Medical Journal of the
Islamic Republic of Iran

Volume 17
Number 4
Winter 1382
February 2004

LOW DOSE PREDNISOLONE WITH INCREASE IN DOSAGE INTERVAL IN FREQUENT RELAPSING NEPHROTIC SYNDROME

MOHAMMAD HOSSEIN FALLAHZADEH, GHAMAR HASHEMI, AND ABBAS MADANI

From the Department of Pediatrics, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

In order to avoid using cytotoxic drugs and to minimize prednisolone side effects in frequent relapsing or steroid-dependent idiopathic nephrotic syndrome, 35 patients, 3 to 15 (mean= 8.1) years of age, were studied. While in remission for at least 6 weeks, the dose of prednisolone was reduced to 0.1-0.37 (mean= 0.23) mg/kg/day as a single dose for 12 to 72 (mean= 27.6) months. It was followed by a tapering method, with gradual increase in the interval instead of decrease in the dose for about 10 to 12 months, and about 18.4 months follow-up without treatment. About 54.3% of the patients had no relapse during the treatment period and the relapse rate per patient per year was 3.94 during the preceding 12 months before the study, 0.51 during treatment ($p<0.001$) and 0.23 after discontinuation of the drug. Each relapse was treated by a standard dose of prednisolone for 2 months and then the low dose regimen was resumed. The patients tolerated the drug well with minimal side effects. It is concluded that long term, low-dose daily prednisolone therapy followed by gradual increase in the interval is a safe, well-tolerated and effective method of maintaining prolonged remission in most children with frequent relapsing idiopathic nephrotic syndrome.

MJIRI, Vol. 17, No. 4, 305-308, 2004.

Keywords: Nephrotic syndrome, Low-dose prednisolone, Tapering, Frequent relapses.

INTRODUCTION

Although nephrotic syndrome is not a common disorder in childhood and is often steroid-responsive, it remains a major cause for referral to pediatric nephrologists due to the chronicity and complexities for evaluation and management.[1]

About 40% of steroid responsive patients suffer from frequent relapses.[2] Although the relapses are usually steroid responsive, the repeated use of large amounts of these agents is followed by significant and sometimes serious side effects. Prolonged alternate days of prednisolone therapy[1,3] or cytotoxic drugs[1,4] have been used to induce a long period of remission in frequent relapsing nephrotic syndrome (FRNS). The former protocol is often ineffective, whereas cytotoxic agents carry the risk of serious toxicity. Long-term, low dose prednisolone therapy (LDT) was used previously in 21 patients, but follow-up was explained only for 12.[5] We report the beneficial results using LDT followed by tapering the drug with gradual increase in the interval, while keeping the daily dose constant, in 35 patients with frequent relapsing or steroid-dependent nephrotic syndrome and mean follow-up of 18.4 months after the discontinuation of treatment.

Mailing Address: M.H. Fallahzadeh, MD, Pediatric Department Office, Nemazee Hospital, Shiraz, Iran, Telephone: 98711-6276972, Fax: 98711-6265024, Email: fallahzadeh@dr.com

PATIENTS AND METHODS

Thirty-five patients with steroid-responsive idiopathic nephrotic syndrome who had at least two relapses during the preceding 6 months or more than three relapses during one year, were used as the subjects of this study.

Informed parental consent was obtained.Twenty-one patients had frequent relapsing and others had steroid-dependent nephrotic syndrome.Ten patients had kidney biopsy and all were in favor of minimal change disease except one with mesangial proliferation. While the patients were in remission for at least 6 weeks, prednisolone was changed to a daily single dose of 0.1-0.37 (mean=0.23) mg/kg for 12 to 72 (mean=27.6) months. Each relapse was treated by the standard treatment method (ST) for 8 weeks, unless an infection was present. With infection, the dose of prednisolone was changed to the stress dose (10 to 30 mg/day) and after eradication of the infection, it was changed to ST, unless proteinuria disappeared spontaneously. After the treatment of each relapse, the previous low dose regimen was resumed. They were followed in the nephrology clinic regularly every 1 to 4 weeks or earlier if necessary. In each visit after a complete history and physical examination a urine sample was tested for the presence of protein and blood. For patients who had relapses during LDT therapy, the duration of treatment was more prolonged. After at least one year of LDT therapy, the drug was tapered very slowly during a period of 10 to 12 months. It was done by gradual increase in the interval (omitting 2 doses per week after 4 weeks, then every other day for 4 weeks and thereafter increasing the interval by one day each month) until it reached one dose per 10 days, then it was discontinued. Each patient was examined by an ophthalmologist two times a year.

Some definitions used in this study are as follows:

Remission: Urinary protein excretion of negative or trace for 3 consecutive days.

Relapse: Urinary protein excretion of 2+ or more for 3 consecutive days.

Frequent relapses (FR): Two or more relapses within 6 months, or more than 3 relapses within a period of 12 months.

