The antihypertensive effects of ketanserin (R 41 468), a novel 5-hydroxytryptamine-blocking agent, in patients with essential hypertension

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Summary

1. In a double-blind placebo-controlled cross-over study a 4 week treatment with ketanserin was shown to reduce systolic and diastolic blood pressure markedly and significantly in 10 patients with essential hypertension. Heart rate remained virtually unchanged during the whole observation period. Systolic time intervals, reflecting cardiac output, did not change during the ketanserin phase, whereas these values deteriorated during the placebo period.

2. Ketanserin, a novel 5-hydroxytryptamine (5HT₂)-receptor antagonist with a high selectivity for blood vessels and thrombocytes, most probably acts by decreasing the venous capacitance bed constriction, and by counteraction of the amplifying effects of serotonin on noradrenaline and other vasoactive amines.

Key words: 5-hydroxytryptamine, ketanserin.

Abbreviation: 5HT₂, 5-hydroxytryptamine.

Introduction

Serotonin was isolated in 1948, in the search for a substance in serum responsible for the increased tone of blood vessels [1]. Nevertheless, little attention has been paid to serotonin in relation to arterial hypertension. The synthesis of a pure 5HT₂-receptor-blocking agent devoid of central effects and with a high selectivity for blood vessels and thrombocytes [2, 3] (ketanserin, R 41 468, Janssen Pharmaceutica, Belgium) prompted us to investigate this agent in elderly hypertensive patients, in whom it proved to normalize systolic and diastolic blood pressure, both after intravenous and oral treatment [4]. In this study, we assessed the oral effect of ketanserin in a double-blind cross-over experiment in patients with essential hypertension.

Methods

Patients

Ten outpatients (four male, six female), aged between 34 and 71 (mean 54.4) years, with a history of essential hypertension varying between 1 and 18 (mean 6.75) years, and without a history of myocardial infarction or cerebrovascular disease, participated in this study. Seven patients received classical antihypertensive treatment, consisting of diuretics or 𝜟-adrenoceptor-blocking agents or a combination of these agents.

Design

Before entering the double-blind cross-over trial all antihypertensive treatments were tapered off during a period of at least 2 weeks. Patients could only enter the double-blind trial if, in the absence of any antihypertensive treatment, hypertension was confirmed on two successive occasions at 1 week intervals (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg). After completion of the pretreatment weaning phase they were allocated in a double-blind fashion and at random sequence to either oral treatment with 20 mg of ketanserin or of placebo thrice daily at meal times. After 4 weeks the alternative medication was given for another 4 weeks. During the double-blind phase, lasting for 8 weeks, blood pressure was measured every other week on the same day of the week and the same time. ECG and systolic time
intervals were investigated before the double-blind phase, and thereafter every other week.

**Study medication**

Tablets with 20 mg of ketanserin or of placebo, identical in appearance, were supplied in two coded boxes for each patient, in random sequence.

**Measurements**

Systolic and diastolic blood pressure were measured with a sphygmomanometer. Measurements were always performed by the same observer on the right arm in the sitting position after a rest of 10 min. The median value of three readings was recorded. Heart rate was evaluated using a peripheral ECG lead from a four-channel Elema recorder (Siemens). Systolic time intervals were measured from simultaneous recordings of a peripheral lead of the ECG, phonocardiogram (TNO, Leiden) and carotid pulse wave (TNO, Leiden). The tracings were obtained on a modified four-channel Mingograph recorder, at a paper speed of 100 mm/s (Elema-Siemens). At least five consecutive cardiac cycles were analysed and averaged for the following parameters: QS, total electromechanical systole; LVET, left ventricular ejection time; PEP, pre-ejection period; ratio PEP/LVET.

All the differences were calculated with the Wilcoxon matched-pairs signed-ranks test, two-tailed probability [5].

**Results**

Systolic and diastolic blood pressure did not markedly increase during the weaning phase in seven patients with essential hypertension. At the start of the double-blind period the mean systolic blood pressure of the 10 patients was 173.5 (range 155-200) mmHg and the mean diastolic blood pressure was 105.5 (range 90-120) mmHg. Ketanserin markedly and significantly reduced systolic and diastolic blood pressure as compared with control values, whereas no significant changes occurred during the placebo period (Fig. 1). Blood pressure values after 4 weeks of ketanserin treatment were significantly lower than after 2 weeks.

No significant changes in heart rate were observed during the whole double-blind period.

Systolic time intervals remained unchanged during the ketanserin period, whereas PEP significantly ($P < 0.05$) increased, LVET significantly ($P < 0.01$) decreased, and the ratio PEP/LVET significantly ($P < 0.01$) increased at the 4 week placebo period, as compared with control values.

No untoward effects were reported during the whole observation period.

**Discussion**

The 10 patients studied had mild to severe hypertension. Six of the seven patients, previously treated with classical antihypertensive agents, had not responded to this therapy. Systolic and diastolic blood pressure significantly and progressively decreased in all these patients during ketanserin treatment, with a slow return to pretreatment blood pressure values during the placebo period. Heart rate remained virtually unchanged throughout the whole period of the study. Systolic time intervals, which are an indirect measure of cardiac output and stroke volume, were not affected by ketanserin, whereas a significant deterioration of these values occurred during placebo treatment. No side-effects or orthostatic hypotension were reported in any of these patients during treatment with ketanserin. From all these data it appears that ketanserin is an effective antihypertensive agent, which was free from side effects in the conditions of this study.

The underlying mechanism initiating the development of essential hypertension is still poorly understood. Recently it has been demonstrated that venous function seems to be impaired in experimental and in essential hypertension [6]. Essential hypertension might be causally related to capacitance bed constriction, due to a deficient stress relaxation of the veins [7]. Serotonin may well be the pressor factor mediating these changes [8, 9]. Indeed, the normalization of systolic and diastolic blood pressure in the absence of reflex changes in heart rate and cardiac output is compatible with the serotonin receptor blockade in peripheral blood vessels. Similar effects have been observed with ketanserin in experimental animals with serotonin-induced hypertension [3]. Serotonin is a potent vasoconstricting and platelet aggregating agent and it is a potent amplifier of vasoconstriction and platelet aggregation induced by other agents such as noradrenaline, angiotensin, prostaglandins etc. [3; F. De Clerck, J. L. David & P. A. J. Janssen, unpublished work]. Ketanserin antagonizes the direct and the amplification effects of serotonin in blood vessels and platelets [3; F. De Clerck et al., unpublished work].

In conclusion, the activity of ketanserin in essential hypertension may be explained by its...
antagonism of the direct vasopressor effect of serotonin at the venous site, but also partially by the abolition of the amplification of serotonin on other vasoactive amines.

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References


