The African Journal of Medicine and Medical Sciences

Volume 17
1988

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Boston Palo Alto Melbourne

Afr. J. Med. med. Sci. (1988) 17, 119–123.

Prolonged prednisolone therapy in adult nephrotic syndrome: a preliminary study

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Summary

Twenty-five adult Nigerian patients suffering from the nephrotic syndrome with normocomplementaemic mesangiocapillary glomerulonephritis were studied. Twelve of these were treated with prednisolone at a dose of 1.5 mg/kg body weight/day, with maximum dose of 90 mg/day initially for 2 weeks. Thereafter, a quarter of the daily dose was given on alternate days for a period varying from 6 to 12 months. The 13 others were similarly followed up on a dietary and diuretic regime alone. Oedema disappeared completely in all the steroid group except one, whilst it persisted in five of the controls. Proteinuria persisted in all the controls but remitted in five of the test patients. Renal function deteriorated with rising plasma creatinine in five of the controls, in contrast with one of the test patients. The beneficial effect of prednisolone observed here calls for further long-term studies.

Résumé

Nous avons étudié 25 adultes Nigérians souffrant de syndrome néphrotique dû à la glomérulonéphrite mesangiocapillaire, avec normocomplémentémie. Douze des malades ont été traités par prédnisolone, 1.5 mg/kg poids de corps par jour au commencement pendant deux semaines. Après cela un quart de la dose a été donné tous les deux jours pendant 6 à 12 mois. Les treize autres malades étaient au régime alimentaire et prenaient de la diurétique en plus. L'oedème était complètement disparu chez 12 des malades traités par prédnisolone lorsqu'il persistait chez cinq malades du groupe contrôlé. La protéinarie persistait chez tous les malades du groupe contrôlé mais elle était disparue chez cinq cas du groupe d'étude. La fonction des reins a détérioré (avec une créatinémie éleveé) chez cinq cas du groupe contrôlé mais chez un seul cas du group d'étude. Il faut étudier davantage l'éfficacité de prédnisolone, ici observée.

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Introduction

The childhood form of the nephrotic syndrome in the tropics is notorious for its poor response to steroids and cytotoxic drugs [1, 2], whilst the effect on the adult form has not been clearly defined [3, 4]. Wing *et al.* [5] reported that prednisolone therapy alone did not influence the onset of diuresis or induce proteinuria amongst their 27 patients.

In an environment where the nephrotic syndrome accounts for a staggering 2–3% of medical admissions to hospitals, and with a general consensus of poor response to known therapeutic regimes, a large percentage of such patients are reduced to virtual helplessness. The reported overall mortality rate of 28% [5] in one 5-year follow-up study thus constitutes a gloomy prognosis, although it must be admitted that figures reflected in such studies include data from the childhood form of the nephrotic syndrome, which does carry a less severe outlook.

The pooling of patients with different age groups and histological types makes meaningful interpretation and comparison of observation of various workers difficult.

In this communication, we set out to report our preliminary observations on the trial of prednisolone in 12 adult Nigerian patients

with the nephrotic syndrome from normocomplementaemic mesangiocapillary glomerulonephritis (MCGN).

In a previous study we observed that a short-term daily course of prednisolone for 8 weeks was not beneficial in the nephrotic syndrome [6]. An alternate-day therapy of prolonged duration similar to that of McAdams *et al.* [7] was, therefore, instituted in this study.

Patients and methods

Twelve newly diagnosed consecutive patients (seven male, five female, age range 17–40 years) with generally accepted criteria for the nephrotic syndrome [8], and whose glomerular histology revealed MCGN on light microscopy with the use of a haematoxylin and eosin, periodic acid–Schiff and modified Jones' methanamine silver stains, were studied.

None of the patients had significant hypertension, whilst their plasma creatinine level was generally below 265.2 μmol/l (3.0 mg%).

Thirteen other patients (nine male, four female, 14–35 years), retrospectively selected from hospital records with the nephrotic syndrome and normocomplementaemic MCGN, served as controls. Patients had normal plasma creatinine level; they were normotensive, and of comparable ages as the test patients, and their plasma creatinine levels were generally below 265.2 μmol/l (3 mg%). These patients had been followed up in the unit on conventional drugs (dietary and diuretic regimen) for periods ranging from 6 to 14 months before the current therapeutic trial of prednisolone commenced.

The clinical parameters, namely age, duration of illness before presentation, blood pressure, plasma creatinine and albumin levels, were statistically comparably similar between the test and control patients.

