Pediatr Nephrol (1992) 6: 247–250

Pediatric Nephrology

Original article

Long-term, low-dose prednisolone therapy in frequently relapsing nephrotic syndrome

Rajendra N. Srivastava[1], Anand S. Vasudev[1], Arvind Bagga[1], and Karimassery R. Sunderam[2]

Departments of [1] Paediatrics and [2] Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Received January 16, 1991; received in revised form October 29, 1991; accepted October 31, 1991

Abstract. The efficacy of daily administration of a small dose of prednisolone was examined in 21 patients with corticosteroid-responsive, frequently relapsing nephrotic syndrome (FRNS). After induction of remission of a third or subsequent relapse with a 6-week course of prednisolone (standard therapy with prednisolone, STP), this drug was continued in a single daily dose of 0.25 mg/kg body weight (low-dose prednisolone, LDP) for 18 months. Relapses occurring during this period were treated with STP, following which LDP therapy was resumed. The historical controls comprised 14 patients with FRNS in whom relapses were treated with STP and who were observed over a minimum period of 30 months. The two groups were comparable for age at the onset of nephrotic syndrome and sex. Twenty patients completed LDP therapy, during which 12 had no relapse, 6 had infrequent and 2 frequent relapses (1 patient became steroid dependent and was taken off LDP). Twelve patients were followed for 12–42 months after stoppage of LDP; during this period 7 had no relapse, 4 had infrequent relapses and 1 showed steroid dependence. The number of relapses during LDP therapy (0.5/patient per year) was significantly less ($P < 0.001$) than in the preceding 12 months (3.62/patient per year), and continued to remain low during the following 12 months (0.6/patient per year). Whereas the frequency of relapses in the LDP group was similar to that in the historical control group in the 1st year of comparison, it was significantly less during LDP therapy (0.5/patient per year versus 2.25/patient per year). No side effects were observed in patients on the LDP regimen, at the end of which the height percentiles improved in 6 patients and remained unchanged in 14. Our observations indicate that long-term therapy with a small daily dose of prednisolone can significantly reduce the number of relapses in patients with FRNS, and that the beneficial effect may continue even after its stoppage.

Correspondence to: R. N. Srivastava

Key words: Nephrotic syndrome – Frequent relapses – Low-dose prednisolone therapy

Introduction

About 40% of children with nephrotic syndrome who respond to corticosteroid therapy suffer from frequent relapses [1]. Although the relapses can be treated with corticosteroids, the repeated use of large amounts of these agents leads to significant and sometimes serious side effects. Prolonged administration of prednisolone on alternate days [2, 3] and cytotoxic drugs [4] have been employed to induce long periods of remission in patients with frequently relapsing nephrotic syndrome (FRNS). The former regimen is often ineffective, whereas cytotoxic agents carry the risk of serious toxicity. Recently cyclosporin A has been found to sustain a remission in such patients [5], but the drug is nephrotoxic and the relapses soon start to recur after its discontinuation [6]. We report beneficial results using a small daily dose of prednisolone for a period of 18 months in patients with FRNS.

Patients and methods

Twenty-one patients with corticosteroid-responsive FRNS, defined as three or more relapses per year, were studied. Informed parental consent was obtained. The definitions and investigative methods have previously been reported [7, 8]. Each relapse was treated with prednisolone 2 mg/kg per day in three to four divided doses for 2 weeks, followed by the same amount given as a single morning dose on alternate days for the next 4 weeks (standard therapy with prednisolone, STP).

After induction of remission of a third or subsequent relapse with the STP regimen, prednisolone was continued in a dose of 0.25 mg/kg daily at 8.00 a.m. for 18 months (low-dose prednisolone therapy, LDP) and then stopped. Relapses occurring during this period were treated with the 6-week course of prednisolone (STP), at the end of which LDP was resumed. The patients were regularly examined at the pediatric nephrology clinic, where records of weekly urine tests for protein (daily if there was proteinuria) were maintained. The height, weight, blood pressure,

Table 1. Clinical and renal histological features in the two groups of patients[a]

	Low-dose prednisolone	Historical controls
Number	21	14
Boys/girls	15/6	9/5
Age at onset of nephrotic syndrome (years)	1–9.5 (3.1)	1–6 (3.1)
Age at start of low-dose prednisolone/ observation period (years)	2.2–11.5 (6.5)	2.5–11 (5.2)
Renal histology	14	9
Minimal change	11	6
Mild mesangial proliferation	3	3

