ORIGINAL ARTICLES

Levamisole treatment in steroid sensitive nephroti syndrome

Hammad O. Alshaya, Jameela A. Kari

ABSTRACT

Objectives: To evaluate the effectiveness of levamisole in maintaining remission in children with steroid-sensitive nephrotic syndrome (SSNS) w had a frequent relapsing or steroid-dependant course.

Methods: All children with SSNS who had a frequent relapsing or steroid dependent course and were treated with levamisole between 1997 and 20 King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia wer reviewed. All patients were treated by the same steroid protocol used in c unit. Levamisole was considered effective if the patient successfully rema remission on Prednisolone 0.5 mg/kg/48 hours or less.

Results: Nine children were treated with levamisole (3mg/kg/48 hours) v median (range) age of 6 (3.5-10) years. Seven received levamisole for m than 6 (6-24) months and 2 were excluded because they did not adhere t treatment. Levamisole was effective in 4 patients (57%) with remarkable reduction in the number of relapses and the steroid maintenance dose. Re biopsy was performed in 4 patients: 2 responders with biopsy findings of minimal change disease (MCD) and mesangioproliferative glomerulonephr and another 2 non responders with biopsy findings of MCD and focal segm glomerulosclerosis. No significant side effect was observed.

Conclusions: Levamisole is effective in maintaining remission in steroid S in Arab children and has few side effects.

Saudi Medical Journal 2002; Vol. 23 (9): 11(

The most common form of childhood idiopathic nephrotic syndrome (INS) characterized by minimal change histology (MCNS), which is usually steroc sensitive (SSNS). However subsequent relapses of NS is the usual course this disease in most patients1,2 and up to 43% will be frequent relapsers Treatment of recurrent relapses is often complicated by the toxicity of the therapeutic regimen with corticosteroids and therefore a substantial propo of steroid sensitive nephrotics will require further immunosuppressive treatment. One or more courses of cytotoxic agent either cyclophospham chlorambucil5 or prolonged course of cyclosprin6 has been shown to be effective in reducing the number of relapses and therefore avoiding steroi effect. However such treatment is hampered with considerable side effect alternative immune-modulating agent is levamisole, which was used sporadically with variable success and minimal side effects in the 80's.7-9 was followed by randomized studies, which showed the high response rat significant steroid sparing effect of levamisole.10-13 In view of the result

these studies, levamisole had been recommended as the treatment of fre
relapsing SSNS and this has led to successful reports from different parts
world,14-16 however, to date there is no report of its use in Arab childrer
treated a group of children (mainly Arab) with frequently relapsing SSNS,
levamisole and report the result of its use. We also discuss the difficulty c
obtaining the medication by some parents, which resulted in non-adherer
treatment.

Methods. Nine children (6 males and 3 females), suffering from frequently
relapsing or steroid dependent INS, aged 3.5-10 years (median 6.5) were
treated with levamisole between 1997 and 2001 at King Abdul-Aziz Unive
Hospital, Jeddah, Kingdom of Saudi Arabia. Median (range) age at the on
the disease was 2.5 (2-7.5) years and median duration of the disease 1.5
8 years). All the patients had frequent relapses as defined by 2 or more
episodes of nephrosis within 6 months of the initial response or 4 or more
within any 12-month period. Some of the patients were steroid dependan
recurrence of nephrosis when the dose of corticosteroids is reduced or wit
weeks after discontinuation of therapy. Levamisole, at a dose of 3 mg/kg
weight on alternate days, was instituted immediately after induction of
remission by daily prednisolone (60mg/m2/day). Prednisolone was then
tapered to alternate days (40mg/m2/48 hours), and by 2.5-5 mg every 4
weeks while levamisole was continued at the same dose. An attempt was
to stop prednisolone after 4-6 months. Base line blood leukocyte counts v
performed at regular 2-month intervals. Neutropenia was defined as a
neutrophil count of less than 1,500/mm3. Relapses that occurred during
administration of levamisole were treated with the prednisolone regimen
mentioned above while levamisole was continued. Levamisole was consid
effective when it was possible to reduce the maintenance dose of predniso
to less than 0.5mg/kg on alternate days. Levamisole was given for at leas
months before considering it ineffective, and defined as occurrence of rela
on prednisolone of more than 0.5mg/kg on alternate days.

