Pediatr Nephrol (2002) 17:355–358

ORIGINAL ARTICLE

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Levamisole: adjunctive therapy in steroid dependent minimal change nephrotic children

Received: 26 February 2001 / Revised: 19 November 2001 / Accepted: 24 November 2001

Abstract In children with minimal change nephrotic syndrome (MCNS), the steroid dependent group constitutes an especially difficult case for management. Patients in this group are prone to serious steroid side effects. Additionally, alkylating agents commonly fail to maintain remission and expose patients to more side effects. Therapy with the immunostimulant drug levamisole may therefore be another option in the attempt to maintain remission with minimal side effects. We prospectively treated 20 of our steroid dependent primary MCNS patients with levamisole. All patients were children, with an age range of 3–15 years; 16 were boys and 4 were girls. Remission was firstly induced by steroids, then levamisole was added in a dose of 2.5 mg/kg body weight on alternate days for 6 months. During this period we attempted to withdraw steroids completely and maintain patients on levamisole alone. We followed up our patients for the occurrence of relapse and side effects during this period and for a further 6 months after stopping levamisole. In 11 out of 20 children (55%), we successfully stopped steroids for more than 2 weeks. At the end of the 6-month treatment period (i.e. after 4 months of steroid discontinuation), ten patients (50%) were maintaining remission on levamisole alone. At the end of the 12-month study period (i.e. after 6 months of levamisole discontinuation), five patients (25%) were still in remission without any treatment for the previous 6 months. No significant side effects were reported during levamisole therapy. None of the patients developed neutropenia, but the leukocyte count showed a significant reduction in those who responded to levamisole treatment. We concluded that levamisole therapy for 6 months is a safe and perhaps effective therapy in a subset of children with steroid dependent MCNS to enable an otherwise infeasible withdrawal of steroids. This may be worth a trial before other types of more hazardous adjunctive therapies are considered.

Keywords Levamisole · Children · Steroid dependent · Minimal change-nephrotic syndrome

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Introduction

In children, the most common variety of primary nephrotic syndrome is minimal change type (MCNS), of which about 95% of cases show an excellent response to steroid therapy. However, the responder group commonly becomes steroid dependent [1–3]. Such patients may experience serious side effects. Therefore, the physician may attempt adjunctive therapy. This may include other immunosuppressive agents such as the alkylating agent cyclophosphamide [4]. However, this commonly fails to maintain a remission. Additionally, the long term immunosuppression in these patients and cumulative risk of further alkylating therapy are worrying in a condition that ultimately has an excellent prognosis. An alternative therapy with an immunostimulant would be an attractive option, especially in MCNS, which is a condition characterised by altered cellular immunity [5].

There are a plethora of reports of the efficacy of levamisole in nephrotic syndrome. However, only few of these studies were exclusively intended to investigate the drug efficacy in steroid dependent patients [6, 7], who are especially prone to serious steroid side effects [4]. The study done by the British Association for Paediatric Nephrology in 1991 [6] was a well designed prospective, randomised, double-blind and placebo controlled study. However, in this study, levamisole was only used for 3 months and patients were followed up for only 3 months after stopping the drug. In other studies, either levamisole was given for different unfixed periods [7, 8] or patients were not followed up after stopping levamisole [7, 9]. Additionally, in all these studies [6–9] neither renal biopsy nor absence of previous treatment with cyclophosphamide was a prerequisite for allocation of pa-

tients. Furthermore, levamisole has not been studied among Egyptian nephrotic syndrome patients in whom environmental, genetic and social factors may alter their pattern of response to therapy.

Therefore, we conducted this prospective trial in 20 steroid dependent nephrotic syndrome Egyptian children, who had a biopsy proven minimal change nephropathy and who had not received any form of adjunctive therapy, to study their pattern of response to a fixed and longer period of levamisole treatment (6 months), following them up for a further 6 months after stopping the drug.

