CLINICAL RESEARCH

Controlled trial of methylprednisolone pulses and low dose oral prednisone for the minimal change nephrotic syndrome

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Abstract

In a multicentre, randomised, prospective trial 89 patients (67 children and 22 adults) with the minimal change nephrotic syndrome were treated with three intravenous pulses of methylprednisolone followed by low dose oral prednisone for six months (group given methylprednisolone) or with high dose oral prednisone for four weeks followed by low dose oral prednisone for five months (control group). Five patients in the group given methylprednisolone and one in the control group did not respond initially. The time to response was shorter in children treated with methylprednisolone. No significant differences between the two groups were observed in the number of patients who relapsed

or number of relapses per patient per year. Patients given methylprednisolone tended to relapse earlier than patients in the control group. Side effects related to treatment were significantly fewer in the group given methylprednisolone than in the control group.

These data suggest that a short course of methylprednisolone pulses followed by low dose oral prednisone is only marginally less effective than a regimen of high dose oral steroids but can improve the ratio of risk to benefit associated with treatment of the minimal change nephrotic syndrome.

Introduction

Proteinuria is completely eliminated in about 80% of adults and in 90% of children with the minimal change nephrotic syndrome after four to eight weeks' treatment with high dose oral prednisone.¹⁻³ Many patients, however, relapse when treatment with the drug is tapered off or stopped. Additional courses of the drug are still effective, but severe and even fatal side effects can occur in patients given repeated courses of high dose steroids. Prolonged administration of steroid on alternate days seems to reduce both the toxicity of the treatment and the number of relapses.⁴ The best regimen for "frequent relapsers" and "steroid dependent" patients is, however, far from established.

In a previous pilot study we achieved prompt remission without side effects in patients given three intravenous pulses of methylprednisolone followed by low dose oral prednisone.⁵ We therefore carried out a multicentre, randomised, prospective trial to compare this schedule with a regimen of oral steroid given at doses similar to those recommended in this condition⁶ and for a period corresponding to that in the group given methylprednisolone.

Patients and methods

PATIENT SELECTION

Patients who satisfied five criteria were admitted to the study. (1) They had proteinuria $> 40 \text{ mg h}^{-1} \text{ m}^{-2}$ (children) or $> 3.5 \text{ g/24 h}$ (adults), persisting for at least two weeks, and a plasma albumin concentration $< 25 \text{ g/l}$. (2) They

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had no evidence of underlying systemic disease, neoplasia, viral hepatitis, or exposure to drugs or toxic agents known to induce the nephrotic syndrome. (3) They had not been treated with steroids or cytotoxic agents for at least one year before admission. Patients with previous episodes of the nephrotic syndrome were included only when they had achieved a complete remission with steroids at least one year before. (4) Adult patients were admitted to the study only after a renal biopsy had shown a clear cut histological picture of minimal change nephrotic syndrome proved by renal biopsy was required for admission only when there was non-selective proteinuria or an erythrocyturia >300 000 red blood cells/h. In addition, a renal biopsy specimen was taken from any child who did not respond after eight weeks of treatment. With these criteria the likelihood of our having included in the study any patient with unproved minimal change nephrotic syndrome was negligible. (5) No children younger than 2 were included.

TREATMENT PROTOCOL

After informed consent had been obtained from the patient or the parents each patient was randomly assigned from a table of random numbers kept in one centre to one of the two steroid regimens. Adults and children were considered separately for random allocation by tables of random numbers. The group given methylprednisolone was given intravenous pulses of methylprednisolone 20 mg/kg daily for three days; then oral prednisone 20 mg/m² (children) or 0.5 mg/kg (adults) daily in a single morning dose for four weeks; then 20 and 10 mg/m² or 0.5 and 0.25 mg/kg every other day for four weeks; and then 20 mg/m² or 0.5 mg/kg on alternate days for four months. The control group was given oral prednisone 60 mg/m² (children) or 1 mg/kg (adults) daily in a single morning dose for four weeks; then 40 mg/m² or 1 mg/kg on alternate days for four weeks; and then 20 mg/m² or 0.5 mg/kg on alternate days for four months.

Patients who relapsed during treatment were treated as follows. Those given methylprednisolone were given a new course of intravenous pulses of methylprednisolone followed by oral prednisone 20 mg/m² (children) or 0.5 mg/kg (adults) daily until remission and then continued the protocol treatment at the dose given before the relapse. Control patients received oral prednisone 60 mg/m² (children) or 1 mg/kg (adults) daily until remission and then continued the protocol treatment at the dose given before the relapse. Patients who relapsed after finishing the protocol treatment were given new complete courses according to their original allocation.

