CLINICAL RESEARCH

Mechanism of antihypertensive action of ketanserin in man

I W REIMANN, J C FRÖLICH

Abstract

A randomised double blind crossover study was carried out to determine whether ketanserin, a serotonin antagonist with an antihypertensive action in animals, has an α_1 adrenergic mediated antihypertensive effect in man. Steady state plasma ketanserin concentrations (mean 88 (SD 19) μg/l) and cardiovascular responses measured in five healthy volunteers showed that therapeutic doses of ketanserin significantly antagonised the α_1 receptor mediated increase in arterial blood pressure after treatment with methoxamine.

Thus the antihypertensive action of ketanserin in man appears to originate from a blockade of peripheral vascular α_1 receptors.

Introduction

Ketanserin, which is under intensive clinical investigation for its antihypertensive effect,[1 2] potently displaces the ligand tritium labelled spiperone from 5-hydroxytryptamine type 2 receptors[3] and is therefore characterised as a highly specific serotonin antagonist at 5-hydroxytryptamine type 2 receptors. As the effects of serotonin on the cardiovascular system are complex, with vasoconstriction in some and vasodilatation in other vascular beds,[4] and as there is only indirect evidence for the existence of 5-hydroxytryptamine type 2 receptors in vascular smooth muscle[5] the assumption that serotonin antagonism at peripheral vascular 5-hydroxytryptamine type 2 receptors is the mechanism of ketanserin's antihypertensive action is open to question and may represent only one of several possibilities. A physiological role of serotonin in centrally mediated regulation of blood pressure is being debated.[7 8] Although some adverse effects of ketanserin, such as dizziness, sedation, and drowsiness, point to central actions of this drug, only one study of ketanserin given intracerebroventricularly has been reported and this did not show a reduction in blood pressure.[11] In addition to its 5-hydroxytryptamine type 2 antagonism ketanserin also has α_1 adrenolytic activity in isolated blood vessels.[12] We therefore carried out a study to determine whether ketanserin has α_1 antagonistic effects in man.

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Patients and methods

Five healthy volunteers (two men and three women, one of whom was a smoker) aged between 23 and 35 years participated in the trial after giving written informed consent. The study, which had been approved by the ethics committee of the Robert Bosch Hospital, was carried out in a double blind randomised crossover fashion. Dose response curves to methoxamine were established on two different occasions separated by at least one week, once during infusion of ketanserin and once during infusion of saline.

With the subjects in the supine position blood pressure (using a Riva-Rocci sphygmomanometer) and heart rate were measured at five minute intervals during a 30 minute equilibrium period. Subsequently, each subject received on one occasion a 10 ml bolus injection of saline (three minutes) followed by an intravenous infusion of saline (30 ml in 3 hours) and on the other occasion a bolus injection (three minutes) of 0·15 mg ketanserin/kg in 10 ml saline followed by an intravenous infusion of 12 mg ketanserin in 30 ml saline (Janssen Pharmaceutica, Beerse, Belgium) in three hours. After 30 minutes' infusion of ketanserin or saline steady state concentrations were achieved and methoxamine hydrochloride (Vasoxyl, Burroughs Wellcome, Research Triangle Park, North Carolina, USA) was injected (15 second bolus) in a fixed dose sequence of 0·5, 1·0, 2·0, 4·0, and 6·0 mg dissolved in 2 ml saline at 30 minute intervals. After each injection of methoxamine blood pressure and heart rate were recorded at one minute intervals for the first five minutes after injection and at five minute intervals during the next 25 minutes until the next higher dose of methoxamine dose was injected. Before and at 30 minute intervals after the infusion had been started blood samples (10 ml) were drawn for analysis of plasma concentrations of ketanserin: blood was collected from the arm opposite the infusion site via an indwelling butterfly needle flushed with heparin in saline. After centrifugation plasma samples were frozen in 5-6 ml aliquots and stored at −20°C. Ketanserin analyses were performed as described.[13]

Blood pressure and heart rate are expressed as means (SD) of the values obtained within the first three minutes after methoxamine injection. Mean arterial blood pressure was calculated as diastolic

blood pressure + (systolic-diastolic pressure)/3. Differences in blood pressure and heart rate with the varying doses of methoxamine and with the infusions of saline for ketanserin were analysed for significance by paired Student's t test. A probability level of $p < 0.05$ was presumed to reflect significance.

