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Bioequivalence Study of CIPOL-N® (Cyclosporine Microemulsion Preparation) in Healthy Adults

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= 국문초록 =

정상 성인에서 Cyclosporine 연질 경구제제 사이폴-엔®의 생물학적 동등성에 관한 연구

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목 적: 국내에서 생산된 cyclosporine 미세 유상액 연질 캡셀인 사이폴-엔(종근당)이 기존에 판매되고 있는 제제인 한국 산도스사의 산디문 뉴오랄과 생물학적으로 동등한가를 확인하기 위하여 국립보건안전연구원에서 제시한 생물학적 동등성 시험기준에 따라 단회 투여후 약물동태학적 검사를 시행하여 확인하였다.

방 법: 총 24명의 건강한 한국 성인 지원자를 대상으로 하였고 이들을 두군으로 무작위로 나누어 2×2 교차 라틴방격법을 사용하였다. 1차 시기에 각각의 약제를 200 mg씩 경구투여하고 약물투여 직전과 투여후 24시간에 걸쳐 정해진 시간에 채혈하였다. 1주간의 휴약기간 후 제 2차 시기에 각 군은 1차 시기와 다른 약제를 투여받고 같은 방법으로 채혈하였다. 전혈내 cyclosporine의 농도는 방사면역법으로 측정하였다. 각 약제에 대한 약물동태학적 비교항목인 혈중농도-시간곡선하 면적 (AUC), 최고혈중농도 (Cmax), 최고혈중농도 도달시간 (Tmax)외에 약물제거 상수 (Ke) 및 반감기 ($T_{1/2}$) 를 산출하였다.

결 과: 사이폴-엔과 산디문-뉴오랄을 각각 200 mg 1회 경구투여후 산출된 최고혈중농도는 1208.93±28.57 ng/ml와 1243.45±35.18 ng/ml; 최고혈중농도 도달시간은 1.60±0.08 h와 1.54±0.07 h; 혈중농도-시간곡선하 면적은 5370.24±176.23 ng · h/ml와 5379.23±194.06 ng · h/ml이었다. 약물제거 상수 (Ke) 및 반감기 ($T_{1/2}$) 는 사이폴-엔이 0.1474±0.0035/h와 4.77±0.12 h, 산디문-뉴오랄은 0.1463±0.0036/h와 4.80±0.11 h 이었다. 유의수준 α=0.05와 검출력(1-β)=0.8에서 최소검출차(△)는 ≤0.2로서 분산분석에 의한 검증상 두 제제 사이에 유의한 차이를 보이지 않았다. 이들 비교항목의 평균치의 차이는 혈중농도-시간곡선하 면적 0.17%, 최고혈중농도 2.78%, 최고혈중농도 도달시간 4.05%로서 대조약의 20% 이내였다.

결 론: Cyclosporine 미세 유상액 연질 캡셀인 사이폴-엔은 기존의 산디문 뉴오랄과 생물학적으로 동등함을 확인하였다.

핵심어: Bioequivalence, Cyclosporine, SANDIMMUN NEORAL®, CIPOL-N®

INTRODUCTION

Cyclosporine is at present the most important immunosuppressive agent in transplantation and in the treatment of selected autoimmune diseases. Clinically, it has been used successfully in the transplantation of kidney, liver, heart, lung and bone marrow[1]. The inhibition of interleukin-2(IL-2) production has been proposed as the main mechanism of immunosuppressive activity. Other proposed

mechanisms are interference with transcription of mRNA coding for IL-2 via cyclophilin binding, and the blockage of Ca^{2+} to calmodulin interaction[2].

Even though cyclosporine has almost no bone marrow toxicity unlike other cytotoxic immunosuppressants, it still has been associated with a number of adverse reactions such as renal and hepatic dysfunction, hypertension, neurotoxicity, lymphoma, abnormal glucose homeostasis, hypertrichosis and gingival hypertrophy[3]. The effect as well as the degree of toxicity are related to the blood concentration of cyclosporine, which is highly variable between individuals. The therapeutic range is narrow and varies among patients.

Since its discovery there has been enormous amount of information gathered in relation to its pharmacokinetic /pharmacodynamic profiles as well as analytical methods for therapeutic drug monitoring; especially because of inter-and intra-individual variability inherent in the drug.

