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TRANSPLANTATION PROCEEDINGS

Switchability of Neoral and Equoral According to Food and Drug Administration Rules and Regulations

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Transplantation Proceedings, Vol. 37, Issue 7, 2988-2993, September 2005

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ABSTRACT

According to the US Food and Drug Administration (FDA), if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted (switchable) for that drug product. Methods used to define bioequivalence as stated by the FDA rules (FDA 21 CFR 320, 24) are (1) pharmacokinetic (PK) studies in healthy volunteers, (2) comparative clinical trials, and (3) pharmacodynamic (PD) studies (bioactivity). We evaluated the switchability of Equoral (IVAX-USA) with Neoral (Novartis Switzerland using all FDA rules. In a single oral dose, we undertook a comparative bioavailability study of Equoral (IVAX, USA) Neoral (Novartis, USA), and Neoral (Novartis UK). The pharmacokinetics of Equoral and Neoral were determined with blood levels at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 42, and 48 hours. The area under curve (AUC), AUC extrapolated to infinity ($AUC_{0-\infty}$), rate of absorption (T_{max}), extent of absorption (C_{max}), half time ($t_{1/2}$) of Equoral and Neoral were all within the 90% confidence interval of 80% to 125% boundaries. A comparative multinational multicenter clinical trial in stable renal transplant patients included 70 patients (22 women and 48 men) of mean age of 33 years (range, 26 to 43) was performed in Turkey, Lebanon, and Pakistan. In this study the ratios of LSM and the 90% confidence intervals for the Nontransformed/Parameters (AUC_{0-t} , AUC_{inf} , T_{max} , and C_{max}) of Equoral and Neoral SGC were 98% and 95%, respectively, which are within the 80% to 125% FDA acceptance range. For immunosuppressive drugs, the site of action is the lymphocyte and the measurable response is the decrease in lymphocyte count caused by the relative concentration of the drug in the lymphocyte. In a controlled switch, fixed-dose study, both Equoral and Neoral achieved the same concentration in the lymphocytes and caused the same degree of lymphocyte count reduction. The results of the testing (bioavailability–bioequivalence, clinical studies, and pharmacodynamic–bioactivity) required by FDA for interchangeability (“switchability”) of immunosuppressive agents suggests that Neoral and Equoral are switchable.

A GENERIC DRUG is identical or bioequivalent to its corresponding brand name drug with respect to dosage form, safety, strength, route of administration, quality, performance characteristics, and intended uses. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. According to the United States Congressional Budget Office, generic drugs save consumers an estimated \$US8 to \$US 10 billion per year at retail pharmacies. Even more is saved when hospitals use generics. It is important for both physicians and patients that strict guidelines for drug approval are followed. For a generic to be approved by US Food and Drug Administration (FDA), it must meet the same rigid standards as the innovator drug.

SWITCHABILITY OF NEORAL AND EQUORAL

To gain FDA approval, a generic drug must contain the same active ingredients as the innovator drug (inactive ingredients may vary; must be identical in strength, dosage form, and route of administration; should have the same indications for use; must be manufactured under the same

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strict standards of the FDA's "good manufacturing practice" [GMP] regulations required for innovator products; must meet the same batch requirements for identity, strength, purity, and quality; and, above all, must be bioequivalent to the brand name product.

Regarding bioequivalence, the FDA has also developed and issued explicit guidelines for a generic products. The manufacturer is required to show that the generic drug is safe, tolerable, effective, and bioequivalent to the pioneer drug, and that it falls within set parameters for bioavailability (the extent and rate at which the body absorbs the agent). The calculated bioavailability is compared to that of the pioneer drug. The FDA's bioequivalence and switchability rule number FDA 505 J 8 states that if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted (switched) for that drug product.

The methods for establishing bioequivalence are defined in FDA Code of Federal Regulations (CFR) rule 21320, 24, and include the following steps: (1) pharmacokinetic studies; (2) comparative clinical trials; and (3) pharmacodynamic (bioactivity) studies.

MATERIAL AND METHODS

The patient details and methods for each of the three segments of our Equoral assessment are outlined below.

