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Pharmacokinetics of a new microemulsion formulation of cyclosporin A (Neoral) in young patients after renal transplantation

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Abstract Pharmacokinetics of the new galenic formulation of cyclosporin A, Neoral, (Sandoz) was examined in 12 stable young patients after renal transplantation. Six of these patients were tested before and 4 weeks after switching from the standard formulation Sandimmun to Neoral. No significant changes were observed in trough levels, t_{max}, C_{max}, and AUC_{0-12h}, but the absorption rate constant (K_a) increased ($P = 0.03$). Glomerular filtration rate, as assessed by inulin clearance, increased by more than 10% in three patients and decreased in two, and was usually associated with a respective drop and rise in C_{max} and AUC_{0-12h} of cyclosporin A. The large interindividual variability in the response to the conversion to the new formulation points to a need for close monitoring of cyclosporin A trough levels and renal function after switching from Sandimmun to Neoral in this age group in order to avoid nephrotoxicity.

Key words Pediatric kidney transplantation, CyA · CyA, pediatric kidney transplantation · Neoral, pediatric kidney transplantation

Introduction

Immunosuppressive regimens following renal transplantation usually include cyclosporin A (CyA). The application of CyA has considerably improved graft survival and reduced the severity of acute rejection episodes [16, 19]. Dosage individualization is required to achieve acceptable clinical results, but treatment with CyA is difficult to monitor due to a pronounced inter- and intraindividual variability of pharmacokinetics, mainly by large variations in intestinal CyA absorption. This is especially true of pediatric patients [1, 7, 18, 22], who generally have an increased CyA clearance compared to adults.

To allow a more consistent absorption, a new oral microemulsion formulation of CyA, Neoral, (Sandoz) was developed, which offers better pharmacokinetic predictability [3]. A number of studies were reported in adult patients after transplantation that seem to confirm the improved pharmacokinetic properties of the new CyA formulation [4, 6, 8]. Corresponding investigations in young transplant recipients are rare [1, 11]. To gain more information regarding the pharmacokinetics of the new formulation in the pediatric population, we examined young transplant recipients before and 4 weeks after a 1:1 conversion from standard CyA (Sandimmun) to the new galenic formulation, Neoral. We also tested the influence of Neoral on glomerular filtration rate (GFR) using a precise marker.

Patients and methods

The pharmacokinetic study comprised 12 stable young transplant recipients (10 male, 2 female) with a median age of 13.9 years who participated after giving informed consent. Ten patients received a cadaveric graft and two a kidney from a living donor. Nine children underwent a first transplantation while three were recipients of a second transplant. All but one patient followed a triple therapy regimen consisting of methylprednisolone, azathioprine, and CyA. In order to enter the pharmacokinetic study, pa-

tients had to meet the following criteria: (1) stable renal graft function defined as serum creatinine (SCr) up to 0.2 mg/dl above the patient's established baseline, (2) no evidence of acute graft rejection for at least 6 months prior to the study, (3) oral administration of a constant amount of CyA in two daily doses (every 12 h) for at least 1 month prior to the study, and (4) no excessive variations in CyA trough levels exceeding 50 ng/ml at least 1 month before the study. The two CyA formulations were administered as soft capsules or as solution. Four patients received calcium channel blockers at a constant dose for at least 3 months: two diltiazem, one nitrendipine, and one nifedipine. Patients receiving other drugs known to interact with CyA or who had liver disease were excluded.

In six patients with a median age of 14.8 years (group 1, Table 1), the bioavailability and pharmacokinetics of CyA were compared following the administration of equal doses of Sandimmun and of Neoral in a nonrandomized order. Transplantation was performed 35–87 (median 59) months prior to the study. The dose of Sandimmun applied in the first pharmacokinetic study corresponded to the same given for treatment. Subsequently, the patients were switched to Neoral on a 1:1 basis, and after 4 weeks the pharmacokinetic study was repeated with Neoral. The mode of administration (i.e., capsules or solution) remained unchanged. The two pharmacokinetic profiles were assessed after an overnight fast of approximately 10 h. A standard lunch was given 4 h after drug intake. Blood samples were obtained at steady-state over the dosing interval of 12 h, before (trough level), and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h after drug administration.

