

## **\*\* BIOEQUIVALENCE OF TWO MICROEMULSIVE PREPARATIONS OF CYCLOSPORINE IN RENAL TRANSPLANT RECIPIENTS WITH STABLE GRAFT FUNCTION**

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A number of cheaper brands of cyclosporine A (CyA) in microemulsion form have hit the Indian market in recent years. However, there is as yet a lurking apprehension amongst transplant physicians on the bioequivalence of these generic.

Preparations: The aim of this study was to compare the bioequivalence of Panimun Bioral © Panacea Biotec, India (with the most commonly prescribed preparation Sandimmun Neoral © Novartis, Switzerland). Renal transplant recipients with stable graft function defined as <20% change in the serum creatinine value in the preceding 4 weeks and having completed at least 6 months after transplantation were studied prospectively in an unblinded, cross over study design and after conversion to Panium Bioral ( $1.32 \pm 0.43$  mg/dl,  $p=0.25$ ). Patients with acute or chronic liver disease or uncontrolled diabetes mellitus. In addition, patients having received any drug known to potentiate the nephrotoxicity of CyA or patients with planned co-administration of nay other drug known to interfere in the CyA pharmacokinetics were excluded. The CyA AUCs were estimated at weekly intervals for 2 weeks before and after the 1:1 dosage switch. For calculation of area under the curve (AUC), whole blood CyA levels while on Sandimmun Neoral and after a 1:1 dosage shift over to Panimun Bioral were taken at 0, 1, 2, 4, 6 and 18 hours after the morning dose. Whole blood CyA levels were analyzed using Cyclo-Trac SP radioimmuno assay kit © Incstar Corporation, USA). Serum creatinine was checked twice a week for 2 weeks before and after the conversion. Patients exhibiting a rise in serum creatinine >20% of baseline values were required to undergo a graft biopsy to look for evidence of rejection/CyA toxicity. Those patients with an episode of rejection of CyA toxicity and responding to dosage reduction were to be excluded from the trial. All results were expressed as mean  $\pm$ 2SD. Paired student's t-test was used to compare differences in means. Eleven patients, all males, with a mean age of  $34.65 \pm 10.9$  years and receiving CyA in a dose of  $3.83 \pm 0.50$  mg/kg/day were included. Various pharmacokinetic parameters evaluated are shown below:

	<b>On Sandimmun Neoral</b>	<b>On Panimun Bioral</b>	<b>p-value</b>
Cmin (ng/ml)	156.9 $\pm$ 210.3	136.9 $\pm$ 93.5	0.36
Cmax (ng/ml)	658.8 $\pm$ 337.0	617.7 $\pm$ 407.5	0.30
Tmax (hour)	2.6 $\pm$ 0.94	3.05 $\pm$ 1.49	0.22
AUC (ng.hr/ml)	2618.1 $\pm$ 1313.7	2474.6 $\pm$ 1500.1	0.28

There was no change in serum creatinine values before ( $1.36 \pm 0.37$  mg/dl) and after conversion to Panimun Bioral ( $1.32 \pm 0.43$  mg/dl,  $p^0.25$ ). There were no episodes of graft dysfunction during and 4 weeks after the conversion to Panimun Bioral. We conclude that the two microemulsive formulations are bio-equivalent and conversion to the cheaper brand 6 months after transplantation is not associated with any adverse short term graft outcomes.