[a] Figures in parentheses indicate mean values

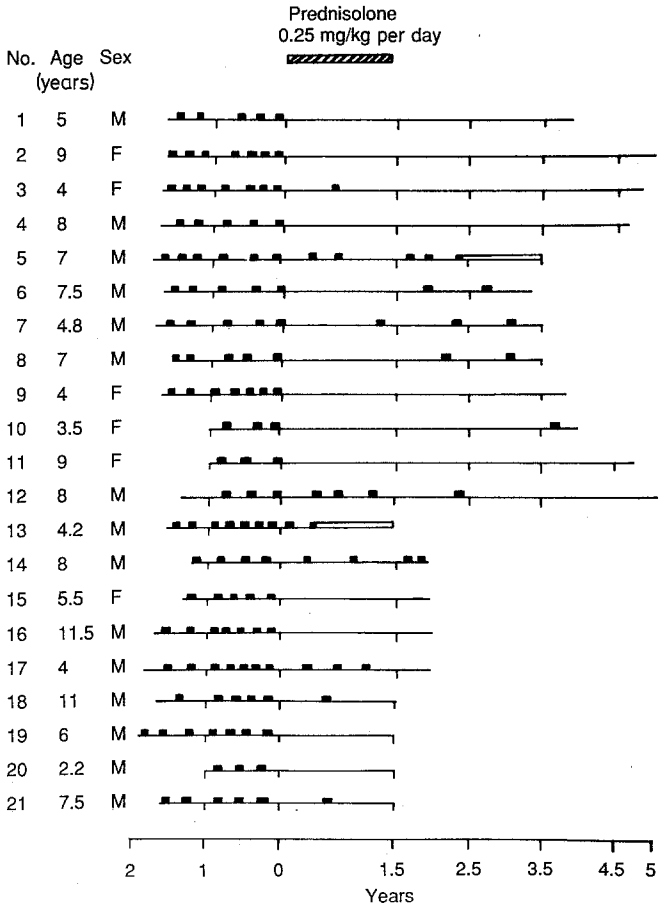

Fig. 1. Clinical course of the patients on low-dose prednisolone therapy. The age represents that at the institution of this regimen. Patients 5 and 13 developed prednisolone dependence; ■, relapse

ocular findings and presence of infections were recorded. Twenty patients completed the 18-month therapy with LDP. Subsequently, 12 of them were followed for 12–42 additional months, and 4 for 6 months.

The historical control group comprised 14 patients with corticosteroid-responsive FRNS. They had been treated earlier with STP,

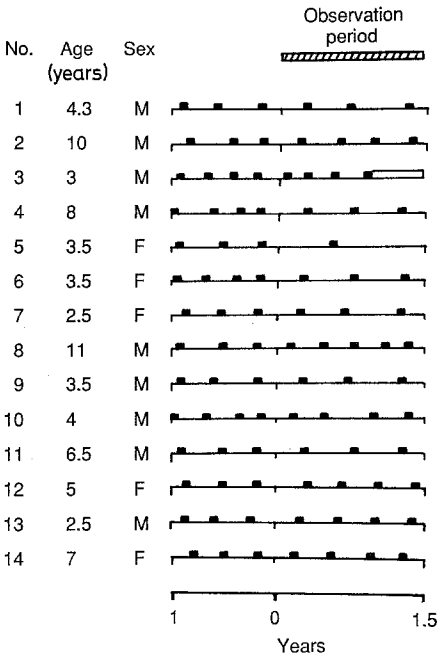

Fig. 2. Clinical course of the historical control patients, on standard prednisolone treatment. The age represents that at the beginning of the observation period. Patient 3 developed prednisolone dependence; ■, relapse

under the supervision of R. N. Srivastava, and were observed for a minimum period of 30 months. None had received long-term prednisolone treatment or cytotoxic drugs. The latter 18 months of their course was regarded as the "observation period", for comparison with the similar period in patients in the LDP group.

The frequency of relapses observed in the patients in the LDP group 1 year before the institution of LDP was compared with the frequency whilst on the LDP regimen and during the year following its stoppage. The relapse rate in the former two periods was compared with that in the corresponding periods in the historical control group. In the historical control group the relapse rate during the observation period was compared with that in the preceding year. Non-parametric Wilcoxon's signed rank test and Wilcoxon's rank sum test were used for statistical analysis. Standards for height for Indian children [9] were used for assessment of linear growth.

Results

Table 1 shows the sex distribution, age at the onset of nephrotic syndrome and age at the start of LDP or the observation period, and the renal histological features in the two groups of patients. Both groups were well matched for these characteristics. Two patients in the LDP group (nos. 1 and 11 in Fig. 1) had received cyclophosphamide for 8 weeks, 2.5 and 5.5 years respectively before they were put on prednisolone. The duration of remission after stoppage of cyclophosphamide was less than 6 months in each case. Another 2 patients (nos. 19 and 21 in Fig. 1) had received levamisole (5 mg/kg on alternate days for 12 weeks), 1.5 years before the institution of LDP, without any benefit.

