

A review of absorption characteristics of microemulsion cyclosporine products over the last 2 years in Indian subjects

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Microemulsion based cyclosporine has demonstrated better absorption with lesser pharmacokinetic variability. For the clinical use of any new microemulsion based product, bioequivalence testing with existing formulation is necessary. Panimun Bioral® (Test) and Sandimmun Neoral® (Reference) were evaluated in different transplant centers using both volunteers as well as renal transplant patients. All these centres have reported that both products are bioequivalent. These reports offer the physician an option to convert the patients to the Test product for economic reasons.

Bioequivalence guidelines applicable to reformulated cyclosporine must address problems associated with pharmacokinetic variability and its suitability within a narrower therapeutic index. Cyclosporine is a critical dose drug and the consequences of underdosing or overdosing the organ transplant patients are severe and often life threatening. Therefore, cyclosporine is usually dosed to achieve whole blood concentrations that fall in a prespecified targeted therapeutic range such that below the therapeutic threshold transplant failure occurs and above the maximum effective concentration nephrotoxicity occurs which can become another fatal adverse effect. Marked variability in blood concentration observed with fixed dose of cyclosporine (Sandimmune®) posed a major problem in the postoperative management of transplant recipients¹. In addition this drug product related factor is critical for patients who are poor absorbers or have high metabolic clearance and therefore, are at higher risk of graft rejection and such patients gain benefit from kinetic analysis. Until 1991 only one oral formulation of cyclosporine was available and in 1992 microemulsion formulation of cyclosporine was introduced with improved absorption characteristics. Various studies have documented that it is possible to predict daily exposure to the drug adequately even by a simplified blood sampling strategy using microemulsion cyclosporine. Panimum Bioral (Panacea Biotec) is a clear transparent microemulsion concentrate comprising cyclosporine together with hydrophilic and lipophilic solvents and co-solvents. With these formulation, available as either an oral solution or soft gelatin capsules, cyclosporine is dispersed faster in the gut thereby increasing the limit of absorption. Therefore, the erratic absorption, which is always assumed to be due to high molecular weight and strong hydrophobicity of the drug, is presumably rectified and these critical physical characteristics will not contribute towards cyclosporine malabsorption. Pharmacokinetics would be effected primarily by the hepatic and gastric extraction after the systemic uptake of the drug is on the pool of drug dissolved in the absorption windows of the gastrointestinal tract.

Substitutions among different formulations of cyclosporine for economic reasons without close monitoring of pharmacokinetics and pharmacodynamics can reduce undesirable toxic effects. A number of reports of adverse drug reactions and acute cellular rejections after conversion between formulations have created uncertainty over the bioequivalence of these agents⁷. Oral bioavailability of cyclosporine has been critically linked with graft survival rates and has a significant bearing on the risk-benefit ratio in designing regimens supporting rejection prophylaxis. The purpose of bioequivalence testing is to ensure that different brands of the same medicine can be interchanged safely.

CURRENT REGULATIONS ON BIOEQUIVALENCE TESTING

Bioequivalence testing in humans is carried out primarily by administering the new product (Test) and existing form (Reference) in a randomized crossover design in a group of volunteers/patients and measuring the drug concentration over a specified period. The extent of absorption is assessed by Area Under the Curve (AUC) and rate of absorption approximated by maximum blood/plasma concentrations (C_{max}) and time to reach the maximum blood concentration (T_{max}). FDA & European Commission guidelines for bioequivalence testing requires the 90% Confidence Interval of the ratio of Test/Reference of AUC values

to fall in the range of 0.80 to 1.25. The Cmax range is required to be specified and Tmax is not normally subject to statistical testing unless clinically relevant.

RESULTS WITH PANIMUM BIORAL .®

Attempts in Panacea Biotec to develop cyclosporine products began with the marketing of conventional cyclosporine, which demonstrated cyclosporine bioequivalence with Sandimmun®¹¹. Due to the consistent in vivo absorption performance of microemulsion cyclosporine. Panacea Biotec also developed a similar product. Panimun Bioral® (Test) and subjected it for multicentric evaluation in volunteers and pre/post renal transplant patients using Sandimmun Neral as a Standard Reference in all Studies. Results at glance are expressed in Table 1.

BIOEQUIVALENCE TESTING IN HEALTHY HUMAN VOLUNTEERS

Bioequivalence of the test of product was recently reported by Gulati et al¹² in 12 healthy adult volunteers. Single dose study was conducted in a randomized crossover manner. Relative of bioavailability of Test product was reported to be 89.6% evaluated from a statistically meaningful data and comparing mean (+ sd) AUC Further bioequivalence testing between Test and Reference was conducted by Gogtay NJ et al¹³ in 12 healthy volunteers at KEM, Mumbai and relative bioavailability of 102.28% was reported towards the Test product using mean (+sd) AUC_{0-2hrs}. The report further stressed of the need of multiple doses studies in volunteers as well as close monitoring of patients treated with Test formulation for regular utility and inter-changeability between formulations.

