Transpl Int (1997) 10: 419–425

ORIGINAL ARTICLE

Michael Melter
Burkhard Rodeck
Rüdiger Kardorff
Peter F. Hoyer
Johannes Brodehl

Pharmacokinetics of cyclosporine in pediatric long-term liver transplant recipients converted from Sandimmun to Neoral

Received: 12 February 1997
Received after revision: 16 May 1997
Accepted: 5 June 1997

M. Melter (✉) · B. Rodeck
R. Kardorff · P.F. Hoyer · J. Brodehl
Kinderklinik,
Medizinischen Hochschule Hannover,
D-30623 Hannover, Germany
Fax: + 49 511 532 3911

Abstract Absorption of cyclosporin from the microemulsion formulation Neoral is less variable than from Sandimmun. Because of a lack of data in pediatric liver transplant recipients, the pharmacokinetic profiles with Sandimmun and Neoral were compared in a conversion study. Thirty-eight children with stable graft function were converted 2–12.3 years post-transplant at a 1:1 ratio. The trough-level (C_{min}) with Neoral was 123 ± 39 ng/ml versus 134 ± 29 ng/ml with Sandimmun (P = NS), the area under the time-concentration curve (AUC) was 3325 ± 1125 ng*h/ml versus 2423 ± 846 ng*h/ml ($P < 0.001$), the peak concentration (C_{max}) was 650 ± 280 ng/ml versus 337 ± 142 ng/ml ($P < 0.001$), and the median time to C_{max} was 2 h (range 0.5–3 h) versus 4 h (range 1–8 h; $P < 0.05$). The weak correlation between C_{min} and AUC with Sandimmun ($r = 0.5$; P = NS) was improved by using Neoral ($r = 0.7$; $P < 0.001$). The best predictor of AUC was the 2-h concentration (C_{2h}) of Neoral ($r = 0.9$; $P < 0.001$). Increased absorption and a more predictable pharmacokinetic profile with Neoral permit safer therapeutic monitoring in children. The exclusive measurement of Neoral-C_{2h} allows one to estimate drug exposure with high precision (> 90 %).

Key words Cyclosporin, conversion, liver transplantation · Conversion, cyclosporin, liver transplantation · Liver transplantation, conversion, cyclosporin · Pediatric liver transplantation, pharmacokinetics · Pharmacokinetics, pediatric liver transplantation

Introduction

The widespread use of cyclosporin as an immunosuppressant has led to a substantial improvement in the outcome of pediatric liver transplantation, with long-term survival rates of up to more than 70 % [5, 9, 19, 22]. The prerequisite for successful immunosuppression and for a low rate of adverse events is the reliable and constant absorption of the drug. The most important factors influencing cyclosporin absorption from the conventional formulation, Sandimmun (SIM), are bile flow, gastrointestinal motility, bowel length, and food intake and composition [10, 12, 13, 14, 18, 25].

Children have been shown to have an increased cyclosporin clearance and lower bioavailability than adults. Therefore, larger doses of oral SIM in relation to body weight (kg) are necessary [4]. Pediatric liver transplant recipients younger than 2 years are especially likely to have variable and unpredictable immunosuppression. The reason is that the most common indication for orthotopic liver transplantation (OLT) in children – biliary atresia after a Kasai procedure – affects at least 50 % of pediatric patients.

The new microemulsion oral formulation of cyclosporin, Neoral (NEO), has been shown in adults to be less influenced by bile flow, food intake, and gastro-

Table 1 Biochemical characteristics of the pediatric liver transplant recipients. Data are expressed as mean ± SD

Test	Prior to switch	3 Months after switch	*n*	*P*
AST (U/l)	19 ± 13	19 ± 17	33	NS
ALT (U/l)	18 ± 16	18 ± 20	33	NS
GlDH (U/l)	7 ± 16	5 ± 6	33	NS
γGT (U/l)	17 ± 25	18 ± 29	32	NS
ALP (U/l)	328 ± 135	306 ± 110	32	≤ 0.05
CHE (kU/l)	5.06 ± 1.06	5.02 ± 0.98	33	NS
Bilirubin (μmol/l)	10 ± 5	9 ± 5	33	NS
Total bile acids (μmol/l)	11 ± 11	12 ± 11	33	NS
Lipoprotein-X (g/l)	0.11 ± 0.08	0.11 ± 0.15	33	NS
MEGX Δ30 (μg/l)	75 ± 20	–		–
S-Creatinine (μmol/l)	63 ± 20	66 ± 20	33	NS
S-Urea (mmol/l)	8.6 ± 2.9	8.1 ± 3.3	33	NS
S-Potassium (mmol/l)	4.6 ± 0.4	4.7 ± 0.5	32	NS
S-Uric acid (μmol/l)	387 ± 90	402 ± 89	27	NS
GFR (ml/min * 1.73 m^2)	89 ± 22	86 ± 25	33	NS

