Effect of the 5-hydroxytryptamine type 2 receptor antagonist, ketanserin, on blood pressure, the renin-angiotensin system and sympatho-adrenal function in patients with essential hypertension

J. R. ZABLUDOWSKI, C. ZOCCALI, C. G. ISLES, G. D. MURRAY¹, J. I. S. ROBERTSON, G. C. INGLIS, R. FRASER & S. G. BALL

M.R.C. Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT and ¹Department of Statistics, University of Glasgow, Glasgow G12 HQQ

1 Ketanserin, a 5-HT type 2 receptor antagonist, was administered intravenously to nine patients with essential hypertension in a double-blind placebo controlled study to investigate the drug's effects on blood pressure, heart rate, the renin-angiotensin system and sympatho-adrenal function.

2 Average blood-pressure for the group prior to injection of the drug was $150 \pm 7/94 \pm 4$ (s.e. mean) mm Hg and decreased significantly ($P < 0.01$) to $137 \pm 8/88 \pm 5$ mm Hg during the 2 h after injection; heart rate increased immediately after injection of ketanserin, reaching a maximum of 81 ± 4 beats/min.

3 After drug administration systolic and diastolic blood pressure decreased on tilting, but the heart rate response was not different from that with placebo.

4 Ketanserin did not affect the blood pressure response to graded infusion of the α_1 -adrenoceptor agonist phenylephrine.

5 Plasma active renin, angiotensin II and aldosterone concentrations increased slightly but not significantly after the drug; plasma noradrenaline increased transiently.

6 5-HT may be important in the maintenance of blood pressure but alternative mechanisms for the action of ketanserin in reducing blood pressure require investigation.

Keywords hypertension ketanserin 5-hydroxytryptamine renin angiotensin

Introduction

5-Hydroxytryptamine (serotonin, 5-HT) is established as a central neurotransmitter involved in the regulation of blood pressure (Kuhn *et al.*, 1980). However, its peripheral role, if any, in the control of blood pressure is unclear (Garrattini & Valzelli, 1965). Administered intravenously it has potent vasoactive properties and potentiates the vasoconstrictor effects of noradrenaline and angiotensin II in isolated perfused vessel preparations (Page & McCubbin, 1953). 5-HT may also regulate the synthesis and release of adrenocortical steroids (Tait *et al.*, 1972; Gross *et al.*,

1981), though much of this evidence comes from *in vitro* studies only.

Drugs which inhibit serotonin have so far shown little consistency in their action on blood pressure in man. However, the recent identification of the 5-HT₂ receptors (Petroutka *et al.*, 1979) and the introduction of ketanserin (Leysen *et al.*, 1981), a new specific 5-HT₂ antagonist devoid of agonist effect, has led to renewed interest in re-exploring the role of 5-HT.

We report the effects of ketanserin given intravenously to nine patients with essential

hypertension, on blood pressure, the renin-angiotensin system, the regulation of sympathetic nerve activity and adrenal function.

Methods

Subjects

Nine patients, six male and three female, aged 20 to 66 years, who had never previously received anti-hypertensive therapy were investigated. None of them had evidence of ischaemic heart disease, cerebrovascular disease, abnormal renal function, or an underlying renal or endocrine cause of hypertension.

Subjects were investigated after a 3 day period of controlled sodium (150 mmol/day) and potassium (60 mmol/day) intake. The protocol of investigation was approved by the Ethical Supervisory Committee of the Western Infirmary, Glasgow, and informed consent obtained from all patients.

Protocol

Supine study Patients fasted overnight and were asked to lie on a tilt table. An indwelling catheter was inserted into a peripheral vein for blood sampling. Blood pressure and heart rate were measured at 5 min intervals. Blood samples (25 ml) were taken for measurement of drug level, plasma active renin concentration, angiotensin II, aldosterone, cortisol, noradrenaline, and electrolytes after 30 min and then 15 min later, immediately before intravenous injection over 3 min of either 10 mg ketanserin or placebo (2 ml of normal saline). The administration of these treatments was double-blind and randomised. Further blood samples (25 ml) were taken 5, 30, 60 and 120 min after ketanserin or placebo injections.

