Chapter VI

Conclusion

1. Our results suggested that there was no single concentrations at any time points including trough level could explain more than 90% of the variability described by the measured AUC calculated by the trapezoidal rule using all seven data points. The single blood concentration that showed the best correlation with AUC was the level measured at 2 hours after drug administration (r^2=0.8845). The actual AUC could be predicted accurately from 2 or 3 sampling times either by stepwise multiple linear regression or by linear trapezoidal rule as shown in table 6.1.

Table 6.1 Regression equations and trapezoidal equations for predicting AUC from 2 and 3 sampling time points

Selected time points (hr after dosing)	Equations: Predicted 12 hr-AUC =	Absolute prediction error (%) Mean ± SE	r^2
2,6	$3.085*C_2 + 6.019*C_6 + 376.893$	5.40 ± 0.88	0.9638
1,2,6	$0.738*C_1 + 2.112*C_2 + 7.02*C_6 + 263.108$	3.01 ± 0.81	0.9823
2,8	$0.5*2*C_2 + 0.5*6*(C_2 + C_8) + 0.5*4* C_8$	9.47 ± 1.57	0.9442
0,2,6	$0.5*2*(C_0+C_2) + 0.5*4*(C_2+C_6) + 0.5*6*(C_6+C_0)$	4.94 ± 0.81	0.9695

It can be seen from our data that regression models provided higher prediction accuracy than trapezoidal rule while used the same number of sampling times. However, multiple linear regression is difficult to visualize what the fitted model looks like, since it requires to plot in more than one dimensions. In addition, it is difficult to interpret what the model means in real life term. On the other hand, two and 3 sampling-point trapezoidal rule, a deterministic model, requires only simple calculation and can be visualized. It is also likely to be a promising method for predicting AUC. Further study could be considered in a large number of patients to concluded the usefulness of the proposed methods.

Applying the model equations proposed by previous studies to the present data also showed good correlation coefficient between the prediction and the full AUC . However, the regression equations which were derived from the present data displayed better correlation than the others.

2. Using CsA-sparing agents was associated with higher AUC/dose, higher C_0/dose, higher C_{max}/dose, longer $t_{1/2}$ and lower Cl/F than not using while t_{max} and Vd were not significantly different in both groups. The postulated mechanism is inhibition of CsA metabolism through the cytochrome P450 system.

Although sampling time point, which showed the best correlation between predicted and actual AUC in a group using CsA-sparing agents was different from a group not using CsA-sparing, there was not much difference in prediction error. Further studies should be made to get a more definite conclusion whether pharmacokinetic drug interaction affecting the optimum sampling time.

3. Trough level, which is generally used for guide CsA dosing, showed poor correlation with CsA dosage (r^2=0.1417) while concentration at 2 hours post dose and AUC displayed the best correlation coefficient with dose whether a group using CsA-sparing agents was excluded or not. Our result suggested that either level at 2 hours after administration or AUC is more appropriate than trough level for using as a tool for guide CsA dosing.

4. Although our result did not show the obvious relationship between CsA levels and the adverse events, concentration at 2 hour-post dose and average steady state level showed a better relationship with adverse events than trough level. Due to the shortage of time duration and the small number of patients were included in this study, further studies are required.