The 12 patients in the test group were placed on oral prednisolone at a dose of 1.5 mg/kg body weight with a maximum dose of 90 mg/day for the first 2 weeks. This was decreased to 40 mg alternate days for 2 weeks, and thereafter to 20 mg alternate days for the rest of the observation period (ranging from 6 to 11 months).

The control group were on the standard dietary regimen of high protein, low sodium intake, and diuretic in the form of daily doses of frusemide varying from 80 to 200 mg, with potassium supplements. Spironolactone (up to 150 mg/day) was added to enhance diuresis in some cases.

All the patients were on admission for at least 2 weeks prior to entering the study for full clinical and laboratory work-up, and the initiation of therapy. Thereafter, further follow-up was on regular out-patient basis. Response to therapy was evaluated by determining the degree of oedema, weight, blood pressure, albuminuria, plasma albumin and creatinine levels. Side-effects of steroids were carefully watched out for.

The following were regarded as contra-indications to containing therapy: (i) rising blood pressure in spite of routine anti-hypertensive therapy and (ii) rising plasma creatinine with hypertension.

Statistical analysis

Statistical significance of the difference between the means of the samples was tested using Student's *t*-test, and the probability level was checked from standard tables. Comparisons were also made between the groups using the Chi-square test where indicated. Values are given in the test as means ± standard error of mean (s.e.m.).

Results

Clinical parameters

Table 1 summarizes the relationship of some of the clinical parameters, namely, age, duration of illness at point of entry into the study, the mean initial weights, diastolic blood pressure, initial plasma creatinine, and albumin levels, between the two groups of patients.

The mean ages of the test and control patients were 25.2 ± 1.9 and 22.6 ± 2.1 years, respectively. There was no significant difference between these ages ($P > 0.1$). The duration of symptoms before therapy varied between 2 weeks and 4 years, the mean values being 16.7 ± 5.2 and 12.7 ± 1.5 months for test and control patients, respectively ($P > 0.1$).

The diastolic blood pressure at time of entry into study was comparable in both test and control patients, with mean values being 80.8 ±

Table 1. Comparison of mean values of clinical parameters at entry into study

Clinical parameter	Steroid-treated group	Dietary and diuretic group	Significance
Mean age (years)	25.2 ± 1.9 *	22.6 ± 2.1	$P > 0.1$
Mean duration of illness before study (months)	16.7 ± 5.2	12.7 ± 1.5	$P > 0.1$
Mean initial diastolic blood pressure (mmHg)	80.8 ± 2.2	78.8 ± 2.5	$P > 0.1$
Mean initial plasma creatinine (μmol/l)	126.8 ± 20.4	145.3 ± 18.9	$P > 0.1$
Mean initial plasma albumin (iu/ml)	67.1 ± 4.0	55.8 ± 2.3	$P > 0.1$
Mean initial weight (kg)	63.2 ± 3.6	62.8 ± 3.4	$P > 0.1$

*Values are given as means ± s.e.m.

2.2 mmHg and 78.8 ± 2.5 mmHg, respectively ($P > 0.1$). The initial mean plasma creatinine levels were also comparable between the two groups, their levels being 126.8 ± 20.4 and 145.3 ± 18.9 μmol/l for both test and control patients, respectively, with no statistically significant difference between them ($P > 0.1$). The mean plasma albumin levels were equally low, that of test patients being 67.1 ± 4.0 iu/ml and 55.8 ± 2.3 iu/ml for controls. There was no significant difference between them.

Oedema

There was regression of oedema in 11 of the steroid-treated group, while this occurred in seven of the control patients. Only partial disappearance of oedema occurred in the remaining one of the test, in contrast to six of the 13 control patients. Comparing these responses in the two groups, a statistically significant association with therapy was obtained ($\chi^2 = 4.8$, $P < 0.05$; Table 2).

Proteinuria

Table 2 also shows the response of proteinuria in the two groups of patients. In the steroid-treated group, proteinuria disappeared completely in five whilst it persisted, but was mild in three, and remained gross in four patients. Gross proteinuria persisted in all the 13 patients on the dietary and diuretic regimen. There was thus a significant difference between the responses of the two groups ($\chi^2 = 12.7$, $P < 0.005$).

Weight

The mean initial weight fell from 63.2 ± 3.6 to 58.9 ± 3.0 kg for the test patients, while a reduction from a mean initial weight of 62.8 ± 3.4 to 59.6 ± 3.1 kg was obtained for the controls. A mean percentage reduction of 6.4 ± 0.58% was thus obtained for the test patients, while a significantly lower mean percentage reduction in weight of 4.8 ± 0.68% was observed for the controls (Table 3).