intestinal motility [3, 23]. From a theoretical point of view, this should translate into clinical benefit. Experience with NEO in pediatric OLT is limited [6, 16, 24]. In order to determine whether this also holds true for children, we performed a conversion study in stable pediatric liver transplant recipients.

Patients and methods

Thirty-eight children (19 girls, 19 boys) with a median age of 10.75 (range 4.9–19) years were enrolled in the study a median of 5.3 (range 2–12.3) years post-OLT. The indications for OLT were: biliary atresia ($n = 14$), Byler's disease ($n = 11$), acute liver failure ($n = 4$), Alagille's syndrome ($n = 3$), hepatoblastoma ($n = 2$), tyrosinemia ($n = 2$), glycogen storage disease I ($n = 1$), and cryptogenic cirrhosis ($n = 1$). Fifteen patients underwent a Kasai procedure prior to OLT, and three had a Roux-en-Y anastomosis during OLT. Thirty-four were primary transplants while four were retransplants. Three girls with Byler's disease had chronic diarrhea.

The conversion ratio from SIM to NEO was 1:1. At the beginning of the study, maintenance immunosuppression consisted of SIM (173 ± 49 mg/m^2 per day) and prednisolone (2 ± 1 mg/m^2 per day). Biochemical liver and kidney function parameters are shown in Table 1. All patients were switched to NEO and had received at least three doses prior to a 12-h absorption profile. Twelve of them had a preconversion SIM profile. Blood samples for the NEO profile were drawn prior to the dose and at 0.5, 1, 1.5, 2, 3, 5, 7, and 12 h; for the SIM profile, they were taken prior to the dose and at 1, 2, 4, 6, 8, and 12 h after oral intake. Trough level (C_{min}) was defined as the cyclosporin concentration in a morning predose blood sample 12 h after the last drug intake. The highest measured concentration and the corresponding sampling time were defined as C_{max} and T_{max}, respectively. Area under the concentration-time curve for 12 h (AUC) was calculated according to the standard trapezoidal rule [11]. Concentrations of cyclosporin were measured in hemolyzed EDTA whole blood by monoclonal-specific radioimmunoassay (SP; Sandoz, Basel, Switzerland) [2]. Additionally, in the C_{min} sample, a monoclonal-nonspecific radioimmunoassay (NSP; Sandoz) was applied in order to determine the capacity to eliminate cyclosporin metabolites [26]. Liver and kidney function parameters were determined by standard methods. Monoethylglycinexylidide (MEGX) was determined by high-performance liquid chromatography (HPLC). The difference in serum concentrations between baseline value and 30 min (MEGX Δ30) after i.v. administration of 1 mg/kg body weight lidocaine was used as a dynamic liver function test [17]. Glomerular filtration rate (GFR) was estimated as: body height × 38 ÷ serum creatinine, according to the formula of Schwartz et al. [20].

Statistical analyses were performed using the SPSS for Windows 6.1 statistical program (SPSS, Chicago, Ill., USA). Data are presented as mean ± standard deviation (SD). Not normally distributed data are presented as median and range. Differences with P values below 0.05 were considered as significant. For comparative analyses, Student's paired t-test and Wilcoxon's test were used; for correlation analyses, Pearson's product moment correlation coefficient (r) was used. The equation for the calculation of the AUC was assessed by linear regression analysis.

Results

Cyclosporin pharmacokinetics

The pharmacokinetic (PK) parameters with NEO and SIM are shown in Table 2. The corresponding 12-h cyclosporin absorption profiles are depicted in Figs. 1, 2, and 4, respectively. C_{min} was not significantly different between SIM and NEO when measured by SP or by NSP (Table 2). AUC as well as C_{max} were significantly higher and T_{max} was reached significantly earlier and with a more consistent interindividual pattern with NEO than with SIM (Table 2). Three patients with flat PK profiles with SIM (one with a Roux-en-Y anastomosis, another with Byler's disease and chronic diarrhea) presented only slight increases in AUC with NEO (Fig. 3).