The reported oral bioavailability of cyclosporine in its conventional soft gelatin capsules varies from less than 5% to 50% depending on the conditions[4,5], while that of newly formulated microemulsion capsules showed the increase of 49% to 140%[6,7]. Perhaps the most prominent improvement of microemulsion would be the significantly reduced intraindividual variability in pharmacokinetic parameters as well as improvements in the correlation between trough concentrations and AUC[8]. However, there seems to be no absorption-related differences in the systemic metabolite profile between two formulations[9].

Cyclosporine binds to erythrocytes and leukocytes by a saturable process depending on the concentration and temperature. Lowering of temperature from 37 to 21°C will cause diffusion of cyclosporine from plasma into blood cells, resulting in the decrease of plasma concentration by 50%. About 97% of cyclosporine is bound to plasma proteins (80% of this bound to lipoprotein). Cyclosporine is widely distributed in various tissues, especially adipose tissue, pancreas, adrenal gland and liver. It distributes according to a three-compartment model with a very large apparent volume of distribution, 4 to 8 L/kg[10].

Cyclosporine is extensively metabolized in the liver by cytochrome P450 enzymes, mainly CYP3A4 and CYP3A5[11]. There are more than 30 metabolites known but three main ones found in man are monohydroxylation products (AM1 =M17 and AM9=M1) and an N-demethylated compound (AM4N=M21)[12]. The major route of elimination is biliary excretion. The urinary excretion accounts for only 6% of an oral dose, and only 0.1% of the dose is excreted unchanged. Terminal elimination half-life ranges from 4 to 50 h[13], while the total clearance from whole blood is 0.27~0.47 L/h/kg[2].

With the development of new generic drugs with the same active ingredients, it is necessary that we should make sure that the newly developed drugs are bioequivalent to the reference drug. The bioequivalence, by the definition given by the US FDA Code of Federal Regulations part 320, is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study"[14]. The best way to prove bioequivalence, as suggested by the FDA, would be an *in vivo* test in humans in which the concentration of the active ingredient or moiety or possibly active metabolites in appropriate body fluids is measured as a function of time. The microemulsion capsule formulation of cyclosporine, with its advantages over the conventional formulation, is now widely used and is accepted as the standard. The newly developed microemulsion capsule of cyclosporine, namely CIPOL-N® (Chong Kun Dang, Korea), was tested for bioequivalence compared with the reference drug of the same formulation, SANDIMMUN NEORAL® (Sandoz, Switzerland).

METHODS

1) Subjects

Twenty four healthy Korean volunteers were enrolled in the study. Written informed consents were obtained from all volunteers after full explanation of the aim, the nature of the study, possible adverse events, and the right to withdraw from the study without any disadvantage. The subjects were of ages 21 to 29 (mean 22.8±0.4 yr) and

of both sexes (M:F=19:5) The body weights of the volunteers were all within 10% of ideal body weight. Prior to the enrollment the volunteers were screened for the presence of underlying illnesses or any abnormalities that may hinder proper conduct of the study as well as the proper interpretation of the results through complete history and physical examinations along with a series of laboratory test [complete blood count with differential, blood chemistry (Ca/P, fasting blood glucose, total protein & albumin, SGOT & SGPT, BUN and Creatinine, total bilirubin, alkaline phosphatase, total cholesterol, serum electrolytes), and urinalysis] and radiological evaluations. All the volunteers had normal values for all the tests listed above. The study subjects refrained from alcoholic beverages or other medications for 1 week before the start of the trial, and fasted for 10 h before and up to 4 h after the administration of the drugs.

2) Study design

2×2 Cross-over Latin square method was used (Table 1). The study subjects were randomly divided into two groups of 12 each. Each group received either the test drug CIPOL-N® or the reference drug SANDIMMUN NEORAL® in the period 1. After one week of wash-out period, each group received the other drug in the period 2. Both drugs were administered at the dose of 200 mg with 200 ml of water. Indwelling venous cannula were inserted into arm veins of the subjects. Through the cannula, 6 ml each of blood was obtained just before drug administration and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h after administration and collected in EDTA tubes. The collected samples were stored frozen at −70°C till the analysis of the whole blood concentrations within one month after collection. Blood pressure and pulse rate were measured before and every hour up to 4 h after administration of the drugs. Any of adverse events were recorded. The study protocol was approved by Institutional Review Board of Severance Hospital Yonsei University College of Medicine (Approval No 9618).

