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Brief report

Improved absorption of cyclosporin A from a new microemulsion formulation: implications for dosage and monitoring

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Abstract. Recently, a new oral microemulsion formulation of cyclosporin A (CsA) – Neoral (Sandoz, Basle, Switzerland) – with a higher bioavailability has become available. Ten stable paediatric renal transplant recipients with excessive variations in CsA trough levels with the original Sandimmun (Sandoz, Basle, Switzerland) preparation were switched to Neoral on a 1:1 basis. Pharmacokinetic studies revealed impaired absorption of Sandimmun in six patients. Compared with equal doses of Sandimmun, the 8-h area under the concentration-time curve increased from 1,422 to 2,657 ng × h/ml and the peak concentration rose from 319 to 824 ng/ml ($P < 0.01$). In six patients with Sandimmun malabsorption, conversion on a 1:1 basis led to a reduction in creatinine clearance which was reversible after dose reduction by 9%–25%. With trough levels at the lower end of the present target range, creatinine clearance stabilised around pre-conversion values.

Key words: Cyclosporin A – Pharmacokinetics – Renal transplant – Side-effects

Introduction

The use of cyclosporin A (CsA) has significantly improved the outcome of renal transplantation [1]. Intestinal absorption of the initial formulation of CsA – Sandimmun (Sandoz, Basle, Switzerland) – requires the presence of bile and shows great variability with food intake [2, 3]. Large variations in CsA absorption carry the risk of both graft rejection and toxicity. Recently, a new oral microemulsion formulation of CsA – Neoral (Sandoz, Basle, Switzerland) – with a more predictable pattern of absorption has become available [4]. We have studied Neoral administration in ten stable renal transplant recipients with excessive variations in CsA trough levels with Sandimmun.

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Patients and methods

In an attempt to screen for possible Sandimmun malabsorption, 66 long-term paediatric renal transplant recipients regularly seen in the transplant unit of Hanover Medical School Children's Hospital were evaluated for variations in CsA trough levels. Excessive variation was defined as at least three unexplained variations of CsA trough level exceeding 50 ng/ml on 12 consecutive outpatient controls. The target range for CsA trough levels was 80 to 140 ng/ml. CsA measurements were performed in hemolysed whole blood either by the EMIT assay (Syva, San Jose, CA, USA) or a monoclonal specific radioimmunoassay (IncStar, Stillwater, MN, USA). The assays had previously been shwon to give concordant results. Creatinine levels were determined by means of an enzymatic assay (PAP Colour Test, Boehringer Mannheim, Mannheim, Germany).

Ten children and adolescents, median age 14.9 years (range 9.8–20.4 years), median time post transplantation 4.1 years (range 2.5–7.2 years), met the criteria of excessive CsA trough level variation. Liver disease or cholestasis were excluded by studies of bilirubin, transaminases, alkaline phosphatase, lipoprotein X and bile acid kinetics in all patients. After informed consent, this group of patients was switched to Neoral at a ratio of 1:1 on an outpatient basis.

Laboratory studies to assure safe conversion included 8-h CsA absorption profiles before and after switching to Neoral, as well as short-term serum creatinine and CsA trough level determinations. Creatinine clearance (C_{Cr}) was estimated according to the formula of Schwartz et al. [5]. An unexplained fall in C_{Cr} of more than 10% from baseline with CsA trough levels in the target range of 80–140 ng/ml was considered as CsA nephrotoxicity, and the Neoral dose was reduced. C_{Cr}, CsA dose and CsA trough levels were compared with pre-conversion values before dose reduction and at the latest visit.

Absorption studies were performed after ingestion of a regular breakfast, the mode of administration (i.e. capsules or liquid) remained unchanged. To characterise absorption, the peak concentration (c_{max}), the time until peak concentration (t_{max}) and the area under the concentration-time curve (AUC) were assessed. AUC was calculated with the trapezoidal rule [6, 7]:

$$\mathrm{AUC} = \sum_{i=1}^{n-1} (c_{ti+1} - c_{ti})/2 \cdot (t_{i+1} - t_i)$$

with c_{ti} denoting the CsA concentration at time ti (in h) post ingestion.

