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TRANSPLANTATION PROCEEDINGS

The Pharmacokinetics of Equoral® Versus Neoral® in Stable Renal Transplant Patients: A Multinational Multicenter Study

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ABSTRACT

We studied the pharmacokinetics (PKs) of the new generic cyclosporine formulation, Equoral® capsules, after the switch from original formulation Neoral® capsules in stable renal transplant patients. The study was carried out in accordance with the basic principles defined in the US 21 CFR Part 312.20 and the principles of the Declaration of Helsinki. The study included clinically stable first renal transplant patients maintained on cyclosporine with no rejection episode during the past 6 months. Hematology, biochemistry, and urine chemistry were determined on day 7, and day 21. The patients were all switched to Neoral® (lot number 416MFD0601) on day 0 when the first sparse sampling PK was performed. On day 14 a 12-hour PK profile included predose, 30 minutes; 1 hour; 1 hour 30 minutes; 2 hours; 3 hours; 4 hours; 5 hours; 6 hours; 8 hours; 10-hours and 12-hour samples. Cyclosporine levels were determined using a CYA kit (Abbott TDx). On day 15 the patients were switched from Neoral® capsules to Equoral® capsules (lot 5T111014) at an equivalent dosage (mg/mg). The second sparse sampling PK was performed on day 21 and a 12-hour PK was performed on day 28. On the morning of day 29 patients were switched from Equoral® capsules to Neoral® capsules at an equivalent dosage (mg/mg). Additional concentrations were measured on days – 7, 18, and 35. Safety parameters were monitored at each visit. The pharmacokinetics of both formulations were equivalent. The mean AUC for Neoral® and Equoral® was 2856 and 2892, respectively. The ratios of *LSM* and the 90% confidence intervals for the in-transformed parameters (AUC_{0-t} , AUC_{inf} , and C_{max}) of Equoral® and Neoral® SGC were 98% and 95%, respectively, suggesting that Equoral® and Neoral® SGC are bioequivalent.

SINCE THEIR INTRODUCTION into transplantation, cyclosporine generic formulations have produced significant cost reduction. The results from many studies indicate similar graft and patient survival rates^{1–7} under treatment with generics versus brand name products.

The US Food and Drug Administration (FDA) regulations stipulate that generics be tested in healthy volunteers in a four-way crossover study.⁸ Such studies are important to compare the bioavailability of the generic to the brand name; however, the drug is really intended to be used in a nonhealthy environment, (“the patient”). We studied the pharmacokinetics of a new generic cyclosporine formulation, Equoral® capsules after the switch from the original formulation Neoral® capsules in stable renal transplant patients.

MATERIALS AND METHODS

Equoral® is a patented macrogel formulation developed by IVAX Pharmaceuticals.⁹ The primary objective of the study was to compare the pharmacokinetics of the new generic cyclosporine formulation, Equoral® capsules, after the switch from original formulation Neoral® capsules. The

secondary objective of the study was to evaluate C1, C2, BTL, and changes in CyA dosage. The study was performed by the CRO Trans Med s.a.l. (Beirut, Lebanon) in accordance with the basic principles defined in the US 21 CFR Part 312.20, the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, Somerset West, 1996) and the ICH harmonized tripartite guidelines regarding good clinical practices. The protocol was also approved by the ethics committee in each center and/or the national ethics committee in each country.

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Table 1. Twelve-Hour Pharmacokinetics of Neoral® and Equoral®

	PK mean concentration profiles											
	T0	T30	T1	T1:30	T2	T3	T4	T5	T6	T8	T10	T12
Neoral®	131	188	569	705	683	473	348	259	220	159	132	116
Equoral®	140	220	514	659	670	481	366	278	226	168	138	123

The inclusion criteria were first renal transplants with no rejection episode during the previous 6 months who were clinically stable with acceptable safety/tolerance to Neoral® capsules; three last whole blood trough cyclosporine levels in the range of 70 to 200 ng/mL (specific) with stable serum creatinine values in the past 3 months with no trend to increase; no hepatic dysfunction during the past 6 months (increase of aminotransferase <100% above the limit) or history of alcohol or drug abuse or signs of alcohol-induced organ damage and no clinical symptoms of CMV infection in the past 6 months; no history or evidence of malignancy or any significant infection; blood pressure in normotensive range with or without antihypertensive medication. The patients were all maintained on cyclosporine in double or triple combination with prednisone, azathioprine, mycophenolate mofetil (doses of cyclosporine ≤8 mg/kg/d). The dose had to be stable over the previous 14 days prior to entry. Doses of concomitant medications had to be stable for 14 days prior to study entry. In addition the subject had to have the ability to communicate with the investigator and to provide written informed consent.

