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Neoral induction in pediatric renal transplantation

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Abstract. Neoral was instituted in pediatric renal transplant patients with the hypothesis it would have more predictable kinetics than Sandimmun. However, significant questions have arisen concerning potential toxicity and dosing interval related to its rapid absorption with subsequent high initial peak. This is compounded by the fact that children appear to metabolize cyclosporine at a greater rate than adults. This combination of a rapid peak and rapid absorption may then result in lower trough levels at 12 h. We compared the trough cyclosporine levels of nine children who received Neoral with nine who received Sandimmun at the time of initial transplantation. More frequent dosing (every 8 h) was required in the Neoral population compared with the Sandimmun population for the 1st month in order to obtain comparable trough levels. Beyond the initial 4–6 weeks, trough levels were similar for Neoral and Sandimmun. Whereas 1-month creatinine levels and blood pressures were similar, the number of blood pressure medications was significantly higher in the Neoral group. At 5.5 $\pm$ 1.1 months' followup, a single patient in the current Neoral group and in the retrospective Sandimmun group each experienced a single OKT3 allograft-treated rejection. We suggest that the area under the curve is different in Neoral than Sandimmun, and the initial dosing frequency may need to be adjusted accordingly.

Key words: Pediatric kidney transplantation – Neoral – Sandimmun

Introduction

Transplantation has become common practice in the pediatric patient with end-stage renal disease (ESRD). Evaluation of immunosuppression protocol demonstrates that cyclosporine (CSA) has been an important medication for both induction and stability of treatment for renal transplantation. Prior to 1996, the available form of CSA was Sandimmun. Since the introduction of Sandimmun, allograft survival has improved compared with historical controls pre CSA [1, 2].

It has been evident over the last decade that, depending upon the age of the patients, the kinetics of the metabolism of Sandimmun varies [3, 4]: the younger the patient the more rapidly Sandimmun is metabolized [2–4]. In order to obtain target trough levels of CSA, one may increase the dose or change the dosing frequency. Increasing the dose of Sandimmun results in a higher peak concentration level. By shortening the dosing interval one may obtain lower peak levels, although a higher total daily dose of CSA may be prescribed.

Data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) have demonstrated that higher Sandimmun dosing has a positive impact on post-transplantation allograft survival [5]. Because the NAPRTCS database does not look at levels but looks at prescribed milligrams per kilogram of Sandimmun per day one cannot say absolutely that higher levels affect outcome. It is evident though that the higher dose most likely results in higher CSA levels improving allograft survival.

Over the last year, a new form of CSA (Neoral), which was developed to provide more reliable absorption, has become available. The concern in the pediatric community is that by more rapid absorption Neoral may give a higher peak but shift the curve to the left (i.e., closer to the time of per os intake) [6]. Due to the fact that children have historically metabolized CSA at a more rapid rate than adults, Neoral may require more frequent dosing in order to obtain the desired target trough levels. With that in mind, we evaluated the use of Neoral in our renal transplant patients.

Materials and methods

Patients who underwent renal transplantation from September 1995 to May 1996 are included ($n = 9$). These children (aged 11.5 $\pm$ 1.5 years;

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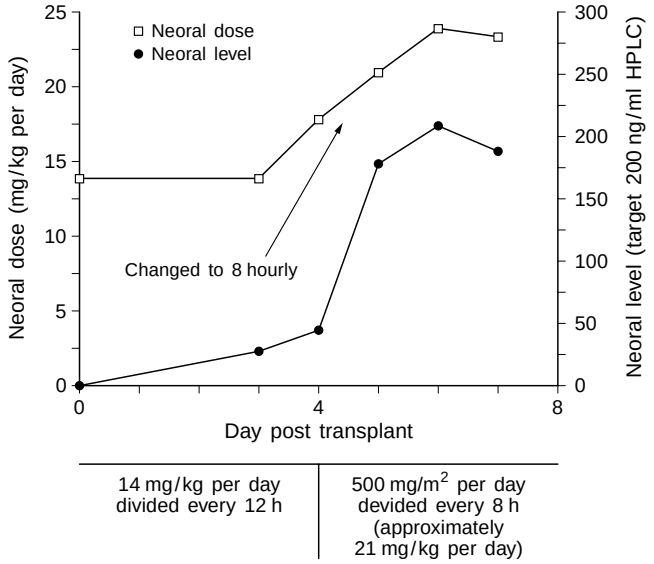

Fig. 1. Cyclosporine levels and Neoral dose in one patient. Therapeutic cyclosporine levels were immediately obtained upon changing from 12-hourly to 8-hourly dosing on day 4 post transplantation. *HPLC,* High-performance liquid chromatography