Results

Ketanserin caused a shift to the right in the response of mean arterial blood pressure to increasing doses of the α_1 adrenoceptor agonist methoxamine (fig 1). The mean arterial blood pressure during the control periods of saline and ketanserin infusion were slightly, but not significantly, different (94·1 (SD 9·1) v 90·0 (SD 4·1) mm Hg (fig 1). Whereas during saline infusion the mean arterial blood pressure increased, depending on the dose, from 94·1 (SD 9·1) mm Hg to 110·6 (SD 15·1) mm Hg with increasing doses of methoxamine up to 4 mg there was no increase in mean arterial blood pressure with this dose during ketanserin infusion. Only at the highest dose of 6 mg did the mean arterial blood pressure rise from 90·0 (SD 4·1) to 98·7 (SD 8·8) mm Hg during ketanserin infusion. This dose was not, however, given during saline infusion because of the adverse effects—such as palpitations, anxiety, and pronounced bradycardia (< 36 beats/minute) —observed in two volunteers. Table I gives the changes in mean arterial blood pressure in each subject with increasing doses of methoxamine during saline or ketanserin infusion. There were significant differences in the changes in mean arterial blood pressure at all dosages when the results for the saline and ketanserin infusions were compared, even though at the lower two doses of methoxamine the differences in pressure were too small to be interpreted. At the 4 mg dose of methoxamine the mean arterial blood pressure response during saline infusion was about 30 times higher than that during ketanserin infusion (table I). During saline infusion systolic and diastolic blood pressures were unchanged after 0·5 and 1·0 mg doses of methoxamine but rose sharply and significantly after the 2 mg and 4 mg doses (table II). By contrast, no significant changes in blood pressure occurred after doses of 0·5-4 mg methoxamine during simultaneous ketanserin infusion. A significant increase in mean diastolic blood pressure from 77·9 (SD 4·5) to 84·7 (SD 9·3) mm Hg was observed during ketanserin infusion only with the 6 mg dose of methoxamine. Whereas mean systolic blood pressure increased significantly from 117·8 (SD 11·2) to 128·0 (SD 9·8) mm Hg after 2 mg methoxamine during saline infusion, even 6 mg methoxamine did not cause a significant increase in systolic blood pressure during ketanserin infusion.

Methoxamine produced significant decreases in heart rate at all the doses given in this study after infusion of saline as well as ketanserin. The fall in heart rate was, however, less during ketanserin infusion, except with the 0·5 mg dose of methoxamine. The difference between the fall after ketanserin infusion and that after saline infusion reached significance ($p < 0.02$) only for the 4 mg dose of methoxamine (fig 2).

The three minute intravenous bolus injection of 0·15 mg ketanserin/kg followed by a continuous infusion at the rate of 4 mg/h resulted in steady state mean plasma ketanserin concentrations of 88·3 (SD 19·1) μg/l. No significant differences could be observed between the plasma ketanserin concentrations measured at 30 minute intervals during the three hours of the study (table II).

TABLE I—*Changes in mean arterial blood pressure (mm Hg) induced by doses of methoxamine during saline or ketanserin infusion*

Case No	Methoxamine dose (mg): 0·5	1·0	2·0	4·0	6·0
Saline infusion					
1	1·2	0·2	7·3	25·6	*
2	−1·5	0·0	7·3	4·2	
3	0·5	3·6	7·8	25·6	
4	2·4	2·5	5·0	8·3	
5	0·9	2·7	7·1	18·9	
Mean (SD)	0·7 (1·4)	0·9 (2·4)	6·9 (1·1)	16·5 (9·9)	
Ketanserin infusion					
1	0·7	1·6	0·0	0·9	16·4
2	−4·9	1·8	2·7	0·7	5·3
3	0·2	1·5	3·5	4·4	17·7
4	1·1	3·6	3·6	6·7	1·0
5	1·0	0·2	0·4	3·3	6·2
Mean (SD)	−1·5 (2·0)	1·1 (2·0)	0·5 (2·8)	0·5 (4·3)	4·9 (7·3)
Significance of difference between infusions: Student's paired t test	$p = 0.01$	$p < 0.001$	$p < 0.001$	$p = 0.006$	

*Not given to volunteers during saline infusion because of side effects.