Materials and methods

Subjects

This prospective study included 20 children with primary nephrotic syndrome selected from patients attending the outpatient clinic or admitted to the Nephrology Department of our centre in the period between May and December 1998. Their age ranged from 3 to 15 years and they comprised 16 boys and 4 girls. The initial corticosteroid protocol for patients at the start of the disease was the ISKDC protocol (short attack treatment). All of them had a steroid dependent pattern of response defined as occurrence of complete remission on steroids but relapse while withdrawing or within 2 weeks after discontinuing steroid treatment [10]. Also, all of them had biopsy-proven minimal change lesions. All patients received more than one steroid course (median = 4.5 and range = 1–24 courses) (Table 1). None of our children had received any type of adjunctive therapy for their nephrotic status before the study. All patients had normal creatinine clearance corrected to surface area [11], normal liver function tests and normal complete blood count at the start of the study. Parental consent was obtained before the study and the study was approved by the Scientific and Ethics Committee of the hospital.

Table 1 Baseline characteristics of patients at the start of the study

Age (years) (mean ± SD)	7.4±2.89
Sex (female/male)	4/16
Duration of steroid treatment (months) (mean ± SD)	41.51±28.91
Number of steroid courses (median/range)	4.5/1–24
Maintenance of every other day steroid dose (mg/kg) (median)	0.36
Hypertension	8/20
Weight (kg) (mean ± SD)	29.65±11.83
Height (cm) (mean ± SD)	123.2±16.24
Height percentile	
5th	1
10th	2
25th	2
50th	6
75th	5
90th	2
95th	2
Cushingoid facies	5/15

Study design

All patients were in relapse at the start of the study. This relapse qualified them for recruitment to the study and was treated by increasing steroid dose to 2 mg/kg/day until remission (protein-free urine on three consecutive days), then decreasing to 1 mg/kg on alternate days for 14 days. At that point levamisole was started in a dose of 2.5 mg/kg on alternate days (the same days as the steroid dose). After the addition of levamisole, steroids were continued at 1 mg/kg on alternate days for a further 14 days, then reduced by 0.25 mg/kg every 14 days until complete withdrawal [6].

Levamisole was continued for 6 months as long as remission was maintained. During this period steroids were gradually tapered to be stopped according to the previously mentioned protocol. Levamisole was stopped if relapse occurred at any time during the treatment period. Relapse was defined as a protein positive urine of +++ for 3 consecutive days [6]. This result was confirmed by a 24-h urinary protein >50 mg/kg [12].

Patients were followed up monthly during the 6-month treatment period and for a further 6 months after stopping treatment. The end point of the study was either a 6-month treatment-free follow-up period or relapse at any time.

At each visit, clinical assessment, urinalysis, 24-h urinary protein, complete blood count, serum creatinine, liver function tests and serum cholesterol were performed for all patients. In addition, parental monitoring was done during intervisit periods based on reappearance of edema, decreased urine output or observation of any complications, and in such cases untimed hospital visits were done. For some children, parental monitoring was also done by performing urine heat tests for protein.

Statistical analysis

Homogeneous data are expressed as means ± SD while non-homogeneous data are expressed as medians. A comparison between leukocytic count before and at the end of levamisole treatment (Table 2) was done by using the paired *t*-test.

Results

Baseline characteristics are shown in Table 1. Hypertension was present in 40% of children at start of the study and was defined as diastolic blood pressure above the 95th percentile for age, sex and height [13]. Three patients were obese as defined by body weight above the 95th percentile for age and sex [14]. Also, five patients were cushingoid at the start of the study. One patient was having personality changes in the form of aggression and

Table 2 Effect of levamisole on leukocytic count (WBCs × 10^3/μl) in levamisole responders and non-responders[a]

	WBCs before levamisole treatment (mean ± SD)	WBCs at the end of levamisole treatment (mean ± SD)	*P* value
Responders (*n*=11)	12.96±5.86	7.91±2.35	0.007[b]
Non-responders (*n*=9)	12.66±4.89	11.76±2.89	0.63

