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Ketanserin in essential hypertension: a double-blind, placebo-controlled study

H.A. Cameron* and L.E. Ramsay

University Department of Therapeutics, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK.

Summary: The antihypertensive effect of the selective serotonin antagonist ketanserin was examined in a double-blind, placebo-controlled, parallel group study in 20 patients with essential hypertension. After 7 weeks treatment with ketanserin (mean dose 71 mg/d) there was a significant fall of both systolic and diastolic blood pressure, as compared to placebo, with a peak effect of 19.1/9.1 mmHg lying ($P < 0.01$/ $P < 0.01$), and 16.5/11.3 mmHg standing ($P < 0.01$/$P < 0.01$); twice daily dosage appeared satisfactory. Subjective side effects were similar in the ketanserin and placebo groups. Ketanserin is an effective antihypertensive drug of moderate potency when given twice daily, with no orthostatic effect.

Introduction

Patients with established essential hypertension have an increase in peripheral vascular resistance with little change in cardiac output (Lund-Johansen, 1980). It has been suggested that serotonin (5-hydroxytryptamine; 5HT) may play some part in the increased peripheral resistance either by amplifying the effects of circulating angiotensin II and noradrenaline (Page & McCubbin, 1953), or by a direct vasoconstrictor effect on vascular smooth muscle (Somylo & Somylo, 1970). This hypothesis has emerged largely from *in vitro* work as 5HT has had variable and inconsistent effects on blood pressure in both animals and man (Garrattini & Valzelli, 1965). The recent characterization of $5HT_2$ receptors (Petroutka & Snyder, 1979) was followed by the development of a selective $5HT_2$ receptor antagonist, ketanserin (DeCrée *et al.*, 1981). This drug has made possible a closer examination of the role of 5HT in the maintenance of blood pressure. In initial open studies ketanserin appeared to lower blood pressure (DeCrée *et al.*, 1981; Wenting *et al.*, 1982), and we have therefore performed a placebo-controlled study to establish that the drug has an antihypertensive effect. We also wished to evaluate its side effect profile and to assess the effectiveness of a twice daily dosage schedule.

Correspondence: L.E. Ramsay, M.B., F.R.C.P.
*Present address: Janssen Pharmaceuticals Ltd., Grove, Wantage, Oxon OX12 DG, UK.
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Patients and methods

Twenty patients with essential hypertension gave written, informed consent, and the study protocol was approved by the Hospital Ethics Committee.

On entering the study all patients had a mean arterial pressure (MAP) of more than 110 mmHg while untreated or taking atenolol 100 mg/d, or taking bendrofluazide 5 mg/d. No other antihypertensive drug had been taken in the preceding 4 weeks. Patients were seen at fortnightly intervals. After a 4 week, single-blind, placebo run-in period they were randomly allocated in parallel groups to either ketanserin 20 mg b.d. or placebo provided the MAP remained above 110 mmHg. The study was rendered double-blind by the use of identical placebo tablets. The randomization was stratified for the existing antihypertensive treatment (untreated, atenolol or bendrofluazide) which was continued unchanged throughout the study. If the MAP remained higher than 110 mmHg 2 weeks after randomization the dose of ketanserin (or placebo) was increased to 40 mg b.d. (or equivalent placebo). If the MAP 2 weeks after randomization was 110 mmHg or less the patients continued on ketanserin 20 mg (or placebo) b.d. Treatment was continued for 7 weeks after randomization. At 2, 4 and 6 weeks patients were seen approximately 2 h after their morning dose (measuring 'peak' effect). At 7 weeks they were seen approximately 14 h after treatment to measure the 'trough' effect.

Blood pressure measurements were made by a single observer with a Hawksley random-zero sphygmoman-

ometer, using the right arm supported at heart level, and measuring phase V diastolic pressure. The means of two values when lying (after 5 min rest) and standing (immediate) were taken. Lying and standing pulse rates were recorded at the same time. Compliance was assessed by counting the tablets returned at each visit. Side effects were assessed by event recording, and by a self-administered questionnaire completed at the end of the study.

The following tests were performed at randomization and at the end of the study: full blood count; erythrocyte sedimentation rate; urea, electrolytes and creatinine; plasma glucose, calcium, urate and cholesterol; anti-nuclear antibody titre; urinalysis and electrocardiogram.