Infrequent relapses: Less than two relapses within 6 months.

Steroid-dependent (SD): Two consecutive relapses occurring during corticosteroid treatment or within 14 days of its cessation.

Standard therapy (ST): Prednisolone 2mg/kg/day in 3 divided doses, decreasing to every other day after the remission and 1mg/kg/day in one dose every other day for a total of 8 weeks.

Statistical analysis was done using Student's t-test, Fisher's exact test, and chi-squared method.

RESULTS

The mean age of the patients when nephrotic syndrome was diagnosed and when LDT was started was 4.7 (2 to 11) and 8.1 (3 to 15) years respectively and the male to female ratio was 4.8/1.The duration of LDT was 12 to 72 (mean=27.6) months and the duration of the follow-up after discontinuation of LDT was 4 to 36 (mean=18.4) months (in 17 patients 1 to 3 years, in 5 patients from 6 to 12 months and in 11 patients the drug was not discontinued at the time of data analysis).

Two patients could not follow the LDT regimen due to frequent relapses, and four had regular follow-up during LDT but irregular follow-up during the tapering phase of prednisolone. One of these patients was admitted due to primary bacterial peritonitis leading to septic shock and death, while he had discontinued LDT a few months before.

The overall response of the patients is illustrated in Table I and the number of relapses during or after the discontinuation of LDT regimen, which occurred in 18 patients, is shown in Tables II and III. The relapse rate before, during, and after treatment was 3.94, 0.51 ($p<0.001$), and 0.23 per patient per year respectively. During the first 6 months of the follow-up without steroid therapy, 4 relapses were detected in 3 patients, and in the subsequent 6 months one of these patients experienced a relapse. The other 2 relapses during this period were observed in 2 patients who had no relapse during the first 6 months of the follow-up.

Drug side effects detected in this study were mild cataract, transient hyperglycemia, and a mild increase in intraocular pressure, each in one patient. The height growth rate before starting LDT was 1.5-10.5 (mean=4.8) and during LDT it was 2.5-9 (mean=5.3) centimeters per year. Acceptable height growth rate was observed in 28 patients as compared to normal values for their age and

Table I. Results of LDT in 35 patients with nephrotic syndrome.

Response pattern	Number of patients (%)
No relapse during or after treatment	15 (43)
Infrequent relapses during treatment	13 (37)
Relapse only after discontinuation of treatment	5 (14)
Frequent relapses	2 (6)
Total	35 (100)

Table II. Number of relapses during LDT in 18 patients.

Relapses with infection	18 (44%)
Relapses without infection	23 (56%)
Total relapses	41 (100%)

Table III. Number of relapses after discontinuation of prednisolone therapy.

First 6 months	4 (57%)
Second 6 months	3 (43%)
First year	7 (100%)

sex. The relation between age, sex, the pattern of disease (SD or FR) and the overall result of LDT was not statistically significant.

At the time of data analysis, 19 patients were free of medication and in remission, 10 patients were on LDT and 6 on high dose prednisolone therapy.

DISCUSSION

The main problem in the long-term follow-up of patients with steroid responsive nephrotic syndrome is its tendency to relapse and the management of relapses. Relapses may be triggered by infection or allergic events.[6] In patients with frequent relapses, renal biopsy will not usually add more information than clinical judgement.[1] If about 0.5mg/kg of alternative day prednisolone therapy is not able to maintain remission, levamisole may be used,[7,8] but most patients will relapse after the cessation of treatment.[7] Some patients may be treated by cytotoxic drugs like cyclophosphamide[9] or chlorambucil.[10] With these alkylating agents, in addition to their side effects (bone marrow suppression, infertility, bladder contraction, alopecia and malignancy), their long term effect (>1year) persists in less than half of the patients.[11] At the present time, cyclosporine may be the last choice of treatment[1,12] but with this drug, the main potential problem is nephrotoxicity, and the renal function must be carefully monitored.[13] Although cyclosporine is effective in maintaining remission, patients relapse soon after the drug is discontinued and then more difficult to control.[14] There is limited experience with mycophenolate mofetil in frequent relapsing nephrotic syndrome.[15]

