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Levamisole therapy in corticosteroid-dependent nephrotic syndrome

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Abstract. The effect of prolonged treatment with levamisole was examined in 43 patients (30 boys) with steroid-dependent nephrotic syndrome (SDNS). The mean age at institution of treatment was 4.0 ± 2.0 years. Fourteen patients had previously received cyclophosphamide with an ensuing remission of 8.5 ± 10 months. Following induction of remission with prednisolone, levamisole was administered at a dose of 2.5 mg/kg body weight on alternate days. Prednisolone was tapered by 2.5–5 mg every 4 weeks to 0.5 mg/kg on alternate days. The duration of levamisole therapy ranged from 6 to 31 months (mean 17.4 ± 8.4 months); 15 patients received levamisole for more than 18 months and 10 for more than 24 months. Prednisolone was discontinued in 18 patients after a mean duration of 11.7 ± 7.1 months, whereas in 21 patients its dose was reduced to 0.2–0.4 mg/kg on alternate days. The mean relapse rate prior to levamisole therapy was 3.0 ± 1.5 relapses/year, which reduced to 0.9 ± 0.7 relapses/year during levamisole treatment ($P < 0.001$). A comparison of the response in 14 patients who had previously received cyclophosphamide with the other 29 patients did not show any significant difference. There were no side effects of levamisole therapy. Our findings suggest that prolonged treatment with levamisole is beneficial and safe in SDNS, with a marked steroid-sparing effect. A significant proportion of these patients can be kept in remission on levamisole alone.

Key words: Minimal change nephrotic syndrome – Levamisole – Cyclophosphamide

Introduction

Nephrotic syndrome which responds to corticosteroid therapy and is characterized by minimal renal histological lesions (minimal change nephrotic syndrome, MCNS) is associated with several abnormalities of the immune system [1]. Based on the assumption that such perturbations may be of pathogenic significance, levamisole, a drug that modulates phagocytic and lymphocytic function [2], has been used for induction and maintenance of remission in patients with MCNS [3, 4]. A few studies have shown a partial steroid-sparing effect of levamisole in frequently relapsing (FRNS) and steroid-dependent nephrotic syndrome (SDNS) [5–8].

We earlier observed that whereas a 12-week course of levamisole reduced the relapse rate in patients with FRNS, the effect was not sustained and most patients relapsed on stopping the drug [9]. We have now examined the effect of a prolonged course of levamisole in 43 patients with SDNS and found that it offers considerable benefit.

Patients and methods

All patients included had corticosteroid-responsive SDNS, defined by the occurrence of two consecutive relapses of nephrotic syndrome while receiving prednisolone 2 mg/kg on alternate days or within 15 days of its discontinuation. The study was approved by the ethics committee of the All India Institute of Medical Sciences and informed parental consent was obtained.

The definitions and methods of investigations have been reported earlier [10]. Levamisole, at a dose of 2.5 mg/kg body weight on alternate days, was instituted immediately at the end of a 6-week course of prednisolone (2 mg/kg body weight daily in 2–3 divided doses for 2 weeks followed by the same amount given as a single dose on alternate days for the next 4 weeks). Prednisolone was then tapered by 2.5–5 mg every 4 weeks to 0.5 mg/kg on alternate days, while levamisole was continued at the same dose. An attempt was made to stop prednisolone after 4–6 months.

The parents maintained records of periodic urine tests for protein (Albustix or heat test). The patients were regularly seen at the pediatric nephrology clinic, where the urinalysis was repeated at each visit. Relapse was defined as sustained proteinuria (3+ to 4+) for at least 3 days, which required daily prednisolone therapy to achieve remission (absence of proteinuria). Blood leukocyte counts were carried out at 2-week intervals. Neutropenia was defined as a neutrophil count of less than 1,500/mm^3.

Relapses that occurred during administration of levamisole were treated with the prednisolone regimen mentioned above while levami-

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Table 1. Baseline clinical and laboratory characteristics of the 43 patients with steroid-dependent nephrotic syndrome

Features	Mean (SD) (n = 43)	Range
Age at onset (years)	3.0 (2.0)	0.9–10
Age at treatment (years)	4.0 (2.0)	1.3–10
Serum cholesterol (mg/dl)	426 (168)	198–770
Serum albumin (g/dl)	1.8 (0.6)	0.7–3.4
Serum creatinine (mg/dl)	0.6 (0.2)	0.1–1.1
Time from completion of alkylating therapy (years)	1.2 (0.9)	0.6–3

Table 2. Relapse rate in patients before and during levamisole therapy

	Number of relapses per year	
	Range	Mean ± SD
Prior to levamisole therapy	1.2 – 7.2	3.0 ± 1.5
During levamisole therapy	0.4 – 3.4	0.9 ± 0.7*

* $P < 0.001$ vs. before therapy

sole was continued. Levamisole therapy was considered effective when it was possible to reduce the maintenance dose of prednisolone to less than 0.5 mg/kg on alternate days. Levamisole was given for at least 6 months before considering it ineffective, defined as occurrence of relapse on prednisolone of more than 0.5 mg/kg on alternate days on two occasions.

The relapse rate (relapses per year) preceding the institution of levamisole was compared with that during therapy; each patient thus served as his own control. Wilcoxon's sign rank test was used for statistical analysis.

Results

Of 43 patients with steroid dependence, 30 were boys. Their clinical data are shown in Table 1. None had hematuria or a reduction in creatinine clearance. Renal biopsy performed in 19 patients showed MCNS. Fourteen patients had previously received cyclophosphamide (2 mg/kg for 12 weeks), with subsequent remission ranging from 1 to 36 months (mean 8.5 ± 10 months). The side effects from prolonged corticosteroid therapy included marked cushingoid features (hirsutism, obesity) in 20, sustained hypertension in 3, and steroid psychosis in 2 patients.