The clinical course of individual patients who were given LDP is shown in Fig. 1. Twelve patients had no relapse and 4 had one relapse each during this treatment.

Table 2. Relapse rate in the two groups of patients (no/patient per year)

Group	Time period		
	Preceding 1 year	Low-dose prednisolone/observation period	Following 1 year
Low-dose prednisolone	3.62*	0.5**	0.6*****
Historical control	3.29***	2.25****	

P <0.001 * versus **; P >0.05 * versus ***; P <0.001 ** versus ****; P >0.05 *** versus ****; P <0.001 * versus *****

Table 3. Effect of low-dose prednisolone therapy on height percentiles

Height percentile before therapy	No. of patients	Height percentile after therapy		Improved percentile
		Unchanged	Improved	
<10	5	4	1	11–25
11–25	5	3	2	26–90
26–50	3	2	1	51–75
51–75	3	2	1	76–90
76–90	2	1	1	90
>91	2	2	0	0
Total	20	14	6	6

One patient (no. 13) had two relapses in the first 6 months of treatment and subsequently became prednisolone dependent. He was taken off prednisolone and considered a treatment failure. On further observation of 10 patients for 12–42 months, 7 were found to have no relapse and 3 had infrequent relapses.

Examination of the clinical course of the patients in the historical control group (Fig. 2) showed that most continued to have frequent relapses. One (no. 4) had four relapses during the observation period and later became steroid dependent.

Table 2 shows the frequency of relapses in the two groups of patients. The relapse rates in the LDP group and the historical control group were not different during the year before the treatment period in the former and the observation period in the latter (P >0.05). The relapse rate in the LDP group during the treatment period was significantly lower than that observed during the preceding year (P <0.001) as well as that noted in the historical control group during the observation period of 18 months (P <0.001). Additionally, the frequency of relapses during the year after discontinuation of LDP was lower than that recorded in the year preceding the treatment (P <0.001).

There were no side effects related to LDP. All except 1 of the 12 patients with cushingoid obesity showed a decrease in their weight. The elevated levels of blood pressure in 7 patients returned to normal. Significant infections were not observed during LDP. None of the patients developed cataract.

Table 3 gives the height percentiles of the patients treated with LDP. At the end of the treatment the height percentiles improved in 6 patients and remained unchanged in 14.

Discussion

In a majority of our patients with FRNS, prolonged administration of a small dose of prednisolone was associated with a significant reduction in the number of relapses. Additionally, in some of them the beneficial effect continued after cessation of the treatment. The results of such therapy can be compared with those using prednisolone, 30–60 mg on alternate days, on a long-term basis [2, 3], or cytotoxic agents [4]. With the former regimen, the side effects of corticosteroids diminish and the number of relapses is reduced in some patients. In others, however, relapses continue to occur during treatment and, in most cases, after stopping the alternate-day therapy [10].

Elzouki and Jaiswal [11] reported beneficial results in patients with FRNS with the administration of 10 mg prednisolone on alternate days for 10–58 months. Of their 37 patients, 32 did not relapse during treatment, whereas in the other 5 the relapse rate was decreased. Improved growth velocity and a decrease in cushingoid obesity was also seen in these patients. In our experience, however, attempts to reduce the dose of alternate-day prednisolone below 1.0–1.5 mg/kg are usually followed by relapses in a large proportion of patients (Srivastava et al., unpublished observations). Significant side effects may develop during alternate day-prednisolone therapy [10].

The efficacy of a small dose of hydrocortisone, 7.5–15 mg administered daily for 6 months, was reported by Schoeneman in four patients with FRNS [12]. Three patients had no relapse during the treatment period. Wingen et al. [13] compared the effect of different prednisone regimens in children with FRNS. They found that long-term daily therapy, consisting of an initial dose of 2 mg/kg per day for 1–3 months followed by a tapering dosage schedule during the subsequent 3–6 months, was most effective in reducing the number of relapses.

There is extensive information on the use of cytotoxic drugs in FRNS and their efficacy is well established [4, 14, 15]. In a study from this centre [8], administration of cyclophosphamide for 8 weeks along with alternate-day prednisolone in patients with FRNS was followed by remissions of more than 3 years in 44% of patients, and between 6 months and 3 years in 31% of patients. Although the acute side effects of cytotoxic therapy are not significant, the gonadal toxicity and carcinogenic potential call for caution in its employment.

