Br. J. clin. Pharmac. (1987), **24**, 705–711

Ketanserin in essential hypertension: use as monotherapy and in combination with a diuretic or β-adrenoceptor antagonist

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1 The antihypertensive efficacy and tolerability of twice-daily treatment with the 5-hydroxytryptamine antagonist ketanserin were examined in a double-blind, placebo-controlled trial of 7 weeks duration in 56 hypertensive patients. Twenty were untreated, 20 were already taking bendrofluazide 5 mg daily, and 16 were already taking atenolol 100 mg daily. Randomisation was stratified to compare ketanserin with placebo as monotherapy ($n = 20$), when added to bendrofluazide ($n = 20$), and when added to atenolol ($n = 16$).
2 The antihypertensive effect of ketanserin in all patients completing the study (mean daily dose 71 mg) was 10/6 mm Hg supine ($P < 0.01/P < 0.01$) and 6/6 mm Hg standing (NS/$P < 0.01$) when blood pressure was measured 2 h after the morning dose. Responses were similar in patients taking ketanserin as monotherapy, in addition to bendrofluazide, and in addition to atenolol, with reductions in mean arterial pressure of 4.6, 7.4 and 8.9 mm Hg respectively.
3 Ketanserin had no antihypertensive effect when measured 14 h after the last dose. The rise in blood pressure between 2 and 14 h after dosing was 11/4 mm Hg supine ($P < 0.01$/NS) and 8/5 mm Hg standing ($P < 0.05/P < 0.05$).
4 The antihypertensive response to ketanserin was positively related to initial blood pressure and, independent of this, to age. It was not related to plasma concentrations of ketanserin or ketanserinol.
5 Five of 28 patients taking ketanserin discontinued treatment because of side-effects, compared with one of 28 patients taking placebo. Ketanserin treatment increased body weight by 1.0 kg ($P < 0.05$) and prolonged the corrected QT interval by 14 ms ($P < 0.01$).
6 Ketanserin has only modest antihypertensive efficacy when used as monotherapy, when added to a thiazide, or when added to a β-adrenoceptor blocker. A twice-daily dosing regimen does not seem satisfactory.

Keywords ketanserin hypertension diuretic β-adrenoceptor antagonist

Introduction

Ketanserin is a selective antagonist of 5-hydroxytryptamine (5-HT) at 5-HT_2 receptors which also has α_1-adrenoceptor antagonist activity (Anonymous, 1982). It lowers blood pressure acutely after intravenous injection (Wenting *et al.*, 1982) and in controlled studies after chronic

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oral dosing (Hedner & Persson, 1984; McGourty *et al.*, 1985). Dose-ranging studies have suggested that 40–80 mg daily given in one or two doses is an appropriate regimen for hypertensive patients (Andren *et al.*, 1983; Hedner *et al.*, 1983). We have performed a 7 week double-blind, placebo-controlled, parallel-group trial of ketanserin in treated and untreated hypertensive patients. The aims of the present study were to assess the efficacy and tolerability of ketanserin; to determine whether the response differed when it is used as monotherapy, in addition to a thiazide or in addition to a β-adrenoceptor blocker; and to examine the suitability of a twice-daily dose regimen. When twenty patients had completed the study an interim analysis was performed, as stipulated in the protocol, to determine that it was safe to continue (Cameron & Ramsay, 1985).

Methods

Patients

Three groups of hypertensive patients were recruited; 20 were untreated and had a mean diastolic blood pressure of 100 mm Hg or higher during the run-in period; 20 were taking bendrofluazide 5 mg daily and had a mean arterial pressure (MAP) of 110 mm Hg or greater during the run-in; and 16 were taking atenolol 100 mg daily and had a MAP $\geqslant$ 110 mm Hg during the run-in. Bendrofluazide and atenolol were continued at constant dosage throughout the study in the appropriate groups. Exclusion criteria were diastolic blood pressure > 120 mm Hg, accelerated hypertension, recent myocardial infarction, unstable angina, serum creatinine > 150 μmol l^{-1}, abnormal liver function, or a history of poor compliance. All patients gave informed consent in writing, and the protocol was approved by the hospital ethics committee.