The correlation between C_{min} and AUC with SIM (Table 3; Fig. 5) was not significant. In contrast, with NEO the correlations between most of the single-point blood concentrations (including C_{min}) and AUC (Table 3; Fig. 6) were significant. The NEO-C_{2h} was found to predict the AUC with the highest precision (Table 3; Fig. 7); thus, NEO-AUC was calculable from the equa-

Table 2 Pharmacokinetic parameters with Sandimmun and with Neoral. Data are expressed as mean ± SD (*SP* monoclonal-specific radioimmunoassay, *NSP* monoclonal-nonspecific radioimmunoassay)

	Neoral ($n = 38$)	Sandimmun ($n = 12$)	Neoral ($n = 12$)	P^a
12-h AUC (ng * h/ml)	3325 ± 1125	2423 ± 846	3484 ± 1050	< 0.001
C_{min} (ng/ml); SP	123 ± 39	134 ± 28	118 ± 32	NS
C_{min} (ng/ml); NSP	517 ± 191	541 ± 195	565 ± 182	NS
C_{min} NSP/C_{min} SP	3.9 ± 1.2	4.63 ± 1.85	4.95 ± 1.44	NS
C_{max} (ng/ml)	650 ± 280	337 ± 142	673 ± 290	< 0.001
T_{max} (h)[b]	2 (0.5–3)	4 (1–8)	2 (1–3)	≤ 0.05

[a] Intraindividual comparison between values with Sandimmun and Neoral in 12 of the 38 patients; [b] Median (range)

tion NEO-AUC = 4.18 * C_{2h} + 1021 ng * ml/h, with a standard error of 417 ng * ml/h.

Taking into account one (C_{2h} + C_{3h} or C_{2h} + C_{5h} or C_{2h} + C_{7h}) or two (C_{2h} + $C_{0.5h}$ + C_{3h} or C_{2h} + C_{3h} + C_{7h}) additional point measurements, r increased to 0.96 and 0.97, respectively.

Whereas a weakly significant relationship ($r = 0.42$; $P < 0.01$) was found between age and NEO dose related to body weight (mg/kg), NEO dose related to body surface area (mg/m^2) was independent of age ($r = 0.24$; P = NS).

C_{min}, C_{max}, T_{max}, and AUC were all found to be independent of NEO dose related to body surface area (mg/m^2) and independent of age (r for each < 0.4).

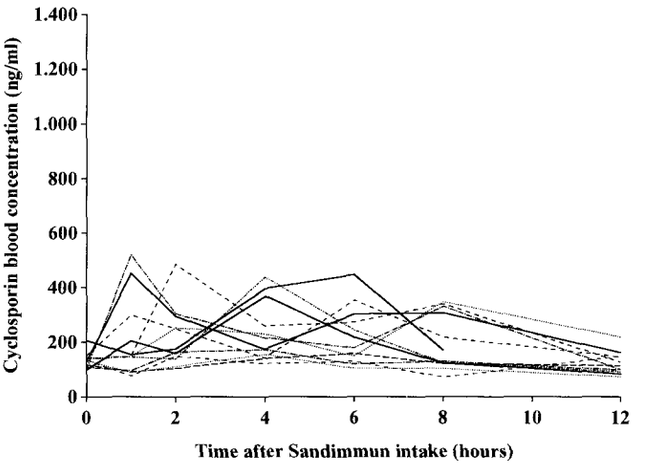

Fig. 1 Cyclosporin profiles with Sandimmun in 12 stable pediatric liver transplant recipients

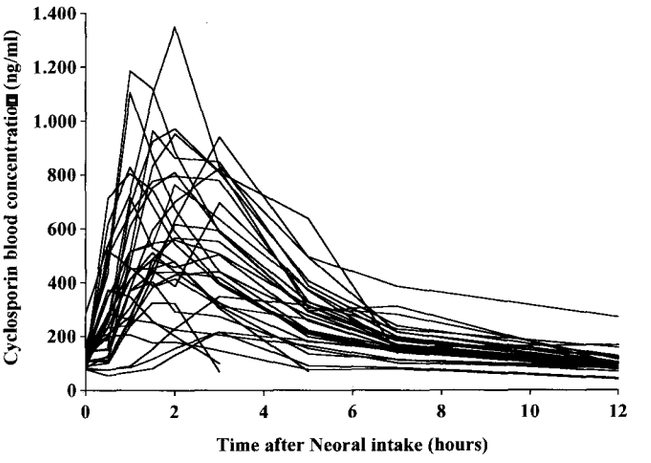

Fig. 2 Cyclosporin profiles with Neoral in 38 stable pediatric liver transplant recipients