Pharmacokinetic Studies

In this part of the assessment, pharmacokinetic studies were performed on healthy male volunteers between the ages of 18 and 45 years who were nonsmokers, weighed at least 60 kg, and were within 15% of their ideal body weight. Each patient was identified as healthy based on medical history, demographic features, physical examination findings, and a normal laboratory profile. Subjects were excluded if they had a history of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease; exhibited hypersensitivity or idiosyncratic reaction to cyclosporine (CsA) or other immunosuppressive agents; or had any form of chronic infection. The study was carried out in accordance with the clinical research guidelines established by the Medical Research Council of Canada, the Basic Principles defined in the US Code of Federal Regulations (CFR) 21 Part 312.20, the principles listed in the Declaration of Helsinki (World Medical Association Declaration of Helsinki, Somerset West, 1996), and the International conference on Harmonization—Good Clinical Practice (ICH-GCP).

Single doses of test and reference drug products were administered and blood levels of the drug were measured over time to determine the following pharmacokinetic parameters: area under the curve (AUC), AUC to the last measured concentration (AUC_{0-t}); AUC extrapolated to infinity ($AUC_{0-\infty}$); rate of absorption (T_{max}); extent of absorption (C_{max}); and half-life ($t_{1/2}$). To meet the FDA criteria, the 90% confidence intervals for AUC and C_{max} had to be entirely within the range of 80% to 125%.

Many pharmaceutical companies have developed and are currently marketing new generic forms of cyclosporine (CyA).¹⁻¹³ In compliance with the requirements of both the FDA and the European Committee for the Propriety of Medicinal Products (CPMP)¹⁴⁻¹⁶ we evaluated the CyA

generic form Equoral¹⁷⁻²⁰ (produced by IVAX Pharmaceuticals) in a three-step sequence of assessments: (1) First, the two CyA formulations, Equoral (IVAX, Miami, USA) and Neoral (Novartis, USA) were tested in healthy volunteers in a comparative, blinded, open-label, randomized, single-dose, four-way crossover study, under fed and fasting states. (2) The second phase of testing was done in stable adult renal transplant patients who had been receiving the original-formulation Neoral capsules but were switched to Equoral at 1:1 dose ratio. (3) The third step was pharmacodynamic (bioactivity) studies, in which the biological effects of both Neoral and Equoral were evaluated and compared in stable renal transplant recipients. Seven studies of healthy volunteers were conducted five of which (namely, SCO 5058, SCO 5057 [International Life Sciences Europe, Czech Republic], MDS 010421, MDS 010422 US [Miami], and Phoenix 992216) in Montreal Canada, were performed for SGC and the other two studies, Phoenix (Montreal, Canada) 138 and 225 were for oral solutions, and were supervised and audited by specialized medical personnel of both Phoenix and International Life Sciences with Trans Med International (Beirut Lebanon) being the consulting Contract Research Organization (CRO).

The formulations tested were Equoral (IVAX) 100 mg/mL oral solution CsA USP (modified) Bath No. 16001QB001 and Neoral (Novartis, USA) 100 mg/mL oral solution CsA for microemulsion. Lot No. 266 A 0099 Sandoz (Neoral, UK) 100 mg/mL oral solution CsA Lot No. 291MFD 0799.

Each subject received a single 200-mg (2-mL) oral dose of study drug, followed by a washout period of 7 days. For each drug, pharmacokinetic profiles were derived for blood levels at a series of time points: 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 42, and 48 hours. This series of time points was established to adequately assess the absorption, distribution, and elimination characteristics in the blood CsA concentration–time profile. Subjects were fasted overnight until 30 minutes prior to their scheduled dosing time (8:00 am), when they were given a standard breakfast. After dosing, each subject fasted for at least 4 hours. Water was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times. Standard meals were provided at approximately 4 and 9 hours after drug administration.

For each subject, we recorded AUC_{0-t} , AUC_{inf} , AUC/AUC_{inf} , C_{max} , T_{max} , and $t_{1/2}$. The ratios between the least-squares means (LSM) for the different drug formulations were calculated for the Nontransformed AUC_{0-t} , AUC_{inf} , and C_{max} .

To assess drug safety, sitting blood pressure and heart rate determinations were performed before the dose was given and within approximately 10 minutes prior to the scheduled blood collections at 2 and 6 hours after drug administration. Vital signs were measured at other times, when deemed necessary. Each subject had a physical examination and underwent hematologic testing, urinalysis, and serum testing at screening with blood urea nitrogen and creatinine levels measured within 24 hours prior to dosing. Much of the initial laboratory testing (hematology, urinalysis, serum levels of blood urea nitrogen, creatinine, liver function tests [liver enzymes]) was repeated at the end of the investigation. Subjects were monitored for adverse events throughout the study.