Study design

All patients completed a 4 week single-blind placebo run-in phase and satisfied the blood pressure criteria stated above. They were then randomly allocated to receive ketanserin at an initial dose of 20 mg twice daily (n = 28) or matching placebo (n = 28). Randomisation was stratified for existing treatment so that ketanserin was compared to placebo as monotherapy (n = 20); in addition to bendrofluazide (n = 20); and in addition to atenolol (n = 16). Randomisation was also stratified for sex. After 2 weeks treatment the dose was increased to ketanserin 40 mg twice daily or equivalent placebo, if the MAP was at or above 110 mm Hg. The dose of ketanserin or placebo was held constant thereafter. Patients were reviewed 2, 4, 6 and 7 weeks after randomisation. At the 2, 4 and 6 week visits blood pressure was measured approximately 2 h after the morning dose of tablets, thus measuring 'peak' effect. At the week 7 visit patients omitted the morning dose of ketanserin or placebo and were seen approximately 14 h after their last dose, thus measuring the 'trough' effect.

Measurements

Supine and standing blood pressure, heart-rate, body weight, compliance as assessed by a count of tablets returned, and side-effects elicited by a non-leading question were measured at each visit. Haematological and biochemical tests, and an electrocardiogram were performed at entry to and exit from the study. Plasma concentrations of ketanserin and its metabolite ketanserinol were measured at 6 weeks, approximately 2 h after dosing ('peak') and at 7 weeks, approximately 14 h after dosing ('trough'). Blood pressure was measured in duplicate by a single observer for each patient using a Hawksley random-zero sphygmomanometer on the right arm supported at heart level, and measuring phase V diastolic. Ketanserin and ketanserinol concentrations were assayed by reverse-phase high-performance liquid chromatography with fluorescence detection using R46594 (Janssen Pharmaceutica, Beerse) as an internal standard. The limit of detection of the assay was 1 ng ml^{-1} and the coefficients of variation were 5.0% (ketanserin) and 2.7% (ketanserinol) at a concentration of 200 ng ml^{-1}.

Statistical analysis

The sample size was chosen to provide a power of 0.8 to detect a difference between ketanserin and placebo of 21/10 mm Hg at the 5% significance level (Freestone *et al.*, 1982) in each of the treatment sub-groups (untreated, bendrofluazide and atenolol). Responses to ketanserin and placebo were examined by analysis of variance after subtracting baseline values. There was no significant interaction between existing treatment and response, so that an overall analysis in all patients (n = 56) was performed in addition to analyses within the three treatment sub-groups.

Results

The patients entered (34 men; 22 women) had a mean age of 50.4 (range 21–67) years and mean

blood pressure at entry of 165/104 mm Hg. The ketanserin and placebo groups were well-matched in all respects except for age (Table 1). Patients randomised to ketanserin were an average of 6.5 years older ($P < 0.05$). The blood pressure at entry was similar in the three treatment subgroups; 161/105 mm Hg for monotherapy; 162/105 for the bendrofluazide group; 171/99 for the atenolol group.

Withdrawals

Eight patients (ketanserin $n = 5$; placebo $n = 3$) were withdrawn after randomisation. Two patients in the placebo group were withdrawn because their diastolic blood pressure exceeded 120 mm Hg, as stipulated in the protocol. The remainder were withdrawn because of side-effects, described later. The main analysis refers to 48 patients (ketanserin $n = 23$; placebo $n = 25$) who completed the study. The final dose of ketanserin was 40 mg daily in seven patients and 80 mg daily in 21 patients.

Blood pressure responses

In the overall analysis ($n = 48$) ketanserin treatment for 6 weeks lowered blood pressure significantly when compared with placebo, by 9.8/5.6 mm Hg supine ($P < 0.01/P < 0.01$) and 6.0/5.7 mm Hg standing (NS/$P < 0.01$), when blood pressure was measured 2 h after dosing (Figure 1). This analysis is biased against ketanserin because two placebo-treated patients were withdrawn because of uncontrolled hypertension (see above). To counter this the final blood pressure achieved by all 56 randomised patients was also analysed, and this showed that ketanserin lowered blood pressure by 9.9/5.7 mm Hg supine and 7.1/5.9 m Hg standing, when compared with placebo. The levels of significance