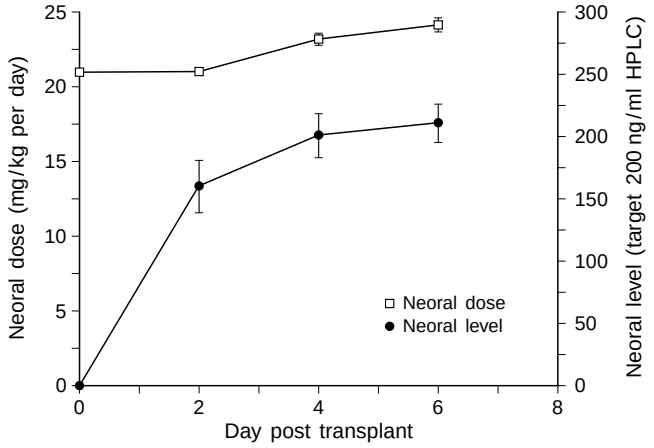

Fig. 2. Cyclosporine dose and trough level in children induced with 8-hourly Neoral

weight 35.1 ± 3.1 kg, mean ± SEM) included five females and four males. Causes of ESRD included: hemolytic uremic syndrome (1), renal dysplasia (4), obstructive uropathy (2), and focal sclerosis (2). Seven of nine children received a living-related donor kidney and none underwent native kidney nephrectomy for hypertension control. The average number of antihypertensive agents each patient was on prior to transplantation was 2.1 per child.

We matched these nine children by age, sex, etiology of ESRD, pre-transplant hypertension, and donor source with nine children transplanted with an identical protocol except for Sandimmun. Seven of nine children received a living-related donor kidney and none underwent native kidney nephrectomy for hypertension control. The average number of antihypertensive agents that each patient was on prior to transplantation was 1.9 per child.

All children (regardless of whether they received Neoral or Sandimmun) underwent our usual induction protocol, including 10 days of ATGAM (15 mg/kg per day, UpJohn, Kalamazoo, Mich., USA), prednisone (2 mg/kg per day with taper), azathioprine (2 mg/kg per day maintaining absolute with blood cell count >4,000), and

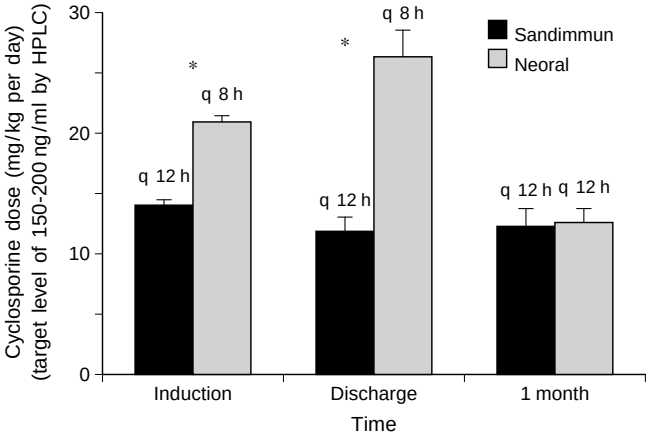

Fig. 3. Cyclosporine dosage and dosing frequency in children matched for age, sex, and cause of end-stage renal disease re-entering either Sandimmun or Neoral according to time post transplantation

Sandimmun [14 mg/kg per day divided every 12 h or 500 mg/m2 per day (in children <6 years) divided every 8 h]. Independent of dosing frequency, the CSA trough target level is 150–200 ng/ml as measured by whole blood trough high-performance liquid chromatography (HPLC). CSA is begun when the post-transplant creatinine is 50% or less of the pre-transplant creatinine, which occurred in 89% of children in both groups within 24 h of transplantation. Experience with this dosing of Sandimmun demonstrated therapeutic levels (i.e., >150 ng/ml) of CSA within 24 h of beginning Sandimmun [4].

Previous experience has demonstrated a 14% incidence of breakthrough rejection during polyclonal T-cell induction when the Sandimmun was begun on days 5 or 6 post transplantation [7]. Since beginning CSA earlier and obtaining therapeutic levels sooner, we have had no further rejection during induction [4].

When applicable, statistical analysis was performed using Student's *t*-test and considered significant at $P < 0.05$.

Results

The first of these children (a 10-year-old female) underwent the usual induction of 14 mg/kg per day Neoral divided every 12 h. Trough levels of Neoral after 3 days of oral administration demonstrated our inability to obtain adequate target trough levels (150–200 ng/ml, HPLC). Upon increasing the dose by 10% and adjusting the frequency from every 12 h to 8 h, therapeutic levels of Neoral were obtained (Fig. 1). Because of the course of this child, the subsequent eight children were induced with Neoral 500 mg/m2 per day (approximately 21 mg/kg per day) divided every 8 h. Therapeutic levels of Neoral were obtained within 24 h of transplant (Fig. 2). At 1 month, with identical target CSA levels obtained, similar dosing of Neoral as Sandimmun is demonstrated (Fig. 3).

In the first 6 months post transplantation, four children underwent a transplant biopsy for suspected rejection (based upon elevated creatinine compared with discharge baseline) and the histology revealed no pathological diagnosis in three. Upon reducing the Neoral dose, creatinine levels stabilized. A single child in each group had OKT3-reversed rejection at 6 weeks post transplantation (Table 1).

