Does long-term low-dose corticosteroid therapy cause hypertension?

S. H. D. Jackson,* D. G. Beevers, and K. Myers†

University Department of Medicine, Dudley Road Hospital, Birmingham, U.K.

Summary

1. One hundred and ninety-five patients undergoing low-dose prednisone or prednisolone therapy were investigated. Blood pressure, weight, serum urea, sodium and potassium were recorded before therapy and again after at least 1 year of therapy.

2. The rise in both mean systolic and mean diastolic blood pressure was paralleled by an increase in the prevalence of arbitrarily defined hypertension.

3. There was no relationship between change of blood pressure and either dose of corticosteroid or duration of therapy. Blood pressure before therapy was the main determinant of the change in blood pressure.

4. Mean serum sodium levels rose slightly but serum potassium levels did not change during the follow-up period. There was no significant weight gain.

5. These results indicate that treatment of asthma and rheumatoid arthritis with prednisolone or prednisone in low dose does not cause hypertension or biochemical features suggestive of mineralocorticoid excess.

Key words: corticosteroid, prednisolone, prednisone.

Introduction

Since the first published trials of corticosteroid therapy in patients with rheumatoid arthritis [1] this group of drugs has been used to treat an increasing variety of diseases. Their well-known, unwanted effects have received much attention [2, 3] and it is generally felt that the risk of complications is related to the dose [4] and duration of treatment [2]. Many authors have suggested that long-term low-dose corticosteroid therapy may lead to the development of hypertension [2, 3, 5], others mention hypertension but fail to define it [6] and others did not detect raised blood pressure in short-term studies [7].

We therefore set out to investigate the relationship between chronic low-dose corticosteroid therapy and blood pressure in a large number of hospital outpatients with asthma and rheumatoid arthritis.

Patients and methods

Outpatients were in two diagnostic groups: (1) 129 with asthma with or without underlying chronic bronchitis and emphysema; (2) 66 with rheumatoid arthritis.

Patients were entered into the study if they had been taking prednisone or prednisolone in a dosage of less than 20 mg daily for a continuous period of at least 1 year.

The following information concerning each patient was recorded: blood pressure, weight, serum urea, sodium and potassium concentrations both before and at least 1 year after starting corticosteroid therapy.

The biochemical methods employed were similar throughout the course of the study.

Data concerning patients before they started corticosteroid therapy were collected retrospectively.

All blood pressures (BP) were taken with a standard mercury sphygmomanometer. Those BP readings collected retrospectively on asthma patients were all made by one physician (G.W.H.) using fifth phase diastolic readings.
This technique was used for all BP readings taken during therapy. Wherever possible they were recorded as the mean of several clinic readings. They were corrected for age and sex by the method of Hamilton et al. [8].

The dose of corticosteroid was calculated by taking the mean dose of prednisone/prednisolone over the previous 12 months.

Statistical analysis was performed by using the Statistical Package for the Social Sciences. Standard deviations are included after means of normal distributions. Probabilities (P) derived from Student’s t-tests are based on paired samples.

Results

Study population

The sexes were equally represented in the asthma group and showed the expected preponderance of females (48/66) in the rheumatoid arthritis group. Mean age at follow up was 56.7 ± 12.7 years, the mean ages for the two diagnostic groups being almost identical. The mean duration of follow up was 8.9 ± 5.3 years. The total number of patient years on corticosteroid therapy was 1702. The mean dose of corticosteroid was higher in the rheumatoid-arthritis patients (8.4 ± 2.7 mg) than in the asthma group (6.7 ± 3.3 mg), although the duration of treatment was longer in the latter group (9.7 ± 5.5 years) than in the rheumatoid-arthritis patients (8.4 ± 2.7).

Urea and electrolytes

There was a significant rise in mean serum urea from 4.8 to 5.9 mmol/l in the 41 patients in whom measurements were made before and after corticosteroid treatment (t = 3.57, P < 0.001). There was no correlation between serum urea and BP either in the whole group or in those who became hypertensive. Although there was a small rise in mean serum sodium there was no significant change in mean serum potassium (Table 1). No patient had a serum potassium below 3.2 mmol/l and only five patients had values below 3.5 mmol/l during corticosteroid therapy.