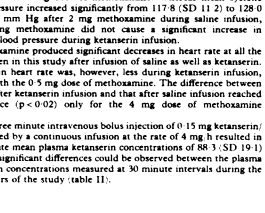

FIG 1—Mean arterial pressure in response to increasing doses of methoxamine in five healthy volunteers given saline (○—○) and ketanserin (●—●) infusions. Bars represent SDs. *$p < 0.01$, ***$p < 0.001$.

TABLE II—*Mean (SD) plasma concentrations of ketanserin and cardiovascular responses to intravenous injections of methoxamine during infusions of ketanserin and saline (n = 5)*

Infusion	Control period	Doses of methoxamine (mg) (minutes after start of infusion): 0·5 (30)	1·0 (60)	2·0 (90)	4·0 (120)	6·0 (150)
Systolic blood pressure (mm Hg)						
Saline	117·8 (11·2)	118·3 (11·3)	119·2 (10·0)	128·0 (9·8)***	143·5 (17·6)***	
Ketanserin	114·2 (8·2)	111·8 (5·0)	111·2 (2·8)	113·0 (3·9)	112·8 (4·4)	126·8 (11·5)
Diastolic blood pressure (mm Hg)						
Saline	78·9 (9·2)	83·1 (8·8)	82·4 (6·6)	87·5 (9·1)**	93·3 (15·1)*	
Ketanserin	77·9 (4·5)	76·8 (7·0)	77·7 (6·1)	77·7 (6·6)	79·3 (7·2)	84·7 (9·3)*
Heart rate (beats/min)						
Saline	64·4 (10·6)	62·8 (9·9)**	56·4 (6·5)*	54·6 (7·6)*	47·0 (8·8)**	
Ketanserin	69·0 (10·9)	65·6 (10·0)*	62·4 (8·8)**	61·6 (10·8)*	54·8 (10·0)**	49·6 (8·3)**
Plasma ketanserin concentration (μg/l)						
Ketanserin		90·0 (21·6)	86·2 (17·7)	87·6 (18·6)	89·8 (20·8)	88·7 (19·6)

Significance of difference compared with control observations: Student's paired t test: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

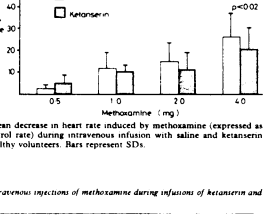

FIG 2—Mean decrease in heart rate induced by methoxamine (expressed as % of control rate) during intravenous infusion with saline and ketanserin in five healthy volunteers. Bars represent SDs.

Discussion

This study clearly shows that ketanserin has an α_1 antiadrenergic action in man. Earlier studies of receptor binding with binding sites isolated from rat brain showed ketanserin to have an affinity to α_1 adrenergic receptors that was, however, only about a fifth of that for 5-hydroxytryptamine type 2 receptors.[4 12] Thus interest focused on the 5-hydroxytryptamine type 2 receptor antagonism as the mechanism of the antihypertensive action of ketanserin. The effect of serotonin on vascular smooth muscle is difficult to predict; it depends on species, type of tissue, vascular beds, and basal vascular tone.[4] The effects of intravenously injected serotonin in man are by no means unequivocal, as shown by Hollander *et al*.[14] In 20 normotensive and 35 hypertensive subjects serotonin given in intravenous doses of 0·25-2·0 mg produced definite but variable pressor, depressor, or biphasic effects on arterial blood pressure. Thus it is difficult to explain the stable reduction of blood pressure observed in animals[15] and clinical studies[1 2] after administration of ketanserin solely on the basis of serotonin antagonism. Furthermore, recent studies in rats have provided evidence in favour of α_1 receptor blocking properties of ketanserin. Fozard[16] showed that in the pithed rat vasoconstriction in response to sympathetic stimulation was attenuated by ketanserin whereas the pure serotonin antagonist BW 501 C67 had no effect, although the doses of the latter were equivalent to those of ketanserin in producing a substantial blockade of serotonin receptors. Kalkman[17] showed that α_1 receptor mediated increases in blood pressure were similarly reduced by prazosin and ketanserin, whereas neither substance changed the α_1 adrenoceptor mediated responses to B-HT 920. Consequently, the hypothesis that the antihypertensive action of ketanserin is based on a blockade of the latter were equivalent amine type 2 receptors is not yet supported by reliable evidence.[18] From the results of our study we conclude that ketanserin shows α_1 adrenoceptor blocking properties in man at plasma concentrations that are normally obtained under therapeutic conditions. The antihypertensive action of ketanserin may thus be caused by its α_1 adrenoceptor antagonism.