Both groups were maintained on a low salt diet and given diuretic and antihypertensive agents as needed.

DEFINITIONS

Complete remission was considered to have occurred when urinary excretion of protein was <4 mg/kg/m² (children) or <100 mg/24 h (adults) for three consecutive days. *Time to response* was defined as the number of days from the beginning of treatment to the first day of remission. *Relapse* was considered to have occurred when a patient had proteinuria >40 mg/h/m² (children) or >3.5 g/24 h (adults) for seven consecutive days. *Patients who did not respond initially* were those whose proteinuria did not change within the first eight weeks of treatment.

FOLLOW UP

During treatment urinary excretion of protein was measured daily with a strip test by the patients or parents up to remission. Clinical and laboratory examinations were performed every month after the end of treatment and every two months for the following six to 18 months. Patients who did not respond initially were dropped from this study and considered for other treatment (a new course of methylprednisolone pulses, high dose oral prednisone, or cytotoxic drugs). All the 89 randomised patients were followed up for 12-24 months.

Side effects and complications were carefully assessed by clinical examination and described on a specially designed form. Criteria for and scoring of the most common side effects related to steroids were consistent for all participating centres.

STATISTICAL ANALYSIS

The median test⁸ was used to compare the age of patients, the times to response, and the number of relapses per patient per year in the two groups. The difference between the two groups in time to response was also evaluated in a stratified analysis by log rank test.⁹ The data (days) were

ranked in ascending order separately for adults and children. Then for each time to response the expected response in the group given methylprednisolone (e_{MT}) and the controls (e_{CT}) was calculated as:

$$e_{MT} = \frac{n_{MT}}{n_{MT} + n_{CT}} \times r_T \text{ and } e_{CT} = \frac{n_{CT}}{n_{MT} + n_{CT}} \times r_T$$

where n_{MT} and n_{CT} indicated the number of patients still with proteinuria at the time (T) considered, and r_T indicated the number of patients who responded within that time. The sums of all e_{MT} and e_{CT} indicated the expected response in each group. The results of the log rank test performed separately for adults and children were combined to produce expected responses adjusted for age. Then χ^2 was calculated to evaluate the effect of treatment adjusted for age. Corrected χ^2 analysis was used to assess the significance of the number of relapses and the incidence of side effects. The proportion of patients still in remission after responding to treatment was calculated from the survival curves, and the difference between the two groups was tested by log rank test.¹⁰ The duration of remission was also evaluated in a stratified analysis, adjusting the data for age group.⁹

Results

CHARACTERISTICS OF PATIENTS

From June 1980 to June 1983, 89 patients entered the study: 44 were assigned to receive methylprednisolone and 45 to serve as controls. There were no differences between the two groups in sex, age, and number of patients with a clinical history of allergic disease (table I). Percutaneous renal

TABLE I—Characteristics of patients

	Group given methylprednisolone (n=44)	Controls (n=45)
Children/adults	33/11	34/11
Male/female	29/15	31/14
Median age (range) (years)	9 (2-54)	8 (2-56)
No with history of:		
Episodes of nephrotic syndrome	24	25
Allergy	8	7

biopsy specimens were taken from all adults and from 10 children given methylprednisolone and nine children in the control group. Light microscopy showed normal glomeruli in all but five cases, in which there was mild mesangial proliferation (three given methylprednisolone and two controls). Focal glomerular obsolescence of about 20% of the glomeruli was observed in one adult in each group.

Immunofluorescence yielded negative results for immunoglobulins, complement, and fibrin in 25 biopsy specimens. Faint, discontinuous, comma like deposits of IgM were detected in glomeruli of specimens taken from 16 patients (nine given methylprednisolone and seven controls). Electron microscopy, performed in 24 cases, showed diffuse effacement of foot processes in all cases. Small mesangial or subendothelial paramesangial electron dense deposits were observed in nine patients.