Table 1. The Ratios of LSM and the 90% Confidence Intervals for the Nontransformed Parameters (AUC_{0-t} , AUC_{inf} , and C_{max}) of Equoral and Neoral Obtained from the EU and USA Studies

Formulation	Study	AUC_{0-t} PE		$AUC_{0-\infty}$ PE		C_{max} PE	
SGC	SCO 5058	97		97		98	
SGC	SCO 5057	90,1		90,5		86,0	
SGC	MDS 010421	94,1		94,2		86,1	
SGC	MDS 010422	105,5		104,5		107,7	
Oral solution	Phoenix (138)	USA 97.3	EU 96.8	USA 96.9	EU 96.8	USA 100.5	EU 96.3
Oral solution	Phoenix (225)	USA 104.1	EU 99.1	USA 105.2	EU 99.9	USA 105	EU 97.8
SGC	Phoenix 992216	USA 95.4	EU 101.2	USA 95.4	EU 100.5	USA 87.7	EU 94.3

Comparative Clinical Trials

The studies on healthy volunteers involved only a single dose. All subjects were adult men (no women or children were tested). However, in reality, most drugs are intended to be used in individuals who are not healthy, as well as children, women, and people of broad ethnic diversity. Moreover, many patients are receiving multidrug therapy, which can affect the pharmacokinetics of CsA.^{21,22} In the clinical trials portion of our research, we investigated the pharmacokinetics of a new generic CsA formulation, Equoral soft gelatin capsules (SGC) in renal transplant recipients. The trial was carried out in accordance with the basic principles listed 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-GCP.

Seventy renal transplant recipients from Turkey, Lebanon, and Pakistan (22 women and 48 men) of mean age 33 years (range, 26 to 43 years) were enrolled and completed the study. Thirty patients were Asian (20 men and 10 women) and 40 were Caucasian (28 men and 12 women). The mean weight of the Asian patients was 60 ± 9.4 kg, and that for the Caucasians 69 ± 13.1 kg. The mean heights for these groups were 155 ± 24.8 cm and 153 ± 35.1 cm, respectively. The patients were selected according to the following criteria: first renal transplant, clinically stable with no rejection episodes for at least 6 months, and acceptable safety with/tolerance of Sandimmun Neoral capsules. The maintenance immunosuppressive regimen for all patients was a CsA-based combination with prednisone and azathioprine, or mycophenolate mofetil. In all cases, the CsA dose was <8 mg/kg/d. In addition to these inclusion criteria, each

subject's CsA dose and the doses of all accompanying medication was stable for the 14 days prior to study entry.

Myocardial infarction within 6 months of enrollment was grounds for exclusion from the study. Any of the following occurring within the 14 days prior to the study were also considered grounds for exclusion: uncontrolled cardiac arrhythmia; any condition that might compromise gastrointestinal tract, kidney, or liver function; any condition that might influence CsA pharmacokinetics; and exposure to any drug known to interfere with CsA pharmacokinetics.

In accordance with the Declaration of Helsinki, each subject was informed that he or she had the right to withdraw from the study at any time and for any reason. The principal investigator had also the right to remove subjects from the study under circumstances such as serious adverse effects, requirement for excluded medications, protocol violations, withdrawal of consent, failure to return for a scheduled visit, and other reasons. Subjects who failed to complete the study were not replaced.

On day 0, the patients who were receiving the commercially available Neoral were switched to the same Neoral lot (number 416MFD0601, expiration date 06/2004). On day 7 the first sparse sampling pharmacokinetics (BTL, C1, and C2), was performed and each recipient underwent hematologic testing, urinalysis, and serum biochemistry testing.

