

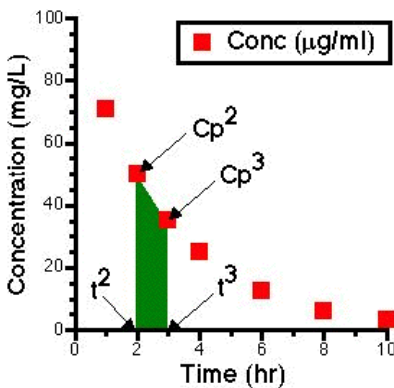
The Determination of Tacrolimus Area Under the Curve (AUC)

Tacrolimus dosing is currently determined by trough blood concentration levels. Unfortunately, there is a lack of correlation between the dose of tacrolimus and trough blood level, and there is great intra- and intersubject variability^{1,2}

It is therefore difficult to predict clinical response, such as nephrotoxicity or graft rejection, which are key components in the monitoring of transplant patients. It is apparent that the tacrolimus trough blood concentration may not be the best predictor of drug exposure. It is necessary to explore different methods of drug monitoring, for more appropriate dosing and therefore have better ability in predicting patient outcomes.

Outlined below is a proposed method of determining the AUC for tacrolimus in adult transplant patients.

1. Dose tacrolimus twice daily
2. Obtain separate blood samples to calculate the AUC
 - a. Be sure that tacrolimus steady state is reached (13 days from first dose)
 - b. The best time points to draw blood are at time 0h (right before dose), 1h (after dose), 4h (after dose), and 8h (after dose) calculate the AUC
 - c. Average AUC: 16-20 ng/dl/hr or 190-250 ng/ml or trough level of 10-15 ng/dl



$$\begin{aligned}
 AUC_{0-\infty} &= AUC_{0-1} + AUC_{1-\text{last}} + AUC_{\text{last}-\infty} \\
 &= \frac{Cp_0 + Cp_1}{2} \cdot t_1 + \frac{Cp_1 + Cp_2}{2} \cdot (t_2 - t_1) \\
 &\quad + \frac{Cp_2 + Cp_3}{2} \cdot (t_3 - t_2) + \dots + \frac{Cp_{\text{last}}}{kel}
 \end{aligned}$$

$$K_{el} = \frac{\ln(Cp_1) - \ln(Cp_2)}{t_2 - t_1}$$

If tacrolimus AUC values correlate better with tissue drug exposure, then we can predict the dose to give patients according to the following equation:

$$\text{Dose} = \text{AUC} \times V$$

$$V = \text{Apparent Volume of Distribution} = 21.3L$$

The clearance (CL) of tacrolimus will affect the AUC of the drug, and hence, tissue exposure. Factors that affect tacrolimus CL in liver transplant patients²:

Increased CL:

Hypoalbuminemia (<3.5g/dL), Low hematocrit (<35%)

Decreased CL:

Coadministration of diltiazem, Coadministration of fluconazole

Factors that do not affect tacrolimus clearance in liver transplant patients:

Demographics (pt's age, weight, gender, ethnicity), Liver function tests (ALT, AST, GGT, bilirubin), Diabetes status, Occurrence of allograft rejection

References:

1. Armendariz Y, Leonor P, Cantarell C, Lopez R, Perello M, Capdevila L. Evaluation of a Limited Sampling Strategy to Estimate Area Under the Curve of Tacrolimus in Adult Renal Transplant Patients. *Ther Drug Monit* 2005;27(4):431-434.
2. Zahir H, McLachlan A, Nelson A, et al. Population Pharmacokinetic Estimation of Tacrolimus Apparent Clearance in Adult Liver Transplant Recipients. *Ther Drug Monit* 2005;27(4):422-430.
3. Equations obtained from: <http://www.boomer.org/c/p4/c02/c0208.html>. Accessed April 18, 2007.