Results. Of the 9 patients with SSNS, 2 patients had levamisole treatment
less than 6 months because of parental discontinuation as a result of diffi
in obtaining the medicine. A10th patient had levamisole prescribed but he
not receive it as the pharmacist told the parents that it was antihelmintic,
another pediatrician who prescribed cyclophosphamide saw the patient. T
other 7 patients received levamisole for a median of (range) 12 (6-24) m
Six patients were Arabs and one was Indian. Four of them had a renal bio
had minimal change disease (MCD), one mesangioproliferative
glomerulonephritis (MePGN) and one focal and segmental glomerulosclero
(FSGS). Four patients (57%) responded to levamisole therapy: 2 with goo
response and 2 with partial response (Table 1). The first patient had no fu
relapses while on levamisole, he did not require any maintenance predniso
for 12 months and he did not have further relapses after stopping the
levamisole. The 2nd patient required low dose maintenance prednisolone
(0.5mg/kg/48 hours) to keep him off relapses while the 3rd and 4th patie
had infrequent relapses despite levamisole and low dose maintenance
prednisolone. The remaining 3 patients did not respond well and continue
relapse frequently despite levamisole and low dose maintenance predniso
Renal biopsy was performed on 2 of the non-responders; one had MCD ar
had FSGS. All non-responders had a course of cyclophosphamide; the pat
with FSGS did not respond and required cyclosporin A to control his recur

relapses. The patient with MCD had no relapses for 8 months followed by frequent relapses. The option of cyclosporin A therapy was discussed with parents but they could not afford it and therefore he was maintained on t lowest possible alternate dose of prednisolone with the plan to give him a dose of cyclophosphamide or chlorambucil if he showed any signs of sterc toxicity particularly growth impairment or sublenticular cataract. The 3rd patient who did not respond to levamisole was assumed to have MCD, wa treated with a course of cyclophosphamide and has responded with no fu relapses for the last 3.5 years. We did not observe any side effects in any our patients who received levamisole.

Discussion. We found like others7-16 that levamisole was effective in maint remission and reducing the number of relapses in children with SSNS. It v effective in 57% of all cases and in 50% of Arab children. This is similar t report from England,17 while others reported a higher response rate.14 T response to levamisole was not sustained in most of our patients which is agreement with previous studies. One patient had sustained remission, w could be explained by levamisole therapy or by the natural spontaneous remission of the disease. Levamisole is a potent antihelmintic with immunomodulatory properties.18 It has a T cell and macrophage activati effect in vitro without any influence on antibody production.18-19 It has b used in patients with frequently relapsing or steroid dependent SSNS to a sustained remission. Previous studies showed that levamisole administrat alternate days or twice weekly caused a decrease in the number of relaps the amount of prednisolone required.7-17 However, it's effect was not sustained as relapses occurred in the majority of cases after the treatmer stopped.12,17

Our case series indicates that levamisole alone or in combination with alte days low dose prednisolone could reduce relapses and maintain remission children with SSNS. We did not observe in any of our patients any side ef such as neutropenia,9 rash20 gastrointestinal upset or convulsions.21 Th similar to observations from previous studies where minimal side effects v recorded.10,15 Some of our patients experienced difficulty in obtaining levamisole for long course administration, which reflects the rarity of it's prolonged use by pediatricians and highlights the need to insure the avail of the medicine when it is prescribed to avoid incomplete course as occur 2 of our patients. Inadequate explanation regarding the history of the me and that it was originally used as an antihelmintic but found to be useful i cases of SSNS resulted in non-adherence to treatment in one patient.

In conclusion, the present case series demonstrates that levamisole thera reduces the overall relapse rate in Arab children with SSNS and minimizes dependency to steroids to keep them in remission. However double blind randomized studies are needed to confirm this conclusion.

From the Department of Pediatrics, King Abdul-Aziz University Hospital, J Kingdom of Saudi Arabia.

Received 10th February 2002. Accepted for publication in final form 1st Ju

2002.