3) Analytical methods

The whole blood concentrations were measured by radioimmunoassay method using Cyclo Trac-SP® RIA kit (Incstar Corp, MI, USA). Briefly, 100 μl of whole blood sample, after thawing and shaking well to achieve homogeneous distribution of red cells, was taken and mixed with 400 μl of methanol on a vortex for 60 sec. It was centrifuged at 1,600×g for 5 minutes. From the supernatant layer containing methanol extract, 50 μl was taken and placed in a test tube for gamma-counting, and added 100 μl of ^{125}I Cyclo-Trac SP® and 1 ml of Anti-Cyclo Trac SP Immunosep®. After fully mixing with a vortex, mixture was left to stand in room temperature for 1 hr. After centrifuging it at 1,600×g for 20 min at room temperature, supernatant was discarded and the test tube was left upside down on a filter paper for 1 minute to allow natural drainage of the remaining fluid. The radioactivity of the precipitate left in the bottom of the test tube was measured with a gamma counter. This value was converted to the actual concentration of cyclosporine(ng/ml) using the standard

Table 1. Allocation of volunteers and administration of two cyclosporine preparations by 2×2 cross-over design in 24 healthy volunteers

Group	Subjects				Period I	Period II
I	LSH CSH HKS	KDH CJH HDK	KSS CYH HIC	LJM CHS YBJ	SANDIMMUN NEORAL®	CIPOL-N®
II	KJH KKT CMH	KYK PKS MHK	JJR CDK PSJ	CSA CSB RJW	CIPOL-N®	SANDIMMUN NEORAL®

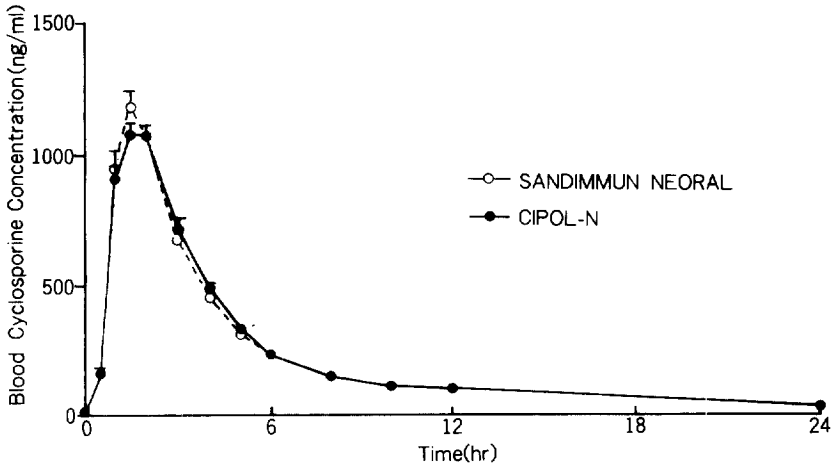

Fig 1. Time-whole blood concentration curve of cyclosporine after oral administration of CIPOL-N® 200 mg or SANDIMMUN NEORAL® 200 mg in 24 healthy Korean volunteers (Each point represents Mean ± SE).

curve obtained by performing the same procedure with a series of cyclosporine of known varying concentrations. This was done by a program built in the gamma counter using RIA mode (logistic curve fit).

4) Pharmacokinetic parameters

For the test of bioequivalence, area under the concentration-time curve (AUC), the maximum concentration (Cmax), and the time to reach the maximum concentration (Tmax) were determined. AUC was calculated using the trapezoidal rule over the time period of 0 h to 24 h after drug administration ($AUC_{0\text{-}24}$). Cmax and Tmax were directly obtained from the concentration-time curve. In addition, elimination coefficient (Ke) and $T_{1/2}$ were also calculated.

5) Statistical analysis

These values were compared between the test and the reference drug using analysis of variance. Power, least significant difference, the confidence interval for the differences of two drugs in the parameters of bioequivalence were determined using Bioequivalence Test Data Analysis Program v. 1.35. Statistical analysis was done according to the guidelines suggested by the National Institute of Safety Research, Korea(Notification 94-1) for the comparison of test drug and the reference drug for the bioequivalence.

