ORIGINAL ARTICLE

The pharmacokinetics and bioequivalence of Gengraf and Neoral in stable renal transplant recipients

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Abstract

Objective: Gengraf capsule, an AB-rated generic cyclosporine for Neoral, has been shown to be bioequivalent in previous studies. The objective of this study was to evaluate the pharmacokinetics and bioequivalence of Gengraf and Neoral in stable Chinese renal allograft recipients

Methods: In a prospective, open-label, two-period design study, 20 renal allograft recipients receiving stable doses of Neoral were recruited. Subjects continued their Neoral regimen during period I (days 1-14). They were then switched from Neoral on a milligram-for-milligram basis to Gengraf during period II (days 15-28). Four-hour pharmacokinetic parameters (concentration before dosing [C_{trough}], maximum blood concentration [C_{max}], time to maximum concentration [T_{max}], and area under the blood concentration-versus-time curve [AUC_{0-4}]) were taken on days 1, 8, 21, and 28. Biochemical parameters were also evaluated.

Results: There was no significant difference in the pharmacokinetics of Gengraf (C_{trough}, T_{max}, C_{max}, and AUC_{0-4}) as compared with that of Neoral in stable renal transplant recipients. The bioequivalent capsules were interchangeable with respect to C_{trough}, C_{max} and AUC_{0-4}. The 90% confidence intervals of the ratio of C_{trough}, C_{max}, T_{max}, and AUC_{0-4} of Gengraf and Neoral were 0.94 to 1.21 for C_{trough}, 0.97 to 1.20 for C_{max}, and 0.97 to 1.20 for AUC_{0-4}. C_{trough} and C_2 remained stable throughout the study without any dosage adjustments. Gengraf was well tolerated, and had a comparable safety profile as Neoral.

Conclusion: Gengraf are bioequivalent to Neoral. Gengraf is well tolerated and interchangeable with Neoral in stable Chinese renal allograft recipients.

Key words: Bioequivalence, Cyclosporine, Gengraf, Pharmacokinetics

中文摘要

目的：在以前的研究中已經表明，環頭孢菌素（Gengraf）膠囊作為 Neoral 的一種 AB 級藥類具有生物等效性。本研究的目的是在接受異體腎移植後狀況穩定的中國患者中評估 Gengraf 及 Neoral 的藥物代謝動力學和生物等效性。

方法：在一項前瞻性、開放、分兩期進行的研究中，共納入了 20 例正在接受穩定劑量 Neoral 的異體腎移植受者。在第一期（第 1 至 14 天），患者繼續接受 Neoral 療法。在第二期（第 15 至 28 天），由 Neoral 改為接受 Gengraf 治療，其劑量保持不變（精確到毫克）。在第 1、8、21、和 28 天，測定 4 小時藥物代謝動力學參數，其中包括給藥前濃度[C_{trough}]，最大血藥濃度[C_{max}]，達峰時間[T_{max}]、和藥 - 時曲線下面積[AUC_{0-4}]。同時也評估生化參數。

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結果：在接受異體腎移植後狀況穩定的患者中，Gengraf的藥物代謝動力學參數 (C_{trough}，T_{max}，C_{max}，及 AUC_{0-4}) 與 Neoral 相比，並沒有顯著差異。從 C_{trough}、C_{max}、和 AUC_{0-4} 來看，這些具有生物等效性的膠囊是可以相互替代使用的。Gengraf 和 Neoral 的 C_{trough}、C_{max}、T_{max}、和 AUC_{0-4} 之比的 90% 可信區間為：C_{trough}，0.94-1.21；C_{max}，0.97-1.20；AUC_{0-4}，0.97-1.2。在整個研究過程中，C_{trough} 和 C_2 保持穩定，未進行劑量調整。Gengraf 的耐受性良好，且其毒副作用與 Neoral 相當。

結論：Gengraf 與 Neoral 具有生物等效性。Gengraf 的耐受性良好，在接受異體腎移植後狀況穩定的中國患者中可以與 Neoral 相互替代使用。

INTRODUCTION

Cyclosporine is a lipophilic cyclic polypeptide that has been used as first-line immunosuppressive therapy for patients undergoing solid organ transplantation. The oil-based formulation of the drug, Sandimmune, (Sandoz, Basel, Switzerland) was characterized by poor and unpredictable absorption and the need for intensive monitoring of blood cyclosporine concentrations and frequent dosage adjustments to obtain the desired therapeutic level after oral administration. In the mid 1990s, however, a novel microemulsion preconcentrate, Neoral, (Novartis, Basel, Switzerland) was introduced. This enhanced the bioavailability of the drug and reduced the variability in pharmacokinetic characteristics (1,2). The introduction of Neoral has prompted much research into therapeutic drug monitoring, with the aim of identifying methods that predict exposure to the drug accurately and thereby assist in the optimization of therapeutic outcomes. This approach, termed "absorption profiling," has the underlying rationale that the 4-hour absorption phase following administration provides measurements that are more informative than cyclosporine trough level (C_{trough}) monitoring in the assessment of likely cyclosporine exposure and subsequent clinical response (3). Achievement of AUC_{0-4} target levels reduced the incidence of acute rejection in early transplant period (4). However, multiple time point AUC_{0-4} sampling is not the most practical solution. Single-time sampling of cyclosporine level at 2 hours (C_2) showed very good correlation with AUC_{0-4} (5). Patient management by Neoral C_2 monitoring in *de novo* renal transplants resulted in a very low incidence of acute rejection with a good safety profile (6).