Experience with other drugs, such as levamisole and cyclosporin A, in the management of FRNS is limited. Mongeau et al. [16] reported that during administration of levamisole for 1 year the relapse rate was decreased by 50%, but on cessation of the treatment relapses occurred in most patients. In a recent multicentre, controlled study [17] levamisole was used in patients with steroid-dependent nephrotic syndrome for a period of 16 weeks, during which a higher number of patients remained in remission than in a matched control group who received a placebo. Further studies are needed to examine the role of this drug in the

treatment of FRNS. Several reports have shown that cyclosporin A can maintain a remission in patients with FRNS [5, 6]. In most cases, however, relapses soon recur after its stoppage [6]. The nephrotoxicity of even small doses of cyclosporin, when given for prolonged periods, remains a matter of concern [18].

We feel that daily administration of a LDP may be effective in preventing relapses in patients with FRNS. The usefulness of even smaller doses than we employed in the present study and the optimum duration of such therapy needs to be investigated. The continued suppression of relapses after stoppage of the treatment in some patients was a surprising observation, since other corticosteroid regimens do no affect the relapse rate once the drug is discontinued [10].

The mechanism by which corticosteroids induce a remission in nephrotic syndrome is not clear [19]. It is possible that they suppress an underlying immunological abnormality (unidentified as yet) that eventually leads to proteinuria. Prolonged administration of low doses of corticosteroids could continue to have such an effect and thereby prevent relapses. Since this regimen seems to be free of significant side effects, we suggest its trial in patients with FRNS before exposing them to cytotoxic drugs.

Acknowledgements. This study was supported by the Indian Council of Medical Research (no. 5/7/15/85 RB). The secretarial help of Ms. Vi Quiroga is gratefully acknowledged.

References

1. Barnett HL, Schoeneman M, Bernstein J, Edelmann CM (1978) Minimal change nephrotic syndrome. In: Edelmann CM (ed) Pediatric kidney disease, 2nd edn. Little Brown, Boston, pp 695–711
2. McEnery PT, Strife CF (1982) Nephrotic syndrome in childhood. Management and treatment in patients with minimal change disease, mesangial proliferation, or focal glomerulosclerosis. Pediatr Clin North Am 89: 875–894
3. Polito C, Oporto MR, Totino SF, LaManna A, DiToro R (1986) Normal growth of nephrotic children during long-term alternate day prednisolone therapy. Acta Paediatr Scand 75: 245–250
4. Trompeter RS (1989) Immunosuppressive therapy in the nephrotic syndrome in children. Pediatr Nephrol 3: 194–200
5. Niaudet P, Broyer M, Habib R (1991) Treatment of idiopathic nephrotic syndrome with cyclosporin A in children. Clin Nephrol 35: [Suppl 1]: S31–S36
6. 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
7. Srivastava RN, Mayekar G, Anand R, Choudhry VP, Ghai OP, Tandon HD (1975) Nephrotic syndrome in Indian children. Arch Dis Child 50: 626–630
8. Srivastava RN, Agarwal RK, Choudhry VP, Moudgil A, Bhuyan UN, Sunderam KR (1985) Cyclophosphamide therapy in frequently relapsing nephrotic syndrome with and without steroid dependence. Int J Pediatr Nephrol 6: 245–250
9. Ghai OP (1990) Growth and development. In: Ghai OP (ed) Essential pediatrics, 2nd edn. Interprint, New Delhi, p 5
10. Arbeitsgemeinschaft für Pädiatrische Nephrologie (1981) Alternate-day prednisone is more effective than intermittent prednisone in frequently relapsing nephrotic syndrome. Eur J Pediatr 135: 229–237
11. Elzouki AY, Jaiswal OP (1988) Long-term small dose prednisolone therapy in frequently relapsing nephrotic syndrome of childhood. Clin Pediatr (Phila) 27: 387–392
12. Schoeneman MJ (1983) Minimal change nephrotic syndrome. Treatment with low doses of hydrocortisone. J Pediatr 102: 791–793
13. Wingen AM, Muller-Wiefel DE, Scharer K (1990) Comparison of different regimens of prednisone therapy in frequently relapsing nephrotic syndrome. Acta Paediatr Scand 79: 305–310
14. Chiu J, McLain PN, Drummond KN (1973) A controlled prospective study of cyclophosphamide in relapsing corticosteroid responsive minimal-lesion nephrotic syndrome in childhood. J Pediatr 82: 607–613
15. 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
16. Mongeau JG, Robiataille PO, Roy F (1988) Clinical efficacy of levamisole in the treatment of primary nephrosis in children. Pediatr Nephrol 2: 398–401
17. British Association for Paediatric Nephrology (1991) Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. Lancet 337: 1555–1557
18. Myers BD, Newton L (1991) Cyclosporine-induced chronic nephropathy: an obliterative microvascular renal injury. J Am Soc Nephrol 2 [Suppl 1]: S45–S52
19. Ponticelli C, Fogazzi GB (1989) Methylprednisolone pulse therapy for primary glomerulonephritis. Am J Nephrol 9: S41–S46