Cardiovascular Profile and Hypotensive Mechanism of Ketanserin in the Rabbit

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SUMMARY Using the radioactive microsphere technique, we studied the systemic and regional hemodynamic effects of ketanserin in conscious renal hypertensive rabbits. To characterize the hypotensive mechanism of the compound, we evaluated its antagonism toward 5-hydroxytryptamine, and \( \alpha_1 \)-adrenergic receptors at hypotensive doses and compared the cardiovascular profile of ketanserin with that of the \( \alpha_1 \)-selective adrenergic receptor antagonist prazosin. Ketanserin (0.1, 0.3, and 1.0 mg/kg i.v.) produced a biphasic effect on the arterial blood pressure. A short, pronounced fall in blood pressure accompanied by tachycardia preceded a more moderate and longer lasting dose-related hypotensive effect. The presence of adequate autonomic nervous system activity seems to be required for the prolonged hypotensive action of ketanserin because, in animals pretreated with hexamethonium (30 mg/kg), the blood pressure, after an initial decrease, returned to baseline values within a few minutes after each ketanserin dose. Ketanserin inhibited the pressor responses produced by 5-hydroxytryptamine (10, 30, and 100 \( \mu \)g/kg i.v.) and phenylephrine (3, 10, and 30 \( \mu \)g/kg i.v.), which indicates that, at hypotensive doses, the compound antagonized both 5-hydroxytryptamine, receptors and \( \alpha_1 \)-adrenergic receptors. At doses that caused a comparable degree of \( \alpha_1 \)-adrenergic receptor blockade, ketanserin (0.1, 0.3, and 1.0 mg/kg i.v.) as well as prazosin (0.01, 0.03, and 0.10 mg/kg i.v.) decreased the blood pressure as a result of a reduction in total peripheral resistance. While cardiac output increased, especially at the lower doses of ketanserin, a moderate decrease in this variable contributed to the hypotensive effect of the highest dose of prazosin. Both compounds decreased the vascular resistance in the kidneys, gastrointestinal tract, and bones, whereas that in the skin and skeletal muscles was not significantly altered. In contrast to prazosin, ketanserin also caused vasodilatation in the coronary and cerebral vascular beds. The results suggest that, in addition to a direct vasodilator effect of short duration, ketanserin has a prolonged hypotensive action in conscious hypertensive rabbits that is predominantly due to \( \alpha_1 \)-adrenergic receptor blockade.

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KEY WORDS • antihypertensive agents • 5-hydroxytryptamine • ketanserin • prazosin • regional blood flow • renal hypertension

KETANSERIN, a selective 5-hydroxytryptamine, (5-HT\(_2\)) receptor antagonist with \( \alpha_1 \)-adrenergic receptor blocking properties,\(^{1,2}\) has been shown to reduce the blood pressure in animals\(^{3-5}\) and humans\(^{6,7}\) by a mechanism that is still a matter of debate. In hypertensive patients ketanserin can lower the arterial blood pressure without causing any attenuation of the pressor response to phenylephrine.\(^7\) This pharmacological evidence has been used to support the concept that a blockade of 5-HT\(_2\) receptors is responsible for the antihypertensive effect of the drug.\(^7,8\) In contrast, studies in spontaneously hypertensive rats provide arguments that ketanserin lowers the blood pressure merely by a competitive blockade of \( \alpha_1 \)-adrenergic receptors.\(^4,5,9\) Moreover, a central action has been suggested to contribute to the hypotensive action of ketanserin.\(^10,11\) To provide further information on the hypotensive mechanism of ketanserin, we studied its blood pressure lowering effect in conscious hypertensive rabbits and tried to relate this effect to the blockade of 5-HT\(_2\) and \( \alpha_1 \)-adrenergic receptors in these animals. In addition, we determined the changes in regional blood flows and resistances after ketanserin administration to characterize the complete hemodynamic profile of this new antihypertensive drug. As we recently have studied the effects of the \( \alpha_1 \)-selective adrenergic receptor antagonist prazosin using the same methodology,\(^12\) we were able to compare the complete hemodynamic profiles of the two compounds in conscious hypertensive rabbits. A preliminary report of this study was presented at a meeting of the British Pharmacological Society.\(^13\)
Materials and Methods

