Effect of pyratrione (a tyrosine hydroxylase inhibitor) in essential hypertension

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Summary
1. A clinical study of pyratrione, a tyrosine hydroxylase inhibitor, has been carried out in essential hypertension.
2. Out of thirty-nine patients who received pyratrione, twenty-eight showed a significant decrease in blood pressure.

Key words: enzyme inhibition, essential hypertension, tyrosine hydroxylase.

Introduction
Tyrosine hydroxylase is an enzyme which limits the rate of catecholamine biosynthesis. Thus inhibition of this enzyme might decrease blood pressure in human hypertension, which may in part be dependent on the sympathetic nervous system.

Several structural analogues of oudenone, a tyrosine hydroxylase inhibitor found in cultured mushrooms, have been synthesized. From about 400 such compounds pyratrione [3-(3-hydroxyhydrocinnamoyl)-6-methyl-2H-2,4-(3H)-dione] was selected for further trial on the basis of its activity against tyrosine hydroxylase (2·4 × 10⁻⁴ mol), dopamine β-hydroxylase (4·3 × 10⁻⁵ mol), its hypotensive effect in spontaneously hypertensive rats and its low toxicity (Fig. 1; Umezawa, 1972).

In this study we have investigated the hypotensive activity of this compound in human subjects.

Methods and subjects
In preliminary experiments we studied the hypotensive effects of pyratrione in five hypertensive patients admitted to hospital. Blood pressure decreased from 5 to 15 mmHg after administration of the drug in a dose of 1·1 mmol/day for 1 week. There were no side-effects and no abnormal laboratory findings.

The effect of the drug administered for a longer period was therefore studied in thirty-nine patients with essential hypertension. The subjects consisted of twenty-three males and sixteen females, fourteen of whom were in the first stage of hypertension according to the WHO classification, ten were in the second stage and fifteen in the third stage. Most of the subjects were between 50 and 69 years old. Blood pressure measurement was carried out twice daily according to the method recommended by WHO.

Fig. 1. Structure of pyratrione [3-(3-hydroxyhydrocinnamoyl)-6-methyl-2H-2,4-(3H)-dione].

The initial doses of pyratrione were 1·1 mmol (300 mg) in eight patients, 1·65 mmol (450 mg) in six patients, 2·2 mmol (600 mg) in twenty-four patients and 3·3 mmol (900 mg) in one patient daily. A reduction of more than 20 mmHg in systolic blood pressure and/or more than 10 mmHg in diastolic blood pressure was regarded as a marked decrease, and a reduction from 10 to 19 mmHg in systolic
blood pressure and/or from 5 to 9 mmHg in diastolic blood pressure was regarded as a significant decrease.

**Results**

The blood pressure decreased significantly in twenty-eight of the thirty-nine patients. No relationship was found between the hypotensive effect and the stage of hypertension.

Out of the twenty-eight cases in which the drug was effective, sixteen showed a decrease in blood pressure within 1 week, nine showed a decrease within 2 weeks and three showed a decrease after 3 weeks.

In seven patients whose blood pressure had not been decreased by the administration of 1.1 mmol of pyratrione, the dose was increased to 2.2 or 3.3 mmol daily. Subsequently, five out of these seven patients showed a decrease of blood pressure.

In all of seven patients who had been treated previously with other anti-hypertensive drugs, such as rauwolfia, chlorothiazide and their derivatives, the blood pressure was lowered by the concomitant administration of pyratrione.

Routine laboratory investigations were performed before and during administration of the drug. Urine testing revealed no abnormalities, apart from one patient showing an increase of casts. None of the subjects developed anaemia. One showed a slight increase of leucocytes. Blood urea nitrogen increased in one patient; serum cholesterol and uric acid increased slightly in three patients; serum creatinine concentrations were not changed. Serum potassium concentrations decreased slightly during treatment in two patients. Total serum proteins, serum transaminases and alkaline phosphatase were increased in only one patient.

Nausea and vomiting were observed in one patient 3 weeks after starting the drug; these symptoms disappeared as soon as it was discontinued.

In two patients pyratrione was administered for 20–21 weeks. In one, the blood pressure was markedly decreased throughout. In the other patient, who had previously been treated with a variety of hypotensive drugs without satisfactory effect, a decrease in blood pressure was observed on addition of pyratrione. There were no side-effects in either instance.

Further clinical studies of pyratrione, including a double-blind trial, are needed. It is also necessary to study catecholamine metabolism in order to clarify the mechanism of the hypotensive effect.

**Reference**