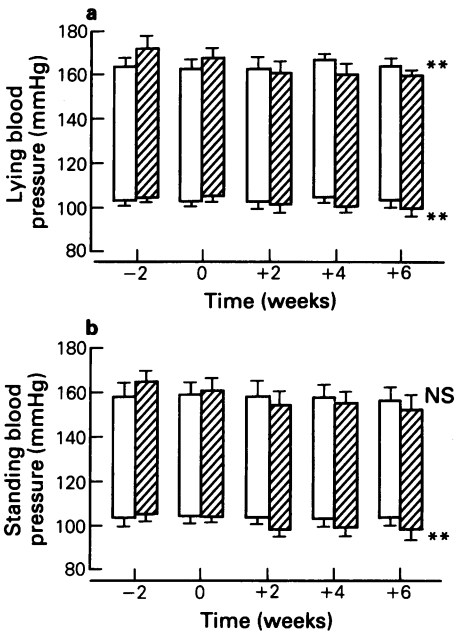

Figure 1 Effect of ketanserin and placebo on (a) lying blood presure and (b) standing blood pressure (mm Hg) during 6 weeks treatment. Mean (s.d.) data. $^{**}P < 0.01$, NS—not significant. ▨ ketanserin, □ placebo.

Table 1 Characteristics of the treatment groups at randomisation mean (s.d.) data

	Ketanserin (n = 28)	*Placebo* (n = 28)
Sex (M:F)	17:11	17:11
Age (years)	53.6 (10.4)*	47.1 (12.4)
Weight (kg)	75.2 (15.5)	76.8 (12.3)
Creatinine (μmol l^{-1})	100.7 (25.0)	94.6 (15.6)
Supine BP (mm Hg)		
Systolic	166.1 (14.1)	163.2 (13.2)
Diastolic	104.8 (7.0)	102.7 (8.9)
Standing BP (mm Hg)		
Systolic	159.6 (16.6)	158.9 (14.9)
Diastolic	105.8 (9.9)	105.6 (9.0)
Existing treatment		
Nil	10	10
Bendrofluazide	10	10
Atenolol	8	8

* $P < 0.05$.

were unaltered. Target blood pressure, which was defined as a mean arterial pressure of < 110 mm Hg at 6 weeks, was achieved by 6/28 patients randomised to ketanserin and 2/28 randomised to placebo. The responses to ketanserin were slightly larger in patients treated with atenolol (fall in MAP 8.9 mm Hg) or bendrofluazide (fall in MAP 7.4 mm Hg) than in those who received ketanserin as monotherapy (fall in MAP 4.6 mm Hg), but these differences did not approach significance.

The data above all refer to the 'peak' response, i.e. measurements 2 h after dosing. When measured 14 h after dosing ('trough' response) ketanserin did not lower blood pressure when compared to placebo. The loss of blood pressure control at 'trough' when compared to 'peak' was significant, with a rise of 10.7/4.2 mm Hg supine ($P < 0.01$/NS) and 7.8/5.1 mm Hg standing ($P < 0.05/P < 0.05$).

Blood pressure response related to age

This was examined because randomisation produced an important imbalance between the two treatment groups as regards age. In the ketanserin group there was a significant positive relation between age and apparent response to ketanserin (Figure 2) and this was independent of initial blood pressure (Δ systolic BP = 62.3 − 0.24 entry BP − 0.6 age, $P < 0.05$; Δ diastolic BP = 23.8 − 0.08 entry BP − 0.42 age, $P = 0.02$). There was no relation between age and apparent response in placebo-treated patients. Since older patients had a larger antihypertensive response the age imbalance at entry would tend to favour ketanserin, and the results presented above may be an overestimate of its efficacy.

Side-effects

One placebo-treated and five ketanserin-treated patients withdrew from the study because of side-effects (Table 2). The mean number of side-effects volunteered in response to non-leading questions was 1.6 per visit in ketanserin-treated patients and 1.0 per visit in placebo-treated patients. Headache and dizziness were the symptoms most frequently reported by ketanserin-treated patients, but no individual symptom was reported significantly more often during ketanserin treatment than on placebo.