Table 2. Serial mean blood concentration of cyclosporine after administration of two cyclosporine preparations in 24 healthy volunteers

Time(hr)	SANDIMMUN NEORAL®	CIPOL-N®
0	9.8 ± 0.9	10.8 ± 1.0
0.5	160.7 ± 18.8	155.2 ± 15.6
1	951.3 ± 62.9	899.3 ± 62.7
1.5	1183.3 ± 42.7	1084.8 ± 35.2
2	1068.7 ± 43.6	1069.1 ± 38.0
3	678.0 ± 33.5	716.6 ± 27.7
4	458.9 ± 24.2	490.6 ± 18.8
5	318.6 ± 18.6	337.2 ± 13.7
6	234.8 ± 12.1	228.5 ± 10.7
8	152.3 ± 6.9	151.4 ± 6.9
10	114.9 ± 4.6	115.3 ± 5.6
12	102.8 ± 5.2	100.9 ± 4.6
24	33.9 ± 2.7	34.2 ± 2.7
Cmax(ng/ml)	1243.4 ± 35.2	1208.9 ± 28.6
Tmax(hr)	1.5 ± 0.1	1.6 ± 0.1
AUC(ng · hr/ml)	5379.2 ± 194.1	5370.2 ± 176.2

Values are means ± S.E.

RESULTS

1) Pharmacokinetic parameters for the test of bioequivalence

The whole blood concentrations of cyclosporine after administration of 200 mg of CIPOL-N® and 200 mg of SANDIMMUN NEORAL® were determined in 24 volunteers as previously described and plotted over time up to 24 h. The time-concentration curves of the test and the reference drugs almost identically matched except for a few points including the peak concentration (Fig. 1 & Table 2). The patterns of the curves were similar. Both drugs were absorbed and accumulated in the blood rapidly showing a steep upward slope, reaching the peak concentrations within 2 h, and thereafter decreased in concentration in a biphasic manner that is, rather rapidly for the first few hours and gradually after 6~8 h.

All the pharmacokinetic parameters determined were comparable for both drugs. The mean maximum blood concentrations of cyclosporine for 200 mg of CIPOL-N®

Table 3. Summary of individual AUC, Cmax and Tmax after administration of two cyclosporine preparations, CIPOL-N® and SANDIMMUN NEORAL® in 24 healthy volunteers

	SANDIMMUN NEORAL®			CIPOL-N®		
SUBJECT	Cmax (ng/ml)	Tmax (hr)	AUC (ng · hr/ml)	Cmax (ng/ml)	Tmax (hr)	AUC (ng · hr/ml)
LSH	1324.9	1.00	4986.62	1165.1	2.00	4798.69
KDH	1091.4	1.50	5414.34	982.0	2.00	5172.91
KSS	1221.3	1.50	4944.53	1178.2	1.50	4754.63
LJM	1505.4	1.00	5801.14	1402.2	1.50	6806.70
CSH	1298.2	1.50	5536.32	1155.1	1.50	5747.61
CJH	1484.6	1.50	7032.29	1421.9	2.00	7743.89
CYH	1390.6	1.50	5284.69	1261.6	1.50	5401.03
CHS	1398.1	1.50	6116.54	1306.5	1.00	5738.38
HKS	1199.9	1.00	4199.24	1071.3	1.00	3826.04
HDK	1225.4	2.00	6445.68	1174.0	2.00	5778.64
HIC	1023.0	1.50	4085.41	1257.4	2.00	5100.83
YBJ	1052.6	1.50	4951.43	1055.6	1.50	4911.36
KJH	919.0	2.00	4755.18	965.6	2.00	4949.34
KYK	1164.7	2.00	5630.98	1059.6	2.00	5462.40
JJR	1257.5	2.00	6240.30	1187.1	1.50	6098.39
CSA	1599.2	1.50	7274.17	1514.2	1.00	6419.16
KKT	1339.9	2.00	6198.24	1378.3	2.00	5823.53
PKS	1403.0	2.00	6224.65	1341.2	2.00	5375.07
CDK	1028.5	1.50	4643.14	1124.4	1.50	5278.00
CSB	1071.3	1.50	4247.32	1122.1	2.00	4607.62
CMH	1076.9	1.00	3795.76	1247.7	1.00	3882.91
MHK	1208.4	1.50	5718.21	1134.5	1.00	5608.67
PSJ	1209.3	1.50	4364.70	1204.3	1.50	4632.82
RJW	1349.6	1.50	5012.59	1304.3	1.50	4967.12
MEAN	1243.45	1.54	5379.23	1208.93	1.60	5370.24
S.E.	35.18	0.07	194.06	28.57	0.08	176.23