RESPONSE TO TREATMENT

Complete remission was observed within eight weeks of treatment in 39 of the 44 patients given methylprednisolone and in 44 of the 45 controls (table II). The six patients who did not respond were given further treatment. In the group given methylprednisolone two children achieved a complete remission after treatment for four to six weeks with oral prednisone 60 mg/m² daily; one adult achieved complete remission after a further course of three methylprednisolone pulses followed by oral prednisone 0.5 mg/kg daily for four weeks; and two adults were treated with cyclophosphamide 2.5 mg/kg daily for six weeks without any effect on proteinuria. The only patient in the control group who did not respond was a 2½ year old child who did not respond either to a further course of oral prednisone 60 mg/m² daily for four weeks or to chlorambucil 0.2 mg/kg daily for the subsequent six weeks. All six patients who did not respond had minimal change nephrotic syndrome proved by renal biopsy. Children treated with methylprednisolone pulses achieved complete remission earlier than those treated with oral prednisone, while no difference was observed in the time to response among adults. An

TABLE II—Response of patients to treatment

	Adults		Children	
	Given methylprednisolone	Controls	Given methylprednisolone	Controls
No of patients who initially responded	8/11	11/11	31/33	33/34
No of patients who relapsed	6/8	7/11	21/31	21/33
No of relapses	13	11	38	42
Median (range) time to response (days)	17.5 (6-60)	15.0 (6-60)	6.0 (2-30)	10.0* (4-45)
Median (range) No of relapses/patient/year†	1.25 (0.6-6.4)	1.30 (0.5-6.0)	1.0 (0.5-4.8)	1.0 (0.5-6.0)

* $\chi^2=5.0674$ ($p<0.05$); all other differences not significant.
† Calculated for patients who had at least one relapse during follow up.

TABLE III—Stratified analysis of times to response for adults and children (figures are numbers of patients)

	Group given methylprednisolone		Controls	
	Observed response	Expected response	Observed response	Expected response
Adults	8	9.12	11	9.88
Children	31	24.33	33	39.67
Total	39	33.45	44	49.55

Log rank test: $\chi^2=22.50$ ($p<0.001$).

overall stratified analysis (table III) adjusted for age group confirmed a significantly shorter time to response in patients treated with methylprednisolone ($p<0.001$).

INCIDENCE OF RELAPSES

Twenty seven patients given methylprednisolone (69% of those who responded; six adults and 21 children) and 28 controls (63% of those who responded; seven adults and 21 children) had one or more relapses during follow up (table II). There were no differences between the two groups in the cumulative number of relapses. The number of relapses per patient per year was similar in the two groups. The number of patients who relapsed for the first time during the six months of treatment was higher in the group given methylprednisolone than in the controls (18/39 v 13/44), but this difference was not significant. The first relapse occurred earlier in the group given methylprednisolone (figure). When calculated from survival curves the

Proportion of patients still in remission after response to treatment calculated by two survival curves, which are not statistically different (log rank test, $\chi^2=2.673$; log rank test adjusted for age group, $\chi^2=2.710$.) Figures are numbers of patients in remission at each month.

proportion of patients still in remission after response to treatment during the first 12 months of follow up was lower in the group given methylprednisolone than in the control group. The differences between the two groups did not reach significance.

SIDE EFFECTS

The number of patients with undesirable effects related to treatment was significantly higher in the control group (table IV); obesity, Cushingoid

TABLE IV—Numbers of patients with side effects due to treatment

	Group given methylprednisolone (n=44)	Controls (n=45)	p*
Obesity	3	17	<0.01
Facies	12	36	<0.01
Striae	1	4	
Hypertrichosis	6	13	NS
Acne	2	7	NS
Retardation of growth	2	4	
Muscular atrophy	1	1	
Gastric pain	4	2	
Behavioural changes	2	7	NS
Minor infections	4	3	
Hypertension	1	2	
Arterial thrombosis		1	
Pulmonary embolism	1		
Fatal myocardial infarction		1	
Patients with side effects	18	39	<0.01

* Corrected χ^2 .

facies, and hypertrichosis being the more common side effects observed among these patients. Three adults (two given methylprednisolone and one control) developed severe thrombotic or embolic complications. A 28 year old man in the control group, under treatment for a relapse, developed thrombotic occlusion of the left popliteal artery and the superior mesenteric artery. The ischaemic ileal loops were resected and the popliteal artery made patent, but subsequently the left foot had to be amputated. Because of persistent nephrotic syndrome he was then treated with cyclophosphamide 2 mg/kg daily for eight weeks, and he showed a slow but progressive decrease in proteinuria until it was eliminated. A 50 year old man in the control group had a fatal myocardial infarction during treatment of the second relapse. A 50 year old man given methylprednisolone had a pulmonary embolism during a relapse before intravenous pulses of methylprednisolone were started again. He recovered from the complication, and proteinuria was eliminated after further treatment with methylprednisolone.

