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A Prospective Study of the Development of Hypertension and Renal Stone Disease in Subjects with Increased Blood Urate

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Summary. The results of a prospective study of the development of hypertension and renal stone disease in subjects with increased blood urate are reported and compared with matched controls. None of the 14 patients on Allopurinol developed a renal stone but one untreated control did. For male patients there was a significant difference ($p < 0.01$) in diastolic blood pressure between the 2 groups over the 5-year study period, with treated patients having higher blood pressures than untreated controls. This suggests that Allopurinol has had no effect on lowering diastolic blood pressure. Long-term therapy with Allopurinol was effective in reducing mean blood urate levels. It is suggested that blood urate levels are more relevant in predicting renal stone formation and of less value in assessing the therapy and prognosis in hypertension.

Key words. Allopurinol, Blood pressure, Renal stones, Hyperuricaemia.

Introduction

The association between hypertension and vascular disease is well recognised [10]. There is a probable link between vascular disease and uric acid [7, 8]. It is well known that increased levels of blood urate can influence the rate of urinary tract stone formation [4] and the development of joint disease, as well as having an association with high blood pressure.

Specific reduction of serum urate values with Allopurinol can affect the recurrence rate of urinary tract stone disease [13]. We have sought to examine the effect on blood pressure and stone incidence in a group of patients treated with Allopurinol and compared this with an untreated control group.

A population survey (Cumbernauld New Town) undertaken in 1976 showed a prevalence rate for upper urinary tract stone disease of 3.5% [11]. Of 3398 people assessed, 329 had an elevated blood urate. We have followed a group of patients treated with Allopurinol for 5 years who initially had significantly elevated blood urate levels and compared them with an untreated control group.

Material

14 patients (5 males and 9 females) with persistently elevated blood urate levels received intermittent treatment with Allopurinol 300 mg each day for 6 months each year during the trial period 1976 to 1981. Age, sex, and weight matched controls also with elevated blood urates were drawn from the parent survey population (Table 1).

Patients and controls were assessed by measurement of blood pressure and blood urate. Details of any intercurrent illness were recorded and a plain abdominal X-ray taken. These results were compared with those obtained at the time of the original survey in 1976. Statistical analysis was carried out using paired t and Wilcoxon signed rank tests.

Table 1. Details of patients and controls: mean age, height and weight

Age (years)	Controls	Patients
males	49.4	50.8
females	60.2	60.7
Height (cm)	**Controls**	**Patients**
males	170.52	171.4
females	154.33	154.22
Weight (kg)	**Controls**	**Patients**
males	77.26	77.4
females	65.25	67.74

Table 2. Initial blood urate levels (μmol/l): mean figures

	Controls	Patients
males	460	534
females	365.56	433.89
males and females	399.29 ($p < 0.001$)	469.6

normal ranges: males 130–430 μmol/l, females 30–340 μmol/l

Table 3. Final blood urate levels (μmol/l): mean figures

	Controls	Patients
males	466	496
females	352.2	412.2
males and females	392.86	442.1

Table 4. Diastolic Blood Pressure (mm/Hg)

	Controls	Patients
males	72.5	87.5 ($p < 0.01$)
females	100.56	96.1
males and females	91.92	93.46

Results

When the initial blood urate levels were compared between the treated and control groups at the start of the survey, it was found that the difference was statistically significant ($p < 0.001$) between the groups and between male and female subjects (Table 2).

At the end of the period of observation (5 years) there was no significant difference between the two groups with respect to blood urate (Table 3).

Systolic Blood Pressure

There was no significant difference between the treated and control groups.

Diastolic Blood Pressure

There was a significant difference ($p < 0.01$) between the two groups of male patients in that the treated subjects had a mean diastolic blood pressure of 87.5 mm Hg and the controls a mean pressure of 72.5 mm Hg. No such difference was found for female patients (Table 4). During the study period one male patient in the treatment group developed evidence of significant cardio-vascular disease viz. angina and hypertension.

Intercurrent Illnesses

One control subject developed diverticular disease and another was diagnosed as having asthma. Seven patients in the treatment group reported symptoms of an "arthritic nature".

Radiology

One patient in the treatment group developed radiological evidence of arthritis. One control subject developed a renal calculus and another developed a gallstone. No patients on Allopurinol developed calculi in their urinary tract or biliary system.

Discussion

It is known that long-term therapy with Allopurinol reduces mean blood urate levels [4] and this is confirmed in the present study. No significant difference could be demonstrated between the treated and untreated groups with respect to blood urate levels at the end of the 5-year period of review.

The present study confirmed that systolic blood pressure between the two groups was not significantly different and that there was also no difference in diastolic pressure in female patients. However, a significant difference ($p < 0.01$) was found between the male groups with respect to diastolic pressures (Table 4). Treated males had a mean blood pressure significantly higher than the control patients. This indicates that treatment with Allopurinol has had no effect on lowering diastolic blood pressure. The opposite result might have been expected since an increased incidence of raised blood pressure has been reported in one study of symptomless hyperuricaemic subjects [6], and serum urate levels are high in over 25% of untreated hypertensive patients [2, 3]. Treatment to reduce blood urate clearly has had no effect in reducing diastolic blood pressure.

It is known that the treatment used to manage hypertension can result in an elevation of blood urate values but whether this can be entirely attributed to diuretic agents used in the management of some cases of hypertension is debatable [1]. In that blood urate values are high in essential and renal hypertension [3], it could be argued that hyperuricaemia is a phenomenon secondary to the elevated blood pressure. The present study, by allowing a direct comparison between two groups of individuals, one of which was treated specifically because they had elevated blood urate values, has shown that despite a significant decrease in urate values there has been no change in the blood pressure differences between the two groups.

It is interesting, however, that in those subjects in whom it could be expected that renal stone disease might be a secondary problem as a result of an elevated blood urate [4] no stones occurred in the 5-year period of treatment. In a survey of gout subjects versus non-gout subjects, it has been shown that no more than 28% of stone subjects could be expected to have hyperuricaemia [5], but myocardial problems and hypertension were significantly more likely to occur in stone subjects. By contrast, in those subjects who at the outset had elevated serum urate values but did not receive any hypouricaemic agent, one developed a renal stone and one a gallstone. There is good evidence to show that with increasing levels of serum uric acid the prevalence of renal stone disease rises [12]. The present study would suggest that in an "at-risk group" with a stone history and an elevated uric acid level, there is merit in reducing serum uric acid levels by Allopurinol. In addition it should be noted that hyperuricaemic subjects are more likely to have evidence of abnormal urinary sediments and proteinuria [9] indicating renal damage of a histological nature which could result in foci being present upon which stone aggregation could occur.

In 19 subjects who were part of the original survey and who were known to have normal serum urates and were reviewed radiologically after 5 years, no new stones occurred. This suggests therefore that serum urate will continue to be a more relevant factor in predicting renal stone formation or as a prognosticator of renal stone formation [4] rather than being of value in assessing the therapy and prognosis in hypertension.

We are not aware of any other study which has been designed to assess the effect of hypouricaemic agents on blood pressure and renal stone disease in subjects who were found to have hyperuricosaemia and who, at the time that the biochemical study was made, were known to be without calcified renal calculi which could be demonstrated by simple radiological techniques.

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