In another group of six patients (group 2), aged 9.8–19.4 (median 12.5) years, who had changed the regimen from Sandimmun to Neoral 41–192 (median 103) days previously, a single pharmacokinetic study on Neoral was performed. This study was conducted 30–111 (median 69) months following transplantation. SCr, GFR, and dose of Neoral given were not significantly different from those in group 1 (Table 2). In group 2, an abbreviated 6-point kinetic profile was obtained by sampling blood before (trough level) and 0.5, 1, 2, 3, and 4 h after Neoral administration. Blood sampling was carried out with an indwelling cannula and was collected in EDTA polystyrene tubes. Whole blood concentration of CyA was measured by monoclonal antibody assay TDxFLx (Abbott Diagnostika, Wiesbaden, Germany). All samples from a given patient were assayed on the same run.

Concomitantly with the pharmacokinetic studies, a single-injection inulin clearance for estimation of GFR was performed in all patients after adequate hydration (20 ml water /kg immediately before the test). Some 2.25 g/m^2 inulin (Inutest, Laevosan-Gesellschaft, Linz, Austria) was injected i.v., and serum samples were collected before and at 3, 15, 30, 45, 60, 90, 120,150, 180, 210, and 240 min after injection, corresponding to the time after CyA administration. Inulin was determined enzymatically [10] and the clearance was evaluated using a biexponential decay model for calculation of inulin distribution and clearance.

Kinetic analysis of concentration-time profiles was performed by applying a two-compartment model with first-order elimination and absorption for repetitive dosing at equal time intervals [21]. The corresponding mathematical equations were fitted to the individual blood concentrations of both Sandimmun and Neoral dispositions at steady state simultaneously using the extended least squares modelling program MKMODEL [5]. To obtain a good fit, it was necessary to include a lag time and a bioavailability factor. Model independent kinetic analysis was performed on blood concentration data of each patient in terms of peak time concentration in blood (C_{max}), the time to peak concentration (t_{max}), and the area under the whole blood concentration-time curve (AUC) obtained over 12 h (group 1) and 4 h (group 1 and 2), respectively.

Table 1 Clinical, laboratory, and pharmacokinetic parameters in six transplant recipients at the time of pharmacokinetic studies with Sandimmun and Neoral (*CyA*, cyclosporin A; *SCr*, serum creatinine; C_{in}, inulin clearance; t_0, CyA trough level; t_{max}, time to peak concentration; C_{max}, peak time concentration in blood; $AUC_{0\text{-}12\,h}$, area under the whole blood concentration – time curve; K_a, absorption rate constant; ΔF, difference in bioavailability for Neoral; *Sol*, solution; *Caps*, capsules)

Patient no.	Age (years)	Sex (F/M)	CyA dose (mg/m^2 per day)	Sandimmun							Neoral							
				SCr (mg/dl)	C_{in} (ml/min per 1.73 m^2)	t_0 (ng/ml)	t_{max} (h)	C_{max} (ng/ml)	$AUC_{0\text{-}12\,h}$ (ng/ml*h)	K_a (h^{-1})	SCr (mg/dl)	C_{in} (ml/min per 1.73 m^2)	t_0 (ng/ml)	t_{max} (h)	C_{max} (ng/ml)	$AUC_{0\text{-}12\,h}$ (ng/ml*h)	K_a (h^{-1})	ΔF (%)
1	11.5	M	94.0 Sol	0.6	114	152	1	852	3823	0.92	0.6	150	82	1	555	2129	1.01	- 44
2	13.8	M	157.1 Sol	1.1	53	154	2	848	4025	0.34	1.1	70	84	1	746	2369	1.25	- 38
3	13.9	F	162.1 Sol	1.0	72	79	1	311	1746	0.33	1.1	62	173	1	924	3534	1.19	+ 104
4	15.7	M	133.4 Caps	1.4	80	41	4	279	1739	0.62	1.6	83	117	1	1034	3362	1.27	+ 59
5	15.8	M	80.0 Sol	0.8	87	74	3	188	1137	1.66	0.9	120	135	2	379	2891	2.05	+ 145
6	20.6	M	182.9 Caps	0.9	151	97	1	790	3058	0.17	0.9	127	205	1	1500	5301	0.15	+ 60
Mean	15.2		134.8	0.96	92.8	99.5	2.0	544.7	2588	0.67	1.03	102	132.3	1.2	856.3	3624.3	1.15	+ 47.7
± SD	± 3.0		± 40.6	± 0.27	± 34.8	± 45.2	± 1.3	± 316	± 1212	± 0.55	± 0.33	± 35.3	± 49.1	± 0.5	± 395	± 1136	± 0.6*	± 75.7
Median	14.8		144.8	0.95	83.5	88	1.5	550.5	2402	0.48	1.0	101.5	126	1.0	855	3126	1.22	+ 59.5

