Controlled trial of ketanserin in hypertension

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- 1 We have completed a double-blind parallel group comparison of the 5-HT₂ receptor antagonist ketanserin with placebo in 22 hypertensive patients.
- 2 Ketanserin (20–40 mg twice daily) lowered sitting blood pressure more than placebo by 6.9 mm Hg systolic (NS), 13.1 mm Hg diastolic ($P < 0.05$) and by 11.4 mm Hg mean arterial pressure ($P < 0.02$). The fall in standing blood pressure was similar and we observed no first dose hypotensive effect.
- 3 Ketanserin lowered the sitting heart rate by 11.1 beats/min ($P < 0.01$).
- 4 The drug was well tolerated.

Keywords ketanserin 5-hydroxytryptamine hypertension

Introduction

Ketanserin is a 5-hydroxytryptamine (5-HT) antagonist which appears specific for 5-HT₂ receptors (Lysen *et al.*, 1981). Preliminary observations have suggested a significant hypotensive effect after acute and chronic dosing but there are few controlled studies in hypertension (De Cree *et al.*, 1981; Wenting *et al.*, 1982; Persson *et al.*, 1983; Fagard *et al.*, 1984; Cameron & Ramsay, 1984). We have completed a double-blind parallel group comparison of chronic treatment with ketanserin and placebo in 22 patients with mild hypertension.

Methods

We studied 22 patients (11 men) with uncomplicated hypertension who were aged 29–66 years (mean 47 years). The entry criterion was a calculated sitting mean arterial pressure (MAP = diastolic + 1/3 pulse pressure) greater than 115 mm Hg. Eighteen were untreated and four were uncontrolled despite treatment with a thiazide diuretic which was not altered throughout the study. After a 4 week (2 visit) run-in period on placebo (one tablet twice daily) those

with a blood pressure satisfying the entry criterion were randomised to one tablet of ketanserin 20 mg ($n = 11$) or identical placebo ($n = 11$). With consent the first dose was administered under out-patient observation ($n = 18$). Supine (5 min) and standing (1 min) blood pressure was measured hourly for 6 h. Dosing was then continued twice daily. Patients were reviewed after 2 weeks and 4 weeks when the dose was increased to 30 mg twice daily and 40 mg twice daily if the sitting MAP was greater than 110 mm Hg. They were reviewed after 8 weeks treatment.

Patients attended an afternoon clinic, therefore blood pressure was measured approximately 8 h after that morning's dose. Assessment of blood pressure was based on sitting (5 min) and standing (1 min) readings using phase V diastolic values. A Hawksley random zero sphygmomanometer was used and the mean of three readings recorded. For each patient the same nurse measured the blood pressure. Sitting pulse and body weight were also noted. Tablet counts confirmed compliance with treatment. Adverse effects were assessed by recording all new events and symptoms during the trial period. In addition

blood and urine were tested before and at the end of the study for changes in blood count, renal and hepatic function. Changes in blood pressure, pulse rate and weight from the end of the run-in period to the end of the trial period were calculated for each patient and significance determined using Students' unpaired *t*-test. The protocol was approved by the Hospital Ethics Committee and written informed consent was obtained.

Results

After randomisation there were four men in the active treatment group compared to seven in the placebo group. Three of the four patients who were taking diuretics were entered into the placebo group. However, patients were well matched for age, diastolic and mean blood pressure. Systolic blood pressure was slightly higher in the placebo group but not significantly so (Table 1). There was no evidence of a first dose effect with ketanserin ($n = 9$). The mean ($\pm$ s.d) standing blood pressure was $156.8 \pm 14.8/106 \pm 8.5$ mm Hg before dosing, $160.6 \pm 15.4/102.8 \pm 12.4$ mm Hg at 1 h and $153.6 \pm 14.8/101.3 \pm 8.9$ mm Hg 2 h after dosing. Supine values and those taken later in the day were similar. Heart rate ($\pm$ s.d) was 84.5 ± 9.0 beats/min before dosing, 77.1 ± 8.2 beats/min at 1 h and 73.3 ± 8.3 beats/min at 2 h which was not significantly different from placebo.

At the end of the chronic dosing period three patients were receiving ketanserin 30 mg twice daily and eight were on 40 mg twice daily. At weeks 2 and 4 there was no significant difference in blood pressure and heart rate when compared to placebo. At 8 weeks (end of trial) sitting and standing blood pressure were lower in the ketanserin group but the change in blood pressure was significant only for diastolic and MAP (Table 1). Although the mean fall in MAP was 11.4 mm Hg the target blood pressure (MAP ≤ 110 mm Hg) was achieved in only four of the 11 patients. There was no postural fall in blood pressure with ketanserin. Heart rate was significantly lower following active treatment but the slight increase in body weight was not statistically significant (Table 1). There were 11 adverse reports in each group (Table 2). One patient receiving ketanserin (80 mg daily) completed the trial but reported lethargy and has since been withdrawn from ketanserin treatment. However, there was no trend towards central nervous system side-effects in the ketanserin group. There was no significant change in blood or urine tests.