Discussion

The minimal change nephrotic syndrome has a favourable long term prognosis. Progression to renal failure is rare and occurs almost exclusively in patients who do not respond to treatment with steroids.^{2,3} Reports of chronic renal failure in patients who previously responded to steroids have been anecdotal.^{11,12} On the other hand, mortality among patients with the minimal change nephrotic syndrome is not negligible. In two studies 2.5% of children¹³ and 20% of adults² died, mainly from infections and cardiovascular diseases. The prognosis depends largely on the occurrence of these complications, which may be due either to the nephrotic syndrome per se or to side effects of repeated courses of steroids. Steroid regimens, including methylprednisolone pulses, have been shown to be useful and fairly safe for various renal diseases due to primary or systemic disorders,¹³⁻¹⁸ but there have been no controlled studies comparing methylprednisolone pulses with high dose oral prednisone.

In this randomised trial we compared the efficacy and side effects in patients with minimal change nephrotic syndrome of three methylprednisolone pulses followed by low dose oral prednisone for six months and oral prednisone given at high dose for four weeks followed by an alternate day regimen similar for doses and duration

to that in the group given methylprednisolone. Although steroid treatment in the minimal change nephrotic syndrome is not universally standardised, the regimen used in our control group corresponds to the schedules that are more often recommended. The 88% response in the group given methylprednisolone, although not significantly lower than that in the control group, is similar to the response observed in other series reported.¹³ A quarter of our patients were adults, and, as the prevalence of patients who initially respond to conventional treatment in the minimal change nephrotic syndrome of adult onset may be as low as 60%,¹⁹ we conclude that this schedule is indeed effective.

Of the five patients in the group given methylprednisolone who did not initially respond, three (two adults and one child) responded to a further course of methylprednisolone pulses or to treatment with high dose oral prednisone. Previous reports have shown that a small proportion of patients does not respond to the first course of eight weeks of treatment but requires more prolonged or higher doses of drugs.¹³⁻²⁰ Renal biopsy specimens taken in patients who respond late, who may represent a variant in the wider range of responsiveness to steroids of the minimal change nephrotic syndrome, often show mesangial hypercellularity.¹³ We did not find this characteristic in any of our patients who did not respond, so we cannot attribute the difference in the rate of response to any unequal distribution of morphological subcategories of the minimal change nephrotic syndrome between the two groups. In some 8% of cases, therefore, methylprednisolone pulses followed by low doses of oral prednisone are possibly less adequate than the high dose oral prednisone regimen for obtaining complete remission within eight weeks.

Among the patients who responded to the treatment the time to response was significantly shorter in children treated with methylprednisolone, while the number of patients who relapsed and the number of relapses per patient per year were similar in the two groups. The first relapse occurred earlier in the patients treated with methylprednisolone, but the difference was not significant. The difference in the duration of remission, evaluated in a stratified analysis, was not influenced by age.

The number of patients who developed side effects related to the steroids was significantly lower in the group given methylprednisolone than in the control group, and this was also true for patients who relapsed several times, who were given repeated courses of treatment. Patients treated with the methylprednisolone regimen had a significantly lower incidence of Cushingoid features than patients in the control group, and only two of the 33 children in the group given methylprednisolone compared with four of the 34 children in the control group showed retardation of growth. In addition, among adults treated with the oral prednisone regimen one patient had a dangerous thrombotic complication and another had a fatal myocardial infarction during treatment of a relapse.

The results of this trial indicate that the regimen of pulses of methylprednisolone and low dose oral prednisone is marginally less effective than a regimen of high dose oral prednisone in achieving and maintaining complete remission but protects the patient from the major side effects of the steroids even when repeated courses are

required. This schedule can, therefore, improve the ratio of risk to benefit associated with steroids in patients who are likely to be at risk from side effects.

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Correction

Long term treatment with luteinising hormone releasing hormone agonists and maintenance of serum testosterone to castration concentrations

An error occurred in this article by Fernand Labrie *et al* (10 August, p 369). The penultimate line of the third paragraph should have read: "We present detailed results in 12 randomly chosen patients who had taken serum luteinising hormone and flutamide for up to two years, having received no previous hormonal treatment."