Ketanserin ampoules were kindly supplied by Janssen Pharmaceutica, Beerse, Belgium. We thank Mrs H Stuber and Mrs P Kopp for performing ketanserin analyses and Mrs B Grözinger for preparing the manuscript. The study was supported by the Robert Bosch Foundation, Stuttgart, Germany.

References

1 DeCree J, Verhaegen H, Symoens J. Acute blood pressure lowering effect of ketanserin. *Lancet* 1981;i:1161-2.
2 DeCree J, Leempoels J, DeCock W, Geukens H, Verhaegen H. The antihypertensive effects of a pure and selective serotonin-receptor blocking agent (R 41 468) in elderly patients. *Angiology* 1981;**32**:137-44.
3 Wenting GJ, Man In't Veld AJ, Wotttiez AJ, Boomsma F, Schalekamp MADH. Treatment of hypertension with ketanserin, a new selective 5-HT$_2$ receptor antagonist. *Br Med J* 1982;**284**:537-9.
4 Leysen JE, Awouters F, Kennis L, Laduron PM, Vandenberk J, Janssen PAJ. Receptor binding profile of (R 41 468), a novel antagonist at 5-HT$_2$ receptors. *Life Sci* 1981;**28**:1015-22.
5 Douglas WW. Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: Goodman Gilman A, Goodman LS, Gilman A, eds. *The pharmacological basis of therapeutics*. 6th ed. New York; Macmillan Publishing Co, 1980:609-46.
6 Cohen ML, Fuller RW, Wiley KS. Evidence for 5-HT$_2$ receptors mediating contraction in vascular smooth muscle. *J Pharmacol Exp Ther* 1981;**218**:421-5.
7 Kuhn DM, Wolf WA, Luvenberg W. Review of the role of the central serotonergic neuronal system in blood pressure regulation. *Hypertension* 1980;**2**:243-55.
8 Browning RA, Bramlet DG, Myers JH, Bundman MC, Smith ML. Failure to produce blood pressure changes following pharmacological or surgical depletion of brain serotonin in the spontaneously hypertensive rat. *Clin Exp Hypertens* 1981;**3**:953-73.
9 Krstic MK, Djurkovic D. Comparison of the cardiovascular responses to intracerebroventricular administration of tryptamine, 5-hydroxytryptamine, tryptophan and 5-hydroxytryptophan in rats. *Arch Int Physiol Biochim* 1981;**89**:385-91.
10 McCall RB, Humphrey SJ. Involvement of serotonin in the central regulation of blood pressure: evidence for a facilitating effect on sympathetic nerve activity. *J Pharmacol Exp Ther* 1982;**222**:94-102.
11 Persson B, Hedner T, Henning M. Cardiovascular effects in the rat of ketanserin, a novel 5-hydroxytryptamine receptor blocking agent. *J Pharm Pharmacol* 1982;**34**:442-5.
12 van Nueten JM, Janssen PAJ, van Beek J, Xhonneux R, Verbeuren TJ, Vanhoutte PM. Vascular effects of ketanserin (R 41 468), a novel antagonist of 5-HT$_2$ serotonergic receptors. *J Pharmacol Exp Ther* 1981;**218**:217-30.
13 Okonkwo PO, Reimann IW, Woestenborghs R, Klotz U. High performance liquid chromatographic assay with fluorometric detection of ketanserin, a new antihypertensive agent and serotonin S_2 antagonist in human plasma, blood and urine. *J Chromatogr* 1983;**272**:411-6.
14 Pertoutka SJ, Snyder SH. Multiple serotonin receptors: differential binding of [^{3}H]-5-hydroxytryptamine, [^{3}H]-lysergic acid diethylamide and [^{3}H]-spiroperidol. *Mol Pharmacol* 1979;**16**:687-99.
15 Hollander W, Michelson AL, Wilkins RW. Serotonin and antiserotonins. I. Their circulatory, respiratory, and renal effects in man. *Circulation* 1957;**16**:246-55.
16 Fozard JR. Mechanism of the hypotensive effect of ketanserin. *J Cardiovasc Pharmacol* 1982;**4**:829-38.
17 Kalkman HO. The antihypertensive effect of the new serotonin antagonist ketanserin in the rat is probably due to antagonism of vascular α_1-adrenoceptors. *Naunyn Schmiedebergs Arch Pharmacol* 1982;**319** (suppl):R 50.
18 Millar JA, Facoory BD, Laverty R. Mechanism of action of ketanserin. *Lancet* 1982;ii:1154.

