One year follow-up of hyperuricaemic hypertensive patients treated with tienilic acid or a diuretic with or without uric acid-lowering drugs

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Summary

1. Fifty-four hypertensive, hyperuricaemic patients were pair-matched for age, sex and current therapy (diuretic, uric acid-lowering drug).

2. One member of each pair was randomly assigned to continue on the previous therapy and the other member to treatment with tienilic acid (ticrynafen). Routine potassium chloride supplements were given only to subjects who were or had previously been on uric acid-lowering drugs.

3. Blood pressure control was equally good in the tienilic acid-treated and control groups. Serum uric acid was significantly lower in patients treated with tienilic acid.

4. In patients (32) not given supplements of potassium chloride, mean serum $K^+$ did not fall but in four patients (three on tienilic acid, one on cyclopenthiazide) serum $K^+$ fell to 3.5 mmol/l or less and potassium chloride was added.

5. Liver-function tests changed from pretrial results in nine patients. In eight of these (four on tienilic acid and four in the control group) minor rises in alkaline phosphatase only occurred. In the ninth patient, who was also taking metoprolol, serum aspartate transaminase rose markedly after 2 months and fluctuated for 4 months. Eventually there were also rises in alkaline phosphatase and bilirubin; these reverted to normal after stopping tienilic acid.

Key words: tienilic acid, uricosuric diuretic.

Introduction

Tienilic acid (ticrynafen) is an ethacrynic acid analogue which combines diuretic and antihypertensive with uricosuric properties. In a short-term crossover trial of tienilic acid and cyclopenthiazide in which 36 hypertensive patients were treated for 3 months with each drug (random order) we found tienilic acid to be an effective drug, which lowered uric acid levels impressively (Bolli, Simpson & Waal-Manning, 1978). However, transaminase activity rose above normal in two men when on cyclopenthiazide and in three women when on tienilic acid, and in one of these women the rise was substantial. The present studies were to determine the effects of long-term treatment with tienilic acid on blood pressure, serum uric acid and liver function.

Methods

Study 1

Thirty-two patients who completed the short-term crossover trial of tienilic acid and cyclopenthiazide without liver-function abnormalities (Bolli et al., 1978) were grouped into 16 sex- and age-matched pairs. One member of each pair was randomly assigned to take cyclopenthiazide, the other to take tienilic acid at the doses previously found to be satisfactory (Bolli et al., 1978). One patient in the thiazide group was treated from the start with hydrochlorothiazide–amiloride instead of cyclopenthiazide because of a tendency to hypokalaemia. Mean dose of cyclopenthiazide of the remaining 15 patients was 0.43 mg/day. Mean dose of tienilic acid was 188 mg/day. Potassium
chloride supplements averaging 1 g/day were stopped in both groups and other antihypertensive drugs were continued unchanged.

**Study 2**

The group comprised 22 pair-matched hypertensive patients (14 male, eight female; mean age 61 years) on long-term uric acid-lowering therapy. Ten had a history of gout. Twenty-one were on allopurinol at a mean dose of 200 mg/day; one was on probenecid 2 g/day; 18 of the patients were on a diuretic (mainly hydrochlorothiazide–amiloride combination). Alcohol intake was moderately heavy in most patients.

One member of each pair was randomly assigned to continue on the previous regimen of an uricosuric agent and (where appropriate) a diuretic, and the other member to stop these drugs gradually and after a 3 day gap to start tienilic acid at 125 mg/day and then to increase the dose until satisfactory control of blood pressure had again been obtained. Other antihypertensive therapy was continued unchanged, as were the potassium chloride supplements, which averaged 775 mg/day.

Measurements of blood pressure, pulse and weight were made and biochemical tests were done monthly for 3 months and thereafter at 3 month intervals. Haematological tests and urine analyses were carried out at 6 months and 1 year and chest X-ray and electrocardiogram at 1 year. All these tests had also been done before the studies were started.

**Results**

Over the 1 year follow-up in both studies lying and standing blood pressure and pulse were similar in the tienilic acid and control patients. Weight was also not significantly different.

**Study 1**

The serum uric acid concentrations at 1 year averaged 0-30 mmol/l (± 0-01 SEM) in patients on tienilic acid (mean dose 188 mg/day) compared with 0-50 ± 0-02 mmol/l (P < 0-0001) in patients on cyclopenthiazide (mean dose 0-45 mg/day). Serum urea, creatinine and K⁺, Na⁺, CO₂ and chloride were similar in the two groups. Linear regression showed a statistically significant but clinically unimportant negative gradient for both groups for serum Na⁺ (−2 mmol/l over a year) and protein (−4 g/l over 1 year). Over the 1 year follow-up only four patients had serum K⁺ values of 3-5 mmol/l or less, which remained at or below this concentration when the blood test was repeated. They were started on potassium chloride supplements; three of these patients were on tienilic acid and one on cyclopenthiazide.

There was no significant difference between liver-function test mean values in the two groups after excluding a tienilic acid-treated patient who developed gross abnormalities. Serum alkaline phosphatase activities rose a little above 90 units (the upper limit of normal) in four patients, three of whom were on cyclopenthiazide and one was on tienilic acid. Gross abnormalities, however, occurred in a woman aged 69 who had felt vaguely unwell in tienilic acid during the crossover trial when serum aspartate transaminase activities, although showing a small rise, had remained within normal values. On resuming tienilic acid for the continuation trial she again felt vaguely unwell and developed abnormal values for the transaminase after being back on the drug for 2 months, as illustrated in Fig. 1. The enzyme activity fluctuated for 4 months with a rise eventually also in alkaline phosphatase to 154 units and bilirubin to 16 µmol/l. Tienilic acid was stopped and cyclopenthiazide restarted. All values have since fallen and remained within normal limits. Tests for hepatitis antigen and antibody were negative. The patient was taking other medication (metoprolol) but no alcohol.