On day 14, pharmacokinetics testing was done over a 12-hour period (predose, and then at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours) following the dose. Thus, in all, 12 samples were collected from each subject. The CsA level in each blood sample was determined using a CsA kit (lot

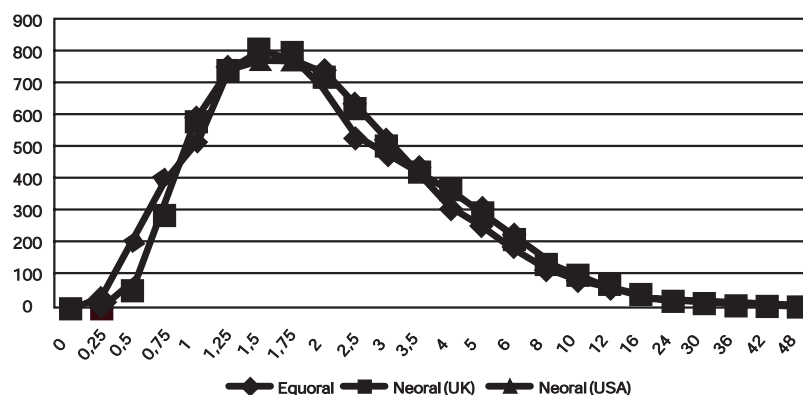


Fig 1. The pharmacokinetic profile of Equoral, Neoral USA and Neoral UK in healthy volunteers.

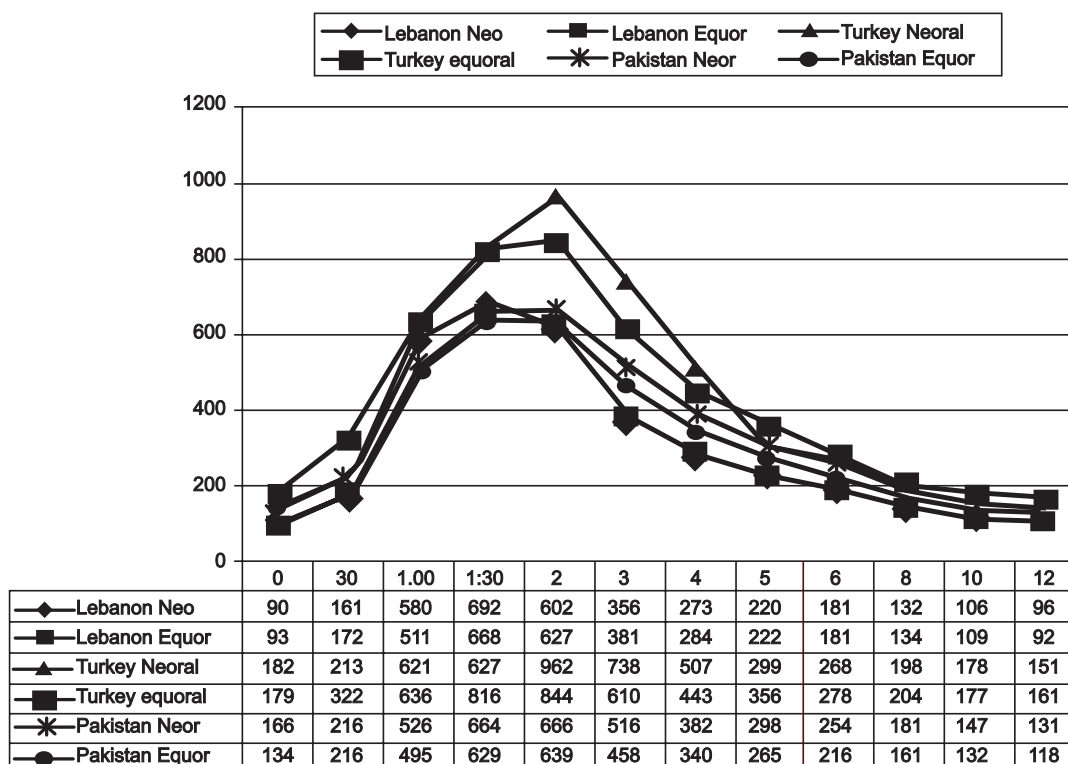


Fig 2. The pharmacokinetics of Equoral and Neoral in Turkish, Lebanese and Pakistani renal transplant patients.

No. 86619Q100), batch No.9797-60 expiration date 20/2/2004, calibrators lot No. 88724Q100, Control lot No. 77414Q100, Abbott TDx). On day 15, the patients were switched from Neoral capsules to equivalent dosages of Equoral capsules (lot 5T111014, expired 11/2003). We performed a second sparse-sampling pharmacokinetic testing, hematologic analyzing, urinalysis, and serum biochemistries on day 21, and a second 12-hour period of pharmacokinetics testing on day 28 (blood drawn at same time points noted). In the morning of day 29, the patients were switched from Equoral SGC back to equivalent dosages of Neoral SGC. Additional blood trough levels were measured on days 7, 18, and 35. Safety parameters were monitored at each visit.