Exclusion criteria included a significant history of hypersensitivity to cyclosporine or related products, such as castor oil, olive oil, or corn oil; pregnancy or lactating females; premenopausal woman of childbearing potential not using safe contraception; more than one renal transplant or grafts of other organs (eg, pancreas); use of routine immunosuppressive therapy other than azathioprine, mycophenolate mofetil, or prednisone; uncontrolled blood pressure (resistant to antihypertensive therapy and despite reduction of cyclosporine dose); history of chronic alcoholism, drug or narcotic abuse; history of myocardial infarction within 6 months of enrollment or uncontrolled cardiac arrhythmia and clinically relevant disease (including nervous system); or other abnormal condition that may compromise function of gastrointestinal tract, kidney, or liver or might influence cyclosporine pharmacokinetic; exposure to any drug interfering with cyclosporine pharmacokinetics or potentially nephrotoxic drug within 14 days prior to study entry.

In accordance with the Declaration of Helsinki, subjects had the right to withdraw from the study at any time for

Fig 1. Twelve-hour pharmacokinetic profiles of Equoral® versus Neoral®.

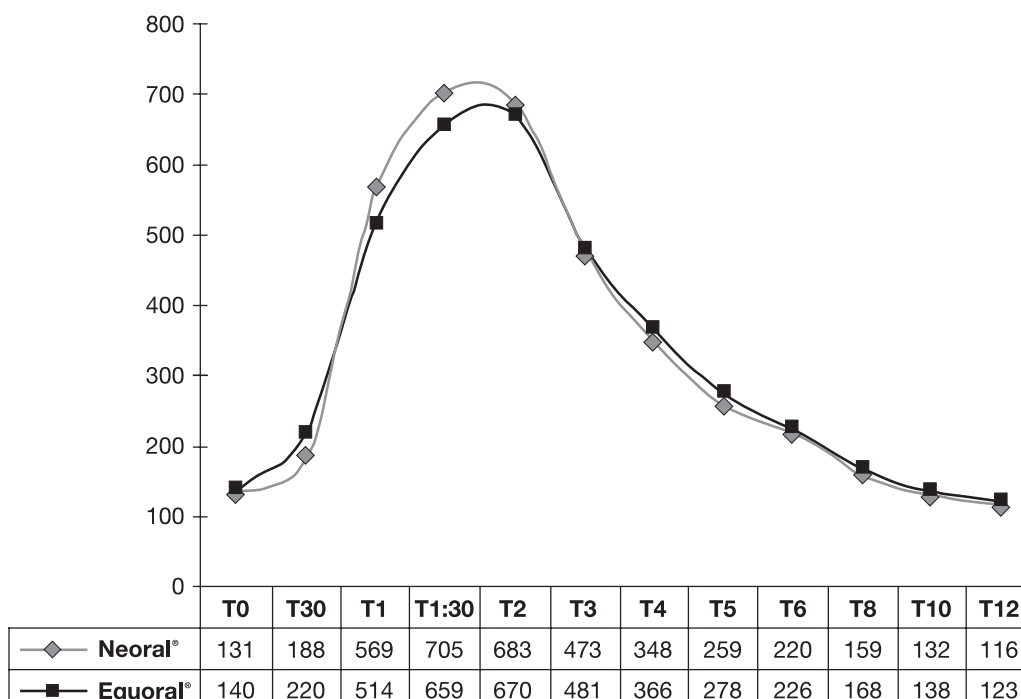


Table 2. Comparison of the T0, T1, T2 of Equoral® and Neoral® at Three Different Occasions

	Neoral®			Equoral®		
	T0	T1	T2	T0	T1	T2
Average	109.80	616.50	680.50	109.30	558.50	689.00
SD	14.41	23.50	0.50	17.26	15.50	6.00
CV	13.13	3.81	0.07	15.80	2.78	0.87

any reason. The principal investigator had the right to withdraw subjects from the study in case of serious adverse events, the necessity to prescribe any excluded medication, protocol violations, withdrawal of consent, failure to return for schedule visit or other reason. The subjects may also be withdrawn if necessary to protect their health and the integrity of the study. In case of a questionable situation the Clinical Trial Monitor or the Medical Contact was consulted. Continued participation of any patient who violated the protocol was decided by the Sponsor's Medical Contact. Patients who were not evaluable due to protocol violations that were within the control of the investigator were not considered as completed subjects. Subjects who did not complete the study were not replaced. Subjects who withdrew due to adverse events were classified as "completed" and not replaced. Should a patient have decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the patient withdrawal was performed with an explanation of why the subject withdrew from the study. Each subject's withdrawal was recorded in a CRF.