Postural changes Two hours after intravenous injection of drug or placebo, subjects were tilted head-up to 45° for 2 min. Heart rate and blood pressure were recorded and blood (5 ml) taken for measurement of plasma noradrenaline and active renin concentrations. The subjects were then returned to the horizontal position for further study.

Phenylephrine infusion Ten minutes after the tilting study was completed the subjects were infused with phenylephrine in incremental dosage of 0.6 to 4.5 $\mu\text{g kg}^{-1} \text{ min}^{-1}$. Each infusion rate was continued for 5 min. Blood pressure and heart rate were measured twice, at 4 and 5 min. Plasma

drug levels were measured at the end of the infusion.

Methods and measurements Blood pressure was measured with a standard mercury sphygmomanometer. Plasma active renin concentration (intra- and inter-assay coefficients of variation, (CV), 6% and 10%, respectively; detection limit (s) 1 $\mu\text{u/ml}$ (Millar *et al.*, 1980), angiotensin II (C.V. 7, 10%; s 3 pmol/l) (Düsterdieck & McElwee, 1971), aldosterone (C.V. 7, 11%; s 100 pmol/l) (Fraser *et al.*, 1973), cortisol (C.V. 4, 7%; s 30 nmol/l) (cortisol kit, Corning Medical, Halstead, Essex) were measured by radioimmunoassay and electrolytes by atomic absorption spectrophotometry. Plasma noradrenaline (C.V. 8, 13%; s 0.1 nmol/l) was measured by a modification (Ball *et al.*, 1981) of the radioenzymatic method of Da Prada & Zürcher (1976); serum ketanserin (C.V. 6, 12%; s 25 nmol/l) by high pressure liquid chromatography (Davies, 1983). Plasma samples were stored at -20°C or -70°C (catecholamines only); samples from each patient were assayed as a single batch within 1 month of collection.

Statistical analyses

Analyses were based on repeated measures of analyses of variance with Greenhouse & Geisser (1954) correction to the *P* values. When appropriate, modified *t* statistics were used. Renin, aldosterone, angiotensin II, cortisol and noradrenaline results were converted to logarithms to attain normal distribution. Blood pressure and heart rate results are expressed as mean $\pm$ s.e. mean.

Results

Drug levels

Plasma ketanserin levels were 500.5 ± 81.9 (range 318 to 986) nmol/l 5 min after injection, 147.9 ± 8.5 (range 116 to 189), 97.6 ± 5.3 (range 80 to 120) at 30, 60 min respectively, and gradually declined to 70.6 ± 4.4 (range 58 to 80) nmol/l at 2 h, immediately prior to infusion of phenylephrine (Figure 1). After phenylephrine infusion plasma ketanserin level was 69.6 ± 5.2 (range 43 to 83) nmol/l.

Blood pressure prior to study

Mean blood pressure for the group was $202 \pm 8/116 \pm 4$ (range 240–170/134–108 sitting position) mm Hg prior to admission; $179 \pm 8/108 \pm 2$ (range 210–140/118–100 lying position) mm Hg on admission; and after 3 days

Figure 1 Blood pressure, heart rate, plasma active renin concentration, angiotensin II, aldosterone, cortisol, noradrenaline and ketanserin (mean $\pm$ s.e. mean) before and after intravenous injection of ketanserin (○) or placebo (●). Arrows indicate time of injection.

*In patient 7 whose blood pressure fell markedly after ketanserin renin increased to 547 μ u/ml and angiotensin II to 142 pmol/l at 60 min. These values are excluded from the figure but included in statistical analysis.

in hospital on a fixed metabolic intake had decreased further (Figure 1, Table 1) to $150 \pm 7/94 \pm 4$ mm Hg prior to ketanserin and $142 \pm 6/87 \pm 3$ mm Hg prior to administration of placebo.

Blood pressure and heart rate

Ketanserin caused a significant ($P < 0.01$) decrease in average blood pressure for the group, from $150 \pm 7/94 \pm 4$ mm Hg in the period prior to drug injection, to $137 \pm 8/88 \pm 5$ mm Hg during the 2 h after administration of ketanserin (Figure 1, Table 1).