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ONE HUNDRED YEARS AGO The throwing open of the competition for the designs of the new War Office and Admiralty has doubtless caused a flutter of excitement amongst architects of every degree. We note that of the judges of designs to be appointed by the Commissioners of Works, one, at least, will be an architect. Is it too much to hope that there will also be placed on the committee a medical man of experience in hygiene and a sanitary engineer? In the conditions of competition, it is indeed laid down that "particular attention must be given to the general sanitary arrangements," which intending competitors will infallibly take to mean that the drains must not be forgotten, that the water-closets must be sufficient in number, and reasonably inodorous, and that the sewage must at any rate have somewhere to go to. But "sanitary arrangements" in a pile of buildings such as is contemplated means much more than this; and if there were sanitary experts on the committee of judges—say, for instance, Dr. Buchanan, the chief medical officer, and Sir Robert Rawlinson, the chief sanitary engineer of the Local Government Board, whose services would cost nothing—we might feel some confidence that the hideous blunders of the new Government offices in Parliament Street would not be repeated. "Sanitary arrangements" in reality involve the whole scheme of the buildings. They comprehend the disposition of the rooms as regards light and ventilation, the area and height of the rooms, the position and construction of the staircases, and other details that may affect very importantly the health and comfort of the inmates. Government officials, even if they be not the hardest worked of beings, have the right to demand reasonable comfort in their work. Moreover, it is a positive economy to the State to keep them in good health, since in their absence their duties must of necessity be provided for. In the new Government offices everything—light, ventilation, and other trifles—was sacrificed to an imposing façade; and as to the drainage, that was a matter not dreamt of in the architect's philosophy. Experience does not, unfortunately, seem to teach Government departments in the same bitter fashion that it does less-favoured mortals who have only their own money to play with; and it may therefore be useful once more to point the moral of the previous Board of Work's undertaking of this kind, and to insist upon the necessity of the plans being critically examined by experts in sanitary science. (*British Medical Journal*, 1883;ii:591.)

Correction

Protective effect of vitamin E (DL-alpha-tocopherol) against intraventricular haemorrhage in premature babies

Two errors occurred in the first sentence of the abstract of this paper by Dr M L Chiswick *et al* (9 July, p 81). The sentence should have read: "Forty four babies, of less than 37 weeks' gestation, were either randomly given 20 mg/kg vitamin E (DL-α-tocopherol acetate) intramuscularly after birth (day 0) and on days 1, 2, and 3 or served as controls."

Acyclovir prophylaxis against herpes virus infections in severely immunocompromised patients: randomised double blind trial

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Abstract

Twenty patients undergoing allogeneic bone marrow transplantation and 39 patients receiving remission induction chemotherapy for acute leukaemia were entered into a double blind, placebo controlled stratified trial of acyclovir prophylaxis against herpes group virus infections. Within the transplant group intravenous acyclovir 5 mg/kg twice daily given throughout the period of granulocytopenia completely prevented oropharyngeal herpes simplex virus infection compared with a 50% incidence in the placebo group ($p = 0.033$). The acyclovir group also had fewer days of fever during the trial and a shorter duration of leukopenia, possibly because of the prevention of herpes simplex virus infections. There was a high incidence of herpes infections after the trial in patients who received either acyclovir or placebo.