Another approach to treatment of frequent relapsing nephrotic syndrome is to use low dose daily prednisolone therapy for a long period. The efficacy of low-dose daily hydrocortisone, for 6 months, was reported by Schoeneman in four patients with FRNS.[16] Three patients had no relapse during the treatment period. Wingen et al.[17] compared the effect of different regimens of prednisone in children with FRNS. They found that the initial dose of 2 mg/kg per day for 1 to 3 months followed by a tapering dosage schedule during the subsequent 3 to 6 months, was most effective in reducing the number of relapses. To our knowledge, the only reported experience with LDT for more than 6 months has been performed on twenty one patients with FRNS,[5] and twelve patients (57%) had a follow-up of 12-42 months. In our study, all the patients had a good follow-up during the treatment and only 4 patients had irregular follow-up during the tapering period or after discontinuing the drug. The mean age of the patients was higher in our study at the time of the beginning of LDT (8.1 versus 6.5 years) and male to female ratio was also higher (4.8 versus 2.5). Their study group used LDT for 18 months, with a dose comparable and relapse rate (during treatment) identical to our study group. They reported no relapse in 12 patients and infrequent relapses in 6 patients during the treatment period (these figures in our study are 20 and 13 respectively). In 12 patients who had follow-up after discontinuation of prednisolone, 7 had no relapse, 4 had infrequent relapses, and one became steroid dependent. With the tapering method used in our study, relapse rate was further decreased (about 50%) after the discontinuation of the drug, so that only 7 relapses were detected in 5 patients during the first one year of the discontinuation of prednisolone. Drug side effects detected in this study were not significant. One of the most important steroid side effects in children with frequent relapsing nephrotic syndrome is disturbance in height growth.[18] Only a few patients in this study had a height growth.[18] Only a few patients in this study had a height growth rate less than expected, and all of these cases had retarded growth before starting LDT. In this study the pattern of response during LDT was compared to the period before and after this treatment protocol. The results indicate that in frequent relapsing or steroid dependent nephrotic syndrome, LDT for at least one year followed by gradual increase in the interval of prednisolone can significantly reduce the number of relapses during and even after the discontinuation of the drug in most of the patients.

REFERENCES

1. Clark AG, Barratt TM: Steroid responsive nephrotic syndrome. In : Barratt TM, (ed.), Pediatric Nephrology, Fourth ed., Williams and Wilkins, pp. 731-743,1999.
2. Nash MA, Edelmann CM, Burnstein J, et al: Minimal change nephrotic syndrome. In: Edelmann CM, (ed.), Pediatric Kidney Disease, 2nd ed., Boston: Little Brown, pp. 1264-1290, 1992.

3. Polito C, Oporto MR, Totino SF: Normal growth of nephrotic children during long term alternate day prednisolone therapy. Acta Pediatr Scand 75: 245-250, 1986.
4. Trompeter RS: Immunosuppressive therapy in the nephrotic syndrome in children. Pediatr Nephrol 3: 194-200, 1989.
5. Srivastava RN, Vasudev AS, Bagga A, et al: Long-term, low-dose prednisolone therapy in frequently relapsing nephrotic syndrome.Pediatr Nephrol 6: 247-250, 1992.
6. Wingen AM, Muller-Wiefel DE, Scharer K: Spontaneous remission in frequently relapsing and steroid dependent idiopathic nephrotic syndrome. Clin Nephrol 23: 35-38, 1985.
7. British Association for Pediatric Nephrology: Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. Lancet 337: 1555-1557, 1991.
8. Bagga A, Sharma A, Srivastava RN: Levamisole therapy in corticosteroid dependent nephrotic syndrome. Pediatr Nephrol 11: 418-422, 1997.
9. Garin EH, Pryor ND, Fennell RS, et al: Pattern of response to prednisolone in idiopathic minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. J Pediatr 92: 304-308, 1978.
10. Williams SA, Makker SP, Ingelfinger JR, et al: Long term evaluation of chlorambucil plus prednisolone in the nephrotic syndrome of childhood. N Engl J Med 302: 929-933, 1980.
11. Barrat TM, Bercowsky A, Osofsky SG, et al: Cyclophosphamide treatment in steroid-sensitive relapsing nephrotic syndrome of childhood. Lancet 1: 55-58, 1975.
12. Niaudet P: French Society of Pediatric Nephrology. Comparison of cyclosporine and chlomrambucil in the treatment of steroid- dependent idiopathic nephrotic syndrome: a multicenter controlled trial. Pediatr Nephrol 6: 1-3, 1992.
13. Hulton SA, Jadresic L, Shah V, et al: Effect of cyclosporin A on glomerular filtration rate in children with minimal change nephrotic syndrome. Pediatr Nephrol 8: 404-407,1994.
14. Hulton SA, Neuhaus TJ, Dillon MJ, et al: Long-term cyclosporin A therapy in minimal change nephrotic syndrome of childhood. Pediatr Nephrol 8: 401-403, 1994.
15. Chandra M, Susin M, Abitbol C: Remission of relapsing nephrotic syndrome with mycophenolate mofetil. Pediatr Nephrol 14: 224-226, 2000.
16. Schoeneman MG: Minimal change nephrotic syndrome. Treatment with low doses of hydrocortisone. J Pediatr 102: 791-793, 1983.
17.Wingen AM, Muller-Wiefel DE, Scharer K: Comparison of different regimens of prednisone therapy in frequent relapsing nephrotic syndrome. Acta Pediatr Scand 79:305-310, 1990.
18. Kitamura M: Growth retardation in children with frequent relapsing nephrotic syndrome on steroid, improvement of height velocity after administration of immunosuppressive agent. Nippon Jinzo Gakkai Shi 34: 117-124, 1992.