Suitability of limited sampling strategy to cyclosporine A oral formulation

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Therapeutic drug monitoring of cyclosporine A in renal transplant patients is normally performed by measuring predose trough levels or doing area under the curve from all possible sampling points. On the basis of good correlation between predicted area under the curve from limited sampling points and actual area under the curve (literature survey), a limited sampling strategy at 1, 3 and 5 hr was used and extended this strategy as a criteria for pilot evaluation of modified cyclosporine A formulations. Hemodialysis patients served as subjects for the study. Panimun Bioral was used as a test formulation while Sandimmun Neoral as standard reference. The study revealed that both formulations had similar restricted $AUC_{0-5\text{ hr}}$ profiles.

During cyclosporine A (CyA) therapy in renal transplant patients, therapeutic monitoring is essential to adjust drug dosage since CyA is a critical dose drug. Therapeutic monitoring of CyA to prevent nephrotoxicity and graft rejection has been traditionally performed over the last 10 years by measuring trough concentrations. Trough level monitoring of CyA is also useful to evaluate patient compliance, drug absorption disturbances, interaction with other drugs and drug handling in altered physiological states. In majority of the renal transplant centers the dose of CyA administered to a patient is adjusted to achieve blood concentrations that fall within a defined predose trough concentration. Several excellent reviews on CyA pharmacokinetics and therapeutic drug monitoring have been published.

On the contrary, results of some available studies prove that for proper CyA dosing, area under the curve (AUC) monitoring is superior to trough level monitoring and therefore, estimation of actual AUC in renal transplant patients becomes mandatory to check the drug exposure. AUC monitoring requires multiple blood sampling which is cumbersome, costly and painful, sometimes resulting in impacts above the minimal risks. Normally AUC of CyA in organ transplant patients is determined from 10-12 disposition points within a dosing interval. Efforts have been directed towards the development of limited blood sampling strategy for the prediction of actual AUC to be used for therapeutic drug monitoring. Limited number of samples to define a non-parametric pharmacokinetic analysis in a larger patient population was analyzed by several investigators and was reported to be adequately predictive ($r = 0.95343$ and 0.994). Since reference and test CyA formulations undergo consistent and similar absorption and elimination in renal transplant patients at steady state, it will afford the physician an opportunity to use a more precise strategy for therapeutic drug monitoring.

In the light of ethical and technical reasons, we decided to implement a limited sampling strategy (previously used by Gaspari et al.) at department of Nephrology, Christian Medical College (CMC), Vellore for the purpose of therapeutic drug monitoring and its extension for comparison of the extents of absorption between two marketed CyA products. The actual purpose of using this limited sampling strategy was to compare the $AUC_{0-5\text{ hr}}$ of Panimun Bioral (test) and Sandimmun Neoral (reference), both micellar solutions in hemodialysis patients to perform pilot investigations for implementing the strategy.

Patients and study design—Patients on hemodialysis receiving blood transfusion were included in this study. Patients with hepatitis and those receiving dilantin, rifampicin, omeprazole or H2 receptors blockers or any other drug known to effect disposition of CyA were excluded from the study. Study design was an open sequential evaluation in which patients functioned as their own controls. Informed consent was obtained before enrollment. Five patients were studied which included 4 males and 1 female.
Fig. 1—Mean whole blood cyclosporine A concentration (C₀-C₅h) in hemodialysis patients (n=5) who received both test and reference product.

Cyclosporine A dosage and analysis—Patients started receiving supervised CyA (5mg/kg either of the formulation) daily, in two equally divided doses, one day prior to blood transfusion. On the 7th day blood samples were drawn for trough levels of CyA and three point sampling was done at 1, 3 and 5 hr after first dose. After the 7th day, washout period of 7 days was given. On day 15, the other formulation was started at 5 mg/kg daily. Second blood transfusion was also given to the patients on the same day. On the 22nd day blood sampling was repeated at 1, 3 and 5 hr after the first dose. Blood samples were collected in glass tubes containing EDTA (ethylenediamine tetraaceticacid). CyA assay was done by a validated Enzyme Multiplied Immune Assay Technique (EMIT) at biochemistry area of CMC Vellore. All samples were analyzed together to avoid batch variation. Area under the curve (AUC₀-₅h) was calculated by linear trapezoidal rule and paired student’s t test was used to compare the groups.

Mean blood CyA concentration (0-5 hr) are shown in Fig.1. Mean±sd AUC₀-₅h for test formulation was 2083±324 ng.h.ml⁻¹, slightly higher than the reference formulation 1774±412 ng.h.ml⁻¹ (P>0.05). None of the patients encountered any adverse effects attributed to the drugs. Both products demonstrated similar distribution while absorption with the test product was found to be more sustained.

Limited blood sampling strategy during CyA therapeutic monitoring in organ transplantation generally requires the following criteria to be clinically applicable: a high degree of correlation between drug levels and clinical outcomes, lesser blood sampling volume with a minimal waiting period for patients and cost effectiveness. Measurement of trough levels alone fails to demonstrate adequate correlation with actual AUC. Based on the earlier findings, Amante and Kahan tested the implementation of abbreviated sampling strategy for AUC analysis of renal transplant recipients and used only 2 time points at 2 and 6 hr. The correlation with abbreviated AUC strategy and full sampling points was r=0.9646 which is technically predictive and similar to reports by other authors. These findings suggest that abbreviated sampling strategy should permit physicians to suggest the appropriate CyA dose more precisely since prediction bias reported with such strategies is low (5-10%). Finally, the abbreviated sampling strategy
reduces by more than half, the length of observation time and reduces the assay costs associated with multiple sampling strategy by up to 80%. All such information will help the physician to adequately check the bioavailability factor and to control the drug related lesser immunosuppression leading to graft rejection. More specifically, previous studies on the pharmacokinetics of CyA in the pediatric population have determined that the absorption and distribution phases require 3-5 hr on average. The limited sampling strategy at 0, 1, 3 and 5 hr used in the present study comprises the essential early distribution phase of CyA disposition. Results of our assessment indicate that both formulations are absorbed to the same extent. We recommend the use of limited sampling strategy to identify absorption differences between CyA products in absence of bioequivalence data established from large patient population. The present results also suggest that the limited sampling strategy adopted for safer therapeutic drug monitoring of reference CyA may also be adopted for test formulation. More studies are required in larger volunteer/renal transplant patient cohorts to further verify the findings for routine and safer therapeutic drug monitoring.

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