The Treatment of Mild to Moderate Essential Hypertension with Tienilic Acid (Ticrynafen)

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SUMMARY

This paper reports a clinical trial of tienilic acid, a new diuretic with uricosuric properties, in 23 patients with mild to moderate hypertension (standing diastolic blood pressure 90 - 120 mmHg). Tienilic acid was compared with hydrochlorothiazide in a variable-dose, double-blind cross-over study, and the duration of therapy was 8 weeks for each drug. The falls in blood pressure (systolic/diastolic) were: 11/11 mmHg supine and 17/11 mmHg standing for tienilic acid, and 8/12 mmHg supine and 9/17 mmHg standing for hydrochlorothiazide. There were no significant differences between the two drugs in their effect on blood pressure and heart rate, and regarding side-effects and laboratory results, except for serum uric acid levels (mean fall of 1,5 mg/dl with tienilic acid and mean increase of 1,1 mg/l with hydrochlorothiazide).

Thiazide diuretics are frequently used in the treatment of hypertension. They are effective antihypertensive agents and potentiate the action of other antihypertensive drugs. Their use is complicated by a number of side-effects, of which hypokalaemia, hyperuricaemia and diabetes mellitus are the most important. Tienilic acid (ticrynafen in the USA), 2,3-dichloro-4-(2-thienylcarbonyl) phenoxyacetic acid (Fig. 1), is a new non-sulphonamide diuretic with powerful antihypertensive effects similar to those of the thiazides. The major mechanism of the diuresis is thought to be interference with the reabsorption of sodium in the cortical diluting segment of the distal nephron. Single-dose studies in normal volunteers have shown that tienilic acid 250 mg has a natriuretic action similar to hydrochlorothiazide 50 mg. Unlike the thiazides, however, tienilic acid inhibits tubular reabsorption of urates in the same manner as other uricosuric drugs such as probenecid. Tienilic acid, therefore, is said to have the advantage of a combination of the diuretic effect of the thiazides with uricosuric properties of probenecid and related agents. Since hyperuricaemia and exacerbation of gout are prominent side-effects of most diuretics presently used for the treatment of hypertension and many oedematous states, the uricosuric property of an antihypertensive diuretic agent is obviously a great advantage.

PATIENTS AND METHODS

Twenty-three patients with essential hypertension were selected from those attending the Hypertension Clinic at the Johannesburg General Hospital. The purpose of the trial was explained to each patient and informed consent was obtained. The mean age of the patients was 61,6 years, and 17 were females and 6 males. All antihypertensive therapy was stopped for 3 weeks in order to establish basal or pretreatment blood pressures and pulse rates, and also to determine the severity of the hypertension. The standing diastolic blood pressure (pretreatment) after 3 weeks off all hypertensive therapy was 90 - 99 mmHg in 7 patients, 100 - 109 mmHg in 14 patients, and 110 - 119 mmHg in 2 patients. The severity of hypertension was classified as mild, moderate or severe according to an index derived from the blood pressure, the optic fundi, an ECG, a chest radiograph, urinalysis, the serum urea level and the cerebrovascular history. No patients in this series were classed as having severe hypertension using these criteria. Secondary hypertension was excluded by clinical examination, testing the urine for protein, cells and bacteria (a colony count), intravenous pyelography, and the measurement of 24-hour urinary vanillylmandelic acid excretion. Serum urea, sodium, potassium, chloride, bicarbonate, uric acid and random glucose levels were determined, and chest radiographs and ECGs were taken.

Patients were seen at the same time of the day by the same investigator at weekly intervals. At each visit the blood pressure and pulse rate were recorded in the recumbent position after the patient had been supine for at
least 3 minutes and in a standing position 2 minutes after rising. Blood pressures were measured with a Hawkesley random-zero sphygmomanometer to minimize observer bias and digit preference. At each visit, the patients completed a self-administered questionnaire which asked whether they had any of the following symptoms, and if so whether these were mild, moderate or severe: headaches, palpitations, cramps in the leg, chest pain, dizziness, breathlessness, ankle swelling, brittle nails, tiredness, sleep disorders, nightmares, a cough, a rash, a stuffy nose, a sore throat, nausea, vomiting, diarrhoea, constipation, a dry mouth, blurred vision, weakness, sleepiness, depression, ringing in the ears, deafness, eye troubles, and impotence or failure of ejaculation in men. Grounds for exclusion from the trial included evidence that the hypertension was secondary to a surgically remediable condition, including phaeochromocytoma; coarctation of the aorta; aldosteronoma; Cushing’s disease; renal artery stenosis; a recent (less than 3 months) history of congestive cardiac failure; grade 4 hypertensive retinopathy; a myocardial infarction within the last 6 months; a cerebrovascular accident or acute hypertensive encephalopathy within the last 6 months; renal failure (defined as a serum urea concentration over 60 mg/dl). Patients requiring treatment with monoamine oxidase inhibitors, β-adrenergic blocking drugs, tranquillizers, or any other drug known to affect blood pressure, those with diabetes mellitus, a history of gout and/or hyperuricaemia, serious haematological, renal or hepatic disease, findings suggestive of neoplastic disease, significant electrolyte abnormalities, psychosis or severe psychoneurosis, and those who were pregnant, were also excluded.