In May 2000, the United States Food and Drug Administration approved Gengraf capsules (Abbott Laboratories, Abbott Park, US) as AB-related bioequivalent to Neoral cyclosporine for the prevention of organ-graft rejection in kidney, liver, and heart transplant recipients. Gengraf has been shown to be bioequivalent to Neoral in stable renal allograft recipients (7). We performed a prospective study of 20 Chinese renal transplant recipients on Neoral maintenance immunosuppressive therapy. The purpose of the study was to evaluate the pharmacokinetics and to establish bioequivalence between Gengraf and Neoral in stable Chinese renal transplant patients.

PATIENTS AND METHODS

Study design

In January 2002, 20 renal transplant patients were recruited for the study after obtaining informed consent for participation. The study was approved by the Ethics Committee of Princess Margaret Hospital. During the screening period, study subjects were evaluated for enrollment on the basis of a complete medical history, physical examination, vital signs, and clinical laboratory testing. Subjects were maintained during screening on their usual stable oral dose of twice-daily Neoral. During period I (days 1-14), study subjects received a 2-week course of twice-daily Neoral cyclosporine capsules. For the next 2-week period (period II, days 15-28), subjects were replaced to twice-daily Gengraf cyclosporine capsules at an equal milligram-for-milligram dose as their usual twice-daily Neoral dose.

Inclusion and exclusion criteria

Men or non-pregnant, non-lactating women aged 18 to 65 years who had undergone renal transplant were allowed to participate in the study. Women of childbearing potential were required to use medically-acceptable methods of contraception and test negative for pregnancy at screening. Subjects were at least 3 months post renal transplant and on a stable twice-daily dosage of Neoral cyclosporine capsules with stable trough cyclosporine levels before the screening period. Subjects demonstrated no gastrointestinal tract, renal or hepatic diseases that might alter cyclosporine metabolism. Subjects were not allowed to take any nephrotoxic drugs or drugs known to significantly change cyclosporine clearance during this study.

Data collection

Four-hour pharmacokinetic evaluations were obtained on days 1 and 8 (period I, Neoral), days 21 and 28 (period

II, Gengraf). Venous whole-blood samples were collected by venipuncture at pre-doses (0 hour) and then at 1, 1.5, 2 and 4 hours after morning dose of cyclosporine. Cyclosporine blood concentrations were measured using a validated enzyme multiplied immunoassay (EMIT assay, Syva Company, Cupertino, US).

Serum biochemical testing, which included electrolytes, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, total protein, and albumin was performed on days 1, 8, 21 and 28. In addition, a complete blood count with differential was collected on these days.

Statistical methods

Biochemical and pharmacokinetic parameters of cyclosporine were compared using paired t test. The concentration before dosing (C_{trough}), the maximum blood concentration (C_{max}), and the time to maximum concentration (T_{max}) were taken directly from blood concentration measurements. The area under the blood concentration-versus-time curve from time 0 to 4 hours after drug administration (AUC_{0-4}) was calculated using the linear trapezoidal method.

Before analysis, values for C_{trough}, C_{max}, and AUC_{0-4} were log transformed. The two one-sided hypotheses were tested at the 5% level for C_{trough}, C_{max}, and AUC_{0-4} by constructing 90% confidence intervals for the ratio of the geometric test and reference means. Bioequivalence with respect to a specific variable was established if the 90% confidence interval of the ratio means fell within the range of 80% to 125% (8).

Intraindividual pharmacokinetic variability was expressed as the percent coefficient of variation calculated as $\sqrt{MSE} \times 100/mean$, where MSE is the mean squared error of the replicated pharmacokinetic values. Intraindividual variations were compared by F tests. Statistical hypotheses were tested at the 0.05 level of significance.

Table 1. Demographic data.

Number of patients	20
Gender	
Male	12
Female	8
Age, years	48.4 ±10.7
Body weight, kg*	65.9 ± 11.2
Time since transplant, months*	7.2 ± 4.8
Dose of cyclosporine, mg/d*	210 ± 49.5
Immunosuppressive regimen*	
Cyclosporine/prednisolone	6
Cyclosporine/prednisolone/MMF	9
Cyclosporine/prednisolone/azathioprine	5

MMF = mycophenolate mofetil

*Data were presented as arithmetic mean ± standard deviation.

