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-hydroxytryptamine₂ and α₁-adrenergic receptors at hypotensive doses and compared the cardiovascular profile of ketanserin with that of the α₁-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 μg/kg i.v.) and phenylephrine (3, 10, and 30 μg/kg i.v.), which indicates that, at hypotensive doses, the compound antagonized both 5-hydroxytryptamine₂ receptors and α₁-adrenergic receptors. At doses that caused a comparable degree of α₁-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 α₁-adrenergic receptor blockade.

Key Words • antihypertensive agents • 5-hydroxytryptamine • ketanserin • prazosin • regional blood flow • renal hypertension

KETANSERIN, a selective 5-hydroxytryptamine₂ (5-HT₂) receptor antagonist with α₁-adrenergic receptor blocking properties, has been shown to reduce the blood pressure in animals and humans 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. This pharmacological evidence has been used to support the concept that a blockade of 5-HT₂ receptors is responsible for the antihypertensive effect of the drug. In contrast, studies in spontaneously hypertensive rats provide arguments that ketanserin lowers the blood pressure merely by a competitive blockade of α₁-adrenergic receptors. Moreover, a central action has been suggested to contribute to the hypotensive action of ketanserin. 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-HT₂ and α₁-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 α₁-selective adrenergic receptor antagonist prazosin using the same methodology, 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.
exception of the skin, skeletal muscles, and bones, for

were counted in their entirety. Data were analyzed on a
tobarbital. All organs and tissues were removed,

20 seconds, starting about 5 seconds before the injection

lyzed, a batch of microspheres was injected. An arterial

arterial blood sample was withdrawn from the carotid

properties were calculated by dividing mean arteri-

Hypertension was induced by bilateral cellophane

Animals and Surgical Procedures

Materials and Methods

Animals and Surgical Procedures

All experiments were performed on conscious hyper-

performed, the left carotid artery was cannulated in these

Arterial blood sample (0.3 ml) was withdrawn immediately after each microsphere injection to measure pH, pressure of CO₂ (Paco₂), and pressure of O₂ (Pao₂) 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; Paco₂, 33 ± 1.32, 31 ± 1, and 30 ± 1 mm Hg; and Pao₂, 94 ± 3.93, 3 ± 9.53, and 95 ± 4 mm Hg. In a previous study we² 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.

Figure 1. Time course of heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) responses after the administration of ketanserin, 0.1, 0.3, and 1.0 mg/kg i.v., in conscious hypertensive rabbits (n = 10).
Figure 2. Effects of i.v. ketanserin, 0.1 (n = 7), 0.3 (n = 7), and 1.0 (n = 5) mg/kg, on systolic and diastolic blood pressure in conscious hypertensive rabbits pretreated with hexamethonium, 30 mg/kg.

Figure 3. Effects of ketanserin and prazosin on mean blood pressure (MBP), cardiac output (CO), and total peripheral resistance (TPR), 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 ($\pm$), 0.03 ($\pm$), and 0.10 (■) mg/kg respectively (n = 10), in conscious hypertensive rabbits. * = significant change from baseline values, p < 0.05. Data for prazosin from Boli and Saxena.12

Figure 4. Effects of ketanserin, 0.1, 0.3, and 1.0 mg/kg i.v. respectively, on regional blood flows (ml/min) 10 minutes after administration in conscious hypertensive rabbits (n = 10). □ = baseline values; □, □, and ■ = values after ketanserin, 0.1, 0.3, and 1.0 mg/kg respectively; GIT = gastrointestinal tract; * = significant change from baseline values, p < 0.05.

whereas that to the skin was not affected. In the skeletal muscles the blood flow decreased after ketanserin, 1.0 mg/kg.

Figure 5 shows the changes in regional vascular resistances 10 minutes after ketanserin, 0.1, 0.3, and 1.0 mg/kg respectively. Ketanserin produced a significant vasodilatation in the heart, brain, kidneys, gastrointestinal tract, and bones (p < 0.05). The decrease in vascular resistance was most pronounced in the latter three vascular beds. The changes were not significant in the skin and skeletal muscles. A more selective vasodilatation was observed with prazosin, 0.01, 0.03, and 0.10 mg/kg i.v., 15 minutes after administration in conscious hypertensive rabbits. A significant reduction in the vascular resistance was measured in the kidneys, gastrointestinal tract, and bones (p < 0.05) while the changes in the heart, brain, skin, and skeletal muscles were not significant.