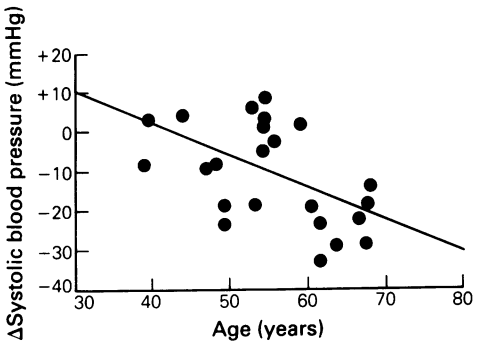

Figure 2 Relation between age and change in systolic blood pressure (mm Hg) during treatment with ketanserin ($n = 23$). Δ systolic BP (mm Hg) = 32.7 − 0.79 age (years) $r = -0.54$, $P < 0.01$.

Compliance and plasma concentrations

Tablet counts suggested that all but one patient took more than 90% of the tablets prescribed. This patient had virtually undetectable concentrations of ketanserin and ketanserinol (Figure 3) and was judged non-compliant. Exclusion of the data for this patient from the analysis had no important effect on the blood pressure responses presented above. Plasma concentrations of ketanserin and ketanserinol were measured at 'peak' and 'trough' (Figure 3). There was no significant relation between plasma concentrations of ketanserin or ketanserinol and blood pressure response.

Other measurements

Treatment with ketanserin caused a slight, but significant increase in weight (mean change from placebo: 1.0 kg, $P < 0.05$) and a non-significant reduction of heart-rate (2.0 beats min^{-1} supine;

Table 2 Withdrawals due to side-effects

Treatment group and dose	*Existing treatment*	*Symptoms*
Placebo	Nil	lethargy, arthralgia
Ketanserin 20 mg twice daily	Nil	headache, lethargy
Ketanserin 20 mg twice daily	Bendrofluazide	limb weakness
Ketanserin 40 mg twice daily	Nil	nausea, dizziness
Ketanserin 40 mg twice daily	Nil	headache, unsteadiness
Ketanserin 40 mg twice daily	Bendrofluazide	headache, depression

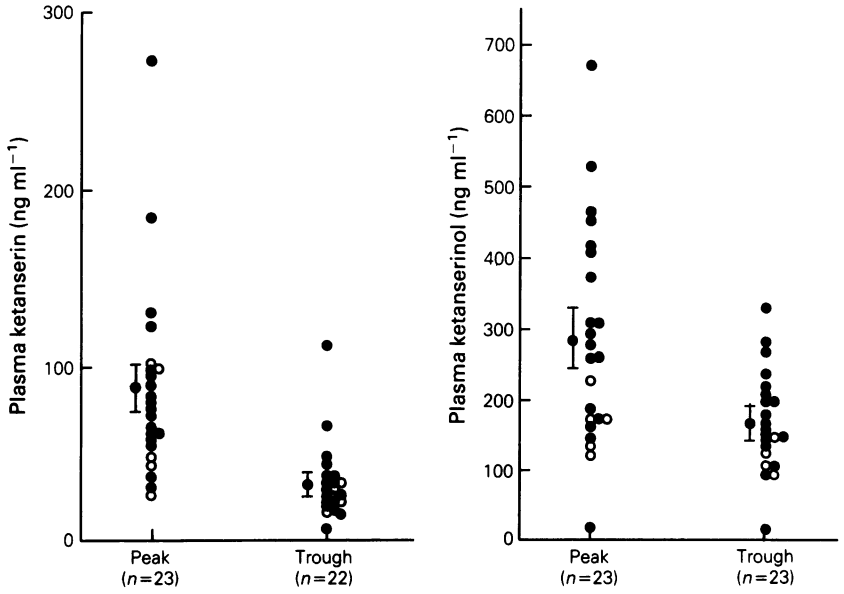

Figure 3 Plasma concentrations of ketanserin and ketanserinol (ng ml^{-1}) during treatment with twice-daily ketanserin (mean daily dose 71 mg) when measured approximately 2 h ('peak') and 14 h ('trough') after dosing. In one patient the 'trough' blood sample was unavailable. Mean (s.e. mean) concentrations: Ketanserin—'peak' 87 (11), 'trough' 33 (4) ng ml^{-1}. Ketanserinol—'peak' 284 (32), 'trough' 166 (15) ng ml^{-1}. ○ ketanserin 20 mg twice daily, • ketanserin 40 mg twice daily.

2.4 beats min^{-1} standing). There were no important changes in the haematological and biochemical tests. Compared with placebo, ketanserin treatment prolonged the corrected QT interval by 14 ms ($P < 0.01$) when measured at 'trough'. No arrhythmias were observed. This is reported in detail elsewhere (Cameron *et al.*, submitted for publication).