RESULTS

Demographic data

Twenty subjects were recruited for the study and they all completed the study. Demographic characteristics for the study subjects were shown listed in Table 1. The average dose of Neoral was 210 ± 49.5 mg/day. They were maintained on their usual stable dosage of twice-daily Neoral during the first 2 weeks. Afterwards, they were switched from Neoral on a milligram-for-milligram basis to twice-daily Gengraf.

After switching from Neoral to Gengraf, the following pharmacokinetic parameters were observed. The C_{trough} increased from 127 ± 50.1 µg/L to 142.6 ± 49.1 µg/L (p=0.052). AUC_{0-4} increased from 2421 ± 722 µg x hr/L to 2637 ± 846 µg x hr/L (p=0.38). T_{max} was delayed from 1.53 ± 0.72 hours to 1.8 ± 0.9 hours (p=0.51) (Table 2).

Concerning the bioequivalence of two formulations of cyclosporine, the point estimates of relative bio-availability for C_{trough}, C_{max} and AUC_{0-4} were 1.12, 1.09, and 1.09, respectively. The 90% confidence intervals of the test reference geometric mean ratio were within the 80% to 125% bioequivalence range. Thus the

Table 2. Pharmacokinetics and bioequivalence analysis of Gengraf and Neoral in stable renal allograft recipients.

Pharmacokinetic parameters	Gengraf (n = 20)*	Neoral (n = 20)*	Ratio†	90% CI‡	*p* value
C_{trough}, µg/L	142.6 ± 49.1	127 ± 50.1	1.12	0.94-1.21	0.052
C_{max}, µg/L	1101.9 ± 425.6	1007 ± 358	1.09	0.97-1.20	0.33
AUC_{0-4}, µg x hr/L	2637 ± 846	2421 ± 722	1.09	0.97-1.20	0.38
C_2, µg/L	913.3 ± 359.7	728 ± 220			0.09
T_{max}, hour	1.8 ± 0.9	1.53 ± 0.72			0.051

CI = confidence interval

*Data were presented as arithmetic mean ± standard deviation.

†Ratio = the ratio of C_{trough}, C_{max} and AUC_{0-4} of Gengraf and Neoral.

‡90% confidence intervals for the ratio of the above pharmacokinetic parameters. Bioequivalence with respect to a specific parameter was established if the 90% CI of the ratio means fell within the range of 80% to 125%.

bioequivalence between Neoral and Gengraf cyclosporine capsules was demonstrated (Table 2). The intraindividual (within subject) variability of C_{trough} of Neoral and Gengraf, as measured by the coefficients of variation, were 18% versus 20% (*p*=0.395)

Safety and tolerability

No dosage adjustments of cyclosporine were required for any subject during study period. No graft rejection or serious adverse event occurred during the study. Evaluation of laboratory parameters, vital signs, and physical findings demonstrated that no clinically significant changes from baseline occurred during the study for any of these parameters. Serum creatinine was 120.4 ± 41.3 µmol/L in Neoral group as compared with 118.5 ± 43.1 µmol/L in Gengraf group (*p*=0.15).

DISCUSSION

The introduction of cyclosporine microemulsion Neoral in renal allograft recipients has enhanced the bioavailability of cyclosporine and reduced the absorption variability (1). Unpredictable absorption of Sandimmune is a common problem encountered in the clinical management of patients with cyclosporine (9). Development of acute or chronic rejection may be associated with the variable absorption of cyclosporine (10). Achievement of Neoral AUC_{0-4} target levels, 4400 to 5500 µg x hr/L, reduces acute rejection in early transplant period (6). C_2 has been shown to have very good correlation with AUC_{0-4} (5). Therapeutic drug monitoring using C_2 is useful and practical in the patient management.

In our study, the bioequivalence between Gengraf and Neoral is established. However, Gengraf C_{trough}, C_{max} and AUC_{0-4} are consistently higher than that of Neoral after conversion although not statistically significant. No dosage adjustment is required during the study period. A larger scale study with longer duration of follow-up is useful to confirm this. The coefficients of variation of Gengraf and Neoral are 20% and 18%, respectively. The fluctuation of Gengraf cyclosporine level is comparable to that of Neoral. There is no acute rejection documented.

In view of the small number of patients involved, larger scale studies in Chinese populations should be conducted over a longer duration to assess the pharmacokinetics and clinical outcomes of Gengraf, including patient and graft survival rate, in *de novo*, and stable renal transplant recipients

CONCLUSION

This study demonstrates that Gengraf is bioequivalent to Neoral in a Chinese population. They can be converted from Neoral to Gengraf on a milligram-for-milligram basis without any dosage adjustments. There is no acute rejection or serious adverse side effects. Gengraf is well tolerated and has a comparable safety profile as Neoral. The availability of bioequivalent and well-tolerated generic formulations provides significant cost savings in allograft recipients receiving immunosuppressive agents.

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