Animals and Surgical Procedures

All experiments were performed on conscious hypertensive New Zealand White rabbits (2.4–4.0 kg). Hypertension was induced by bilateral cellophane wrapping of the kidneys, 6 to 10 weeks before the experiment, according to the method of Page.14 In the animals used for the microsphere experiments a left-sided thoracotomy was performed 9 to 14 days before the experiment to cannulate the left atrial appendage with a nylon catheter for the administration of microspheres.15 Subsequently, 4 to 8 days before the experiment the left carotid artery was cannulated in these animals for the measurement of blood pressure and heart rate during the experiments and the withdrawal of arterial blood samples. The different surgical procedures together with the systemic and regional hemodynamic characteristics of bilateral cellophane perinephritis hypertension in rabbits have been described in detail elsewhere.16

Measurement of Hemodynamic Variables

On the day of the experiment the animals were placed in a rabbit restrainer box. The marginal ear vein was cannulated under local anesthesia (2% lidocaine) for the administration of the drugs. Subsequently, a catheter was inserted into the central ear artery in the animals used for the 5-hydroxytryptamine (5-HT) and phenylephrine experiments. A Statham P23De pressure transducer (Statham Laboratories, Hato Rey, Puerto Rico) was connected to either the central ear artery catheter or the carotid catheter (microsphere experiments) for the recording of the arterial blood pressure and the heart rate with a Grass model 7 polygraph (Grass Instruments, Quincy, MA, USA). Mean blood pressure was obtained by electronically damping the blood pressure signals.

Cardiac output and regional blood flows were measured with the radioactive microsphere technique, using the reference blood sample method.17-19 For each measurement 0.5 ml of a suspension, containing about 100,000 microspheres (Nen-Trac, Dreieich, W. Germany) with a nominal diameter of 15 ± 1 (sd) µm and labeled with either 141Ce, 113Sn, 103Ru, 99Nb, or 46Sc, was injected and flushed with 1.5 ml of saline into the left atrial catheter over a 20-second period. A reference arterial blood sample was withdrawn from the carotid artery at a rate of 1.85 ml/minute for a period of 60 seconds, starting about 5 seconds before the injection of microspheres. At the end of the experiment the animals were killed with an overdose of sodium pentobarbital. All organs and tissues were removed, weighed, cut into small pieces, and placed into plastic vials. The radioactivity (counts per minute, cpm) in the vials was counted with a Gamma-scintillation counter (Packard, Model 5986) attached to a multichannel analyzer (Conrac, Packard Instruments, Downers Grove, IL, USA) to discriminate isotope energies. With the exception of the skin, skeletal muscles, and bones, for which an aliquot of at least 30% was taken, all organs were counted in their entirety. Data were analyzed on a PDP-11/70 computer (Digital Equipment Corporation, Maynard, MA, USA) using a set of computer programs especially designed for the radioactive microsphere technique.20 The fraction of cardiac output received by the tissues was calculated as the ratio of tissue radioactivity ($I_{t}$) and total body radioactivity ($I_{b}$): the latter was determined by adding together the radioactivity in all body parts and in the withdrawn blood sample ($I_{w}$). Cardiac output (CO) was calculated as $CO \times (ml/min) = (I_{b}/I_{w}) \times Q_{a}(ml/min)$, where $Q_{a}$ is the rate of withdrawal of the arterial blood sample (1.85 ml/min). Blood flows to individual organs and tissues ($Q_{o}$) were calculated in a similar manner: $Q_{o}(ml/min) = (I_{o}/I_{w}) \times Q_{a}(ml/min)$. Peripheral vascular resistances were calculated by dividing mean arterial blood pressure (mm Hg) by respective tissue blood flows (ml/min).