Table 4. Summary of the statistical analysis of the bioequivalence test for two cyclosporine preparations, CIPOL-N® and SANDIMMUN NEORAL®

	AUC	Cmax	Tmax
Percent difference in mean against reference drug	0.17%	2.78%	4.05%
Least significant difference	5.79%	4.60%	13.46%
Noncentrality	10.136	12.736	4.356
Confidence interval for difference in bioavailability	$-3.93\% \leq \leq 4.26\%$	$-0.48\% \leq \leq 6.03\%$	$-5.47\% \leq \leq 13.59\%$

(at the level of α=0.05 and 1-β=0.8)

and 200 mg of SANDIMMUN NEORAL® were 1208.93 ±28.57 ng/ml and 1243.45±35.18 ng/ml, respectively. Tmax of CIPOL-N® was 1.60±0.08 h, whereas that of SANDIMMUN NEORAL® 1.54±0.07 h. $AUC_{0\text{-}24}$ was 5370.24±176.23 ng · h/ml for CIPOL-N® and 5379.23± 194.06 ng · h/ml for SANDIMMUN NEORAL®(Table 3). Ke and $T_{1/2}$ were also comparable for both drugs; that is, 0.1474±0.0035/h and 4.77±0.12 h for CIPOL-N® and 0.1463±0.0036/h and 4.80±0.11 h for SANDIMMUN NEORAL®. Statistical analysis using unpaired *t*-test and ANOVA revealed that there were no significant differences between two drugs in mean values as well as in variance for all these pharmacokinetic parameters.

Based on the pharmacokinetic parameters given above, we calculated the difference between the mean values of two drugs against the mean values of the reference drug to see whether these were within 20% to satisfy the conditions for bioequivalence. The difference of AUC, Cmax, and Tmax was 0.17%, 2.78%, and 4.05%, respectively. At the significance levels suggested by the regulation, α=0.05, and power (1-β)=0.8, the least significant difference ($\triangle$) for AUC, Cmax, and Tmax was 5.79%, 4.60% and 13.46%, respectively. The confidence intervals for the BA difference of AUC, Cmax, and Tmax were −3.93% ~4.26%, −0.48% ~6.03%, and −5.47% ~13.58%, respectively(Table 4).

2) Adverse events

There were no serious adverse events during the study period. The changes in blood pressure and pulse rate were negligible and all in the normal ranges. Beginning from 30 minutes to 2 hours, heat sensation of face, hands and feet, and sometimes generalized, was observed in 91.7% of the subjects for both drugs (data not shown). But none of the subjects showed actual elevation of body temperature. The symptoms subsided spontaneously within 0.5 to 3 hours without medical management.

DISCUSSION

In the history of transplantation, cyclosporine would be one of the most monumental milestones, which allowed surgeons a breakthrough in improving the success rate as well as in extending into transplantation of various other organs. Unlike other immunosuppressive agents cyclosporine gives benefit of effectively suppressing graft rejection while preserving immune functions necessary for the defense against invading organisms. In addition to its use in the organ transplantation, cyclosporine has been used in other fields of medicine, such as for the treatment of autoimmune diseases[15]. But the most disturbing aspects of cyclosporine and perhaps the major reasons why therapeutic drug monitoring has become a must are narrow margin of safety with a number of serious dose-dependent adverse reactions, incomplete absorption through gastrointestinal tract and high inter- as well as intra-individual variability, depending on the type of transplant, time after transplant, presence or absence of external biliary drainage, liver function, presence of food or intestinal dysfunction[16].

Recently produced cyclosporine in the formulation of

microemulsion capsules SANDIMMUN NEORAL® by Sandoz exhibits improvement in many aspects over the conventional soft gelatin capsule SANDIMMUN®; that is, enhanced absorption and bioavailability along with lower degree of variability. SANDIMMUN NEORAL® showed a consistently shorter time to reach peak concentration and a mean increase in peak concentration by 67% and an overall mean increase in drug exposure (AUC) by 34% compared with SANDIMMUN®, whose Tmax is about 3 to 4 h[2]. The inter-and intraindividual variation of the pharmacokinetic parameters were significantly lowered from 19~41% of SANDIMMUN® to 3~22% of SANDIMMUN NEORAL®[17]. The results of this study are generally in agreement with the reported results; for both SANDIMMUN NEORAL® and CIPOL-N®, Tmax (1.54 and 1.60 h, respectively) was shorter and Cmax (1243 and 1208 ng/ml for a single-dose of 200 mg) was higher compared with the published values for the conventional gelatin capsules or oral solutions[2].