There were only five other events in tienilic acid-treated patients: muscle cramps (one patient) and indigestion (one patient), both of which subsided on reducing the dose of tienilic acid; paroxysmal tachycardia (one patient), which occurred in association with a serum K⁺ of 3-5 mmol/l and which subsided after resumption of potassium chloride supplements; disappearance of cyclopenthiazide-induced kidney pain (one patient); a mild attack of gout (one patient) 1 month after starting tienilic acid.

**Study 2**

Over the 1 year follow-up there was no difference between tienilic acid and control groups in lying and standing blood pressure, pulse, weight, serum K⁺, Cl⁻, creatinine and urea, liver-function tests and haematology except for platelet count, which was significantly increased on tienilic acid (P < 0-05). Minor rises in alkaline phosphatase occurred in four patients who admitted to heavy alcohol intake and of whom only one was taking...
One year tienilic acid therapy

FIG. 1. Serum aspartate transaminase activity in a patient from study 1 while on tienilic acid. When she was withdrawn from the trial at 5½ months alkaline phosphatase had also risen to 154 units and bilirubin to 16 μmol/l.

tienilic acid. No rise in aspartate transaminase activities above normal was seen in these 22 patients. Linear regression analysis showed a statistically significant but clinically unimportant negative gradient for Na⁺ (−5 mmol/l in 1 year) in tienilic acid-treated patients only.

In the tienilic acid-treated group mean serum uric acid at 1 year was significantly lower (P < 0.01) on tienilic acid than on the previous regimen (0.31 vs 0.46 mmol/l) and significantly lower (P < 0.01) than in the control group (0.31 vs 0.41 mmol/l).

Most of the events in the tienilic acid group occurred in the change-over period: these included slight oedema in two patients, headache associated with a rise in blood pressure (one patient) and mild left ventricular failure (one patient). All settled when the dose of tienilic acid was increased. One patient after a dose increase of 125–250 mg of tienilic acid experienced bilateral loin ache, diarrhoea and indigestion for 5 days. These symptoms subsided and he continued on 250 mg of tienilic acid daily. On the established dose of tienilic acid the following were reported: better daytime diuresis (one patient), nocturia less than on cyclopenthiazide (one patient), improvement in joint aches (two patients). A virile dark 'beard' growth occurred in a male patient who also had the highest blood concentration of tienilic acid.

Discussion

Tienilic acid has proved to be a useful drug in this 1 year trial. It was as effective as a thiazide in maintaining control of blood pressure and very effective in lowering serum uric acid. In areas such as New Zealand, where hyperuricaemia and gout are relatively common, tienilic acid represents a major advance in diuretic therapy. The drug was, in general, very well tolerated and the only problem was the marked asymptomatic rise in serum asparatate transaminase activity in one patient. The whole episode was very similar to the rise in the enzyme seen in a patient in our short-term crossover trial (Bolli et al., 1978). Both these patients were female and both were taking metoprolol in addition to tienilic acid. Coincidence cannot be ruled out and apparently no other similar cases have been reported (V. G. Balmer, personal communication). However, the two episodes suggest that although most people can take tienilic acid without problems, occasional individuals react with abnormalities of liver function. The part played by metoprolol is not clear; conceivably a drug interaction could be involved. On the basis of our experience we would recommend that, in the meantime at least, patients should have liver-function tests carried out before they start tienilic acid and after 2–3 months of treatment with the drug.
The uricosuric effect is extremely powerful and a great deal of uric acid is poured out in the urine after the first dose (Wood, Bolli, Waal-Manning & Simpson, 1978). This can lead to crystalluria and tubule disorders (Le Lievre, Raviart, Le Poutre & Tacquet, 1978). Loin pain may occur in the early stages of therapy in spite of the fact that a water diuresis also occurs. We adopted the following policy: (1) gradual withdrawal of the previous diuretic over the space of a week, (2) a gap of 3 days without a diuretic and (3) introduction of tienilic acid at a relatively small dose (125 mg). This policy enabled the change to tienilic acid to be made without uric acid precipitation causing clinical problems. On the other hand, the cautious approach had its drawbacks in that a few patients clearly had an insufficient diuretic effect at the changeover. The lack of uric acid-precipitation problems may also have been partly due to the administration of a uric acid-lowering drug to some patients, so that the body pool of urate in these patients would have been relatively small. Conceivably the loin pain noted by one patient when the dose was increased from 125 mg to 250 mg daily could have been due to transient crystalluria.

Gout was expected during the changeover period, with the huge mobilization of urate. However, only one patient developed gout 1 month after starting tienilic acid.

Acknowledgments

The authors are aided by a grant from the Medical Research Council of New Zealand. We are grateful to Mrs G. Hobbs and her team of technicians for efficient day-to-day help in running the trial and coding of the results, to Mr M. Hayworth, biostatistician, Department of Preventive and Social Medicine, for computer analysis of the results and to Dr V. G. Balmer of Smith Kline and French Laboratories (Australia) Ltd for supplies of tienilic acid.

References