Systemic and Regional Hemodynamics

The effects of ketanserin on systemic and regional hemodynamic variables were studied in 10 conscious hypertensive rabbits with the use of the radioactive microsphere technique. After a stabilization period of at least 30 minutes the first batch of microspheres was injected to determine baseline values of cardiac output and regional hemodynamic variables. Heart rate and arterial blood pressure values were recorded continuously. After baseline values were obtained, each animal received three cumulative doses (0.1, 0.3, and 1.0 mg/kg i.v.) of ketanserin. Ten minutes after each dose, when heart rate and blood pressure response had stabilized, a batch of microspheres was injected. An arterial blood sample (0.3 ml) was withdrawn immediately after each microsphere injection to measure pH, pressure of CO2 ($P_{CO2}$), and pressure of O2 ($P_{O2}$) with an ABL-2 (Radiometer, Copenhagen, Denmark). Values of arterial blood gases and pH were not affected by ketanserin. Before and 10 minutes after the successive doses of ketanserin (0.1, 0.3, and 1.0 mg/kg), the respective values were: pH, 7.41 ± 0.01, 7.41 ± 0.01, 7.39 ± 0.02, and 7.40 ± 0.01; $P_{CO2}$, 33 ± 1.32, 31 ± 1, and 30 ± 1 mm Hg; and $P_{O2}$, 94 ± 3, 93 ± 3, 95 ± 3, and 94 ± 4 mm Hg. In a previous study we12 measured the effects of prazosin (0.01, 0.03, and 0.10 mg/kg i.v.) in conscious hypertensive rabbits using the same experimental protocol, except that the microspheres were injected 15 minutes after the subsequent doses of prazosin when stable heart rate and blood pressure responses were measured.

We have validated our methodology by showing that under control conditions four successive microsphere injections do not consistently alter any of the systemic or regional hemodynamic variables measured.19

Determination of 5-Hydroxytryptamine Blocking Properties

The effects of 5-HT on the heart rate and arterial blood pressure were studied in seven conscious hypertensive rabbits. After an appropriate equilibration period increasing doses of 5-HT (10, 30, and 100 µg/kg...
i.v.) were administered at 5-minute intervals. Hexamethonium (30 mg/kg i.v.) was administered 30 minutes after the measurement of the control responses. When steady baseline values of heart rate and blood pressure were reached the three 5-HT doses were again administered. This procedure was repeated twice at 30-minute intervals in the presence of ketanserin, 0.1, and 0.3 mg/kg i.v. respectively. Lastly, a dose of 1 mg/kg of ketanserin was injected to observe its hypotensive effect in the presence of hexamethonium. Since the pressor effects of 5-HT already were almost completely blocked by the previous doses of ketanserin, 5-HT was not injected after the highest dose.

Determination of α₁-Adrenergic Receptor Blocking Properties

The effects of ketanserin and prazosin on the pressor response induced by phenylephrine, 10, 30, and 100 μg/kg i.v., administered at 5-minute intervals were studied in two groups of eight rabbits. In the first group the subsequent doses of phenylephrine were administered four times at 30-minute intervals in the absence and presence of ketanserin, 0.1, 0.3, and 1.0 mg/kg i.v. respectively. In the second group the effects of prazosin, 0.01, 0.03, and 0.10 mg/kg i.v., on the phenylephrine pressor response were measured using the same experimental protocol.

Statistical Evaluation

All data, expressed as mean ± SE in the text, have been statistically evaluated with nonparametric tests. Initially, Friedman's two-way analysis of variance was used to establish whether the samples represented different populations. The Wilcoxon matched-pairs signed ranks test was applied to test the significance (p < 0.05, two-tailed) of the changes in hemodynamic variables from baseline values.

Drugs

The following drugs were used: 5-hydroxytryptamine creatinine sulfate (Merck, Darmstadt, W. Germany), hexamethonium bromide (Fluka, Buchs, Switzerland), phenylephrine hydrochloride (Sigma Chemical Company, St. Louis, MO, USA). Ketanserin tartrate and prazosin hydrochloride were generously supplied by Dr. J. M. Van Nueten of Janssen Pharmaceutica (Beerse, Belgium) and by Pfizer B. V. (Brussels, Belgium) respectively. The 5-HT, phenylephrine, and hexamethonium were dissolved in physiological saline. Ketanserin and prazosin were dissolved in distilled water. Concentrations were such that a volume less than 0.5 ml was injected at a time.