Three-month follow-up with Neoral

During the 3 months of follow-up with NEO, no death, graft loss, rejection episode, or relevant adverse event occurred. The mean daily NEO dose related to body surface area remained the same, but C_{min} measured both by SP and by NSP were significantly lower after 3 months (Table 4). The SP/NSP ratio remained unchanged (Table 4). Serum aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), glutamate dehydrogenase (GlDH), gamma glutamyl transpeptidase (γGT), cholinesterase activity (CHE), total bile acids, and lipoprotein X (LPX) remained stable during the study period (Table 1), whereas alkaline phosphatase (AP) decreased significantly ($P \leq 0.05$; Table 1). Serum concentrations of creatinine, urea, uric acid, and potassium, as well as calculated GFR, remained unchanged (Table 1).

Discussion

Currently, cyclosporin is the predominant immunosuppressive drug for pediatric organ transplant recipients. However, the clinical use of SIM is associated with highly variable PK parameters, especially following pediatric OLT [21, 27]. This has been associated with an unpredictable response to therapy [15]. Several studies have shown an improved absorption and a more consistent bioavailability of cyclosporin from NEO than from SIM in adults and in pediatric kidney recipients [3, 6, 8]. Overall tolerability of NEO is regarded to be very good.

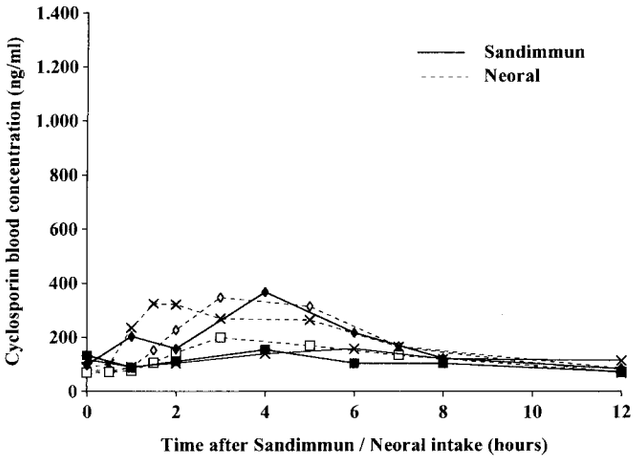

Fig. 3 Cyclosporin profiles with Sandimmun and Neoral in three poor absorbers of Sandimmun. Same markers represent corresponding profiles

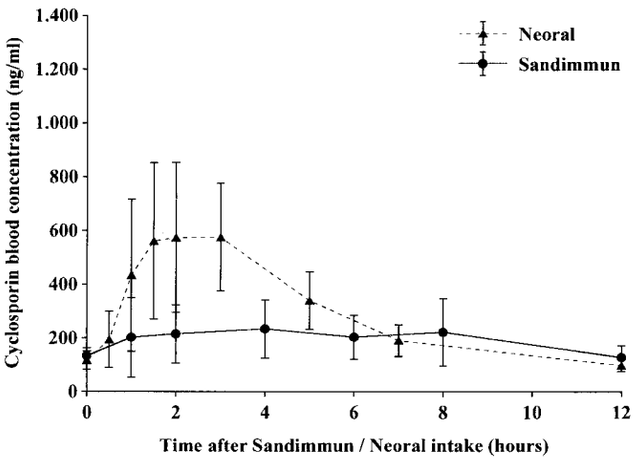

Fig. 4 Cyclosporin profiles (mean ± SD) with Sandimmun and Neoral in 12 stable pediatric liver transplant recipients

These promising results, together with the announcement from Sandoz that SIM will be withdrawn from the market, motivated us to compare PK parameters from SIM and NEO in stable pediatric long-term liver recipients in a conversion study. This study revealed an increased and more consistent absorption of cyclosporin from the NEO formulation, expressed as a shorter time to achieve maximum concentration (T_{max}), increased peak concentration (C_{max}), increased drug exposure (AUC), and an improved correlation between single-point concentrations and AUC. For AUC, C_{min}, C_{max}, and T_{max}, similar results were found in de novo-treated pediatric liver transplant recipients [24]. It has been suggested that NEO converts all so-called poor absorbers of SIM to good absorber status [7]. In contrast, in the group of 12 patients with SIM and NEO profiles, 3 with poor cyclosporin absorption from SIM remained poor absorbers under NEO, although on a higher level (Fig. 3).