5-Hydroxytryptamine, and $\alpha_1$-Adrenergic Receptor Blocking Properties

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-
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 production of ketanserin and 5-HT, which indicates the presence of an effective ganglionic blockade after hexamethonium, 30 mg/kg (see Figure 6). The pressor response produced by 5-HT in the ganglion-blocked animals was rather small, probably in part because of the opposing vasodilator response of 5-HT. Nevertheless, ketanserin, 0.1 and 0.3 mg/kg, effectively antagonized the increase in blood pressure as shown by the shift in the pressor response curve produced by 5-HT (Figure 7).

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 vasodilation 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

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**FIGURE 7.** Changes in mean blood pressure produced by 5-HT, 10, 30, and 100 \( \mu \)g/kg i.v., in conscious hypertensive rabbits (\( n = 7 \)) pretreated with hexamethonium (30 mg/kg) in the absence (open circles) and presence (closed circles) of ketanserin, 0.1 and 0.3 mg/kg (from top to bottom respectively).

**FIGURE 8.** Changes in mean blood pressure produced by phenylephrine, 3, 10, and 30 \( \mu \)g/kg i.v., in conscious hypertensive rabbits in the absence (open circles) and presence (closed circles) of ketanserin, 0.1, 0.3, and 1.0 mg/kg (from top to bottom respectively; \( n = 8 \)), and prazosin, 0.01, 0.03, and 0.10 mg/kg (from top to bottom respectively; \( n = 8 \)).
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\(^1\) may possibly be attributed to a direct vasodilator effect of the drug.

5-Hydroxytryptamine\(_2\) Receptor Blockade

The pressor response to 5-HT, though only moderate, could be visualized after ganglion 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.\(^25\) The pressor response to 5-HT has been attributed to a direct vasoconstriction mediated by 5-HT\(_2\) receptors aided indirectly by an augmentation of noradrenaline and angiotensin II responses.\(^1\) These effects can be antagonized by ketanserin because of the 5-HT\(_2\) receptor blocking properties of the compound, which may play an important role in the hypotensive mechanism.\(^1\)\(^7\)\(^8\) 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,\(^22\)\(^26\)\(^27\) an important physiological role for 5-HT-H\(_2\) receptors 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-HT\(_2\) receptor antagonists.\(^3\)\(^5\)\(^27\)\(^28\) Finally, Amery et al.\(^29\) have shown that, although long-term treatment with ketanserin reduced the blood pressure in hypertensive patients, 5-HT\(_2\) 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-HT\(_2\) receptor blockade in the hypotensive action of ketanserin remains to be established.

\(\alpha\)-Adrenergic Receptor Blockade

Ketanserin also possessed \(\alpha\)-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 \(\alpha\)-selective adrenergic receptor stimulants methoxamine\(^3\) and phenylephrine\(^5\) were measured. The decrease in blood pressure produced by the \(\alpha\)-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,\(^4\)\(^5\)\(^9\) the blockade of \(\alpha\)-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\(^7\) which suggests that ketanserin may lower blood pressure independently of \(\alpha\)-adrenergic receptor blockade. A certain degree of \(\alpha\)-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.\(^7\) In addition, after chronic treatment with ketanserin, Fagard et al.\(^30\) 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 \(\alpha\)-adrenergic receptor blockade, than they did after a single i.v. administration of 10 mg ketanserin.\(^7\)\(^31\)

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,\(^12\) 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 dilation of venous capacitance vessels,\(^7\)\(^12\)\(^32\) 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 \(\alpha\)-adrenergic receptor blocking properties in the hypotensive mechanism of ketanserin. It is tempting to attribute the additional vasodilatory production by ketanserin in the coronary and cerebral vascular beds to the 5-HT\(_2\) 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.\(^33\) 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 \(\alpha\)-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 \(\alpha\)-adrenergic receptor blocking activity of ketanserin at hypotensive doses and the similarities in the cardiovascular profile of
ketanserin and prazosin, blockade of $\alpha_1$-adrenergic receptors probably plays a predominant role in the hypotensive mechanism of ketanserin in conscious hypertensive rabbits.

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