Results

Systemic Hemodynamic Variables

The cumulative doses of ketanserin (0.1, 0.3, and 1.0 mg/kg) administered at 10-minute intervals in conscious hypertensive rabbits produced transient falls in systolic and diastolic blood pressure of about 2 minutes' duration that were followed by a more moderate and longer lasting dose-related hypotensive effect (Figure 1). A transient tachycardia accompanied the initial fall in blood pressure and reached a maximum within 30 seconds after each ketanserin administration. By 2 minutes the changes in heart rate were no longer significant.

In animals pretreated with hexamethonium, 30 mg/kg, only a transient fall in blood pressure was observed after ketanserin, 0.1, 0.3, and 1.0 mg/kg; baseline values were reached within 4 minutes after each ketanserin dose (Figure 2).

The effects of ketanserin, 0.1, 0.3, and 1.0 mg/kg, on mean arterial blood pressure, cardiac output, and total peripheral resistance 10 minutes after administration in conscious hypertensive rabbits are shown in Figure 3. The hypotensive effect of ketanserin resulted from a reduction in total peripheral resistance. Especially at the lower doses of ketanserin, an increase in cardiac output opposed the ketanserin-induced reduction in total peripheral resistance. Figure 3 also shows the effects of prazosin (0.01, 0.03, and 0.10 mg/kg i.v.) on mean blood pressure, cardiac output, and total peripheral resistance measured 15 minutes after the successive administrations in conscious hypertensive rabbits. In contrast to ketanserin, a moderate fall in cardiac output contributed to the hypotensive effects of the highest dose of prazosin.

Regional Hemodynamic Variables

Figure 4 shows the regional blood flow values before and after the successive administration of ketanserin, 0.1, 0.3, and 1.0 mg/kg i.v., in conscious renal hypertensive rabbits. The three doses of ketanserin increased the blood supply to the kidneys and gastrointestinal tract. After the first and second dose, the blood flow to the heart, brain, and bones was enhanced.
Ketanserin: a 5-Hydroxytryptamine2 and α1-Adrenergic Receptor Blocking Property

A transient bradycardia accompanied by a fall in blood pressure was observed after the intravenous administration of 5-HT (10, 30, and 100 μg/kg) in conscious hypertensive rabbits (Figure 6). This effect was followed by a more prolonged hypotensive response accompanied by tachycardia. Pretreatment with a ganglionic blocker (hexamethonium, 30 mg/kg), which led to an increase in heart rate and a decrease in blood pressure, antagonized the first phase of the 5-HT responses; the amine caused a moderate increase in blood pressure, again followed by a prolonged hypotensive effect (see Figure 6). Pretreatment with hexamethonium prevented the alterations in heart rate pro-
FIGURE 5. Effects of ketanserin and prazosin on regional vascular resistances in conscious hypertensive rabbits, expressed as percentage change from baseline values 10 minutes after ketanserin, 0.1 ( ), 0.3 ( ), and 1.0 ( ) mg/kg respectively (n = 10), and 15 minutes after prazosin, 0.01 ( ), 0.03 ( ), and 0.10 ( ) mg/kg respectively (n = 10). GIT = gastrointestinal tract; * = significant change from baseline values, p < 0.05. Data for prazosin have been adapted from Bolt and Saxena. 12

The effects of ketanserin and prazosin on the pressor response produced by phenylephrine (10, 30, and 100 µg/kg) in the conscious untreated hypertensive rabbits are shown in Figure 8. Ketanserin (0.1, 0.3, and 1.0 mg/kg) shifted the three-point curve dose dependently. A comparable α₁-adrenergic receptor blocking action was observed with prazosin, 0.01, 0.03, and 0.10 mg/kg.

Discussion
Cardiovascular Profile of Ketanserin
The fall in blood pressure observed after ketanserin administration in conscious hypertensive rabbits was biphasic; an initial pronounced but transient decrease in blood pressure preceded a more moderate and longer lasting dose-related hypotensive effect. The transient tachycardia, which accompanied the initial fall in blood pressure, probably resulted from the hypotension-induced activation of the baroreceptor reflex and the subsequent increase in sympathetic activity and--
withdrawal of vagal tone. Indeed, the ketanserin-induced changes in heart rate were not observed after ganglionic blockade. The absence of reflex tachycardia during the prolonged hypotensive action of ketanserin may be related to the reported interference of the drug with the autonomic nervous system activity, where it causes a decrease in sympathetic outflow. Remarkably, a similar heart rate response has been observed with hypotensive doses of the $\alpha_1$-selective adrenergic receptor antagonist prazosin in conscious normotensive and hypertensive rabbits. Pronounced tachycardia was only observed during the first few minutes after the acute administration of prazosin despite sustained hypotension.