In contrast average blood pressure for the group increased slightly but significantly ($P < 0.01$) after placebo from $142 \pm 6/87 \pm 3$ to $150 \pm 5/92 \pm 3$ mm Hg (Figure 1, Table 1). The average fall in mean blood pressure during the 2

h after drug administration was 7.9 ± 2.5 mm Hg. However, this was almost certainly an underestimate of the drugs hypotensive action as pressure increased by 5.9 ± 1.5 mm Hg after placebo. When change in average mean blood pressure in the 2 h after placebo was compared with that after drug there was a significant ($P < 0.01$) decrease of 13.8 ± 2.9 mm Hg.

Analysis of previously determined time points using a conservative procedure (Greenhouse & Geisser, 1954) found the decreases in both systolic and diastolic pressures were statistically significant ($P < 0.05$) only at 50, 60 and 120 min after the drug was given whereas mean arterial pressure was significantly lower at 20, 30, 50, 60, 70, 90 and 120 min.

Heart rate rose immediately after injection of ketanserin, reaching a maximum of 81 ± 4 beats/min within 10 min and remained signifi-

Table 1 Systolic and diastolic blood pressures (mm Hg supine) of individual patients at last out-patient clinic visit prior to admission, at admission, prior to study (mean $\pm$ s.e. mean of five readings) on fourth or fifth day of admission before administration of ketanserin (K) or placebo (P), at 5, 10, 30, 60, 90 and 120 min after ketanserin or placebo, and average blood pressure during 2 h after ketanserin or placebo.

Patient	Pre-admission	Admission	Basal	5 min	10 min	30 min	60 min	90 min	120 min	Average
1	225/110	202/108	P 151 $\pm$ 2/79 $\pm$ 1 K 160 $\pm$ 5/80 $\pm$ 1	150/80 170/74	154/72 150/68	154/76 150/72	148/76 138/70	164/72 138/70	160/76 138/72	158 $\pm$ 2/76 $\pm$ 1 145 $\pm$ 2/74 $\pm$ 1
2	200/110	188/118	P 123 $\pm$ 1/81 $\pm$ 1 K 142 $\pm$ 2/97 $\pm$ 2	122/86 142/100	124/80 146/98	134/98 140/100	130/88 136/100	132/100 150/104	140/96 150/106	133 $\pm$ 1/95 $\pm$ 1 140 $\pm$ 1/99 $\pm$ 1
3	215/108	156/98	P 146 $\pm$ 1/83 $\pm$ 1 K 121 $\pm$ 2/67 $\pm$ 2	150/82 128/70	144/80 108/62	154/100 96/58	144/84 100/64	152/88 100/56	158/86 104/56	151 $\pm$ 1/86 $\pm$ 1 102 $\pm$ 1/59 $\pm$ 1
4	180/132	162/104	P 129 $\pm$ 1/90 $\pm$ 1 K 136 $\pm$ 1/96 $\pm$ 1	132/94 142/96	128/92 140/98	132/100 142/96	136/102 134/96	138/96 132/102	136/92 132/100	135 $\pm$ 1/97 $\pm$ 1 136 $\pm$ 1/97 $\pm$ 1
5	170/120	164/108	P 139 $\pm$ 1/95 $\pm$ 1 K 148 $\pm$ 1/102 $\pm$ 2	136/98 134/92	140/94 128/94	136/94 134/96	134/100 138/98	140/100 132/94	148/98 124/96	141 $\pm$ 1/98 $\pm$ 1 132 $\pm$ 1/94 $\pm$ 1
6	205/115	140/100	P 122 $\pm$ 1/74 $\pm$ 2 K 132 $\pm$ 1/91 $\pm$ 1	122/78 130/78	120/76 110/70	134/68 104/78	150/94 104/84	150/80 84/68	156/88 120/84	143 $\pm$ 3/81 $\pm$ 1 103 $\pm$ 3/71 $\pm$ 2
7	170/105	185/110	P 140 $\pm$ 1/89 $\pm$ 1 K 179 $\pm$ 5/102 $\pm$ 2	146/96 162/100	148/92 162/92	152/98 156/96	150/94 162/100	150/86 148/92	150/92 166/100	149 $\pm$ 1/93 $\pm$ 1 156 $\pm$ 2/97 $\pm$ 1
8	240/110	210/110	P 181 $\pm$ 2/97 $\pm$ 2 K 185 $\pm$ 2/108 $\pm$ 2	182/96 170/110	180/98 172/102	182/98 174/104	190/104 178/108	202/110 178/108	194/110 190/114	188 $\pm$ 1/105 $\pm$ 1 179 $\pm$ 2/107 $\pm$ 1
9	214/134	204/112	P 149 $\pm$ 1/99 $\pm$ 1 K 142 $\pm$ 1/95 $\pm$ 1	148/98 120/90	154/98 124/92	148/102 130/94	154/100 134/94	148/100 132/90	146/102 132/88	152 $\pm$ 1/100 $\pm$ 1 132 $\pm$ 1/93 $\pm$ 1