Discussion

The antihypertensive response to ketanserin was modest, averaging 10/6 mm Hg supine and 6/6 mm Hg standing, and only 6/28 patients treated with the drug attained normal blood pressure, defined as mean arterial pressure < 110 mm Hg (equivalent to 150/90 mm Hg). The disappointing response could not be attributed to poor compliance, nor to the significant difference between the groups in age. The response to ketanserin did increase with age as observed in some previous studies (DeCree *et al.*, 1985; Hedner *et al.*, 1985) but not others (Staessen *et al.*, 1985). If the initial blood pressure was 165/104 mm Hg one would predict a response of 7/6 mm Hg in a 50 year old, and 15/11 mm Hg in a 65 year old, from our data. However, the imbalance in age between the treatment groups favoured ketanserin, and would not bias the findings against the drug. The response to ketanserin was similar whether it was used as monotherapy or in addition to bendrofluazide or atenolol.

The antihypertensive effect of ketanserin has varied widely in published placebo-controlled studies, ranging from 19/12 mm Hg (Hedner *et al.*, 1984) to 5/4 mm Hg (Waal-Manning *et al.*, 1985) (Table 3). Such variability is to be expected when comparing studies which have included only small numbers of patients. The average antihypertensive response to ketanserin, weighted according to sample-size, in the studies listed in Table 3 was 8.9/7.6 mm Hg, a response very similar to that observed in the present study. It is clear that ketanserin has a significant but only modest antihypertensive action.

As ketanserin has an elimination half-life of approximately 17 h (Heykants *et al.*, 1986), one would expect a twice-daily dose regimen to prove satisfactory, and one study (Hedner *et al.*, 1983) appeared to support this. However our data suggest that a twice-daily regimen may not be satisfactory. Blood pressure measurements 14 h after dosing with ketanserin were significantly higher than those taken 2 h after dosing, and indeed were indistinguishable from placebo values. Further work is required to establish an appropriate dosage regimen.

Table 3 Placebo-controlled, double-blind trials of ketanserin in the treatment of essential hypertension

Reference	n†	*Mean age (years)*	*Mean dose (mg day^{-1})*	*Duration (weeks)*	*Blood pressure* *Initial (mm Hg)*	*Response (mm Hg)*
Fagard *et al.* (1984)	14*	40	120	6	150/84	9/7
Hedner *et al.* (1984)	10*	62	80	4	164/99	19/12
McGourty *et al.* (1985)	11	47	75	8	166/101	7/13
Waal-Manning (1985)	11*	63	125	4	171/100	5/4
Wing *et al.* (1985)	17*	59	80	6	152/88	7/4
Present study	23	50	73	6	165/104	10/6

† number of patients analysed who were treated with ketanserin.
* Cross-over studies ('initial' BP refers to BP during placebo treatment).

We observed no serious adverse reactions to ketanserin, but the drug was not well tolerated. 18% of patients treated with ketanserin had to discontinue treatment within 7 weeks, compared with 4% of placebo-treated patients. Ketanserin treatment was associated with significant weight gain averaging 1 kg, probably because of expansion of the extracellular fluid volume (de Leeuw & Birkenhager, 1985). Ketanserin treatment prolonged the QT interval, an observation previously reported in healthy subjects (Stott *et al.*, 1985) and confirmed by us in other studies (Cameron *et al.*, 1987). QT interval prolongation may predispose patients to life-threatening ventricular arrhythmias (Soffer *et al.*, 1982). We have not observed arrhythmias during ketanserin treatment, but three cases have been reported (Verstraete, 1984).

In conclusion, this study and the other placebo-controlled studies available (Table 3) all suggest that ketanserin is a weak antihypertensive agent. It is not particularly well tolerated and causes substantial prolongation of the QT interval, which is a major concern in a drug designed for lifelong use. Ketanserin is unlikely to have a role as a first or second line antihypertensive drug, and indeed we doubt whether it will have any useful place in the management of hypertension.

Financial support for H.A.C. and P.C.V. from Janssen Pharmaceutical Ltd, is gratefully acknowledged.

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(Received 11 May 1987, accepted 6 August 1987)