After the washout period, patients received, according to a randomized prescription list, either tienilic acid 250 mg/d or hydrochlorothiazide 50 mg/d before breakfast, during an initial active treatment period of 8 weeks. After this period of active treatment each patient then received one placebo tablet a day for 2 weeks, followed by a crossover into a second active treatment period with the alternate drug for 8 weeks. At the end of the study there was a further 1-week placebo period. If, during each 8-week period of active treatment, there was less than a 10 mmHg decrease in the standing diastolic blood pressure, or if there were no side-effects attributable to the therapy, the dose was doubled to one tablet twice a day.

The results are summarized in Fig. 2. The mean blood pressure during the placebo period, excluding week 1, was $173/103 \pm 3/1$ (SEM) mmHg supine and $160/100 \pm 3/1$ mmHg standing. There was a progressive reduction in both supine and standing systolic and diastolic pressures with both tienilic acid and hydrochlorothiazide; the tienilic acid values at week 8 were $162/92 \pm 10/3$ mmHg supine and $143/89 \pm 6/4$ mmHg standing, and the hydrochlorothiazide values at week 8 were $165/91 \pm 7/3$ mmHg supine and $151/83 \pm 7/2$ mmHg standing. During the hydrochlorothiazide treatment period the blood pressure control at the end of week 6 was somewhat better than that at the end of week 8.

**RESULTS**

**Blood Pressure**

The same data are shown in Fig. 3, this time expressed as a change in arterial blood pressure from the pretreatment or placebo period. This figure also shows the levels of significance, based on paired t-testing against the pretreatment values for weeks 2, 4, 6 and 8 of the treatment period, for both the supine and standing systolic and diastolic pressures for tienilic acid and hydrochlorothiazide. It can be seen that both agents produced a highly significant fall in blood pressure within 2-4 weeks; the systolic pressures fell more rapidly with the hydrochlorothiazide than with tienilic acid, but the final values achieved after 8 weeks were not significantly different. The hydrochlorothiazide-induced fall in the standing diastolic blood pressure was greater than that in the supine position, indicating a significant postural component in the thiazide group. This was not present in the tienilic acid group, where both supine and standing diastolic pressures fell to about the same extent as the standing diastolic pressure during hydrochlorothiazide therapy. Put another way, the supine diastolic pressure response to tienilic acid was significantly greater than the response during the period of treatment with hydrochlorothiazide. With this exception, there were no significant differences between the responses to tienilic acid and hydrochlorothiazide.
Heart Rate

There were no significant differences or changes in the heart rate responses in both groups of patients.

Laboratory Tests

Table I shows the mean plasma potassium and uric acid values during the initial washout period and at the end of the tienilic acid and hydrochlorothiazide treatment periods. There was a small but statistically non-significant decrease in the serum potassium level at the end of both the tienilic acid and hydrochlorothiazide treatment periods compared with the placebo period. Tienilic acid produced a 1.5 mg/dl decrease in the mean serum uric acid value, significant at the 0.5% level. Conversely, hydrochlorothiazide increased the mean serum uric acid value by 1.1 mg/dl, also significant at the 0.5% level.

No significant or consistent changes were observed in any of the other electrocardiographic, radiographic or laboratory data during either treatment period.

Side-Effects

Side-effects were usually mild and did not require cessation of therapy. Tienilic acid therapy was associated with dizziness (3 patients), palpitations (2), headache (2), nausea and vomiting, dyspepsia, blurring of vision and ankle oedema. Patients on hydrochlorothiazide developed palpitations (2 patients), constipation (2), dizziness, angina, nausea and vomiting, and abdominal cramps.