As evident from the history, drugs with the same active ingredients as the reference drug do not necessarily have the same pharmacologic properties in respect to the pharmacokinetic and pharmacodynamic profiles. Therefore, it has become absolutely necessary to assure the bioequivalence of new drugs in order to safeguard against possible deviations that may result in catastrophic situations as in the past, such as with phenytoin intoxication among epileptic patients in Australia in the late 1960s[18]. In order to show the bioequivalence or, in other words, that new drugs can be used in place of the reference drug as a substitute without making any adjustment to the prescription, a number of requirements have to be satisfied. The Korean National Institute of Health and Safety Research suggests the following guidelines for bioequivalence: a) measures of bioavailability, such as AUC, Cmax and Tmax, b) difference in mean values of the above parameters of the test drug should be less than $\pm 20\%$ of the reference drug values, c) at the significance level of analysis of variance $\alpha=0.05\sim0.1$ and $1-\beta>0.8$, least significant difference ($\triangle$) is <0.2, and d) the overall evaluation on the basis confidence interval for the difference of bioavailability of two drugs and the results of above c) is to be done[19].

The pharmacokinetic profiles of SANDIMMUN NEORAL® and CIPOL-N® were compared. The time-concentration curves of the both drugs matched almost identically, thus proving by itself the similarity of the bioavailability as well as the pattern of elimination. There was no statistically significant difference between the drug concentrations over time, analyzed by repeated-measure ANOVA. The mean values and the variances of Cmax, Tmax and AUC of two drugs was not significantly different (unpaired *t*-test and ANOVA). Furthermore, Ke and $T_{1/2}$ were also comparable. The differences in mean values of these parameters were all less than 20% of SANDIMMUN NEORAL® values (0.17% for AUC, 2.78% for Cmax, and 4.05% for Tmax). At the significance levels of analysis of variance $\alpha=0.05\sim0.1$ and $1-\beta>0.8$, least significant differences ($\triangle$) were all less than 0.2 (0.058 for AUC, 0.046 for Cmax, and 0.13 for Tmax. The 95% confidence intervals of the difference of AUC, Cmax and Tmax ranged from -3.93% ~4.26%, -0.48% ~6.03%, and -5.47% ~13.58%, respectively.

Concerning the analytical methods used to detect cyclosporine whole blood concentrations, there are a few popular methods currently accepted worldwide. Even though high performance liquid chromatography (HPLC) may be the most accurate method in isolating and measuring the parent compound cyclosporine, a number of commercially available specific immunoassays, such as radioimmunoassay (RIA), fluorescence polarization immunoassay and enzyme multiplied immunoassay technique have proved their usefulness in the determination of trough blood level as acceptable therapeutic drug monitoring methods as well as for the measurement of pharmacokinetic profiles[20]. It has been made possible by the introduction of selective antibodies which detect parent cyclosporine molecules with little cross-reactivity with the metabolites. Another benefit of immunoassays may be the improved reproducibility compared to HPLC. The method we used in this study was RIA using Cyclo Trac-SP® RIA kit (Incstar Corp, MI, USA), which is one of the most popular methods reported to be used for therapeutic drug monitoring in the UK as well. Although its specificity for the parent cyclosporine is high, it is still known to give con-

sistently higher results than HPLC, due to cross-reactivity with the major metabolites[20]. Nevertheless, in this study for the test of bioequivalence, the analytical method did not impose any problems, because the whole blood samples were analyzed with the same RIA kit for both the test and the reference drugs.

CONCLUSION

In summary, the test drug CIPOL-N® satisfied all the requirements listed in the guidelines for the test of bioequivalence to the reference drug SANDIMMUN NEORAL®. However, it does not mean that therapeutic drug monitoring can be precluded from the clinical use of cyclosporine. Therapeutic drug monitoring continues to be a necessary measure for optimization of the use of cyclosporine for each patient in whom there are so many factors influencing its pharmacokinetic profiles, unlike the study settings for bioequivalence.

We conclude that CIPOL-N® and SANDIMMUN NEORAL® are bioequivalent and can be safely used as a substitute for each other.

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