cantly ($P < 0.05$) above basal readings for 40 min (Figure 1).

Phenylephrine infusion

The blood pressure response to incremental doses of phenylephrine was not modified by ketanserin treatment (Figure 2). During infusion of phenylephrine the rises in mean arterial pressure were 1 ± 1 , 3 ± 1 , 6 ± 2 , and 16 ± 4 mm Hg after administration of ketanserin, and 2 ± 1 , 3 ± 1 , 6 ± 3 , and 13 ± 4 mm Hg after placebo.

Figure 2 Mean arterial pressure (MAP) induced by infusion of phenylephrine 120 min after i.v. injection of ketanserin (○) or placebo (●).

Response to tilting

Systolic blood pressure decreased from 155 ± 5 to 146 ± 9 mm Hg, and diastolic blood pressure rose from 93 ± 3 to 104 ± 5 mm Hg on tilting after placebo. After ketanserin, both systolic and diastolic pressures decreased respectively from 144 ± 10 to 123 ± 15 mm Hg and from 91 ± 7 to 89 ± 8 mm Hg (Figure 3). One patient on tilting after ketanserin felt faint and diastolic blood pressure could not be recorded. Heart rate increased on tilting by 16.6 ± 3.6 beats/min after placebo and 16.4 ± 4.5 beats/min after ketanserin.

Noradrenaline

Five minutes after injection of ketanserin there was a significant ($P < 0.05$) increase in plasma noradrenaline from 1.7 ± 1 to 2.5 ± 0.2 nmol/l. No increase occurred in plasma noradrenaline in the subjects after placebo (Figure 1). On tilting, plasma noradrenaline increased significantly ($P < 0.01$) from 1.7 ± 0.2 to 2.6 ± 0.2 nmol/l after

placebo and from 2.1 ± 0.2 to 3.4 ± 0.4 nmol/l after drug (Figure 3).

Renin

Plasma renin concentration increased after ketanserin injection but the rise was not significantly different from the smaller increase observed after placebo injection (Figure 1).

Angiotensin II, aldosterone and cortisol

No significant changes were observed after ketanserin or placebo administration over the 2 h observation period (Figure 1).

Electrolytes

Plasma electrolyte concentrations were unchanged after administration of the drug or placebo.

Discussion

Our study shows that ketanserin administered intravenously caused a fall in blood pressure during the 2 h after injection. Patients were studied on the fourth and fifth days after admission during which time there had been a considerable reduction in blood pressure in individual patients compared to both out-patient and admission blood pressures (Table 1). This well documented phenomenon of decrease in blood pressure after admission illustrates the importance of placebo controls during sequential studies of blood pressures. At the time of administration of ketanserin two patients had diastolic pressures less than 90 mm Hg and three patients systolic pressures below 140 mm Hg (Table 1); individual responses to the drug were variable and did not in this small study relate to blood pressure before admission, at admission or immediately prior to the study (Table 1). These findings support recently published studies in which ketanserin has been shown to lower blood pressure in man (Wenting *et al.*, 1982a) and animals (Van Neuten *et al.*, 1981).