The prolonged fall in blood pressure observed after ketanserin administration in the conscious hypertensive rabbits was due to a decrease in total peripheral resistance, which illustrates the arterial vasodilator properties of ketanserin. An increase in cardiac output, possibly as a result of the reduction in afterload secondary to the fall in total peripheral resistance, was observed after ketanserin, 0.1 and 0.3 mg/kg. The less pronounced increase in cardiac output after ketanserin, 1.0 mg/kg, may be due to a reduction in venous return as a result of dilatation of venous capacitance vessels. In comparison, a transient increase in cardiac output has been observed after ketanserin administration in hypertensive patients despite the fact that a reduction in cardiac filling pressure indicated a reduced venous return.

Because of the ketanserin-induced vasodilatation in the heart, brain, kidneys, gastrointestinal tract, and bones, the increase in cardiac output resulted in an enhanced blood supply to these vascular beds. An increase in renal blood flow and a fall in vascular resistance in the kidneys have also been observed after ketanserin administration in hypertensive patients. In the cutaneous vascular bed the vascular resistance and blood flow remained unchanged, whereas in the skeletal muscles the vascular resistance tended to increase and resulted in a reduced blood flow to the muscles at the higher ketanserin doses. Apparently ketanserin has minor effects in the two latter vascular beds; however, it is possible that reflex-mediated vasoconstriction and tissue autoregulation obscured a direct vasodilator activity of ketanserin in certain vascular beds in the conscious animals.

**Hypotensive Mechanism of Ketanserin**

**Direct Vasodilator Action**

The biphasic blood pressure response after ketanserin administration in conscious hypertensive rabbits also has been observed in anesthetized rats, in which the initial fall in blood pressure was ascribed to a possible direct vasodilator action of ketanserin. A vasodilator effect of ketanserin that could not be blocked by methysergide or sympathetic denervation also has been demonstrated in the dog hindleg, which indicates that this effect is not mediated by either 5-HT$_2$ or $\alpha_1$-adrenergic receptors. In the present study the transient decrease in blood pressure was still observed after ganglionic blockade, which indicates that the initial fall in blood pressure does not depend on an autonomic nervous tone and may be due to a direct vasodilator action of ketanserin that has also been shown for other structurally related quinazolinedione derivatives. Although in the present study this initial vasodilatation did not play a role in the prolonged hypotensive action of ketanserin, it is possible that when higher doses are given or when a different route
of administration is used, the direct vasodilator action may contribute to the antihypertensive properties of the compound. In this respect, the observed hypotensive effect of ketanserin in patients with autonomic insufficiency may possibly be attributed to a direct vasodilator effect of the drug.

5-Hydroxytryptamine, Receptor Blockade

The pressor response to 5-HT, though only moderate, could be elevated after ganglionic blockade, which prevents the fall in heart rate and blood pressure that result from the changes in autonomic nervous activity secondary to activation of the Bezold-Jarisch reflex. The pressor response to 5-HT has been attributed to a direct vasoconstriction mediated by 5-HT receptors aided indirectly by an augmentation of noradrenaline and angiotensin II responses. These effects can be antagonized by ketanserin because of the 5-HT₁ receptor blocking properties of the compound, which may play an important role in the hypotensive mechanism. Indeed, at hypotensive doses ketanserin effectively antagonized the 5-HT-induced pressor responses in the conscious hypertensive rabbits pretreated with hexamethonium. Although this antagonism may facilitate the vasodilator effect of 5-HT mediated by “atypical” 5-HT receptors, an important physiological role for 5-HT in the maintenance of the arterial blood pressure has not been demonstrated previously. In addition, hypotensive properties have not been shown for other selective 5-HT₁ receptor antagonists. Finally, Amery et al. have shown that, although long-term treatment with ketanserin reduced the blood pressure in hypertensive patients, 5-HT₂ receptor blockade could not be demonstrated when assessed by platelet aggregation. Thus, despite the 5-HT antagonistic properties at hypotensive doses of ketanserin, a contribution of 5-HT₁ receptor blockade in the hypotensive action of ketanserin remains to be established.

