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Assessment of Bioequivalence of a Generic Cyclosporine (Equoral) by a Prospective Randomized Controlled Trial on Allogeneic Stem Cell Transplant Recipients

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ABSTRACT

Introduction. Bioequivalence of Equoral has been suggested by measurements of pharmacokinetic parameters in healthy volunteers and in stable renal transplant recipients, but not study in allogeneic stem cell transplant (ASCT) recipients. The aim of our study was to compare the pharmacokinetics and safety of Equoral to Neoral solution among ASCT recipients.

Patients and methods. Our open-label, two-way crossover, randomized controlled trial compared Equoral versus Neoral solutions in ASCT recipients. The 30 enrolled patients from June 2007 to November 2008 had a 7 to 14-day duration of the test period. A 10-point blood sampling from 0 to 12 hours measured Cmax (extent of absorption), tmax (rate of absorption) and AUC_{0-12h} (area under the concentration-time curve) calculated by the linear trapezoid rule. The study protocol was approved by the ethics committee.

Results. Median age was 26 years (range = 6–47). The mean pharmacokinetic features were: AUC_{0-12h}: Equoral 4162 ± 1231 ng · mL/h vs Neoral 4370 ± 1059 ng · mL/h (P = .50); Cmax: Equoral 821 ± 244 ng/mL vs Neoral 834 ± 298 ng/mL (P = .86); and tmax: 105 minutes for both formulations. Comparable toxicities and rates of graft-versus-host disease were recorded in both groups.

Conclusion. We suggest that Equoral and Neoral solution can be considered interchangeable in ASCT recipients.

CYCLOSPORINE (CsA) is extensively used in child and adult bone marrow transplantation.[1,2] This population shows more digestive problems than solid transplant patients, due to mucositis and diffuse inflamation of the intestinal tract related to the preparative regimen. In addition, these patients frequently develop both a digestive graft-versus-host disease (GVHD) and an intestinal viral disease affecting the absorption of CsA.[3]

Studies comparing the pharmacokinetics of Equoral, which is a generic microemulsion formulation of CsA, and Neoral, which is the original formulation of CsA, have been conducted in healthy volunteers[4] and in renal transplant recipients,[5,6] showing similar profiles. In addition, the generic formulation confers a significant economic advantage compared with Neoral. Since our knowledge no study has been performed on allogeneic stem cell transplant (ASCT) recipients, we compared the pharmacokinetics and safety of Equoral solution (IVAX, USA) with Neoral solution (Novartis, USA).

PATIENTS AND METHODS

Study Design

This open-label, two-way crossover, randomized controlled trial of Equoral solution (100 mg/mL) versus Neoral solution (100 mg/mL) in 30 ASCT recipients was performed from June 2007 to November 2008. CsA (Sandimmum) was started by continuous intravenous (IV) infusion from day −1 upto 15 to 21 days after transplantation, when patients were randomized to oral CsA (Equoral or Neoral) at twice the IV dose. At the end of the study, all patients received Neoral solution. A measure of whole blood concentration was performed 1 day before the switch. The daily dose was taken in two equally divided portions at 12-hour intervals. Laboratory and

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clinical variables identified before randomization, were repeated at days 7 and 14 after randomization. CsA levels were determined using the fluorescence polarization immunoassay (FPIA-Axym).

The dose conversion was 1:1. The duration of the test period was between 7 and 14 days (Fig 1). In each study period, a 10-point blood samplings included: before administration (C0) as well as 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours thereafter. The study measures included Cmax (extent of absorption), tmax (rate of absorption), and AUC_{0-12h} (area under the concentration-time curve). Cmax and tmax were identified directly from the observed concentration-time curves and AUC_{0-12h} calculated by the linear trapezoid rule. The study protocol was approved by our ethics committee.

Inclusion and Exclusion Criteria

Patients were included in the study if they were aged between 3 and 50 years, clinically stable after a first ASCT, and receiving oral CsA for GVHD prophylaxis with last whole blood through CsA level ranging between 150 and 300 ng/mL. Patients must have had a stable serum creatinine value (<2 baseline value) and no history of hepatic dysfunction (bilirubin and aminotransferases < twofold the normal value).

Patients were excluded if they developed GVHD or microangiopathy, received another drug that interferes with CsA pharmacokinetics, or showed evidence of noncontrolled digestive problem, or renal (2× creatinine baseline value) or hepatic dysfunction (bilirubin and aminotransferases > 2× normal value).

Statistical Analysis

The pharmacokinetic data (AUC_{0-12h}, Cmax, tmax) were derived from analysis of variance. To evaluate bioequivalence, we calculated 90% confidence intervals yielding accepted bioequivalence ranges between 80% and 125% for AUC_{0-12h} and Cmax.

