Pediatr Nephrol (1993) 7: 249–252

Pediatric Nephrology

Original article

Long-term ciclosporin treatment in children with steroid-dependent nephrotic syndrome

Ryojiro Tanaka[1], Norishige Yoshikawa[1], Yoshitaka Kitano[1], Hiroshi Ito[2], and Hajime Nakamura[1]

[1] Department of Paediatrics, Kobe University Hospital, Kobe, Japan
[2] Department of Paediatrics, Tokyo Metropolitan Children's Hospital, Tokyo, Japan

Received May 21, 1992; received in revised form and accepted November 5, 1992

Abstract. We report the effect of 18-month ciclosporin (CS) treatment in 19 children with steroid-dependent frequently relapsing nephrotic syndrome. CS was started at 3–5 mg/kg per day after remission with steroid therapy, was adjusted to maintain a trough blood level of between 200 and 600 ng/ml and was administered for 6 months (high-dose CS). Then, the dosage of CS was decreased and 2.5 mg/kg per day was administered for the subsequent 12 months (low-dose CS). Only 2 patients had relapses during the initial 6 months of CS therapy. Eight patients had infrequent relapses, 4 had frequent relapses and 7 had no relapses during the 12 months of low-dose CS. Not only did continuation of CS at a lower dosage decrease the relapse rate, it also reduced steroid toxicity, allowed increased growth in 16 of the 19 patients and also decreased obesity scores in 12 of these patients. All of the side-effects that occurred during the 18-month period of CS treatment were reversible and none was serious enough to necessitate discontinuation of therapy. Our 18-month CS treatment was helpful in preventing relapses and reducing steroid toxicity in children with steroid-dependent frequently relapsing nephrotic syndrome.

Key words: Ciclosporin – Steroid-dependent nephrotic syndrome – Growth – Obesity – Steroid toxicity

Introduction

Recent studies suggest that ciclosporin (CS) may be efficacious in the treatment of children with frequently relapsing nephrotic syndrome [1–6]. We have reported that a 6-month course of CS in children with steroid-dependent frequently relapsing nephrotic syndrome was effective in preventing relapses during the CS treatment [7]. However, after the cessation of CS treatment, the nephrotic syndrome relapsed as frequently as before and most patients again showed steroid dependence. The effect of CS in maintaining remission in steroid-dependent nephrotic syndrome was CS dependent [4, 7].

Our previous study showed that no relapse occurred even during the period of CS tapering. This suggests that it may be possible to maintain longer remission with a lower dosage and a longer period of CS administration. We therefore report the effect of low-dose 12-month CS treatment following high-dose 6-month CS treatment in children with steroid-dependent nephrotic syndrome.

Patients and methods

Nineteen children with frequently relapsing and steroid-dependent nephrotic syndrome, identified at our hospitals from 1987 to 1988, were studied. The definition and criteria for nehprotic syndrome were the same as those used by the International Study of Kidney Disease in Children [8, 9]. Remission was denoted by a reduction of urinary excretion of protein to <4 mg/h per m^2 body surface area for 3 consecutive days. Relapse was denoted by a reappearance of proteinuria $\geq$40 mg/h per m^2 for 3 consecutive days. A frequently relapsing course was defined as two or more relapses in the preceding 6 months. Steroid dependence was defined as a relapse when the dose of prednisolone was reduced or within 2 weeks of discontinuation of therapy.

For steroid therapy, only prednisolone was used. The initial attack and relapses were treated with 2 mg/kg per day prednisolone, given in three divided doses (total dose $\leq$80 mg/day) for the first 4 weeks, followed by alternate-day prednisolone with 2 mg/kg given as a single dose on the morning of every other day for 8 weeks, after which dosage was decreased by 0.5 mg/kg every 2 weeks (total 18 weeks).