As the data were not normally distributed, they are presented as median and range. The Wilcoxon signed rank test was used for comparison of Sandimmun and Neoral and stepwise linear regression for the analysis of factors influencing renal function after conversion to

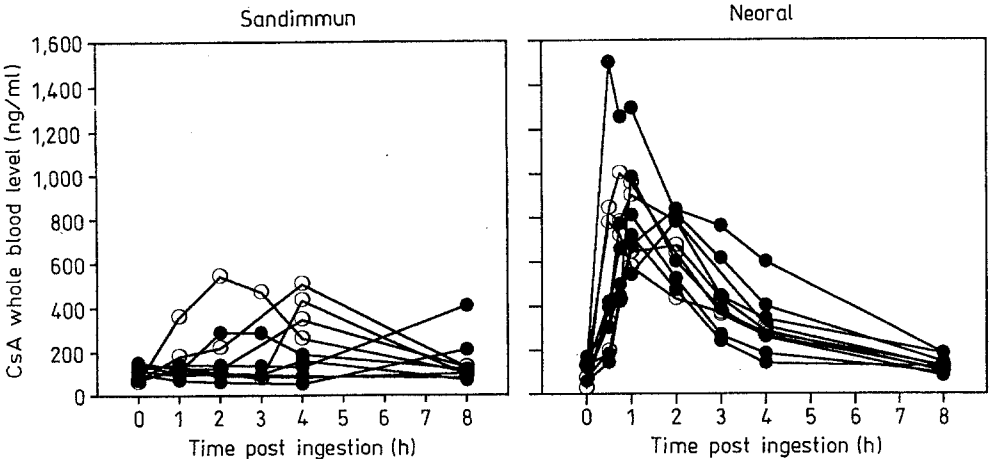

Fig. 1. Cyclosporin A (*CsA*) following ingestion of *equal* doses of Sandimmun and Neoral. ○, Patients without dose reduction on follow-up; ●, patients with dose reduction on follow-up

Neoral. To study changes in C_{Cr} after conversion, the ratio of $C_{Cr\ Sandimmun}/C_{Cr\ Neoral}$ was calculated. A P value of less than 0.05 was considered statistically significant.

Results

CsA absorption profiles after ingestion of *equal* doses of Sandimmun and Neoral in the same patients are presented in Fig. 1. Impaired absorption of CsA from the Sandimmun preparation was found in six children with peak levels below 300 ng/ml [2]. The median peak level c_{max} following ingestion of Sandimmun was 319 ng/ml (range 143–542 ng/ml), which was observed after 4 h post ingestion (range 0–8 h). After administration of Neoral, the patients showed a uniform pattern of absorption. Median c_{max} increased significantly to 824 ng/ml (range 672–1,500 ng/ml, $P < 0.01$), median t_{max} was 1 h (range 0.5–2 h, $P < 0.05$). The AUC was also significantly higher with Neoral (2,657 ng × h/ml, range 2,099–4,402) than Sandimmun (1,422 ng × h/ml, range 659–2,269, $P < 0.01$).

Follow-up after conversion was 124 days (range 73–143 days). With equal doses of Neoral, C_{Cr} decreased from 48.5 to 43.5 ml/min per 1.73 m² ($P < 0.05$) (Table 1). CsA trough levels 12 h post ingestion remained in the same range after 1:1 conversion. In six patients a fall in C_{Cr} exceeding 10% of baseline (i.e. from 49.5 ml/min per 1.73 m² (24–83) to 40 ml/min per 1.73 m² (19–67)) led to Neoral dose reduction at 67 days post conversion (4–100 days). Following reduction of Neoral dose by 19.5% (9%–25%), C_{Cr} returned to baseline [50 ml/min per 1.73 m² (30–77)]. Follow-up after dose reduction was 55 days (16–84). Compared with pre-conversion values, CsA trough levels were lower at the last visit, although this did not reach statistical significance (90.7 vs. 72.3 ng/ml, $P = 0.06$).

Factors possibly influencing the change in C_{Cr} (i.e. $C_{Cr\ Sandimmun}/C_{Cr\ Neoral}$) were studied by stepwise regression analysis at 8 weeks post conversion or before Neoral dose reduction, as applicable. These were AUC, c_{max} and trough levels both before and after conversion to Neoral. A low c_{max} after ingestion of Sandimmun was the best predictor for a fall in C_{Cr} after 1:1 conversion to Neoral ($r = 0.762$, $P < 0.01$). None of the parameters reflecting Neoral absorption (i.e. AUC, c_{max} or trough levels) correlated with the change in C_{Cr} after 1:1 conversion. At the latest visit, i.e. after Neoral dose reduction in six patients, higher CsA trough levels correlated with a fall in C_{Cr} compared with baseline ($r = -0.695$, $P < 0.05$).