Blood pressure

Blood pressure remained normal in all but one of the prednisolone-treated group, whilst three patients on the diet and diuretic regimen required anti-hypertensive therapy. The mean diastolic blood pressure fell from an initial

Table 2. Illustration of response of oedema and proteinuria in relation to therapy

Parameter	Assessment	Treatment group: Prednisolone group	Treatment group: Dietary/diuretic group	χ^2	Significance
Oedema	Complete disappearance of oedema	11	7	4.8	$P < 0.05$
	Partial disappearance of oedema	1	6		
Proteinuria	Complete disappearance of proteinuria	5	0	12.8	$P < 0.005$
	Partial disappearance of proteinuria	3	0		
	Persisting gross proteinuria	4	13		

value of 80.8 ± 2.2 to 72.5 ± 3.7 mmHg after therapy in the test patients, while a rise from the initial mean diastolic blood pressure value of 78.8 ± 2.5 to 85.3 ± 3.0 mmHg was obtained in the controls. Comparing the diastolic blood pressure at the end of the study revealed a statistically significant difference ($P < 0.01$) between the prednisolone-treated and the diuretic/dietary-treated patients.

Plasma creatinine level

There was no significant change in the mean plasma creatinine from the normal initial level in the test patients ($P > 0.6$), whilst a statistically significant rise of mean plasma creatinine value from 145.3 ± 18.9 to 265.3 ± 52.8 μmol/l ($P < 0.05$) was obtained in the control group, at the end of the study. A comparison of the mean plasma creatinine levels at the end of the study thus revealed a statistically significant difference between the two groups ($P < 0.05$; Table 3).

Plasma albumin

In the test patients, mean plasma albumin rose significantly from the initial value of 67.1 ± 4.0 to 93.1 ± 5.2 iu/ml ($P < 0.01$), whilst it remained essentially unaffected ($P > 0.1$) in the control group at the end of the study.

The mean plasma albumin levels at the end of the study were compared for both groups, and a statistically significant difference ($P < 0.005$) was obtained between them (Table 3).

Discussion

Previous experience in tropical Africa [1, 5, 6] has shown that a short-term daily course (lasting not more than 8 weeks) of prednisolone therapy, as well as cytotoxic agents, offers little benefit in patients with nephrotic syndrome in the tropics.

In a previous limited study in the Renal Unit at the University College Hospital, Ibadan [6], a 2-month course of prednisolone, at a dose of 1.5 mg/kg body weight/day to a maximum dose of 90 mg, was administered to eight adult Nigerians with the nephrotic syndrome and with renal histology of mesangiocapillary glomerulonephritis. Only one patient showed some response, as defined by moderate loss of proteinuria and oedema. A similar response was, however, observed in an equal proportion of a control group of patients on the diuretic and dietary regime alone.

Long-term alternate-day prednisolone therapy has been shown by McAdams *et al.* [7] to be beneficial, in their limited study of eight patients with mesangiocapillary glomerulonephritis.

Table 3. Comparison of clinical parameters at the end of the study period

Parameter	Treatment group		Significance
	Prednisolone group	Dietary/diuretic group	
Mean diastolic blood presure (mmHg)	72.5 ± 3.7	85.3 ± 3.02	$P < 0.01$
Mean plasma albumin (iu/ml)	93.1 ± 5.2	59.6 ± 2.5	$P < 0.005$
Mean plasma creatinine level (μmol/l)	148.6 ± 28.4	265.3 ± 52.8	$P < 0.05$
Mean percentage reduction in weight (% of initial weight)	6.4 ± 0.6%	4.8 ± 0.7%	$P < 0.05$

Our preliminary study has demonstrated a significant diuretic effect of this regime in patients with the nephrotic syndrome. It has also enhanced the possibility of a favourable response to therapy in this form of glomerulonephritis. In differing from our previous observations of poor response in a similar group of patients on a 2-month course of daily prednisolone, it is conceivable that the positive response evident in the present study is due to the prolonged therapy.

The commonly feared complication of hypertensive encephalopathy was not a feature of this study, perhaps because of our rigid criteria, which eliminated existing significant hypertension, and strict observation resulted in quick institution of anti-hypertensive therapy immediately an elevated blood pressure was noticed.

The information on the effect of therapy on histology awaits repeat biopsies but we are prompted to report this preliminary study as a favourable outcome of a disease that is otherwise regarded as progressively fatal.

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(*Accepted* 21 *May* 1987)