The results were analysed by calculating for each variable the changes from baseline values in each treatment group, then comparing the results for the two groups by Student's t test for unpaired samples. The predetermined principle end point was the change in blood pressure 6 weeks after randomization. The sample size was calculated to give the study a power of 0.8 to detect a difference between treatments of 21/10 mmHg, accepting $P < 0.05$ in a two-tailed test as significant (Freestone *et al.*, 1982).

Results

The 20 patients (12 men) had a mean age of 55 y (s.d. 9.9), mean body weight 76.3 kg (s.d. 13.2), and mean lying blood pressure at randomization 170.4(9.2)/105.8(6.9) mmHg systolic/diastolic. None had renal impairment. Table I compares the treatment groups at randomization; they were well matched in all respects except age, with patients receiving ketanserin being on average 10 y older than those receiving placebo. However, the responses in both groups showed no relation to age and we do not believe that this difference influenced the results.

Two patients were withdrawn from the study 2 weeks after randomization. One placebo patient had a diastolic blood pressure greater than 120 mmHg and was withdrawn for safety as specified in the protocol. One ketanserin patient was withdrawn because of headaches and lethargy. The analysis therefore refers to the 18 patients who completed the study. The final dose of ketanserin reached was 40 mg/d in 3 patients and 80 mg/d in 7. All those treated with placebo required the higher dose 2 weeks after randomization apart from the patient who was withdrawn.

The results for lying blood pressure are shown in Figure 1. Compared to placebo, patients treated with ketanserin showed a significant fall of both systolic and diastolic blood pressure at 2 weeks, and after 6 weeks the blood pressure had fallen further, with a peak antihypertensive effect of 19.1/9.1 mmHg ($P < 0.01$).

Figure 2 shows the results for standing blood pressure. The findings were similar, with patients treated with ketanserin having a peak antihypertensive effect of 16.5/11.3 mmHg after 6 weeks ($P < 0.01$/$P < 0.01$). There was no significant orthostatic response to ketanserin treatment. While acknowledging the small number of patients involved, the ketanserin-bendrofluazide combination was as effective as the ketanserin-atenolol combination in terms of lowering blood pressure.

The withdrawal of the placebo patient with a diastolic blood pressure higher than 120 mmHg caused a slight underestimate of the antihypertensive effect of ketanserin. An analysis of the final blood pressure reached, including the withdrawn patient, resulted in a smaller placebo effect and thus a slightly

Table I Characteristics of the two treatment groups at randomization, mean (standard deviation) data

	Placebo (n = 10)	*Ketanserin* (n = 10)
Men:Women	7:3	6:4
Age (y)	50 (9.6)	60 (7.8)*
Body weight (kg)	78.0 (12.5)	74.7 (14.4)
Plasma creatinine (μmol/l)	90.9 (16.1)	107.9 (30.8)
Lying blood pressure – systolic	170.3 (8.4)	170.1 (10.7)
(mmHg) – diastolic	107.4 (4.7)	105.3 (8.6)
Standing blood pressure – systolic	163.4 (8.8)	160.4 (14.8)
(mmHg) – diastolic	108.9 (8.1)	106.9 (11.7)
Existing treatment†		
Untreated	3	3
Atenolol 100 mg	3	4
Bendrofluazide 5 mg	4	3

* $P < 0.02$ versus the placebo group.

† Patients taking atenolol or bendrofluazide continued these drugs at the same dose throughout the study.

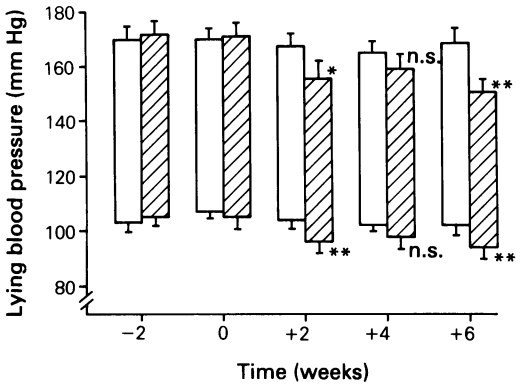

Figure 1 Change in lying blood pressure for patients taking ketanserin (▨ $n = 9$) and placebo (□ $n = 9$). Vertical bars represent mean (s.e.m.) systolic and diastolic blood pressure. $*P < 0.05$; $**P < 0.01$.