[a] Levamisole responders are those in whom steroids could be successfully stopped for more than 2 weeks
[b] Significant using *t*-test

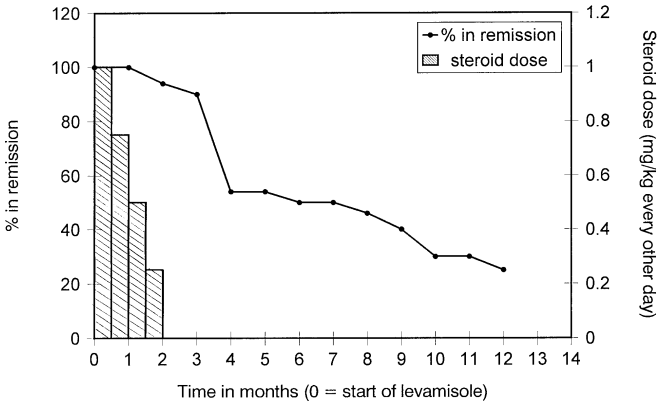

Fig. 1 Percentage of patients in remission throughout the study period beginning from the time of start of levamisole treatment

nervousness, which was noticed by parents and schoolteachers after commencement of steroid therapy. Another child had a history of recurrent urinary tract infection and a radioisotope study revealed the presence of coincidental first degree right vesicoureteric reflux. Fifteen children (75%) were at or above the 50th percentile for height.

During the 6-month period of levamisole treatment, 11 out of 20 children (55%) were able successfully to stop steroids for more than 2 weeks, i.e. became no longer steroid dependent (levamisole responders). Throughout the rest of the study period, this remission was maintained for variable durations (median 6.83 months, range 0.23–11.67 months).

Percentage of patients in remission throughout the study is shown in Fig. 1. At the end of the 6-month treatment period with levamisole (i.e. 4 months after steroid discontinuation), ten patients (50%) were in remission on levamisole alone. At the end of the 12-month study period, five patients (25%) were still in remission without any treatment for the previous 6 months.

As already mentioned, only 5 out of 20 children (25%) maintained their remission throughout the study. The remaining 15 children (75%) experienced relapse at some time during the study.

During levamisole therapy, none of our patients developed neutropenia, gastrointestinal manifestations or any of the reported levamisole side effects. At the end point of the study – which was either the occurrence of relapse or the 6 months continuation without relapse after stopping treatment – only 3 patients were hypertensive and none of the patients was cushingoid compared to 11 hypertensive patients and 5 cushingoid patients at the start of the study. None of the patients developed neutropenia, but the leukocyte count was lower at the end of levamisole treatment than that before the start of treatment in both levamisole-responders and non-responders. As shown in Table 2, such a reduction in leukocyte count was significant in levamisole responders (P=0.007) and non-significant in levamisole non-responders (P=0.63).

Discussion

One of the most difficult problems in the care of patients with MCNS is the multiplicity of relapses. Attempts to maintain remission and to prevent relapses often result in several hazards. The immunomodulatory agent levamisole has been used in such cases as an adjunctive therapy [6, 15] as a good alternative to major immunosuppressives [16]. However, long term levamisole treatment may be hampered by side effects such as vasculitis [17, 18], granulocytopenia, psoriasis-like cutaneous reaction [19], leukemia [20] and gastrointestinal manifestations [6].

We conducted this prospective trial to study the efficacy and safety of levamisole as an adjunctive therapy in steroid dependent MCNS children.

The initial steroid course was given to patients 41.51±28.91 months before the start of the study. At the commencement of the study, 40% of our MCNS children were hypertensive. This incidence is far above that reported by ISKDC in 1978 (13%). This big difference may be due to differences in definition of hypertension (ISKDC defines it as diastolic blood pressure above the 98th percentile). It may also be attributed to steroid therapy in our patients (the ISKDC report is concerned with patients at the time of diagnosis of their nephrotic syndrome). Other side effects of steroid therapy included obesity and cushingoid facies. In the child who was having personality changes, although this may be attributed to steroid therapy because these changes were noticed after starting steroid treatment, the psychosocial impact of the disease itself cannot be excluded. Fortunately, 75% of children were at or above the 50th percentile of height. This may reflect our policy of turning to every other day steroids as soon as remission has occurred in the treatment of relapse.