One patient, a 71-year-old man, developed acute gouty arthritis of the left big toe after 6 weeks of tienilic acid therapy (at this stage he was taking 2 tablets a day). He had no previous history of gout. His serum uric acid level during the placebo period had been 7.7 mg/dl; it had risen to 13.5 mg/dl during the period of treatment with hydrochlorothiazide, during which he had no symptoms of gout. The serum uric acid level at the time of his acute gout attack was 6.3 mg/dl.

DISCUSSION

Tienilic acid is a diuretic and uricosuric drug which is as effective an antihypertensive drug as hydrochlorothiazide. Hyperuricaemia is an important and sometimes limiting side-effect of most of the diuretics currently available — this is thought to be related to contraction of extracellular fluid volume and competition with uric acid by diuretics for a common secretory site. Breckenridge found in a large study that 27% of untreated hypertensives have hyperuricaemia, and that this increased to 58% for those under treatment. Cannon et al. found that 26% of untreated hypertensives with normal serum urea values had hyperuricaemia and that of all hypertensive patients treated with thiazides 67% became hyperuricaemic (in contrast to those receiving other forms of treatment, in whom the incidence of hyperuricaemia was only 48%). Acute attacks of gout have been induced in some patients. Many feel that hyperuricaemia may be one of the risk factors associated with atherosclerosis and coronary disease, although this is still controversial. An antihypertensive drug that would eliminate this risk would consequently be desirable.

It is clear from the current data that tienilic acid is as effective an antihypertensive agent as hydrochlorothiazide, but that a further useful property is its uricosuric action. Despite the prominent uricosuric effect, no patient described any symptom associated with the urinary excretion of uric acid crystals. In this regard tienilic acid should be safer than other uricosuric agents, since it is also a diuretic and increases the volume of urine at the same time as urinary excretion of urate is maximal.

In a large Veterans Administration co-operative study, it was thought that a lower dose (250 mg/d) of tienilic acid was both less effective than a large dose (500 mg/d) or than hydrochlorothiazide (50 and 100 mg/d) in terms of reducing blood pressure. There was, however, no difference in uricosuric activity between the patients taking tienilic acid 250 mg/d and those taking 500 mg/d. This would suggest that the dose-response curve for the uricosuric action had flattened out between 250 and 500 mg/d, whereas antihypertensive efficacy is very much greater at 500 mg/d than at 250 mg/d and may be greater still at higher doses.

Unlike the findings in the Veterans Administration study, there would seem to be no difference in the degree of reduction of the serum potassium level in response to tienilic acid and hydrochlorothiazide in the present study.

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Both tienilic acid and hydrochlorothiazide caused serum potassium values to fall significantly, but there were no changes in serum glucose and triglyceride values with either drug (Table I). Treatment compliance appeared to be similar in both series, and the incidence of side-effects was extremely low in both groups.

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<thead>
<tr>
<th>TABLE I. SERUM POTASSIUM AND URIC ACID LEVELS</th>
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<tr>
<td>Potassium</td>
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<td>Mean (mEq/l)</td>
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<td>Uric acid (mg/dl)</td>
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*P values refer to paired r-testing.

Tienilic acid is an important new antihypertensive drug. It should be of great importance in the treatment of hypertensive patients with gouty diathesis or hyperuricaemia. This drug also does not produce the hyperuricaemia which is so often a problem with other diuretics. While the importance of asymptomatic hyperuricaemia as a cardiovascular risk factor is still a matter of some controversy, it would seem wise to avoid inducing this condition by the use of a thiazide diuretic when an effective uricosuric diuretic is available. Attention should be paid, however, to the potential hypokalaemia induced by tienilic acid, which does not appear to be any less common than that caused by thiazide. The importance of tienilic acid in unmasking diabetes mellitus or inducing abnormalities of carbohydrate tolerance, in the same way as thiazide diuretics, has yet to be assessed. The risk of inducing acute gout with tienilic acid, presumably via the rapid mobilization of uric acid secondary to its uricosuric activity, also needs to be determined as part of larger phase III studies. In the present series there was 1 patient who developed acute gouty arthropathy while on tienilic acid at a time when the serum uric acid level was normal, in contrast to the period of treatment with hydrochlorothiazide, when he had a serum uric acid level of 13.5 mg/dl with no symptoms at all.

**ADDENDUM**

Since this study was completed, reports of hepatotoxicity of tienilic acid have resulted in the temporary withdrawal of this agent from the market in the USA. There was no clinical or biochemical evidence of liver damage in any patient in this study.

**REFERENCES**