Chapter I

Introduction

Cyclosporin (CsA) is a potent immunosuppressive drug widely used in organ transplantation and some autoimmune diseases. Since it has a major impact on organ transplantation, significantly improving one or two year graft-survival rates, CsA is chief to many immunosuppressive regimens (Shoker, 1996). However, dosage of CsA is complicated by intra- and interindividual variability of its pharmacokinetics, and by the narrow margin between adequate immunosuppression and toxicity. For this reason, attention to the CsA concentration in blood is essential for optimization of therapy.

The consensus panels on CsA monitoring recommended trough concentration monitoring since trough levels far outside a therapeutic range tend to predict adverse events and it is practical (Kahan et al., 1990; Shaw et al., 1990; Oellerich et al., 1995). However, as a consequence of the variability of its pharmacokinetics, patients titrated to similar trough levels could be exposed to different extents of the drug, as assessed by area under the concentration versus time curve (AUC) profiles and this is the reason for the overlap in trough concentrations associated with either graft rejection or good graft function (Kasiske et al., 1988; Nankivell, Hibbins and Chapman, 1994). Because of such limitations of trough level monitoring, a pharmacokinetic strategy based on serial concentration-time profiles was applied to determine appropriate drug dose (Kahan and Grevel, 1988). Monitoring of the AUC, calculated from the individual pharmacokinetic profile, has been reported to be more effective than trough level in dosage adjustment to control CsA therapy (Grevel, Welch and Kahan, 1989). Furthermore an average steady-state concentration, obtained by dividing the steady-state AUC by the oral dosing interval, affords a prediction of the probability of rejection, which is not reached by conventional trough-level monitoring (Grevel et al., 1991). Nevertheless, despite a complete pharmacokinetic profile (AUC) could provide more precise information, it is expensive and time consuming because of multiple blood sampling. Thus a careful choice of only few sampling times is desired.

To decrease the number of blood samples for pharmacokinetic profiles, Johnston et al. (1990) used multiple regression to derive an equation that provided a good estimate of the AUC from the minimum number of time

points. AUC was taken as the dependent variable, and blood concentrations grouped by time as the independent variables. It was found that the predicted AUC, calculated from three times points 3.5, 8, and 10 hours after dosing (twice daily) correlated well ($r^2 = 0.9898$) with the full AUC calculated from 13 data points. Likewise, Grevel and Kahan (1991a) suggested that a model equation based on three concentrations obtained at 2, 6, and 14 hours after oral administration (once daily) predicted a 24-h AUC with r^2 equal to 0.963. Meyer et al. (1993), also reported that only three blood samples taken at 2, 6, and 24 hours after once daily drug administration provided good prediction with r^2 equal to 0.986. In 1993, Lindholm et al. recommended the abbreviated AUC studies at 0, 2, and 6 hours in case of twice-daily dosing ($r^2 = 0.96$) or 0, 2, 4, 6, and 24 hours ($r^2 = 0.94$) for patients receiving daily dose. Since this sampling schedule required the patient to be available for 6 hours per day, it suits for outpatient setting. In 1993 Gaspari et al. applied the published models to their data to evaluate which equations were predictive of AUC. They found a very poor correlation with the actual AUC with major error ranges and suggested that the regression equation depended on the set of selected data and was not generally applicable. However, the regression method still being used to derive AUC prediction equations in many studies (Serino et al., 1994; Foradori et al., 1995; Kahan et al., 1995; Tsang et al., 1996; Serafinowicz, Gaciong, Baczkowska et al, 1996; Serafinowicz, Gaciong, Majchrzak et al., 1997).

Nevertheless, it is quite clear that inconsistent absorption of CsA in its classical oral formulation, crude emulsion (Sandimmun®), is a major cause of the tremendous inter and intraindividual pharmacokinetic variation. To optimize the bioavailability of CsA, a new microemulsion formulation of the drug has been developed (Neoral™). It has shown an increased rate and extent of drug absorption with lower inter- and intraindividual pharmacokinetic variability when compared with the conventional formulation (Kovarik et al., 1994; Holt et al., 1995; Kahan et al., 1995). Moreover, an improved correlation between trough concentrations and AUC was demonstrated with Neoral (Mueller et al., 1994; Kovarik et al., 1994) . Theoretically, these advantages should allow a better correlation between a limited sampling strategy and total drug exposure, which is best estimated by the AUC. Besides, it may be possible to predict AUC by simply using limited time points in linear trapezoidal rule.

There are few studies of CsA therapeutic drug monitoring in Thailand and besides, the abbreviated AUC study has never been done before. The present study was thus performed in order to establish optimum sampling time that yields a good estimate of the AUC by trapezoidal rule and regression method. Also, to determine correlation between CsA dose and

CsA blood level at different time points. In addition, this research would investigate the pharmacokinetics of CsA microemulsion formulation in stable kidney transplant Thai patients. These would be a useful information for application of CsA therapy monitoring in Thailand.

Objectives

1. To determine the optimum sampling time points for predicting CsA area under the concentration versus time curve (AUC) by multiple linear regression and by trapezoidal rule.
2. To compare correlation between CsA dose and CsA blood level at different time points including average concentrations at steady state calculated from measured AUC.

The significance of the study

First, the study will determine the optimum sampling time to estimate the AUC from limited number of blood samples. This abbreviated pharmacokinetic profile will make the procedure quicker and easier than a complete pharmacokinetic profile, while reducing cost and patient discomfort. Second, this study will provide the information of the correlation between CsA dose and CsA blood level including pharmacokinetics in Thai patients which might be different from those reported in foreign countries and could be use as a guide for therapeutic drug level monitoring in Thai patients.