We next compared the serum creatinine levels, blood pressures, and the number of blood pressure medications

Table 1. Creatinine levels, blood pressure (BP), number of BP medications, and biopsy results in Neoral and Sandimmun groups[a, b]

	Neoral group	Sandimmun group	Significance
n	9	9	NS
Dose at discharge (mg/kg per day)	25 ± 2.3	12.4 ± 1.9	$P < 0.05$
Dose at 1 month (mg/kg per day)	13.7 ± 0.9	13.3 ± 1.2	NS
Creatinine at 1 month	1.1 ± 0.2 mg/dl	1.1 ± 0.2 mg/dl	NS
Mean BP at 1 month	122/70 mmHg	131/78 mmHg	NS
No. of BP medications at 1 month	2.7 ± 0.2	0.75 ± 0.5	$P < 0.05$
No. of biopsies/first 6 months	4/9	1/9	Not applicable
No. of biopsies with rejection	1/4	1/1	Not applicable
No. of biopsies compatible with CSA toxicity[c]	3/4	0/0	Not applicable

CSA, Cyclosporine
[a] Results are mean ± SEM
[b] Statistical analysis performed using Student's *t*-test
[c] Normalization of creatinine with decreasing Neoral dose with no subsequent evidence of allograft rejection

between the Neoral and the Sandimmun group at 1 month post transplantation. The serum creatinine levels were 1.1 ± 0.2 versus 1.1 ± 0.2 mg/dl (NS), the number of blood pressure medications was 2.7 ± 0.2 versus 0.75 ± 0.5 ($P < 0.05$), and the mean blood pressure was 122/70 versus 131/78 mmHg (NS) in the Neoral and the Sandimmun group, respectively (Table 1).

At 5.5 ± 1.1 months followup, one child in the Neoral group has had a rejection episode. The mean creatinine level of the Neoral group is 1.1 ± 0.2 mg/dl as compared with 1.0 ± 0.2 mg/dl for the Sandimmun group (NS). The number of blood pressure medications is 2 ± 0.9 versus 0.5 ± 0.3 ($P < 0.05$), while the mean blood pressures are similar (115/69 vs. 133/78 mmHg) in the Neoral and Sandimmun group, respectively.

Discussion

Experience suggests that a trough level in a known therapeutic range (in our case 150–200 ng/ml by HPLC) provides adequate immunosuppression in most patients receiving Sandimmun. An alternative method for monitoring CSA exposure would be to measure the area under the curve (AUC). The correlation between trough CSA levels and AUC is not well established, but appears to vary significantly from patient to patient [8]. The factors that affect the AUC would obviously be the peak level as well as the metabolism and clearance rates. Those patients with a high peak level with a slow metabolism will have a higher AUC than patients with low peak levels and a rapid metabolism. Since calculation of AUC requires multiple samples, trough levels have been used in most transplant centers.

The use of Neoral in patients has been suggested to give improved immunosuppression because of more-reliable absorption. Certainly data on patients being transitioned from Sandimmun to Neoral suggest that the AUC may be increased by almost 40% in the Neoral arm as opposed to the Sandimmun arm [9, 10]. Bokenkamp et al. [9] converted ten children on a one-to-one basis from Sandimmun to Neoral; 60% of those children exhibited a diminished creatinine clearance which normalized after the Neoral dose was decreased. They found that they could prescribe 3%–5% less CSA by decreasing the Neoral dose using the child's previous serum creatinine as the judge of adequacy (and toxicity) of CSA therapy. This suggests that by lowering the target CSA trough levels, adequate immunosuppression from Neoral can be obtained while minimizing CSA toxicity. This might be explained by a higher AUC for Neoral than Sandimmun when similar trough levels are achieved. Neoral may provide higher exposure to CSA, which may be beneficial for immunosuppression but potentially toxic.

In our experience when we administer Neoral every 12 h we are unable to achieve therapeutic CSA levels within 3–4 days of transplant. Only by increasing the frequency of dosing from every 12 to 8 h are we able to obtain a therapeutic trough level.

More frequent dosing of Neoral may affect compliance as well as require more planning by families and healthcare givers. Within 1 month post transplantation all patients were able to change from 8-h to 12-h dosing. We presume this may be related to saturation of lipid stores and/or alterations in metabolism of CSA.

Comparative data of blood pressure, number of blood pressure medications, and serum creatinine levels suggest more CSA toxicity in the Neoral than the Sandimmun group. Biopsies in four of nine of the Neoral recipients demonstrated no rejection in three (based upon Banft criteria), and suggested CSA toxicity. We are in the process of lowering our target CSA trough levels to aim for a 10% reduction in CSA trough level with Neoral compared with Sandimmun. We believe that by doing this we will see fewer acute side effects of Neoral and at the same time provide adequate immunosuppression.

In summary, Neoral has been developed to improve absorption and to deliver a greater AUC for CSA. Because children metabolize/eliminate CSA at a higher rate than adults, they may initially require more frequent dosing of Neoral. In those patients who do require more frequent dosing, most can be changed to twice daily dosing within 1 month post transplant.

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