We performed our study on 30 ASCT recipients, which was the number shown by statistical data for the assessment of bioequivalence between the two formulations with coefficient of variation of −20% to +25% and power test calculations at 80%.

RESULTS

Characteristics of the Study Population

We analyzed 30 from out of 47 ASCT recipients excluding 17 patients after randomization because of renal dysfunction ($n = 8$), acute GVHD ($n = 8$), or cytolysis ($n = 1$). The study group median age was 26 years (range = 6–47) and their diseases were: acute myeloblastic leukemia ($n = 16$), acquired aplastic anemia ($n = 6$), acute lymphoblastic leukemia ($n = 4$), Fanconi's anemia ($n = 2$), multiple myeloma ($n = 1$), and Gaucher disease ($n = 1$). Their conditioning regimens consisted of: IV busulfan + cyclophosphamide ($n = 18$), fractionated total body irradiation + etoposide ($n = 4$), horse antithymocyte globulin + cyclophosphamide ($n = 6$), fludarabine + cyclophosphamide ($n = 2$). All patients received oral antimicrobial prophylaxis with amoxicillin or spiramycine, fluconazole, and acyclovir.

Pharmacokinetic Data

Pharmacokinetic data showed no significant difference between the AUC_{0-12h}, Cmax, and tmax for both CsA formulation (Fig 2). The mean AUC_{0-12h} estimates of Equoral versus Neoral were 4162 ± 1231 versus 4370 ± 1057 ng · mL/h, respectively ($P = .50$). Their mean Cmax values were 821 ± 244 and 834 ± 298 ng/mL ($P = .86$). The 90% confidence limits for AUC_{0-12h} and Cmax were within the accepted bioequivalency range compared with Neoral. Both formulations showed similar median of tmax determinations (105 minutes). Pharmacokinetic data are summarized in Table 1. The doses required to achieve these levels were similar for the two formulations (mean: 107 ± 37 mg twice a day).

Safety Profile

No significant difference in safety profile was observed between the two formulations (Table 2). No serious adverse event or death occurred during the study period.

DISCUSSION

CsA was introduced as an immunosuppressive agent more than 15 years ago.[7] Beside organ transplantation, CsA has proved to be effective for prophylaxis or treatment of GVHD and for prevention of rejection following hematopoietic stem cell transplantation. This molecule is a critical dose drag with a narrow therapeutic index;[8–10] therefore, clinicians should be aware of the prescription and the switchability of this drug.[11]

Equoral solution, the generic CsA, seems to be bioequivalent to Neoral solution in healthy human volunteers after a single oral dose, and in stable renal transplant recipients.[4,5] However, extrapolation findings from these two populations to ASCT recipients have been questioned, because of the particularity of their gastrointestinal problems, especially during the first month after bone marrow transplant.[3] Our patient model was unique to test switchability of formulations.

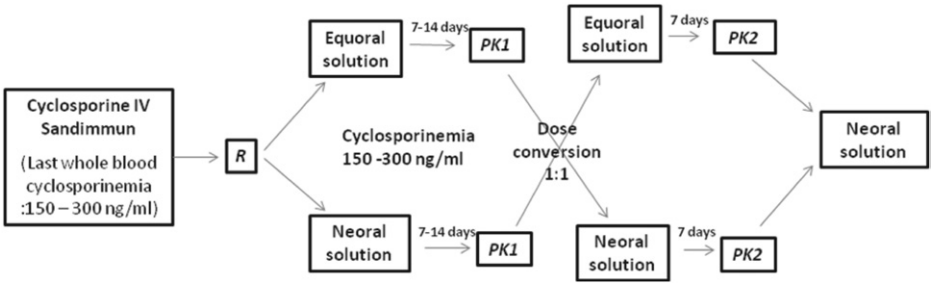

Fig 1. Study protocol. R, randomization; PK1, first pharmacokinetic study; PK2, second pharmacokinetic study.