Weight

Measurements were available both before and during therapy in 75 patients. Although there was no significant change in mean weight (Table 1) there was a weight gain of 6 kg or more in 19 (25.3%) patients. Positive correlations were found between weight and both systolic BP (r = 0.16, P < 0.05) and diastolic BP (r = 0.23, P < 0.005) during corticosteroid treatment.

Blood pressure

Blood pressure rose during the treatment period. The rise in systolic BP reached statistical significance (Table 1). The prevalence of systolic hypertension in the whole group before therapy, taking an arbitrary dividing line of 160 mmHg, was 17.7%. This rose during treatment to 29.8% (chi square 5.77, P < 0.02). The prevalence of diastolic hypertension, taken as a diastolic pressure of 100 mmHg or greater, rose from 15.3% to 20.2% (not significant). These changes occurred over an average of 8.9 years. There were no significant differences in the behaviour of the two diagnostic groups.

Both systolic (r = 0.36, P < 0.001) and diastolic (r = 0.19, P < 0.02) BP during treatment correlated with age although the relationship was less marked for BP before treatment. There was no significant correlation between BP and either corticosteroid dosage or duration of therapy.

When all blood pressures were corrected and expressed as if for a 60 year old the rise in both blood pressure and prevalence of hypertension was no longer apparent.

| TABLE 1. Data on 195 patients with asthma or rheumatoid arthritis receiving long-term low-dose corticosteroid therapy |
|---------------------------------|---------------|---------------|
|                                | Before corticosteroid therapy | At follow up   |
|                                | Systolic BP (mmHg) | *             | 147.0 ± 26.1 |
| Diastolic BP (mmHg)            | 85.1 ± 11.7     | N.S.          | 86.6 ± 13.2  |
| Serum sodium (mmol/l)          | 137.7 ± 3.9     | **            | 139.6 ± 3.7  |
| Serum potassium (mmol/l)       | 4.5 ± 0.6       | N.S.          | 4.4 ± 0.5    |
| Weight (kg)                    | 63.0 ± 11.6     | N.S.          | 64.6 ± 11.8  |

Values are means ± SD. Significance: *P < 0.001; **P < 0.01; N.S., not significant.
Corticosteroid therapy and hypertension

Multiple regression analysis showed no significant effect of either dose or duration of therapy on the change in systolic or diastolic BP. Only systolic BP before therapy [regression coefficient \( B = -0.62, P < 0.001 \)] and age at follow up \( B = +0.57, P < 0.05 \) had significant effects on the change in systolic BP, explaining 22.5% of observed variance. Diastolic BP before treatment \( (B = +0.53, P < 0.001) \) was the only variable to have a significant effect on the change in diastolic BP during treatment, explaining 21.1% of observed variance. Other variables that did not contribute to the regression equation predicting the change in BP were body weight, sex and underlying diagnosis.

Discussion

Despite the problems associated with a partially retrospective study we have demonstrated a prevalence of hypertension at least as high as that reported in other studies [2, 3, 5]. In these studies the authors have implied a relationship between low-dose corticosteroid therapy and the development of hypertension without examining the effects of other variables such as the height of the BP before therapy and age.

We used multiple regression analysis to look for the effects of underlying diagnosis on change in BP as well as variables more generally accepted as affecting BP such as age, sex [9] and weight [10]. The results of this analysis do not support the generally accepted hypothesis that low-dose corticosteroid therapy causes blood pressure to rise. The much simpler and cruder technique of age correction confirms the findings of multiple regression analysis.

Long-term corticosteroid treatment does carry many hazards which must be considered before embarking on therapy. However, we have found no evidence that prednisone (or prednisolone) in the doses utilized in the management of rheumatoid arthritis or asthma is an important cause of hypertension.

Acknowledgments

We are grateful to Dr B. McConkey, Consultant Physician, and Dr G. W. Hearn, Honorary Consulting Physician, for permission to include their patients in this study. This work was supported by grants from Pfizer Ltd and Merck Sharp and Dohme Ltd.

References