Informed consent was obtained from all of the patients before CS treatment. Patients who had received immunosuppressive agents within the past 6 months were not included in the study. CS therapy was started at a dosage of 3–5 mg/kg per day, given in two divided doses after the patients had attained remission with prednisolone. The dose of CS was adjusted to maintain a trough whole blood level between 200 and 600 ng/ml as measured by polyclonal antibody radioimmunoassay for the initial 6 months (high-dose CS treatment). The dosage of CS was then decreased to 2.5 mg/kg per day given for 12 months (low-dose CS treatment) and subsequently was tapered by 1 mg/kg per day every week. The protocol for prednisolone therapy during CS treatment was the same as above.

Correspondence to: N. Yoshikawa, Department of Pediatrics, Kobe University Hospital, 5-1 Kusunoki-cho 7 Chome, Chuoku, Kobe, Japan

Table 1. Clinical data before ciclosporin (CS) treatment[a]

No. of patients	19
Boys/girls	14/5
Age at onset (years)	6.0±3.7 (1.7–12.7)
Age at the time of study (years)	9.9±4.0 (2.4–15.5)
Duration of illness (years)	3.9±3.2 (0.6–10.9)
Relapses:	
Total	7.1±3.7 (2–15)
1 year before CS	3.1±0.8 (2–5)
Therapy before CS:	
steroid only	6
steroid/cyclophosphamide	11
steroid/cyclophosphamide/chlorambucil	2

[a] Values are mean ±1 SD, with range in parentheses

Patients were treated in hospital during the first 2 or more weeks of CS treatment. The following tests and measurements were performed at baseline every alterante day for the first 2 weeks and every 2 weeks thereafter: blood count (including haemoglobin, white blood cells, differential cell count and platelets), serum creatinine, blood urea nitrogen, total bilirubin, glutamic oxaloacetic transaminase, alkaline phosphatase, uric acid, electrolytes, urinalysis, blood pressure, body weight and body height. Side-effects were monitored at 2 week intervals.

To evaluate the degree of growth retardation and obesity in patients, the standard deviation score for height and obesity score were used. Standard deviation score for height = (height-expected height at that age)/standard deviation for expected height at that age. Obesity score = (weight-expected weight at that height)/expected weight at that height ×100–100 (%).

Two-way analysis of variance (ANOVA) followed by the method of Bonferroni was performed for comparisons of multiple groups. Student's paired or unpaired *t*-test was performed for comparisons between two groups. Results are presented as the mean *plus or minus one* standard deviation.

Results

All subjects completed the full trial. They had had 2–15 relapses prior to the study. Thirteen patients had previously received alkylating agents: cyclophosphamide (2–3 mg/kg per day for 8–12 weeks) and/or chlorambucil (0.2 mg/kg per day for 8 weeks). All had relapsed soon after cessation of these treatments. Renal biopsy was performed in 8 patients before the study; 7 patients showed minimal change and 1 had focal segmental glomerulosclerosis. Additional clinical data obtained before CS treatment are summarized in Table 1.

The average number of relapses per patient in the 6-month period before CS treatment was 2.2±0.4 (Table 2). The number of relapses decreased to 0.1±0.3 during the initial 6 months of CS therapy (P <0.001 vs. CS pre-treatment rate), 0.3±0.5 during the second 6 months of CS therapy (P <0.001) and 0.6±0.6 during the last 6 months of CS therapy (P <0.001). Seven patients had no relapses during the 18-month CS therapy; 8 had either 1 or 2 relapses and 4 had more than 2 relapses. All patients required prednisolone therapy during the 6 months prior to CS treatment. In contrast, all patients were able to discontinue prednisolone 44–120 (87±22) days after starting CS treatment. The duration without prednisolone during CS treatment was 70–501 (372±120) days. The cumulative prednisolone dosage was therefore reduced from 140±58 mg/kg for the 6 months before CS treatment to 50±34 mg/kg during the first 6 months of CS treatment (P <0.001), 23±38 mg/kg during the second 6 months of CS treatment (P <0.001) and 60±65 mg/kg during the last 6 months of CS treatment (P <0.005). During the 6 months after discontinuation of CS treatment, 5 of the 7 patients without relapse during the 18-month CS treatment maintained remission. Nephrotic syndrome relapsed in 14 patients within 6 months of discontinuation of CS treatment, with 8 patients reverting to their pre CS treatment pattern, namely frequent relapses with steroid dependence.