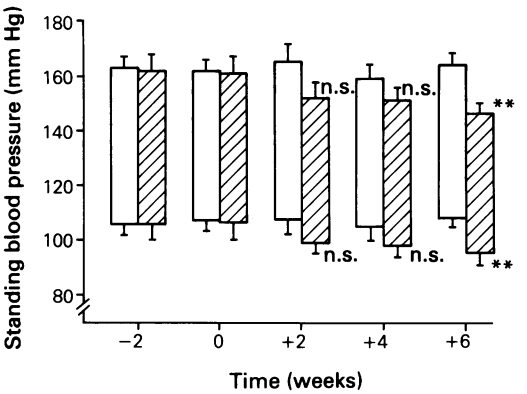

Figure 2 Change in standing blood pressure for patients taking ketanserin (▨ $n = 9$) and placebo (□ $n = 9$). Vertical bars represent mean (s.e.m.) systolic and diastolic blood pressure. $**P < 0.01$; n.s., not significant.

larger response to ketanserin (20.3/10.8 mmHg; $P < 0.01/P < 0.01$).

The adequacy of twice daily dosage was examined by comparing peak (2 h) and trough (14 h) measurements in patients treated with ketanserin and placebo. There was no loss of effect on lying blood pressure after 14 h (MAP rose by 0.5 mmHg; n.s.). However, in the standing position there was a small, though significant, loss of the antihypertensive effect of ketanserin (MAP rose by 4.6 mmHg; $P < 0.05$).

After 6 weeks treatment with ketanserin there was a significant fall in the lying heart rate (mean 6.4 (4.5) beats/min; $P < 0.01$). Body weight increased by 0.8 (1.9) kg but the change was not significant. There were no significant or important changes in haematological or biochemical tests during ketanserin treatment.

Electrocardiograms showed a statistically not significant trend for the QTc interval to increase (mean + 0.01 s; 95% confidence limit − 0.004 to + 0.030 s), but no other abnormality.

There were no serious side effects during the study. One patient stopped treatment after 2 weeks of ketanserin 20 mg b.d. because of headaches and lethargy. The side effect questionnaire administered at the end of the study showed no difference between the treatment groups.

Discussion

This study establishes that ketanserin is an effective antihypertensive drug, with a mean response of 19/9 mmHg lying and 17/11 mmHg standing compared with placebo. It had no orthostatic effect. With twice daily treatment there was no loss of lying blood pressure control 14 h after treatment, but there was a slight loss of control of the standing pressure. Twice daily dosage may therefore be satisfactory as suggested by the results of other studies (Anderson *et al.*, 1983; Andren *et al.*, 1983) and by a plasma half-life of about 13 h (Reimann *et al.*, 1983). A significant antihypertensive effect was also observed with a dose of 20 mg b.d. after 2 weeks.

There was no difference in subjective side effects recorded in the ketanserin and placebo groups, but one of 10 patients treated with ketanserin had to be withdrawn because of headaches and lethargy. Similar side effects have been reported with ketanserin treatment in other studies (Andren *et al.*, 1983; Hedner *et al.*, 1983) and suggest a central effect of the drug. There is some evidence that the incidence of side effects is lower when ketanserin is started at a dose of 20 mg b.d. and then increased to 40 mg b.d., and higher when a dose of 40 mg b.d. is used from the outset (Anderson *et al* 1983; Andren *et al.*, 1983; Hedner *et al.*, 1983).

Interest has been focussed recently on the mechanism by which ketanserin lowers blood pressure. In the spontaneously hypertensive rat considerable α_1 blockade with ketanserin was reported (Cohen *et al.*, 1983), but the relevance of this model to human hypertension is in some doubt (Wenting *et al.*, 1982; Cohen *et al.*, 1983). Studies in man have produced conflicting reports of the effects of ketanserin on the pressor response to methoxamine (Reimann & Frölich, 1983) and phenylephrine (Zoccali *et al.*, 1983), and the contribution (if any) of α_1 receptor blockade to the pharmacological action of ketanserin in man is not clear. There may also be a difference in the contribution of α_1 blockade during acute and chronic adminis-

tration of ketanserin (Ball *et al.*, 1983). The present study does not address directly the question of the relative role of $5HT_2$ and α_1 receptor blockade in the response to ketanserin. However, the significant reduction in heart rate suggests that α_1 blockade is not the only, or principal, mechanism of the antihypertensive effect. The absence of an orthostatic effect is also noteworthy.

In conclusion ketanserin is an antihypertensive drug of moderate potency and may prove a useful addition to the antihypertensive drugs currently available. In combination with beta-blockers and diuretics it appears safe and effective. It merits further evaluation in larger studies, with emphasis particularly on the frequency and severity of subjective side effects and the safety of long-term treatment.

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