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Levamisole treatment in steroid-sensitive and steroid-resistant nephrotic syndrome

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Abstract. Since 1992 we have treated 11 children with frequently relapsing steroid-sensitive (*n*=6) or steroid-resistant (*n*=5) nephrotic syndrome with levamisole. All had been non-responsive to other immunosuppressive medication before levamisole treatment. All steroid-sensitive patients had signs of steroid toxicity. At least 1 kidney biopsy had been performed prior to study in each patient. Five children had minimal glomerular changes and the other 6 focal segmental glomerular sclerosis. The patients were treated with levamisole (2.5 mg/kg per 48 h) for at least 2 months (up to 18 months, median 10 months). Two patients had additional immunosuppression (cyclosporine A) during levamisole treatment. All patients with steroid-sensitive nephrotic syndrome became free of proteinuria within 2 months and have remained in remission after discontinuation of levamisole (follow-up time 8–50 months, median 24 months). None of the children with steroid-resistant nephrotic syndrome experienced a remission. Side effects were observed in 2 patients and included a granulocytopenia and a severe psoriasis-like cutaneous reaction; both were reversible after discontinuation of levamisole. We conclude that levamisole is of benefit in steroid-sensitive nephrotic syndrome but not in steroid-resistant nephrotic syndrome.

Key words: Levamisole – Steroid-sensitive nephrotic syndrome – Steroid-resistant nephrotic syndrome

Introduction

Treatment of recurrent idiopathic nephrotic syndrome (INS) is often complicated by the toxicity of the therapeutic regimen with corticosteroids, alkylating substances, and/or cyclosporine A (CyA). An alternative is treatment with levamisole, a potent anthelmintic with immune-modulating properties [1–3]. Levamisole has been used sporadically in the treatment of INS with variable success [4–15]. This led to a prospective randomized study of the British Association of Paediatric Nephrology, which showed a high response rate and a significant steroid-saving effect of levamisole [16]. In the light of these data, levamisole has been recommended for the treatment of relapsing steroid-sensitive INS by some authors [17], but to our knowledge current treatment regimens vary considerably between different centers [18].

In contrast, experience in the treatment of steroid-*resistant* INS with levamisole is limited. There is only one published report, including three children with partially steroid-sensitive INS treated with levamisole. Two of these had a complete remission [19]. Since 1992 we have used levamisole in patients with INS and normal renal function as rescue therapy, i.e., only if other medications (steroids, CyA, alkylating agents) had been tried without lasting success. Our single-center experience indicates that levamisole treatment is of considerable clinical benefit, but only in patients with steroid-sensitive INS.

Patients and methods

A total of 11 patients (aged 4–18 years, median 12.5 years) were treated with levamisole (Table 1). Clinical course and response to treatment were classified according to criteria established by the German "Arbeitsgemeinschaft für Pädiatrische Nephrologie" (APN) [20]. Six children were classified as frequent relapsers and 4 as primarily steroid resistant. One initially steroid-sensitive patient (no. 7) acquired steroid resistance after 5 years and was classified as secondarily steroid resistant. All patients had been treated with at least one additional immunosuppressive agent before levamisole therapy (Table 1). All patients had previously undergone at least 1 kidney biopsy (Table 1). Histology in 5 patients showed minimal glomerular changes, while 6 patients had focal segmental glomerular sclerosis (FSGS).

Before starting levamisole therapy, remission was achieved in steroid-sensitive patients using a standard course of prednisone (60 mg/m² per day). After 3 days of protein-free urine, levamisole was introduced at a dosage of 2.5 mg/kg every 48 h and prednisone was reduced according to the APN protocol (40 mg/m² per

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Table 1. Responses of 11 patients with idiopathic nephrotic syndrome (INS) to levamisole treatment