STUDY DESIGN

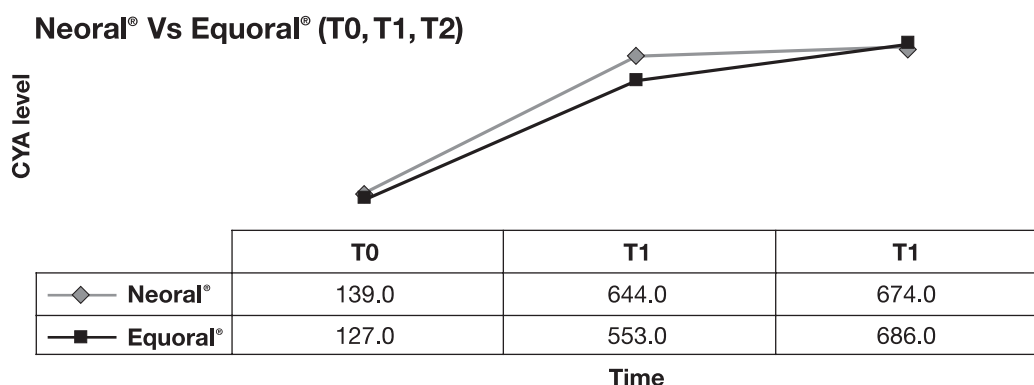
On day - 7 and day 21 hematology, biochemistry, and urine chemistry, were determined as well as the first sparse sampling PK on Neoral® (lot no. 416MFD0601, expiry date 06/2004) on day 0. On day 14 the 12-hour PK included

predose, 30 minutes; 1 hour; 1 hour 30 minutes; 2 hours; 3 hours; 4 hours; 5 hours; 6 hours; 8 hours; 10-hours and 12-hours samples. The 12 cyclosporine levels were determined using the same CYA kit (lot no. 86619Q100, batch no. 9797-60, expiry 20/2/2004, calibrators lot no. 88724Q100, control lot no. 77414Q100, Abbott TDx). On day 15 the patients were switched from Neoral® capsules to Equoral® capsules (lot 5T111014, expiry 11/2003) at an equivalent dosage (mg/mg). The second sparse sampling PK was performed on the day 21 with a 12-hour PK performed on day 28. On day 29 in the morning the patients were switched from Equoral® capsules to Neoral® capsules at an equivalent dosage (mg/mg). Additional BTL were measured on days - 7, 18, and 35. Safety parameters were monitored at each visit. The dose of cyclosporine was not adjusted throughout the study.

RESULTS

The pharmacokinetics of both formulations were equivalent at all times during the 12-hour period (Table 1; Fig 1). Seventy percent of the patients displayed a C_{max} at 1:30 minutes, 20% at T1, and only 10% at T2. The C_{max} in all centers was far lower than those reported from European or US patients. The mean AUC for Neoral® and Equoral® was 2856 and 2892, respectively. The C_{max} for Equoral® was 743 ng/mL and for Neoral® 773 ng/mL, respectively. There were no significant changes in the creatinine levels for both Equoral® at 1.24 mg/dL and

Fig 2. T0, T1, T2 of Neoral® versus Equoral® at two different time intervals: day 7 and day 14 for Neoral® and day 21 and day 28 for Equoral®.



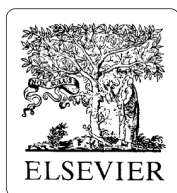
Neoral® at 1.23 mg/dL. There were no serious adverse effects during the study; none of the patients withdrew from the study. The stability of the pharmacokinetics was also similar as determined by the CV of three consecutive measurements performed 7 days apart (Table 2).

Both formulations had similar T₂ (C₂) for the two measurements performed on day 7 and day 14 for Neoral® and day 21 and day 28 for Equoral® (Fig 2).

The ratios of *LSM* and the 90% confidence intervals for the in-transformed parameters (AUC_{0-t} , AUC_{inf} and C_{max}) of Equoral® and Neoral® SGC were 98% and 95%, respectively, which were within the 80% to 125% FDA acceptance range. These results indicate that Equoral® and Neoral® SGC are bioequivalent.

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