* $P = 0.03$ vs K_a after Sandimmun

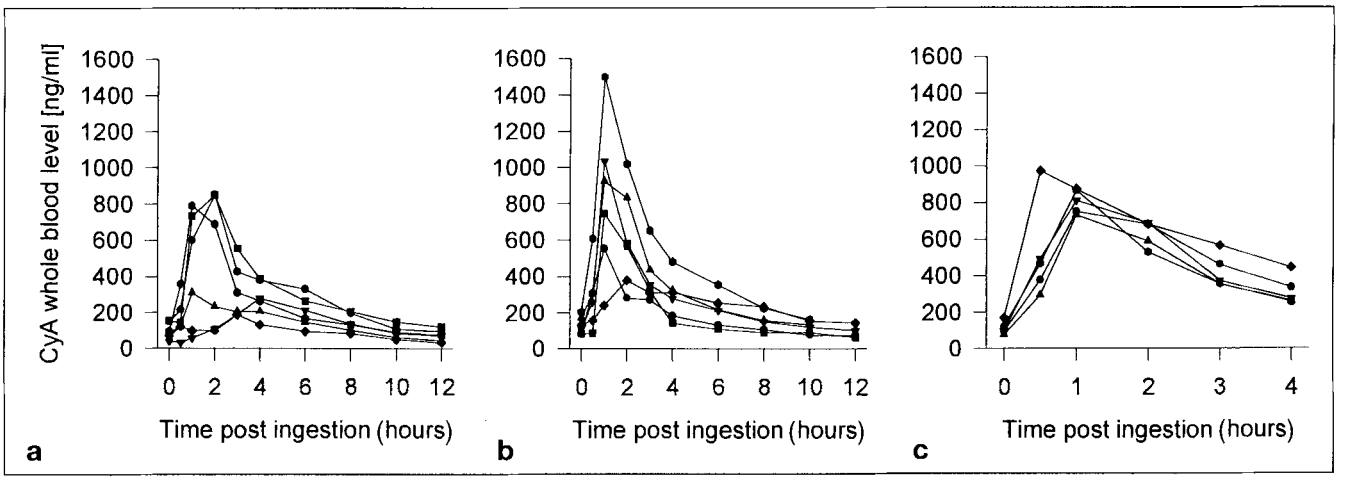

Fig. 1a–c Individual blood concentrations of CyA versus time profiles followed up to: **a** 12 h after oral administration of Sandimmun and **b** 12 h after oral administration of Neoral in patients from group 1; **c** 4 h after Neoral administration in patients from group 2

Table 2 Laboratory and pharmacokinetic parameters in 12 patients undergoing pharmacokinetic testing with Neoral (mean ± SD) (*SCr*, serum creatinine; C_{in}, inulin clearance; C_{max}, peak time concentration in blood; $AUC_{0\text{-}4\,h}$, area under the whole blood concentration – time curve; K_a, absorption rate constant)

	Group 1 ($n = 6$)	Group 2 ($n = 6$)	Significance
SCr (mg/dl)	1.03 ± 0.33	0.99 ± 0.48	NS
C_{in} (ml/min per 1.73 m^2)	102 ± 35.3	83.3 ± 19.4	NS
Neoral dose (mg/m^2 per day)	134.8 ± 40.6	152 ± 0.37	NS
Trough level (ng/ml)	132.3 ± 49.1	112 ± 32.4	NS
C_{max} (ng/ml)	856.3 ± 395	892.8 ± 181	NS
$AUC_{0\text{-}4\,h}$ (ng/ml*h)	1947 ± 840	2224 ± 409	NS
K_a (h^{-1})	1.15 ± 0.6	1.72 ± 1.15	NS

Nonparametric Wilcoxon statistics were applied to assess the significance of within-group (signed rank test) and between-group differences (analysis of variance on ranks). A P value of less than 0.05 was considered statistically significant.

Results

Throughout the study, the new galenic formulation of CyA, Neoral, was well tolerated by the patients. In group 1, hemograms and biochemistry profiles remained stable from the first to the second pharmacokinetic study; Neoral had no effect on blood pressure or serum concentrations of urea, uric acid, or potassium. At the time of the first pharmacokinetic study and 4 weeks after switching to Neoral, mean SCr was 0.96 ± 0.27 mg/dl and 1.03 ± 0.33 mg/dl (mean ± SD), respectively (P = NS). No rejection episodes were noted in the interval.