At the end of the 6-month treatment with levamisole, 10 out of 20 children (50%) were in remission in spite of steroid discontinuation after the first 2 months and continuing on levamisole alone for the subsequent 4 months. This number gradually decreased so that 6 months after stopping treatment, five of our patients (25%) were still in remission. Nevertheless, our results are higher than the results obtained by the British Association for Paediatric Nephrology study with 14 out of 31 patients (45.16%) maintained on remission after 3 months of levamisole treatment and only 4 of them (12.9%) maintained on remission 3 months after stopping the drug. This difference may be attributed to the longer duration of levamisole treatment and the follow-up period in our study. It may also be attributed to variations in steroid dependent nephrotic patients who were included in both studies. While we included any steroid dependent MCNS child regardless of the dose of steroids on which they were maintained (median = 12.5 mg every other day), the British Association for Paediatric Nephrology study included only those nephrotic children who were dependent on high-dose steroids (=0.5 mg/kg on alternate days). Furthermore, differences may be due to genetic and racial factors, which may alter the pattern of re-

sponse to therapy. Ksiazek and Krynski [9] reported a higher number (45.5%) of steroid dependent nephrotic patients who were able to withdraw from steroids and maintain remission for more than 6 months after levamisole therapy perhaps because they did not stop levamisole throughout the study.

In our study, patients who were able successfully to stop steroids maintained this remission for a median period of 6.83 months. This period was far less than that reported by Dayal et al. [15] (12 months). This big difference may be attributed to differences in patient selection. Dayal et al. tried levamisole in steroid sensitive nephrotic syndrome children after induction of steroid-induced remission for their first attack. Also Tenbrock et al. [19] reported a longer median duration of remission than that reported by our study (10 vs 6.83 months) perhaps because they studied levamisole in frequently relapsing and not steroid dependent patients.

Fortunately, in our study, throughout the 6-month treatment period with levamisole, no side effects were attributed to the drug. This agrees well with the safety of using levamisole for 3 months reported by the British Association for Paediatric Nephrology [6] and may suggest that extending treatment with levamisole to 6 months can be safely tried. Side effects reported by other authors [17–20] seem to be due to protracted levamisole use or idiosyncrasy. Additionally in our patients, as was expected due to withdrawal of steroids, some steroid side effects decreased such as hypertension and cushingoid facies. None of our patients developed neutropenia. However, levamisole treatment did result in a reduction of leukocyte count. This reduction was significant in levamisole responders but insignificant in levamisole non-responders. This difference may be correlated with the pattern of response. Nevertheless, it may be due to a longer duration of treatment with levamisole in levamisole responders (6 months in all patients but one, who relapsed before continuing this period) than that in levamisole non-responders (only until relapse has occurred).

In conclusion, our study indicates that levamisole may be safely tried for 6 months in children with steroid dependent MCNS before adopting other types of adjunctive therapy which may cause serious side effects. This may be effective in withdrawing steroids in a subset of these patients.

Our protocol entailed the use of levamisole for 6 months. Longer treatment periods may be expected to induce longer remission. Moreover, a short course resulting in a return to steroid therapy will not impact on reducing steroid toxicity in the long run. Therefore, further studies are necessary to study the effects of long term levamisole therapy. However, the balance between the possible prolongation of the treatment period and the frequency of complications (not constant but unpredictable) should be considered.

Acknowledgements The authors express their gratitude to Fathya Gado and Atalla Al-Kot for their technical assistance. In addition, the authors acknowledge Sahar Abdel-Rahman for her statistical assistance and Ola Ali for typing this work.

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