Table 3 Correlation between single-point cyclosporin blood concentrations and AUC

Time after oral intake (h)	Sandimmun AUC		Neoral AUC	
	r	*P*	*r*	*P*
0	0.50	NS	0.70	< 0.001
0.5			0.48	< 0.01
1	0.52	NS	0.58	< 0.001
1.5			0.84	< 0.001
2	0.65	< 0.01	0.94	< 0.001
3			0.88	< 0.001
4	0.47	NS		
5			0.83	< 0.001
6	0.70	< 0.01		
7			0.81	< 0.001
8	0.93	< 0.001		
12	0.50	NS	0.49	< 0.01

There were no significant differences between percentage of variability of C_{min}, C_{max}, or AUC with SIM and NEO. However, there was a significantly decreased variability of T_{max}, and the PK profiles from NEO followed a uniform pattern with a peak concentration at around 2 h in all patients (Figs. 1, 2, and 4).

With regard to the anthropometric differences, it is more sensible to administer drug doses according to body surface area than to body weight, especially in young children. Our results showed that NEO dose adjusted to C_{min} was age-dependent related to body weight but independent from age related to body surface area. The pharmacokinetic parameters (C_{min}, C_{max}, T_{max}, AUC) of NEO were independent of the dose related to body surface area and independent of age.

In view of the increased AUC with NEO, a significant dose reduction for NEO was postulated [3, 24]. This was not supported by our findings. In contrast, we found a gradual decline in mean C_{min} during 3 months of follow-up in our patients, while dose in relation to body surface area remained unchanged.

It is, as yet, not known whether an increased peak concentration or drug exposure may improve immunosuppression or result in more frequent side effects. It has been shown that a higher C_{max} and AUC are not necessarily correlated with more side effects. On the contrary, while C_{max} increased with NEO, a decrease in renal proximal tubular toxicity was found [1]. It could be speculated that a relatively short, but high, peak concentration with a subsequent sharp decrease may be less toxic than a PK profile with a lower peak, but more persistent and relatively high concentration plateau.

Our results have shown that there is no relationship between the trough level and AUC with SIM. This

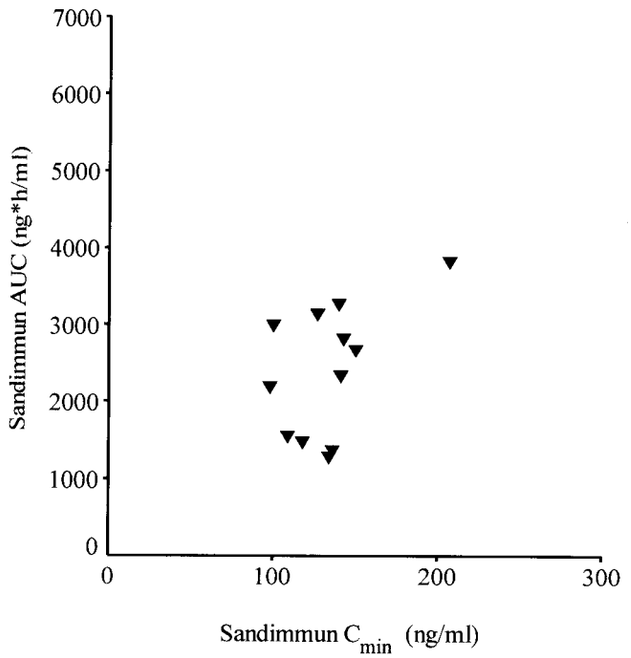

Fig. 5 Correlation between C_{min} and AUC with Sandimmun in 12 stable pediatric liver transplant recipients (*AUC* area under the cyclosporin time-concentration curve, C_{min} cyclosporin trough level). $r = 0.5$, P = NS