α₁-Adrenergic Receptor Blockade

Ketanserin also possessed α₁-adrenergic receptor blocking properties at hypotensive doses, as was shown by the shift in the three-point phenylephrine pressor response curve after ketanserin, 0.1, 0.3, and 1.0 mg/kg, in conscious hypertensive rabbits. Similar results were obtained in studies in pithed rats, in which the inhibitory effects of ketanserin on the pressor responses to the α₁-selective adrenergic receptor stimulants methoxamine and phenylephrine were measured. The decrease in blood pressure produced by the α₁-selective adrenergic receptor antagonist prazosin at doses that caused a comparable shift in the phenylephrine pressor response curves indicates that in conscious hypertensive rabbits, as in rats, the blockade of α₁-adrenergic receptors alone can be held responsible for the prolonged hypotensive action of ketanserin. In addition, in the animals pretreated with hexamethonium the blood pressure returned to baseline values within a few minutes, which indicates the requirement of an autonomic nervous tone for the prolonged hypotensive action of ketanserin. In contrast, in hypertensive patients hypotensive doses of ketanserin did not alter the pressor effects of phenylephrine, which suggests that ketanserin may lower blood pressure independently of α₁-adrenergic receptor blockade. A certain degree of α₁-adrenergic tone seems to be required for the compound to exert its full antihypertensive action in humans because pretreatment with prazosin blunted the antihypertensive effect of ketanserin in hypertensive patients. In addition, after chronic treatment with ketanserin, Fagard et al. observed a reduction of the pressor response to methoxamine in patients with essential hypertension. However, it may be that after chronic oral treatment with ketanserin (120 mg/day) plasma levels were higher and caused a more pronounced α₁-adrenergic receptor blockade, than they did after a single i.v. administration of 10 mg ketanserin.

In contrast to prazosin, ketanserin moderately increased the cardiac output in the present study. It may be that the direct vasodilator action of ketanserin, which is not observed with prazosin, contributed to the relatively more pronounced cardiac stimulation during the prolonged hypotensive phase of ketanserin. On the other hand, both the less pronounced increase in cardiac output after ketanserin, 1.0 mg/kg, and the decrease in this variable after prazosin, 0.1 mg/kg, can be explained by a reduction in venous return secondary to dilatation of venous capacitance vessels, which becomes more prominent when higher doses of the drugs are used.

The remarkable similarities in the regional hemodynamic profile of ketanserin and prazosin also indicate an important role for the α₁-adrenergic receptor blocking properties in the hypotensive mechanism of ketanserin. It is tempting to attribute the additional vasodilatory action of ketanserin in the coronary and cerebral vascular beds to the 5-HT₁ receptor blocking properties of ketanserin that prazosin does not have; however, other explanations are possible. Myocardial autoregulation plays an important role in the blood flow to the heart. If we consider the decrease in the cardiac output and the more pronounced reduction in blood pressure observed with prazosin, it is possible that the myocardial metabolic demands are less than those occurring after ketanserin administration. This may explain the difference between the effects of the two drugs on the coronary vascular bed. In addition, possible differences in the pharmacokinetic properties of ketanserin and prazosin as well as the direct vasodilator action unique to ketanserin may contribute to the differences in the cardiovascular profiles of the two compounds.

In conclusion, as after ganglion blockade only a transient fall in blood pressure that probably was not mediated by α₁-adrenergic receptors or 5-HT receptors was observed, an autonomic nervous tone seems to be required for the prolonged hypotensive action of ketanserin. In addition, considering the α₁-adrenergic receptor blocking activity of ketanserin at hypotensive doses and the similarities in the cardiovascular profile of
ketanserin and prazosin, blockade of α₁-adrenergic receptors probably plays a predominant role in the hypertensive mechanism of ketanserin in conscious hypertensive rabbits.

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