Table 1 and Fig. 1 give the individual pharmacokinetic data in group 1. In most patients, T_{max} occurred earlier for Neoral than for Sandimmun. In four children, C_{max} and $AUC_{0\text{-}12\,h}$ were higher after Neoral, but the difference between all patients was not significant. The bioavailability of Neoral compared to Sandimmun ranged from –44 % to +145 %. The absorption rate constant (K_a) was higher for Neoral than for Sandimmun in five of six patients ($P = 0.03$). The correlation between trough levels and $AUC_{0\text{-}12\,h}$ was similar for Neoral ($r^2 = 0.84$) and Sandimmun ($r^2 = 0.80$). GFR decreased by more than 10 % after switching to Neoral in two patients (nos. 3 and 6) and there was an increase in C_{max} and $AUC_{0\text{-}12\,h}$. Another two patients (nos. 1 and 2) showed an increment of GFR after conversion to Neoral that was associated with a reduction in trough levels, C_{max}, and $AUC_{0\text{-}12\,h}$. Such a change was not observed in another patient (no. 5) who presented an increase in GFR after the introduction of Neoral.

The 4-h pharmacokinetic profile of Neoral obtained in group 2 was similar to that in group 1, without significant differences between trough levels, C_{max}, $AUC_{0\text{-}4\,h}$, or K_a (Table 2, Fig. 1).

Discussion

Several reports in adult patients have indicated that the new microemulsion formulation Neoral exhibits a better and more predictable pattern of intestinal absorption [8, 20]. Mueller et al. [13] demonstrated that the pharmacokinetic differences between the two formulations of CyA were absorption-related. Our study in 12 young patients appears to confirm previous observa-

tions on the pharmacokinetics of Neoral after transplantation [8, 13]. Four weeks after conversion from Sandimmun to Neoral on a 1:1 basis, four of six stable transplant recipients presented an increase and two a reduction in C_{max} and AUC_{0-12h}, indicating a wide range of absorption. T_{max} was shorter with Neoral than with Sandimmun in half of the patients, pointing to a more rapid absorption.

The improved bioavailability of CyA after switching to Neoral may, in some patients, lead to enhanced drug exposure and an augmented risk of side effects including renal dysfunction [12]. In an earlier study in young transplant recipients, it was shown that GFR is reduced after a 1:1 conversion from Sandimmun to Neoral [1]. It is assumed that CyA-induced nephrotoxicity is related to increased resistance in afferent glomerular arterioles, leading to reduced renal blood flow [2, 14] and a decline in GFR, probably by excessive synthesis of endothelin [17]. In our study, the conversion from Sandimmun to Neoral was accompanied by a fall in GFR in two of our patients (nos. 3 and 6) with higher trough levels, C_{max}, and AUC_{0-12h} under Neoral. The opposite was also true, namely, two other patients (nos. 1 and 2) with lower trough levels, C_{max}, and AUC_{0-12h} under Neoral showed an improved GFR after conversion from Sandimmun, possibly due to reduced nephrotoxicity. Overall GFR did not change significantly after conversion in our young transplant population.Our observations are compatible with those of Bökenkamp et al. [1] who, after 1:1 conversion to Neoral, observed a fall in creatinine clearance by 9 %–25 % in six children previously presenting a low C_{max} (< 300 ng/ml) after Sandimmun. In another study, about 1/3 of stable adult transplant recipients studied showed some increase in CyA trough levels after switching from Sandimmun to Neoral on a 1:1 basis, paralleled by a slight decrease in creatinine clearance, which was reversible after reducing the Neoral dose [15]. However, in a recent study, Kovarik et al. [9] found that the higher exposure to CyA after conversion from the standard formulation to Neoral does not directly influence creatinine clearance in stable adult transplant recipients. We believe that in order to detect changes in GFR in the near-normal range, precise markers are required, such as inulin clearance as used in this study.

We confirmed the good correlation between trough levels and AUCs for Neoral observed earlier [13]; in our study, the correlation was similar to that obtained for Sandimmun. It would seem that trough levels of CyA under Neoral are a good predictor of systemic CyA exposure [6].

In conclusion, our pharmacokinetic study demonstrates that 4 weeks after switching stable young transplant recipients from Sandimmun to Neoral, the bioavailability of CyA increased in four of six patients and was associated with a decrease in GFR in only two. The large interindividual variability of CyA pharmacokinetics in this age group makes further studies necessary to optimize the dosage and reduce the risks of systemic overexposure to CyA after switching to Neoral. Clearly, close monitoring of trough levels and renal function after switching from Sandimmun to Neoral is mandatory.

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