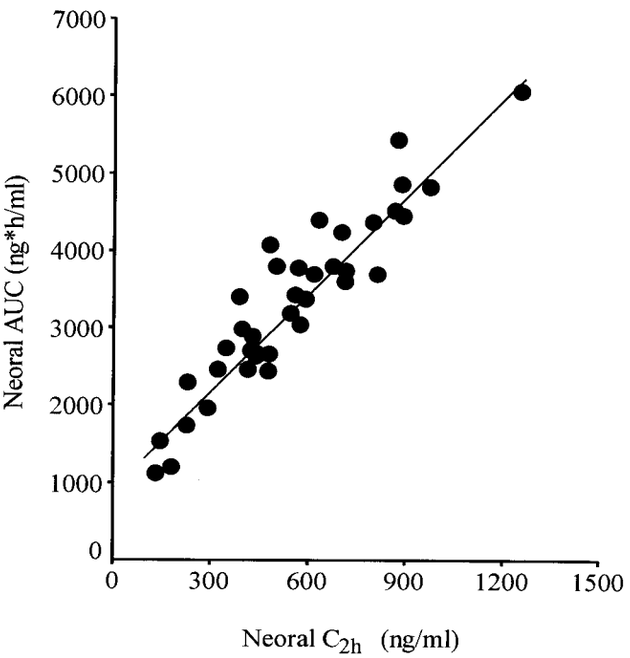

Fig. 7 Correlation between C_{2h} and AUC with Neoral in 38 stable pediatric liver transplant recipients. (*AUC* area under the cyclosporin time-concentration curve, C_{min} cyclosporin trough level). $r = 0.94$, $P < 0.001$

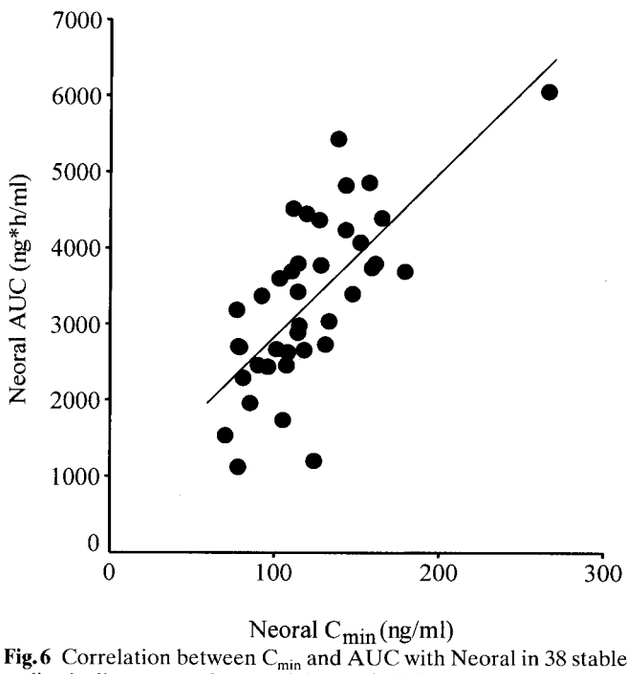

Fig. 6 Correlation between C_{min} and AUC with Neoral in 38 stable pediatric liver transplant recipients. (*AUC* area under the cyclosporin time-concentration curve, C_{min} cyclosporin trough level). $r = 0.7$, $P < 0.001$

might be due to the undefined interval between cyclosporin intake and blood sampling for C_{min}, especially in outpatients. Therefore, C_{min} is an unreliable parameter of individual cyclosporin exposure with SIM. Although the correlation between C_{min} and NEO-AUC was better, a remarkable increase in predictability of AUC was obtained using the NEO 2-h concentration (C_{2h}). The NEO-AUC can be estimated by C_{2h} (AUC = 4.18 * C_{2h} + 1021 ng * ml/h) with a precision error of less than 10 %. Therefore, C_{2h} measurement offers a practical alternative for routine cyclosporin monitoring. In particular, it is easy to administer NEO in the outpatient clinic and to take the blood sample exactly 2 h later. Holmberg recently reported that the shape of any individual NEO profile for pediatric liver recipients remains reproducible over a 1-year period (personal communication; Madrid, Spain; 1996). Thus, if the individual AUC is evaluated at baseline, it could again be calculated exactly by C_{2h} at follow-up. Two and three-point measurements have been suggested as most predictive for AUC [15]. In our cohort, one or two further point measurements, in combination with the 2-h concentration, improved the predictive ability only slightly. Then again, a routine monitoring strategy with repeated blood sampling is expensive, impractical, and would not be accepted by patients and their parents. Currently, cyclosporin dose adjusting to C_{min} is the most widely ac-