Table 2. Effect of CS treatment[a]

	6 months before CS	18 months during CS		
		Months 1–6	Months 7–12[b]	Months 13–18[b]
Relapses:				
Total	42	2	6	10
No./patient	2.2±0.4	0.1±0.3*	0.3±0.5*	0.6±0.6*,**
Prednisolone dosage (mg/kg)	140±58	50±34*	23±38*	60±65***

* P <0.001 compared with 6 months before CS;
** P <0.05 compared with months 1–6 during CS;
*** P <0.005 compared with 6 months before CS
[a] Values are mean ±1 SD
[b] Low-dose CS treatment

Table 3. Laboratory data before and during CS treatment[a]

	Before	6th month	12th month	18th month
CS (mg/kg per day)		5.2±1.6	2.6±0.2	2.6±0.2
Trough level (ng/ml)		264±107	150±70*	118±65**
BUN (mg/dl)	12±3	14±4	13±4	13±3
Creatinine (mg/dl)	0.6±0.3	0.6±0.1	0.6±0.2	0.5±0.1
ALP (units/l)	246±93	540±237***	447±270***	385±191

* P <0.005 compared with 6th month; ** P <0.001 compared with 6th month; *** P <0.05 compared with before CS
BUN, Blood urea nitrogen; ALP, alkaline phosphatase
[a] Values are mean ±1 SD

Group data for CS trough blood levels were related to the dose of CS (Table 3). Mean trough levels during low-dose CS treatment were not significantly different between patients with relapse and those without relapse (146±81 and 140±54 ng/ml, respectively). The standard deviation scores for height and obesity scores before and after CS treatment were estimated in 19 patients (Figs. 1, 2). The mean standard deviation score for height during the 18-month CS treatment increased from −0.34±1.14 to 0.02±1.01 (P <0.005). The mean obesity score during the 18-month CS treatment decreased from 22.1±17.0% to 14.0±12.7% (P <0.005). All 7 patients who were obese (obesity score >20%) before CS treatment reduced their obesity.

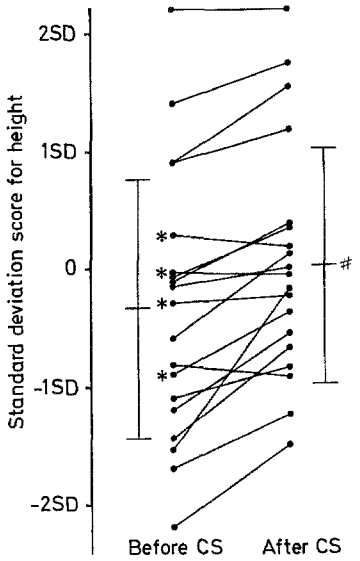

Fig. 1. Standard deviation score for height before and after ciclosporin (*CS*) treatment. *Bars* indicate mean (1 SD). $P < 0.005$ after vs. before CS treatment. * Frequent relapses occurred during CS

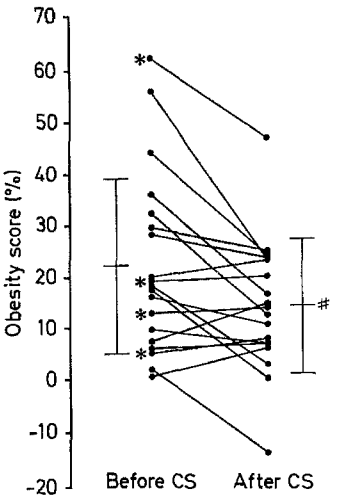

Fig. 2. Obesity score before and after CS treatment. *Bars* indicate mean (1 SD). $P < 0.005$ afer vs. before CS treatment. * Frequent relapses occurred during CS treatment