Pharmacodynamic Studies (Bioactivity)

To assess the bioactivity of any drug, the site of action must be known, and the investigator must be able to make accurate, specific, and reproducible measurements of drug concentration at the site of action, and also identify and measure the response. For CsA, and indeed, for all immunosuppressive drugs, the site of action is lymphocytes.

Thirty patients enrolled in the clinical study were also enrolled in the pharmacodynamic study. We measured the concentrations of both Equoral and Neoral in each patient's

lymphocytes using the methods previously described by Masri et al.²³⁻²⁶ Specifically, lymphocytes were isolated from each blood sample collected on day 14 of dosing with Neoral (predose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours postdose), and then again after the switch to Equoral on day 28. The CsA levels in the isolated lymphocytes were determined using the same CsA kit noted (lot No. 86619Q100, batch No.9797-60 expired 20/2/2004, calibrators lot No. 88724Q100, Control lot No. 77414Q100, Abbott TDx). We correlated the lymphocyte CsA concentration results with the degree of reduction observed in the patients' lymphocyte counts.

RESULTS

Pharmacokinetic Studies

Under fasting conditions, the AUC C_{max} of Equoral and Neoral SGC and oral solutions were similar in healthy volunteers. There was no significant difference between the

Parameter	Neoral			Equoral		
	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂
Average	109.8	616.5	680.5	109.3	558.5	689
SD	14.41	23.50	0.50	17.26	15.5	6.00
CV	13.13	3.81	0.07	15.80	2.78	0.87

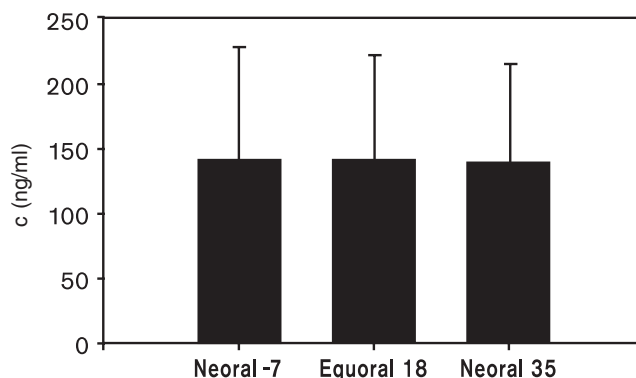


Fig 3. The T0 levels for Neoral at day-7 and day 35 and for Equoral at day 18

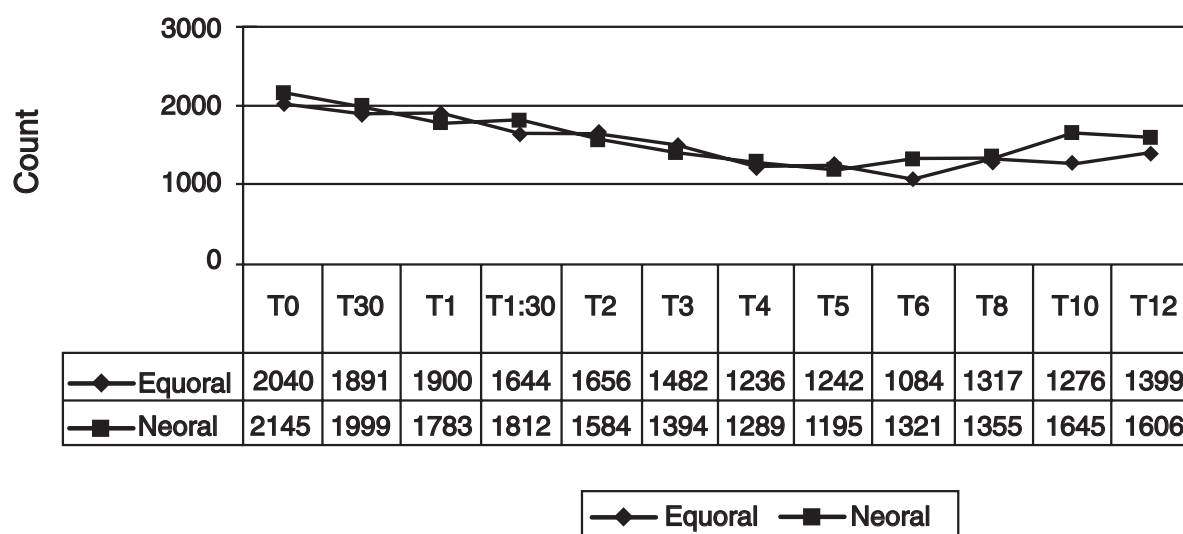


Fig 4. The lymphocyte counts corresponding to Equoral and Neoral lymphocyte levels during the pharmacokinetics profiles.

