equations were derived for all time points individually and for the time points selected by the stepwise regression procedure. These equations were then used to predict the AUC values of the remaining 36 patients and these data from the second group of patients were used to determine the accuracy and precision of the predictions. The agreement between the predicted and measured AUC was examined and the prediction error calculated as shown in Eq. 1.

$$\% \text{ Prediction error} = \frac{\text{Predicted AUC} \quad \text{Measured AUC}}{\text{Measured AUC}} \times 100 \quad (1)$$

Results

The stepwise linear regression procedure indicated that only two points were needed to account for 97 % of the variance in AUC in the first group of patients. These time points were 2 and 8 h post-dose. Using the derived regression equation (Eq. 2) to predict the AUC values for cyclosporin after Neoral in the remaining 36 patients at 8, 12 and 52 weeks following conversion from Sandimmun resulted in highly accurate predictions. The mean (95 % CI) prediction error of the three occasions were 1.7 % (−2.1–5.4 %), 3.3 % (−2.6–9.2 %) and 0.4 %(−3.4–4.2 %), respectively. These data are shown in Fig. 1.

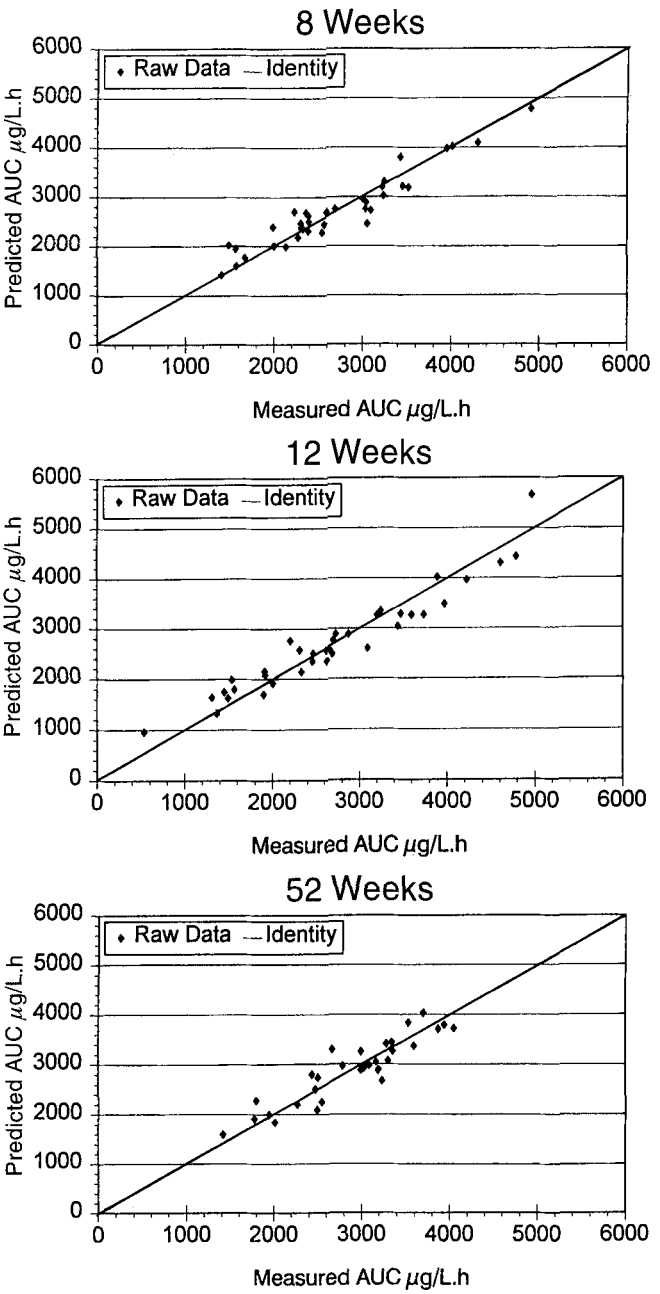

Fig. 1 Predicted area-under-curve *(AUC)* versus measured AUC at 8, 12 and 52 weeks in 36 patients after conversion from Sandimmun to Neoral. The predictions were made using Eq. 2. The raw data are plotted as a *filled diamond* and the line is the line of identity, i. e. one-to-one agreement

$$\text{AUC} = 1.96 \times [2\text{ h}] + 11.5 \times [8\text{ h}] + 355.2 \quad (2)$$

The variance in AUC explained by cyclosporin concentrations at individual time points varied between 18 % and 85 %. Using the regression equations derived for all time points individually in the first group of patients to predict the AUC in the second group resulted in a minimum mean predictive error of 0.4 % and a maximum of 35.7 %. The coefficient of determination (r^2), the mean and standard deviation of the prediction error at each time point are shown in Fig. 2.

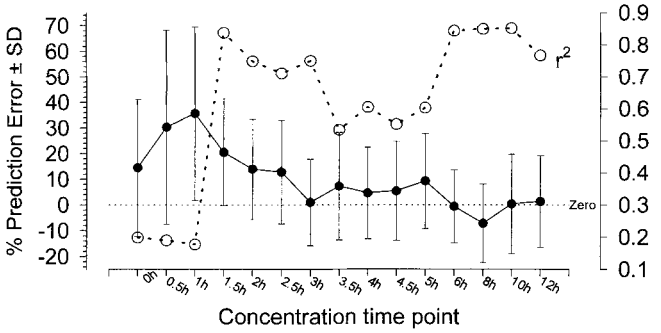

Fig. 2 The mean ± standard deviation of prediction error after using the regression equations derived for all time points individually in the first group of patients to predict the AUC in the second group (*filled circles* and *error bars, left-hand y*-axis scale). The corresponding coefficients of determination (r^2) at each time point are shown as *open circles (right-hand y*-axis scale)

Discussion

It is clear from the results of this study that cyclosporin AUC after Neoral can be determined with a high degree of accuracy and precision with only two concentration measurements in renal patients. The choice of blood concentrations at 2 and 8 h post-dose was made for statistical reasons rather than clinical utility and with other data sets different authors have shown similar correlations with 2 and 6 h [5] and with 0 and 2 h post-dose [6]. Following Neoral administration, AUC prediction error is smaller, less variable and requires one less concentration measurement than that shown previously for Sandimmun [4]. However, the use of two accurately timed blood samples would still present practical difficulties in many clinical setting.

A more practical method would be to use only one sample which could be taken at any of a given range of time after dosing. The data shown in Fig. 2 suggest that this approach would be feasible since prediction error falls to less than 10 % when blood cyclosporin concentrations measured in samples between 3 and 12 h are used to predict AUC. Thus, a series of equations could be derived to calculate AUC from a single, timed, blood cyclosporin concentration measurement. This could be further simplified for clinical use by using a programmable calculator or by means of a graphical display from which AUC could be read given a cyclosporin concentration measured at a specific time.

Using this approach, it would be possible to use a less restrictive range of blood sampling times and this would allow AUC estimation in routine clinical settings. It would also overcome some of the problems associated with trough concentration measurement when the times of medical out-patient clinics do not correspond with the start or end of patients' cyclosporin dosing regimens. However, it is obvious that before this method could be introduced it would require further testing to confirm its accuracy in a wider range of patients and cyclosporin indications. It is also likely that the derived equations would be unique to Neoral due to the particularly good absorption characteristics of that formulation coupled with its low within- and between-patient variability.

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