Address correspondence and reprint request to: Dr. Jameela Kari, Associa
Professor, Pediatrics Department, King Abdul-Aziz University Hospital, PO
80215, Jeddah 21589, Kingdom of Saudi Arabia. Tel. +966 (2) 55677904
+966 (2) 6743781. E-mail: jkari@doctors.org.uk

References

1. Tejani A. Relapsing nephrotic syndrome. Nephron 1987; 45: 81-85.

2. Nephrotic syndrome in children: Prediction of histopathology from clini
and laboratory characteristics at time of diagnosis. A report of the Interna
Study of Kidney Disease in Children. Kidney Int 1978; 13: 159-165.

3. Barnett HL. International study of kidney disease in children. Nippon Ji
Gakkai Shi. Japanese Journal of Nephrology 1979; 21: 1141-1144.

4. Barratt TM, Bercowsky A, Osofsky SG, Soothill JF. Cyclophosphamide
treatment in steroid-sensitive nephrotic syndrome of childhood. Lancet 19
1: 55-58.

5. Grupe WE, Makker SP, Ingelfinger JR. Chlorambucil treatment of frequ
relapsing nephrotic syndrome. N Engl J Med 1976; 295: 746-749.

6. Tejani A, Suthanthiran M, Pomrantz A. A randomized controlled trial of
dose prednisone and ciclosporin versus high-dose prednisone in nephrotic
syndrome of children. Nephron 1991; 59: 96-99.

7. La Manna A, Polito C, Del Gado R, Foglia AC. Levamisole in childrens
idiopathic nephrotic syndrome. Child Nephrol Urol 1988; 9: 200-202.

8. Tanphaichitr P, Tanphaichitr D, Sureeratanan J, Chatasingh S. Treatme
nephrotic syndrome with levamisole. J Pediatr 1980; 96: 490-493.

9. Niaudet P, Drachman R, Gagnadoux MF, Broyer M. Treatment of idiopa
nephrotic syndrome with levamisole. Acta Paediatr Scand 1984; 73: 637-

10. Levamisole for corticosteroid-dependent nephrotic syndrome in childh
British Association for Paediatric Nephrology. Lancet 1991; 337: 1555-15

11. Tejani A, Suthanthiran M, Pomrantz A. A randomized controlled trial c
dose prednisone and ciclosporin versus high-dose prednisone in nephrotic
syndrome of children. Nephron 1991; 59: 96-99.

12. Durkan AM, Hodson EM, Willis NS, Craig JC. Immunosuppressive ager
childhood nephrotic syndrome: A meta-analysis of randomized controlled
Kidney Int 2001; 59: 1919-1927.

13. Dayal U, Dayal AK, Shastry JC, Raghupathy P. Use of levamisole in

maintaining remission in steroid-sensitive nephrotic syndrome in children
Nephron 1994; 66: 408-412.

14. Fu LS, Chi CS. Levamisole in steroid-sensitive nephrotic syndrome chi
with steroid-dependency and/or frequent relapses. Acta Paediatr Taiwan 2
41: 80-84.

15. Bagga A, Sharma A, Srivastava RN. Levamisole therapy in corticoster
dependent nephrotic syndrome. Pediatr Nephrol 1997; 11: 415-417.

16. Alsaran K, Grisaru S, Stephens D, Arbus G. Levamisole vs
cyclophosphamide for frequently-relapsing steroid-dependent nephrotic
syndrome. Clin Nephrol 2001; 56: 289-294.

17. Neuhaus TJ, Fay J, Dillon MJ, Trompeter RS, Barratt TM. Alternative
treatment to corticosteroids in steroid sensitive idiopathic nephrotic syndr
Arch Dis Child 1994; 71: 522-526.

18. Renoux G. The general immunopharmacology of levamisole. Drugs 19
20: 89-99.

19. Taki HN, Schwartz SA. Levamisole as an immunopotentiator for T cell
deficiency. Immunopharmacol Immunotoxicol 1994; 16: 129-137.

20. Rongioletti F, Ghio L, Ginevri F, Bleidl D, Rinaldi S, Edefonti A et al. Pu
of the ears: A distinctive vasculopathy with circulating autoantibodies
complicating long-term treatment with levamisole in children. Br J Derma
1999; 140: 948-951.

21. Palcoux JB, Niaudet P, Goumy P. Side effects of levamisole in children
nephrosis. Pediatr Nephrol 1994; 8: 263-264.