Patient no.	Sex	Age at therapy (years)	Clinical course	Biopsy	Therapy before levamisole	Duration of levamisole therapy	Side effects of levamisole	Results
1	M	14	Steroid-sensitive INS since 07/82	Minimal change 10/84 Minimal change 10/87 FSGS 11/92	Cyclophosphamide 1984 CyA 86/87 and 88/89	10/93–03/95	None	Remission
2	M	16	Steroid-sensitive INS since 1980	Minimal change 1979 1983/1986/1987	Chlorambucil 04–08/80 Cyclophosphamide 12/83–02/84 CyA 86–88	03/93–10/94	None	Remission
3	M	13	Steroid-sensitive INS since 1983	FSGS 07/87	CyA 10/89–03/93	03/93–10/94	None	Remission
4	M	12	Steroid-sensitive INS since 05/86	Minimal change 10/86	Cyclophosphamide 03/87–05/87, 03/89 CyA 09/90–10/92	06/92–10/92	Cutaneous reaction	Remission
5	F	18	Steroid-sensitive INS since 1980	Minimal change 08/81	Cyclophosphamide 1981	10/96–12/96	Agranulcytosis	Remission
6	F	8	Steroid-sensitive INS since 1988	Minimal change 11/92	CyA 12/96–03/96	04/96–04/97	None	Remission
7	F	18	Steroid-sensitive INS 1995 Secondarily steroid-resistant since 1995	Minimal change 1988	Cyclophosphamide 1988 CyA 03/90–10/93 11/93–03/95	10/93–12/94 05/95–07/95	None	Initial remission, relapse after 10 months no remission
8	F	4	Steroid-resistant INS since 05/93	Minimal change 01/94 FSGS 07/95	CyA 08/93–10/96/since 05/97 Cyclophosphamide 07/94–09/94	08/95–02/97	None	No remission with levamisole, remission after 2nd course of CyA
9	M	7	Steroid-resistant INS since 1991	Minimal change 1991 FSGS 07/96	CyA 08/93–10/95 Chlorambucil 1993	08/96–02/97	None	No remission
10	M	14	Steroid-resistant INS since 03/95	FSGS 04/95	CyA 04/95–02/96	10/96–03/97	None	No remission
11	M	13	Steroid-resistant INS since 03/96	FSGS 07/96	CyA 1996	11/96–03/97	None	No remission

FSGS, focal segmental glomerular sclerosis; CyA, cyclosporine A

48 h) during the following 4 weeks. Two patients received additional therapy with CyA during treatment with levamisole.

In patients with steroid-resistant INS, the same dose of levamisole was introduced and steroid therapy was tapered regardless of proteinuria. Renal function of all patients was normal (creatinine clearance calculated from a 24-h urine collection). Two patients had additional immunosuppressive treatment with CyA while on levamisole; 3 patients did not receive any other immunosuppressive treatment at that time (Table 1).

Before starting therapy informed consent was obtained from the patient and/or parents. The patients were seen weekly in the outpatient clinic during the first few weeks for a physical examination and control of laboratory data (white blood cell count, serum electrolytes, serum total protein, creatinine, urea, liver enzymes, and coagulation parameters). Levamisole therapy was stopped after a minimum of 2 months, if no decrease in proteinuria (urine dipstick, 24-h urine collection) was apparent. In responders, it was continued for at least 12 months, but in 3 patients treatment was extended to 18 months (median 12 months).

Results

All 6 patients with steroid-sensitive INS experienced a remission during the first 2 months of therapy (100%). All additional immunosuppressive treatment could be discontinuated during levamisole treatment. The duration of levamisole therapy was 2–18 months (median 10 months). In 1 patient who was treated for 2 months only, treatment had to be stopped because of an adverse side effect (neutropenia); however, the patient had no relapse of proteinuria. In another patient, a severe psoriasis-like skin reaction was observed. The patient required hospitalization and levamisole was stopped immediately. Symptoms disappeared gradually after several weeks. This side effect was retrospectively also attributed to the discontinuation of CyA leading to an exacerbation of the pre-existing psoriasis. At present, all patients are still in remission after a follow-up period of 8–50 months (median 24 months).

All 4 patients with primarily steroid-resistant INS had no remission (0%). The duration of therapy was between 6 and 18 months (median 9 months). One patient (no. 7) went into remission lasting for 10 months with levamisole. After a relapse, steroids were reintroduced without obtaining a remission, and the patient was classified as secondarily steroid resistant. A second trial of levamisole had no effect and was stopped after 2 months.

Discussion

Levamisole is a potent anthelmintic with immunomodulatory properties which were first described in clinical studies in the 1970s [1–3]. The drug has a T-cell- and macrophage-activating effect in vitro without any influence on antibody production [1, 2]. The use of levamisole thus seems contradictory to the normal therapeutic rationale of immunosuppression applied in patients with INS. This might be one of the reasons why levamisole has not been used widely. There is only one published prospective trial with levamisole in patients with nephrotic syndrome [16]. In Germany, its use has been regarded rather critically [18]. Although levamisole has been tried for many years, there is no information available regarding long-term safety and there are no official recommendations for dosage and duration of therapy in INS. We have adopted the dose and duration of therapy from the British study [16].