The rise in heart rate after ketanserin injection coincided with a significant rise in plasma noradrenaline, confirming another report (Wenting *et al.*, 1982b) and is compatible with increased sympathetic nerve activity in response to the fall in blood pressure.

Plasma ketanserin levels were most variable as would be expected at 5 min after injection but at subsequent time points were within a narrow range and no relationships to blood pressure or hormonal changes could be found. An increase in heart rate occurred shortly after injection of drug when plasma ketanserin levels were markedly elevated.

Figure 3 Blood pressure, heart rate, plasma active renin and noradrenaline concentrations before and after head up tilting to 45° for 2 min. Results for individual patients and mean $\pm$ s.e. mean are shown.

The rises observed in renin and angiotensin II after drug, but not placebo, failed to achieve statistical significance. However, within the series, the individual with the largest fall in blood pressure, had the greatest rise in renin and angiotensin II, suggesting these increases may have been largely mediated by the change in blood pressure.

The modest overall increase in aldosterone after drug administration, again not achieving statistical significance, was maximal 30 min after the rise in renin and angiotensin II suggesting an appropriate adrenal response and was largely accounted for by these subjects who had the greatest increases in plasma renin and angiotensin II. 5-HT may stimulate aldosterone

secretion by a direct effect on the adrenal or by hypothalamic action (Gross *et al.*, 1981; Epstein & Hamilton, 1977). Antagonism of 5-HT's action would be expected therefore to impair the aldosterone response to angiotensin II. Our results neither support nor refute a direct action and cannot exclude a composite response to stimulation by circulating angiotensin II and direct antagonism of aldosterone secretion.

Ketanserin can act as an α_1 -adrenoceptor antagonist in man (Reimann & Frölich, 1983) and animals (Fozard, 1982). Furthermore, some of its haemodynamic effects in the present study are similar to those seen after administration of prazosin (Lund-Johansen, 1974). However, at a time when mean plasma ketanserin levels were

between 69.6 and 70.6 nmol/l, infusion of phenylephrine induced the same rise in blood pressure as observed in the placebo period. Similar findings have been reported by others (Wenting *et al.*, 1982b), but Reimann & Frölich (1983) using large doses of ketanserin given intravenously by infusion and bolus injections of methoxamine in five normal subjects have offered evidence of an α_1 adrenolytic effect and we have observed also a shift of the dose response curve of blood pressure to phenylephrine infusion after administration of the drug orally for 3 days to normal subjects (Ball *et al.*, 1983). Ketanserin could act directly or indirectly to modify α -adrenoceptor response to sympathetic nerve stimulation reducing both arteriolar resistance and perhaps venous tone.

In spite of the fall in systolic and diastolic blood pressures in subjects tilted to 45° after receiving ketanserin the increases in heart rate and plasma noradrenaline in the drug treated patients were similar to those observed in the placebo group. These findings suggest an altered baroreflex response, but the changes in pulse intervals during phenylephrine infusion were the

same after ketanserin or placebo, arguing against interference with baroreflex function. However, the baroreflex response to reduction of pressure may not be comparable to that in response to an increase in pressure.

Intravenous ketanserin caused a fall in blood pressure when administered to patients with essential hypertension. An immediate and transient rise in heart rate, and of plasma noradrenaline were also observed, probably as a result of reflex sympathetic stimulation. Ketanserin as given in this study did not affect the blood pressure response to graded infusion of the α_1 -adrenoceptor agonist phenylephrine. The responses of blood pressure, heart rate and noradrenaline to tilting suggest the drug may modify baroreflex function.

S.G.B. is a British Heart Foundation Senior Research Fellow.

We thank Dr G. R. Venning and Dr Susan Gould (Janssen Pharmaceutical Ltd, Marlow, Bucks) for supplying ketanserin, and Dr C. L. Davies for the measurement of plasma ketanserin.

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(Received June 29, 1983,
accepted November 18, 1983)