Hypertrichosis occurred in 9 patients, becoming apparent 2–3 months after starting CS, but it was not severe enough to necessitate discontinuing CS treatment. Elevation of alkaline phosphatase to >500 units/l was observed in 8 patients. Values returned to normal after discontinuation of CS treatment. Hypertension (defined as diastolic pressure >90 mmHg) occurred during the first 2 weeks of CS administration in 6 patients. It was controlled either by loop diuretics or by calcium channel blockers or β-blocking agents. One patient had an elevated serum creatinine (1.6 mg/dl) after 3 months of CS administration; values returned to normal after a decrease in CS dosage. Two patients had perionyxis. No tremors, convulsions, hyperkalaemia, gingival hyperplasia, hypomagnesaemia or malignancy were noted in any of the patients. All side-effects associated with CS treatment disappeared after CS was discontinued or its dosage reduced. Repeat renal biopsies after CS therapy were performed in 6 patients who showed minimal lesions in their pre CS biopsy. None of the specimens showed interstitial fibrosis, tubular atrophy or arteriolopathy changes, which have been attributed to CS toxicity.

Discussion

Although nephrotic syndrome in children is usually a benign disease, one of the major problems in its management is steroid toxicity. Alkylating agents such as cyclophosphamide and chlorambucil may induce longer remissions of nephrotic syndrome. For example, 80% of frequently relapsing non-steroid-dependent patients were in remission at 1 year following an 8-week course of one of these drugs. However, the same drug regimen was less effective in steroid-dependent children [10, 11]. Extending treatment for 12 weeks may be beneficial, but there is still a high relapse rate with this regimen [12] and side-effects of these drugs (which appear to be dose dependent and include gonadal toxicity, bone marrow suppression and oncogenicity) restrict their use.

CS treatment of nephrotic syndrome in children has been reported by a number of investigators [1–6]. Although the results of recent trials using CS suggest a beneficial effect in frequently relapsing nephrotic syndrome, these studies used various protocols, the numbers of patients enrolled were small and most did not evaluate separately the effects of CS treatment on patients with and without steroid dependence. The present study confirms our previous observation that high-dose CS treatment, resulting in trough blood levels of between 250 and 600 ng/ml as measured by polyclonal antibody radioimmunoassay, will maintain remissions in steroid-dependent nephrotic syndrome [7]. Shortly after discontinuation of CS treatment, most patients reverted to their previous pattern of frequent relapses and steroid dependence. Thus, these patients appeared to be CS dependent as well as steroid dependent [4, 7]. However, we noted that no relapses occurred during the period when the dose of CS was tapered [7]. This suggested that it may be possible to maintain longer remission using long-term, low-dose CS administration.

In the present study, the number of relapses during the 12 months of low-dose CS treatment significantly decreased compared with that before CS treatment. Indeed 37% of the patients remained in remission during the 12 months of low-dose CS treatment compared with only 6% in our earlier study in which CS was discontinued after the 6-month period of high dosage [7]. Not only did continuation of CS at a lower dosage decrease the relapse rate, it also reduced the steroid toxicity, allowed increased growth in 14 of the 15 patients with no or infrequent relapses and also decreased obesity scores in 12 of these patients.

Relapse rates were higher on low-dose compared with high-dose CS treatment. Even though the mean trough levels of CS were lower on low-dose than high-dose CS,

trough blood levels of CS during low-dose CS treatment were not significantly different between the patients who relapsed and those who did not. Trough blood levels of CS necessary to maintain remission may vary in different patients.

Of the 7 patients who had no relapses during the 18-months of CS treatment, 5 maintained remission after discontinuation of CS therapy. This suggests that the CS regimen we used might be effective in inducing sustained remissions even after discontinuation of CS. However, it is well known that many children with steroid-dependent nephrotic syndrome will improve with time. All of the side-effects that occurred during the 18-month period of CS treatment were reversible and none was serious enough to necessitate discontinuation of therapy. One patient developed impairment of renal function (creatinine 1.6 mg/dl) at a time when the CS trough blood level was 600 ng/ml. Niaudet et al. [3] have reported that repeat renal biopsies in children with nephrotic syndrome treated with CS may show tubulointerstitial abnormalities. It remains unclear whether these changes are due to CS toxicity or to progression of the primary disease. None of our post-CS renal biopsies demonstrated changes attributable to CS, but the patient with impairment of renal function was not one who had a repeat biopsy.