We started treating our patients with levamisole as “rescue-therapy” in 1992. All children were steroid sensitive and had signs of steroid toxicity. Other medications (CyA, alkylating agents) had been tried without lasting success. These patients were cured by levamisole without any further relapses. This supports the results reported by other groups in patients with steroid-sensitive INS [4–15]. This seems a remarkably high success rate if one considers that all patients had been unsuccessfully treated with other immunosuppressive agents previously. However, our study was uncontrolled and, since spontaneous remissions are known to occur in patients with INS, especially during puberty, we cannot rule out spontaneous resolution of the disease in our patients with steroid-sensitive INS.

Because of these encouraging results, we started to treat children with steroid-resistant INS associated with FSGS. One of these patients had a secondary steroid-resistant INS with minimal glomerular changes in a previous kidney biopsy. All children had normal renal function which was not adversely affected by levamisole treatment. However, none of these patients went into remission or showed reduction of proteinuria. To our knowledge this is the first report of levamisole treatment in patients with steroid-resistant INS. Although levamisole therapy was apparently of no benefit, we felt justified in trying this form of treatment, since anecdotal observations suggest that some steroid-resistant patients may respond to a large variety of therapeutic methods including intravenous gamma globulin and lipid-lowering agents, amongst others [21, 22].

The encouraging results of others as well as our study should lead to more prospective studies to optimize duration and dosage of therapy in steroid-sensitive nephrotic syndrome. In our opinion levamisole is a reasonable treatment option in steroid-sensitive nephrotic syndrome, especially if signs of steroid toxicity have appeared.

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Literature abstract

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Potassium metabolism in extremely low birth weight infants in the first week of life

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Objective. Nonoliguric hyperkalemia has been reported to occur in the first week of life in as many as 50% of extremely low birth weight (ELBW) infants. We studied potassium balance and renal function in the first 5 days of life to characterize potassium metabolism during the three phases of fluid and electrolyte homeostasis that we have described in ELBW infants and to elucidate the factors that contribute to the development of nonoliguric hyperkalemia.
Study design. Plasma potassium concentration (PK), potassium intake and output, and renal clearances were obtained for the first 6 days of life in 31 infants with a birth weight of 1000 gm or less. Collection periods in which urine flow rate was greater than or equal to 3 ml/kg per hour and weight loss was greater than or equal to 0.8 gm/kg per hour were denoted to be diuretic. Prediuresis includes all collection periods before the first diuretic period; diuresis includes all collection periods between the first and last diuretic periods; postdiuresis includes all collection periods after the last diuretic period. Infants with a PK greater than 6.7 mmol/L on at least one measurement were denoted to have hyperkalemia.
Results. PK increased initially after birth – despite the absence of potassium intake – and then decreased and stabilized by the fourth day of life. Diuresis occurred in 27 of 31 infants. The age at which PK peaked was closely related to the onset of diuresis. PK decreased significantly during diuresis as the result of a more negative potassium balance, despite a significant increase in potassium intake. In fact, PK fell to less than 4 mmol/L in 13 of 27 infants during diuresis. After the cessation of diuresis, potassium excretion decreased even though there was a significant increase in potassium intake, potassium balance was zero, and PK stabilized. Hyperkalemia developed in 11 of 31 infants. The pattern of change in PK with age was similar in infants with normokalemia and hyperkalemia: PK initially increased (essentially in the absence of potassium intake) and then decreased and stabilized by the fourth day of life. However, the rise in PK after birth was greater in infants with hyperkalemia than in those with normokalemia: 0.7+/–0.2 versus 1.8+/–0.2 mmol/L ($P<0.001$). No differences in fluid and electrolyte homeostasis or renal function were identified as associated with hyperkalemia.
Conclusions. PK increases in most ELBW infants in the first few days after birth as a result of a shift of potassium from the intracellular to the extracellular compartment. The increase in the glomerular filtration rate and in the fractional excretion of sodium, with the onset of diuresis, facilitates potassium excretion, and PK almost invariably decreases. Hyperkalemia seems to be principally the results of a greater intracellular to extracellular potassium shift immediately after birth in some ELBW infants.