Table 1 Mean s.d. values for blood pressure, heart rate and body weight at the end of the run-in period and after 8 weeks treatment with placebo or ketanserin. CL represents the 95% confidence limits for the difference in blood pressure reduction between ketanserin and placebo.

Blood pressure (mmHg)	Placebo		Ketanserin		Δ	P value	Confidence limits (CL)
	Run in	Week 8	Run in	Week 8			
<i>Sitting</i>							
Systolic	172.5 $\pm$ 17.2	169.4 $\pm$ 22.2	160.3 $\pm$ 11.5	150.3 $\pm$ 14.4	-10	NS	+4.7 -18.5
Diastolic	100.7 $\pm$ 11.0	104.5 $\pm$ 12.4	102.1 $\pm$ 7.3	92.8 $\pm$ 7.1	-9.3	<0.05	-1.4 -24.8
MAP	124.6 $\pm$ 8.4	126.4 $\pm$ 13.1	121.5 $\pm$ 4.5	111.9 $\pm$ 6.7	-9.6	<0.02	-1.7 -21.1
<i>Standing</i>							
Systolic	173.9 $\pm$ 19.2	167.7 $\pm$ 18.2	161.3 $\pm$ 13.0	147.9 $\pm$ 11.2	-13.4	NS	+4.9 -19.3
Diastolic	108.8 $\pm$ 10.5	111.6 $\pm$ 11.0	110.3 $\pm$ 11.8	96.8 $\pm$ 9.2	-13.5	<0.01	-5.3 -24.5
MAP	129.9 $\pm$ 6.7	130.2 $\pm$ 9.9	127.3 $\pm$ 8.5	113.8 $\pm$ 7.8	-13.5	<0.01	-5.1 -22.5
Pulse rate (beats/min)	86.5 $\pm$ 7.7	90.1 $\pm$ 13.1	82.2 $\pm$ 13.1	74.7 $\pm$ 7.7	-7.5	<0.01	
Weight (kg)	70.7 $\pm$ 11.8	70.4 $\pm$ 11.2	71.3 $\pm$ 10.6	72.0 $\pm$ 10.2	+0.7	NS	

Table 2 Adverse effects reported by patients in both treatment groups throughout the study period.

New event	Ketanserin	Placebo
Mild depression/irritability	0	2
Transient impairment of memory and judgement	1	0
Lethargy/sleepy	1	1
Photophobia/blurred vision	1	0
Headache	1	2
'Detached'/muzzy	1	0
Faint/dizzy	1	1
Palpitations worsened	2	0
Chest discomfort/heartburn	1	2
Hot flushes	0	1
Bruising	1	0
Muscle cramps	0	1
Others	1	1
Total	11	11

Discussion

We have shown ketanserin lowers blood pressure in hypertensive patients. However, the effect on systolic pressure was modest which is at variance with some but not all preliminary studies (Persson *et al.*, 1983; Hedner *et al.*, 1983; Andren *et al.*, 1983; Fagard *et al.*, 1984; Staessen *et al.*, 1984; Cameron & Ramsay 1984). One reason for this may be the wide 95% confidence limits for the difference in systolic pressure reduction between ketanserin and placebo (Table 1). Although our patients had mild hypertension

only four out of 11 (36%) achieved the target MAP of 110 mm Hg which contrasts with uncontrolled reports at this dose (Hedner *et al.*, 1983). Higher drug doses may have been slightly more effective in reducing blood pressure, but doses above 120 mg/day are poorly tolerated (Andren *et al.*, 1983) whereas we found no increase in side effects over placebo.

There is considerable interest in ketanserin because it may possess a novel mode of action. It is uncertain whether the antihypertensive effect results from a direct action on 5-HT vascular receptors or via peripheral α -adrenoceptor antagonism (Reimann & Frolich, 1983; Ball *et al.*, 1983; Wenting *et al.*, 1984). Ketanserin is not associated with postural hypotension or a first dose effect, furthermore like others (Persson *et al.*, 1983; Cameron & Ramsay, 1983) we observed a bradycardia instead of the tachycardia often seen with α -adrenoceptor antagonists. The cause of this phenomenon is unknown. Our observations support the view that ketanserin may lower blood pressure by a direct effect on 5-HT receptors peripherally or by modulating the vasoconstrictor responses to other pressor agents such as noradrenaline or angiotensin II rather than by significant adrenoceptor antagonism.

In conclusion, ketanserin 40 mg twice daily was associated with a significant reduction in blood pressure and heart rate with minimal side effects. It may prove useful in the treatment of mild hypertension but the modest reduction in blood pressure suggests that it is likely to be inferior to existing first line agents.

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