BIOEQUIVALENCE TESTING IN PRETRANSPLANT PATIENTS

Therapeutic drug monitoring of cyclosporine in renal transplant patients is normally performed by measuring predose Trough Levels or doing AUC profiles from full sampling points. On the basis of good correlation between predicted AUC from limited sampling points and actual AUC^{3,4,5} a limited sampling strategy was used at 0, 1, 3 & 5 hours to calculate AUC and was extended as a criteria for pretransplant pilot assessment of the Test formulation. Hemodialysis patients were enrolled as patient volunteers. Both Test and Standard Reference repeated statistically similar mean (+sd) AUC_{0-5hrs} and the investigators recommended a 1:1 product switch in these prerenal transplant patients awaiting actual renal transplant¹⁴.

BIOEQUIVALENCE TESTING IN RENAL TRANSPLANT PATIENTS

After collection of the bioequivalence data in healthy volunteers same dosage strength of Test formulation (Reference Standard stabilized dose) was tested on renal transplant patients by switching from Reference of Test Product¹⁵. Renal transplant recipients with stable graft functions defined as <20% changes in the serum creatinine value in the preceding 4 weeks and have been completed 6 months after transplantation were studied. The cyclosporine AUC (s) were estimated at steady state concentration before and after product switch generating multiple pharmacokinetic profiles. The authors

reported statistical bioequivalence between formulations and recommended 1:1 product switch at 6 months post renal transplant. All results were expressed as mean (+2sd). The study also highlights the significance of bioequivalence testing in renal transplant patients as bioavailability stands variable in patients and volunteers¹⁶.

Table 1 : Bioequivalence Studies on Test Product Conducted in India

Center	Subject	Dosing (mg/kg)	RA (%)	SD/SS	Assay Method	Cm ax (ng/ml)	Tmax (hrs)	AUC (ng.h.ml ⁻¹) T/R	*TL (ng/ml)
MAMC	V	10	89.6	SD	HPLC	1571.7/ 1600.6	2.29/2.46	13727.1/ 15321.6	-
KEM	V	300	102.28	SD	RIA	1074.5/ 1046.2	2.08/1.67	8659.5/ 8466.8	-
CMC	HP	5	-	SS	KMT	-	-	2083/ 1774	-
PGIMER	RTP	3.83±0.5	94.5	SS	RIA	617.7/ 658.8	3.05/2.60	2474.6/ 2618.1	-
NMC	RTP	2.73-7.65	-	SS	HPLC	-	-	-	134.8/ 321.7

MAMC: Maulana Azad Medical College, New Delhi, INDIA

KEM: Seth GS Medical College & KEM Hospital, Mumbai, INDIA

CMC: Christian Medical College, Dept. of Nephrology, Vellore, INDIA

PGIMER: Post Graduate Institute of Medical Education & Research, Chandigarh, INDIA

NMC: NOIDA Medicare Center, INDIA

HPLC: High Performance Liquid Chromatography

RIA: Radio Immuno Assay

EMIT: Enzyme Multiplied Immuno Assay Technique

RA: Relative Bioavailabilily

HP: Hemodialysis Patients

RTP: Renal Transplant Patients

V: Volunteers

SS: Steady State

SD: Single Dose

T/R: Test Reference

*TL: Trough Levels 2years/initial

TROUGH CONCENTRATIONS

Cyclosporine Trough levels for therapeutic success after bioequivalence confirmation both in volunteers transplant patients was evaluated in 103 renal transplant patients by Jauhari et al¹⁷. Trough Levels observed with Panimun Bioral® at various post renal transplant period were reported as mean (±sd). The authors reported observations, which were comparable with Reference product^{18, 21} and demonstrated that the test product generated Trough Levels required to prevent drug related transplant rejections with adequacy. The only limitation with this evaluation is the lack of the model, which can correlate Trough Levels with episode of rejection. The study however provides a guides to device a dosage adjustment policy for clinicians using Panimun Bioral®.

Discussion

The studies conducted so far demonstrate the bioavailability aspects but further studies are needed to identify whether the Test product undergoes linear or nonlinear absorption, which requires dose range studies. Food effects & pediatric testing with the test product would be other important determinants of all bioavailability. The current studies provide a proof that the consistent pharmacokinetic profile of tested cyclosporine offers the opportunity of adequate day by day therapeutic monitoring with lesser confusion for clinicians and reduced discomfort for the patient. Given the equal absorption of cyclosporine microemulsion, AUC values are equivalent for 1:1 conversion from Standard Reference to Test product and this conversion is also unlikely to affect renal function¹⁵. Panimun Bioral® looks promising to alleviate some of the difficulties of inter & inpatient variability by use of a galenic formulation in a micellar form. Now the reality is that the conversion in actual renal transplant patients at Post Graduate Institute of Medical Education and Research, Chandigarh, have demonstrated a safe 1:1 product switch with equivalent systemic absorption and therapeutic equivalence may also be demonstrated since no patient experienced any rejection episode and no uncommon side effect could be identified after the product switch. Similar kinds of studies have been reported in the development of Sang-35, which also is a novel cyclosporine formulation. More exhaustive evaluation of the test product are still going on in renal transplant patients in other premier institutes of the Country and abroad and their results would be made available in due course of time.

Importantly all these studies which have been checked out in Indian subjects and patients also demonstrate the clinical suitability of efficacy & tolerability resulting in the fact that Panimun Bioral® is now marketed with strong acceptability. These findings assume importance for all transplant physicians who wish to change cyclosporine brands for economic reasons.

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