Table 4 Immunosuppressive course with Neoral. Data are expressed as mean ± SD
(*SP* monoclonal-specific radioimmunoassay, *NSP* monoclonal-nonspecific radioimmunoassay)

	1st week	3 months	*n*	*P*
Daily dosage (mg/m^2)	174 ± 40	172 ± 43	33	NS
C_{min} (ng/ml); SP	124 ± 37	97 ± 25	33	< 0.001
C_{min} (ng/ml); NSP	511 ± 170	402 ± 109	26	< 0.01
C_{min} NSP/C_{min} SP	4.4 ± 1.4	4.4 ± 0.9	25	NS

cepted method. However, in the future, it would seem reasonable to establish a 12-h profile as the baseline and parallel C_{min} and C_{2h} measurements in routine cyclosporin monitoring to gain experience with these new kinetic parameters in comparison to the trough level. Data from such prospectively conducted follow-up trials (at least 1 year) are necessary to determine which pharmacokinetic parameter (and which target range for that parameter) is most reliable and the most practical and which should be routinely used.

While further pharmacokinetic data are being collected, we recommend continuing to adjust the cyclosporin dose to the locally established target range for C_{min}, and we consider any recommendations to reduce C_{min} with NEO [3, 24] as premature.

In this trial, no death, graft loss, or rejection episode occurred after the switch. Although the mean AUC increased by 44 % and C_{max} by 100 %, no evidence of increased toxicity, especially nephrotoxicity, was found after 3 months with NEO. The relevance of the decrease in mean AP remains vague, but has been reported by others [7].

In conclusion, the main difference between NEO and SIM is their absorption. In NEO, it is greater, as reflected in a shorter T_{max}, higher C_{max} and higher AUC; there is also a strong relationship between AUC and corresponding single-point blood concentrations. These guarantee a better predictability of systemic drug exposure, especially from C_{2h}, and permit less drug monitoring and fewer dose adjustments. Consequently, NEO is expected to improve the management of pediatric liver recipients, in whom unstable and unpredictable SIM absorption is frequently observed. Long-term follow-up trials should be done to evaluate the significance of C_{2h} or other limited sampling strategies as a routine cyclosporin monitoring approach and to develop target ranges for them.