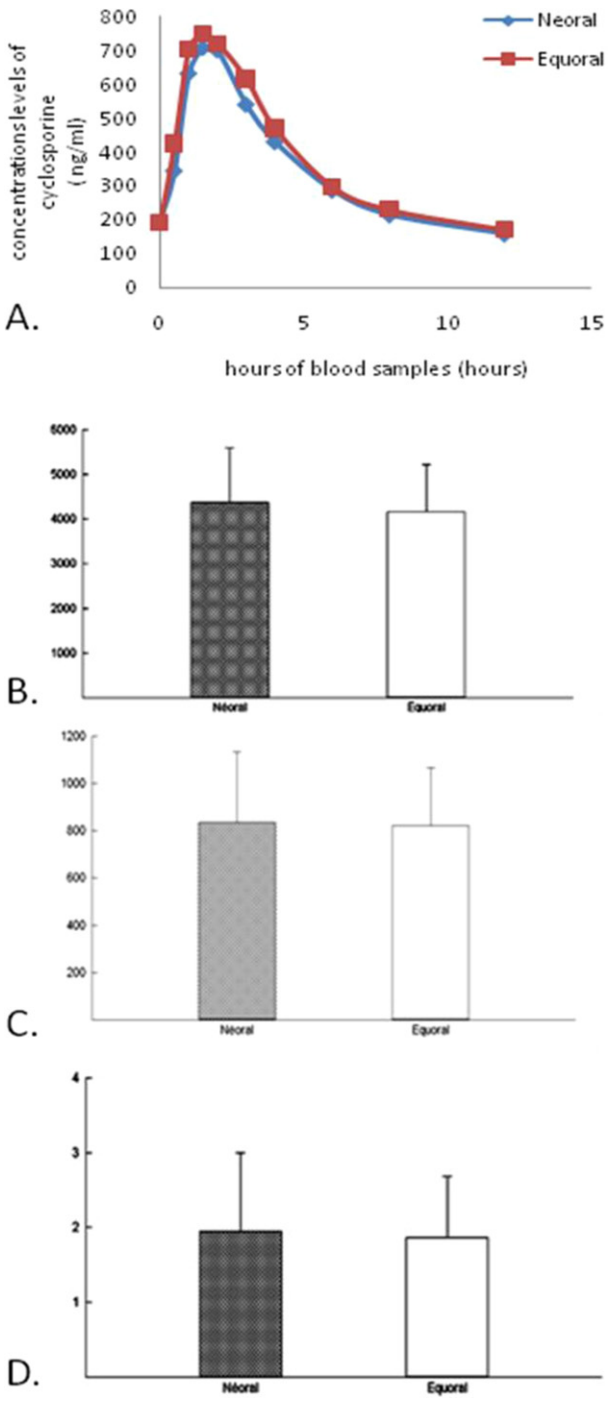

Fig 2. **(A)** Twelve-hour pharmacokinetic profiles of Equoral and Neoral. **(B)** mean ± standard deviation of area under the concentration-time curve (ng · h/mL). **(C)** mean ± standard deviation of extent of absorption. **(D)** mean ± standard deviation of rate of absorption (h).

Our results showed that pharmacokinetic data for the nontransformed parameters (AUC_{0-12h}, Cmax, tmax) of Equoral microemulsion and Neoral solutions were within

Table 1. Summary of Pharmacokinetic Data

Formulations	Patients	Mean	SD	Median	Min	Max
AUC_{0-12h} (ng · h/mL)						
Formulation						
Neoral	30	4370.69	1231.31	4245.06	2462	8062
Equoral	30	4162.56	1057.13	4171.39	2229	6631
C_{max} (ng/mL)						
Neoral	30	834.97	298.41	784	453.4	1544
Equoral	30	821.80	244.69	767	350.2	1279
T_{max} (min)						
Neoral	30	117	63	105	60	360
Equoral	30	112	49	105	60	240

AUC_{0-12h}, area under the concentration-time curve; C_{max}, extent of absorption; T_{max}, rate of absorption; SD, standard deviation; min, minimum; max, maximum.

Table 2. Safety Profile

	Neoral Solution	Equoral Solution	*P*
Serum creatinine (μmol/L)	58 ± 28	55 ± 20	.74
Serum cholesterol (mmol/L)	3.79 ± 1.15	3.84 ± 1.12	.82
Serum triglyceride (mmol/L)	1.88 ± 0.69	1.68 ± 0.89	.63
Uricemia (μmol/L)	178 ± 89	187 ± 109	.70

Values are mean ± standard deviation.

the 80% to 125% FDA acceptance range, indicating bioequivalence in ASCT recipients. Regarding the bioequivalence criteria of narrow therapeutic index drugs,[12] the 90% confidence interval of nontransformed AUC_{0-12} is within the 90% to 112% range, which is the accepted interval of AUC recommended by the European Medicine Agency and the Health Protection Board of Canada. Both formulations were well tolerated; the number of adverse events was consistent with the generally known incidences related to CsA therapy.[5,6] No serious adverse events or death occurred during the study.

In conclusion, an analysis of our study in ASCT recipients demonstrated that Equoral solution was safe and pharmacologically bioequivalent to Neoral solution.

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