AUC, C_{max} , and T_{max} of both formulations under fasting or fed conditions. The LSM values of the AUC_{0-t} , AUC_{inf} , and C_{max} in all the studies for both the SGC and oral solutions were within the FDA defined and accepted limits (Table 1). The mean concentration–time (pharmacokinetics) profiles were superimposed on each other (Fig 1). The correlation between the C_2 and AUC for Neoral and Equoral were $r = 0.74$ and $r = 0.76$, respectively.

Comparative Clinical Trials

In stable renal transplant recipients the pharmacokinetics of Equoral (AUC_t , PTF, C_{max-ss} , C_{min-ss} , t_{max} , C_2) was indistinguishable from the corresponding Neoral values under standard conditions. Both bioequivalent formulations were interchangeable with respect to AUC_t , PTF, and C_{max-ss} at steady state. There were no statistically significant differences in blood trough levels across the entire study regardless of the formulation administered and no need for dosage adjustment in any of transplant recipients after switch to Equoral. The safety profile of Equoral was comparable to that of Neoral in both the Asian and Caucasian populations.

Lebanese and Pakistani patients had similar pharmacokinetics profiles. However, the C_{max} and AUC of Turkish patients were 16% higher than the Lebanese and Pakistani patients (Fig 2). Seventy percent of the patients had their C_{max} at 1:30 minutes, 20% at T_1 and only 10% had their C_{max} at T_2 . The mean of the 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 either Equoral at 1.24 mg/dL or Neoral at 1.23 mg/dL. There were no serious adverse side effects reported during the study and 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 which were performed 7 days apart (Table 2). Both formulations had similar T_2 (C_2) for the two different measurements performed on day 7 and day 14 for Neoral and day 21 and day 28 for Equoral.

The T_0 (C_0) of the patients remained the same following the switch from Neoral to Equoral and following the switch back to Neoral (Fig 3). The 90% confidence intervals (CI) for the Equoral versus Neoral comparison at steady state were 0.99 to 1.06 for AUC_t , 0.93 to 1.01 for C_{max} , and 0.90 to 1.01 for PTF, respectively, which is within the 80% to 125% FDA acceptance range.

Pharmacodynamic Studies (Bioactivity)

Both formulations caused a similar decrease in the lymphocyte count. Correlating the intralymphocyte CsA concentration with the lymphocyte count indicated that the highest degree of inhibition occurred 6 hours postdose (Fig 4).

DISCUSSION

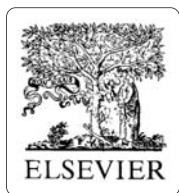
The ratios of LSM and the 90% confidence intervals for the nontransformed Parameters (AUC_{0-t} , AUC_{inf} , and C_{max}) of Equoral and Neoral SGC and the oral solution under fasting and fed conditions were within the 80% to 125% FDA acceptance range. These results indicate that Equoral and Neoral 100 mg SGC and 100 mg oral solutions are bioequivalent under fasting and fed condition.

The administration of food decreased the AUC_{0-t} , AUC_{inf} , and C_{max} and delayed the T_{max} of the three CsA formulations. The pharmacokinetics of the formulations tested were the same under all the conditions tested. The formulations Equoral SGC, Equoral oral solution, Neoral SGC, Neoral oral solution are bioequivalent under fasting and fed conditions. The pharmacokinetics of Equoral were equivalent and indistinguishable from those of Neoral in stable renal transplant patients.

There was no difference in the C_2 level, which is now being used as the standard blood level monitoring of Neoral.²⁷⁻²⁹ Equoral was well tolerated and interchangeable with Neoral in stable renal patients. The bioactivity of Neoral was similar to Equoral, both resulting in the same decrease in the number of lymphocytes over the inter-12-hour pharmacokinetics.

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