References

1. Ahlmén J, Sundberg A, Gustavsson A, Strömborn U (1995) Decreased nephrotoxicity after the use of a microemulsion formulation of cyclosporine A compared to conventional solution. Transplant Proc 27: 3432–3433
2. Ball PE, Munzer H, Keller HP, Abisch E, Rosenthaler J (1988) Specific 3H radioimmunoassay with a monoclonal antibody for monitoring cyclosporine in blood. Clin Chem 34: 257–260
3. Bökenkamp A, Offner G, Hoyer PF, Vester U, Wonigeit K, Brodehl J (1995) Improved absorption of cyclosporin A from a new microemulsion formulation: implications for dosage and monitoring. Pediatr Nephrol 8: 196–198
4. Burckart G, Starzl L, Williams A, Sanghvi A, Gartner C Jr, Venkataramanan R, Zitelli B, Malatack J, Urbach A, Diven W, Ptachcinski R, Shaw B, Iwatsuki S (1985) Cyclosporine monitoring and pharmacokinetics in pediatric liver transplant patients. Transplant Proc 17: 1172–1175
5. Calne RY, White DJG, Thiru S, Evans DB, McMaster P, Craddock GN, Pentlow BD, Rolles K (1978) Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet II:1323–1327
6. Dunn SP, Cooney GF, Kulinsky A, Falkenstein K, Pierson A, Elder CA, Melingeni J (1995) Absorption characteristics of a microemulsion formulation of cyclosporine in de novo pediatric liver transplant recipients. Transplantation 60: 1438–1442
7. Färber L, Maibücher A, Geissler F, Gutzler F, Wiesinger FO, Winkler M (1994) Favourable clinical results of Sandimmun-Neoral in malabsorbing liver and heart transplant recipients. Transplant Proc 26: 2988–2993
8. Frei U, Taesch S, Niese D (1994) Use of Sandimmun Neoral in renal transplant patients. Transplant Proc 26: 2928–2931
9. Gordon RD, Bismuth H (1991) Liver transplant registry report. Transplant Proc 23: 58–60
10. Gupta SK, Manfro RC, Tomlanovitch SJ, Gambertoglio G, Garovoy MR, Benet LZ (1990) Effect of food on the pharmacokinetics of cyclosporine in healthy subjects following oral and intravenous administration. J Clin Pharmacol 30: 643–653
11. Holt DW, Mueller EA, Kovarik JM, Bree JB van, Kutz K (1995) The pharmacokinetics of Sandimmun Neoral: a new oral formulation of cyclosporine. Transplant Proc 27: 1434–1437
12. Hoyer PF, Brodehl J, Ehrich JHH, Offner G (1991) Practical aspects in the use of cyclosporin in paediatric nephrology. Pediatr Nephrol 5: 630–638
13. Klompmaker IJ, Wierda JMKH, Sluiter WJ, Uges DRA, Haagsma EB, Verwer R, Slooff MJH (1993) Pharmacokinetics of cyclosporine after intravenous and oral administration in liver transplant patients measured with high-performance liquid chromatography. Ther Drug Monit 15: 60–64
14. Lemaire M, Fahr A, Maurer G (1990) Pharmacokinetics of cyclosporine: inter- and intraindividual variations and metabolic pathways. Transplant Proc 22: 1110–1112
15. Lindholm A, Kahan BD (1993) Influence of cyclosporine pharmacokinetics, trough concentrations, and AUC monitoring on outcome after kidney transplantation. Clin Pharmacol Ther 54: 205–218
16. Melter M, Rodeck B, Kardorff R, Hoyer PF, Wonigeit K, Brodehl J (1996) Neoral and Sandimmune pharmacokinetics in pediatric liver transplanted long-term survivors. J Pediatr Gastroenterol Nutr 22: 442

17. Oellerich M, Raude E, Burdelski M, Schulz M, Schmidt FW, Ringe B, Lamesch P, Pichlmayr R, Raith H, Scheruhn M, et al (1987) Monoethylglycinexylidide formation kinetics: a novel approach to assessment of liver function. J Clin Chem Clin Biochem 25: 845–853
18. Ptachcinski RJ, Venkataramanan R, Rosenthal JT, Burckart GJ, Taylor GJ, Hakala TR (1985) The effect of food on cyclosporine absorption. Transplantation 40: 174–176
19. Rodeck B, Melter M, Kardorff R, Burdelski M, Ringe B, Oldhafer KJ, Pichlmayr R, Brodehl J (1996) Lebertransplantation im Kindesalter. Monatsschr Kinderheilkd 144: 490–495
20. Schwartz GJ, Brion LP, Spitzer A (1987) The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am 34: 571–590
21. Shaw LM, Bowers L, Demers L, Freeman D, Moyer T, Sanghvi A, Seltman H, Venkataramanan R (1987) Critical issues in cyclosporine monitoring: report of the task force on cyclosporine monitoring. Clin Chem 33: 1269–1288
22. Starzl TE, Demetris AJ, Van Thiel D (1989) Liver transplantation (second of two parts). N Engl J Med 321: 1092–1099
23. Trull AK, Tan KKC, Uttridge J, Bauer T, Alexander GJM, Jamieson NV (1993) Cyclosporin absorption from microemulsion formulation in liver transplant recipients. Lancet 341: 433
24. Van Mourik IDM, Thompson M, Kelly DA (1996) Neoral an effective alternative immunosuppressant drug in children post liver transplant? J Pediatr Gastroenterol Nutr 22: 434
25. Whitington PF, Emond JC, Whitington SH, Broelsch CE, Baker AL (1990) Small bowel length and the dose of cyclosporine in children after liver transplantation. N Engl J Med 322: 733
26. Wonigeit K, Kohlhaw K, Winkler M, Schaefer O, Pichlmayr R (1990) Cyclosporine monitoring in liver allograft recipients: two distinct patterns of blood level derangement associated with nephrotoxicity. Transplant Proc 22: 1305–1311
27. Wood AJ, Maurer G, Niederberger W, Beveridge T (1983) Cyclosporine: pharmacokinetics, metabolism and drug interactions. Transplant Proc 15: 2409–2412