The duration of levamisole therapy ranged from 6 to 31 months (mean 17.4 ± 8.4 months). Fifteen patients received treatment for more than 18 months and 10 for more than 24 months. In 2 patients levamisole was discontinued after 28 and 31 months, with continued remission for 8 and 12 months, respectively. Levamisole was considered beneficial in 39 patients. Prednisolone was discontinued in 18 of these after a mean duration of 11.7 ± 7.1 months (range 4–25 months); they have remained in remission on levamisole alone for a mean duration of 16 ± 8.2 months. Five of these patients had earlier received cyclophosphamide with ensuing remissions of 3–24 months (11.9 ± 6.9 months). In the remaining 21 patients, the dose of prednisolone was reduced to 0.2–0.4 mg/kg on alternate days, with continued remission for 20.5 ± 8.7 months.

Table 3. Relapse rate (relapses per year) in patients with and without previous cyclophosphamide therapy[a]

	With previous cyclophosphamide therapy (n = 14)	Without cyclophosphamide therapy (n = 29)
Prior to levamisole therapy	2.7 ± 0.8 (1.4–4.8)	3.0 ± 1.1 (1.2–7.2)
During levamisole therapy	0.8 ± 0.3* (0–1.6)	0.9 ± 0.3* (0–3.4)

* $P < 0.001$ vs. before therapy
[a] Mean ± SD with range in parentheses

The relapse rate in the 43 patients prior to levamisole treatment ranged between 1.2 and 7.2/year (mean 3.0 ± 1.5 relapses/year). During levamisole treatment, the number of relapses significantly reduced to 0.4–3.4/year (mean 0.9 ± 0.7 relapses/year, $P < 0.0001$) (Table 2).

Cushingoid features, hirsutism, and steroid psychosis resolved in 15, 5, and 2 patients, respectively and hypertension was controlled by atenolol treatment in 3. No episodes of neutropenia were seen. None of the patients had any other side effects of levamisole treatment, such as rash, gastrointestinal upset, or convulsions.

Levamisole was considered ineffective in 4 patients, all of whom required more than 1 mg/kg prednisolone on alternate days to prevent relapses, and was discontinued after 6–10 months (mean 7.3 months) of treatment. These patients did not show any difference in their clinical and laboratory characteristics (including age at onset of nephrotic syndrome, age at treatment with levamisole, and previous relapse rate) from those who benefitted from this drug. One had earlier received cyclophosphamide, with a remission of 17 months. Renal biopsy in 2 of these patients showed MCNS, with mesangial IgM deposits in 1.

The relapse rate, prior to the institution of levamisole, in patients who had previously received treatment with cyclophosphamide was similar to those who had not (Table 3). Following therapy with levamisole, there was a significant reduction in relapse rates in the two groups.

Discussion

Patients with SDNS present difficult problems in management. Prolonged or repeated use of corticosteroids often results in serious side effects, such as cushingoid obesity, striae, hypertension, growth failure, and psychoemotional changes [11]. Cyclophosphamide has been extensively employed in such patients and, whereas it induces extended remissions in 30%–40% of cases, many others get short remissions and continue to have a corticosteroid-dependent course. Moreover, the beneficial effect of cyclophosphamide is less impressive in young children [12], in whom the management of SDNS is particularly difficult.

Levamisole has been used in patients with FRNS or SDNS to achieve a sustained remission. In previous studies administration of levamisole at 2.5 mg/kg on alternate days

or twice weekly for 6–18 months concurrently with alternate-day prednisolone caused a decrease in the number of relapses and the amount of prednisolone required [4–7]. Niaudet et al. [7] treated 30 SDNS patients with levamisole for a mean duration of 9.9 months. The treatment was effective in almost half the patients, who had no relapses despite a significant reduction in the dose of prednisolone. The British Association for Pediatric Nephrology reported prolonged remissions in patients with SDNS given alternate-day levamisole for 16 weeks [8]. However, relapses occurred in a majority of cases after the treatment was stopped. Neuhaus et al. [13] also showed that levamisole at a dose of 2.5 mg/kg on alternate days for 6–18 months was effective in inducing remission in more than half the patients.

Our findings indicate that long-term levamisole therapy with low-dose prednisolone can lead to a significant reduction of the relapse rate in SDNS patients. Furthermore, prednisolone can be discontinued or its dose reduced to less than 0.5 mg/kg on alternate days in a majority of patients. No side effects were observed in our patients, some of whom received levamisole for over 2 years. The chief hazard of levamisole therapy is neutropenia, which is uncommon and reversible. Considering our data with previous reports, in only 4 of 228 patients who received levamisole was a neutrophil count below 2,000/mm^3 documented [7–9, 14]. However, the occurrence of neutropenia is not dose dependent, and periodic blood cell counts are necessary.

The options for treatment of patients with SDNS are limited. Further administration of large doses of corticosteroids would be contraindicated. Second courses of cyclophosphamide or chlorambucil carry the hazard of gonadal toxicity. Cyclosporin has been used in patients who continue to be steroid dependent despite treatment with cyclophosphamide [13, 15]. While a majority of patients remain in remission during cyclosporin therapy, relapses occur when this drug is stopped [16]. Cyclosporin, besides being nephrotoxic, is an expensive drug and its use requires monitoring of blood levels. Levamisole appears to be effective in reducing relapses in patients with SDNS, including those previously treated with cyclophosphamide. The cost of treatment with levamisole is considerably lower than cyclosporin and its extended use is usually not associated with significant side effects. We suggest that prolonged levamisole therapy may be considered in patients with SDNS before exposing them to cytotoxic drugs or cyclosporin.

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