Table 1. Kidney function, cyclosporin A (CsA) dosage and trough levels with Sandimmun and Neoral[a]

	Sandimmun	Neoral after 1:1 conversion (before dose reduction)	Neoral at the latest visit[b]
C_{Cr} (ml/min per 1.73 m²)	48.5	43.5*	46.5
range	24–83	19–67	30–77
CsA trough (ng/ml)	90.7	88.3	72.3
range	60–134	56–117	44–99
CsA dose (mg/m² per day)	162.4	162.4	160.3**
range	121–222	121–222	101–222

C_{Cr}, Creatinine clearance calculated according to Schwartz et al. [5]
* $P < 0.05$; ** $P < 0.01$ compared with pre-conversion. Statistical analysis by Wilcoxon test
[a] Median and range
[b] After dose reduction in six patients

Discussion

Adequate absorption is crucial for the immunosuppressive effect of CsA. With Sandimmun, the large intraindividual and interindividual variability of CsA pharmacokinetic parameters in kidney transplant recipients is well known [8]. First reports in adult patients indicate that the new oral microemulsion formulation of CsA – Neoral – exhibits a more predictable pattern of absorption [6, 7]. At present, no data on the pharmacokinetics of this preparation in paediatric renal transplant recipients are available.

In an attempt to improve CsA absorption in a group of stable adolescent long-term kidney transplant recipients with documented large trough level variations, ten patients were switched to Neoral in a controlled fashion. Absorption studies showed Sandimmun malabsorption [2] in six of the

ten children. This could be overcome with the Neoral preparation, so that a uniform absorption pattern was found in all patients. This is reflected by the large increase in both c_{max} and AUC after switching to Neoral. AUC, c_{max} and t_{max} values in our children are in the range reported in adult kidney transplant recipients treated with Neoral [6].

Although CsA trough levels remained in the same range following conversion to Neoral on a 1:1 basis, C_{Cr} decreased in all patients. A pronounced fall in glomerular filtration rate of 20% was observed in the six children with the lowest c_{max} values for Sandimmun, i.e. the Sandimmun malabsorbers. This reflects the increase in drug bioavailability in the order of 300% in this group of patients, which is much higher than the increase of 34% (AUC) and 67% (c_{max}) observed in adult renal transplant recipients switched to Neoral [6]. This reduction in glomerular filtration rate was reversible following reduction of Neoral dose by 9%–25%. Lindholm and Kahan [8] observed a correlation between hypertension and CsA peak levels in patients treated with Sandimmun. It is noteworthy that blood pressure was stable after conversion to Neoral in all our patients.

The question of which parameter should be used to monitor CsA therapy is as yet unanswered [2, 8]. This is even more unclear for the conversion from Sandimmun to Neoral. Even with a marked fall in glomerular filtration rate, CsA trough levels remained in the target range for Sandimmun therapy. In the present study kidney function stabilised after reduction of Neoral trough levels to the lower end of the present target range.

In conclusion, Sandimmun malabsorption in paediatric renal transplant recipients can be overcome with the new microemulsion formulation; 1:1 conversion to Neoral leads to a fall in C_{Cr} from drug overexposure in Sandimmun malabsorbers, which is reversible after Neoral dose reduction. In order to screen for Sandimmun malabsorption, it might be prudent to determine the CsA concentration at 4 h post ingestion of Sandimmun, prior to conversion to Neoral. After conversion, CsA trough levels at the lower end of the present target range should be aimed at.

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Literature abstract

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Eosinophils in urine revisited

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The finding of eosinophils in the urine has been suggested to be useful in establishing the diagnosis of acute interstitial nephritis (AIN). The diagnostic accuracy of this test has not yet been defined. It is the purpose of this study to define the specificity, sensitivity, and the predictive positive and negative values for the presence of eosinophils in the urine. One hundred forty-eight patients with pyuria were tested for the presence or absence of urinary eosinophils. In this group consecutively admitted to the hospital with WBC in the urine, 4% of patients had urinary eosinophilia of greater than 1 eosinophil per 100 cells. Since none of this group had the diagnosis of AIN, the false positive rate was 4% and the specificity was 96%. In a selected group of patients in which the diagnosis of AIN was suspected by a nephrology consultant, urinary eosinophils were found in 6 of 15 patients with a confirmed diagnosis of AIN but were also found in 10 of 36 patients with another renal diagnosis. The sensitivity for eosinophiluria was 40% and the specificity was 72% with a positive predictive value of only 38%. We conclude that eosinophiluria is not an accurate test for the diagnosis of AIN. The false positive and negative rates are too high to confirm an AIN diagnosis.