Recently Niaudet et al. [13] reported that chlorambucil at a cumulative dose of 8 mg/kg body weight was more effective in inducing a sustained remission in nephrotic syndrome than CS treatment. We believe there is a role for CS especially in steroid-dependent frequently relapsing patients who have failed to respond alkylating agents. Use of CS in low doses enabled all our patients to discontinue steroid therapy during CS treatment and reduced steroid side-effects, especially impaired growth. More observations are required to determine the optimal dosage schedule for CS and to identify whether this drug in low doses has untoward side-effects.

Acknowledgements. This study was supported by a grant from the Ministry of Health and Welfare (Research on the System for Long-Term Management of Pediatric Renal Disease), Japan.

References

1. Hoyer PF, Krull F, Brodehl J (1986) Cyclosporin in frequently relapsing minimal change nephrotic syndrome. Lancet II: 335
2. Capodicasa G, De Santo NG, Nuzzi F, Giordano C (1986) Cyclosporin A in nephrotic syndrome of childhood – a 14 month experience. Int J Pediatr Nephrol 7: 69–72
3. Niaudet P, Tete MJ, Broyer M, Habib R (1988) Cyclosporine and childhood idiopathic nephrosis. Transplant Proc 20: 265–268
4. Brodehl J, Hoyer PF, Oemar BS, Helmchen U, Wonigeit K (1988) Cyclosporine treatment of nephrotic syndrome in children. Transplant Proc 20: 269–274
5. Tejani A, Butt K, Trachtman H, Suthanthiran M, Rosenthal CJ, Khawar MR (1988) Cyclosporine A induced remission of relapsing nephrotic syndrome in children. Kidney Int 33: 729–734
6. Brandis M, Burghard R, Leititis J, Zimmerhockl B, Hildebrandt F, Helmchen U (1988) Cyclosporine A for treatment of nephrotic syndromes. Transplant Proc 20: 275–279
7. Kitano Y, Yoshikawa N, Tanaka R, Nakamura H, Ninomiya M, Ito H (1990) Ciclosporin treatment in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol 4: 474–477
8. International Study of Kidney Disease in Children (1982) Early identification of frequent relapsers among children with minimal change nephrotic syndrome. J Pediatr 101: 514–518
9. International Study of Kidney Disease in children (1981) Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. Kidney Int 20: 765–771
10. Garin EH, Pryor ND, Fennell RS, Richard GA (1978) Pattern of response to prednisone in idiopathic, minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. J Pediatr 92: 304–308
11. Arbeitsgemeinschaft für Pädiatrische Nephrologie (1982) Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. N Engl J Med 306: 451–454
12. Arbeitsgemeinschaft für Pädiatrische Nephrologie (1987) Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course. Arch Dis Child 62: 1102–1106
13. Niaudet P (1992) The French Society of Paediatric Nephrology: comparison of cyclosporin and chlorambucil in the treatment of steroid-dependent idiopathic nephrotic syndrome: a multicentre randomized controlled trial. Pediatr Nephrol 6: 1–3

Literature abstract

Acta Paediatr (1992) 81: 345–350

Effect of phenylpropanolamine on incontinence in children with neurogenic bladders. A double-blind crossover study

P. Åmark and O. Beck

In children with myelodysplasia and a low-level spinal cord lesion (low lumbar-sacral), detrusor hyperactivity together with dyssynergic urethral function forms the main pathophysiological basis for incontinence. Pharmacological treatment of incontinence due to neurogenic bladder dysfunction has been tried, mainly with anticholinergics and alpha-adrenoceptor antagonists. In this study, the effects of the alpha-adrenoceptor agonist phenylpropanolamine on urodynamic parameters and incontinence were investigated in 10 patients. Effects on incontinence were evaluated in a double-blind crossover trial. Plasma concentrations of phenylpropanolamine were measured by means of gas chromatography-mass spectrometry. Phenylpropanolamine reduced detrusor hyperactivity and improved continence, but the effect was not so pronounced as to make the patients continent.