In the non-transplant group there was also a significant reduction of herpes simplex virus infection in the oropharynx and oesophagus (two out of 19 patients as compared with 10 out of 20; $p = 0.018$). Herpes simplex virus was isolated in the acyclovir arm within a day after starting the trial in one patient, and the other failure was due to a virus with reduced sensitivity to acyclovir in a patient who had had several previous courses of the drug. The incidence of herpes infections after stopping treatment was low.

The influence of acyclovir on excretion of Epstein-Barr virus in saliva in either group was inconclusive. One patient (transplant group) developed a cytomegalovirus infection while receiving acyclovir.

Acyclovir provides effective prophylaxis against oropharyngeal and oesophageal herpes simplex virus infection in severely immunocompromised seropositive ($\geq 1/8$) patients. In patients given bone marrow transplants this may have the additional benefit of reducing the time to recovery of an adequate blood count and the number of days of fever.

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Introduction

Patients with bone marrow failure either as a primary condition or after intensive chemotherapy or radiotherapy or both have a high incidence of herpes virus infections owing to reactivation of latent virus.[1 2] Usually these are superficial—for example, oropharyngeal and oesophageal for herpes simplex virus or in cutaneous dermatome distribution for varicella zoster virus. These severely immunocompromised patients, however, frequently fail to contain the infection, which leads to dissemination such as pneumonia or encephalitis for herpes simplex virus and chickenpox with pneumonitis for varicella zoster virus. In addition, patients undergoing bone marrow transplantation have a high incidence of cytomegalovirus infection (leading to hepatitis) and pneumonia (often fatal).[3]

The incidence of herpes simplex virus infections in patients given bone marrow transplants was roughly 50%, in a previous group of 40 patients in our unit. A report from the Johns Hopkins unit quotes a figure of 45%,[4] and from Seattle the combined incidence of herpes simplex virus and varicella zoster virus infections was 50%.[5] The Johns Hopkins Hospital report emphasised that acute lesions of herpes simplex occurred in only 14% of patients with a pretrial anti-herpes simplex virus serological titre of less than 1/8, whereas those with "positive" serological titres had an incidence of 73%. This supports the hypothesis that most herpes simplex virus infections after bone marrow transplantation are due to reactivation of latent virus. In a series of 525 transplant recipients in Seattle 12 died with herpes simplex virus pneumonia and eight with varicella zoster virus pneumonia.[6] The authors also noted that most herpes simplex virus infections occurred within the first month after transplantation but that infection with varicella zoster virus occurred with a median onset of five months and cases continued to present for three to four years. Cytomegalovirus infection occurred mainly in the period three to six months after transplantation, and attempts at prophylaxis with adenine arabinoside (vidarabine) and treatment with human leucocyte interferon were unsuccessful.[7]

Acyclovir (9-[2-hydroxyethoxymethyl]guanine) is a guanine derivative with an acyclic side chain which is preferentially incorporated into cells infected with herpes simplex virus and transformed to its monophosphate by a specific viral thymidine kinase.[8] After further phosphorylation acyclovir triphosphate competes with deoxyguanosine triphosphate for incorporation into DNA and inhibits viral DNA polymerase to a greater extent than host DNA polymerase.[9] Acyclovir thus has a high "therapeutic index" and has proved active against herpes simplex virus and varicella zoster virus in vitro, against herpes simplex virus in laboratory animals, and against herpes simplex virus and varicella zoster virus in man,[10 11] including the immunocompromised.[12 13] Epstein-Barr (EB) virus and cytomegalovirus do not code for a specific viral thymidine kinase, but nevertheless in vitro activity is documented against EB virus with less against cytomegalovirus.[14 15] Therapeutic trials of acyclovir against cytomegalovirus, EB virus, and hepatitis B virus are at an early stage.[16 17]

The present study was designed to determine whether a twice daily infusion of acyclovir 5 mg/kg given throughout the period of granulocytopenia would prevent infection by the herpes viruses in immunocompromised patients.