Hypertension

Brief Review

Serotoninergic Mechanisms in Hypertension
Focus on the Effects of Ketanserin

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SUMMARY Aggregating platelets release serotonin, which induces contraction of most vascular
smooth muscle by activation of S2-serotoninergic receptors. Serotonin released in the circulation may
contribute to the increase in peripheral resistance of hypertension as the responsiveness of blood
vessels from hypertensive animals and humans to the vasoconstrictor action of the monoamine is
augmented. The data obtained with the new antihypertensive agent ketanserin may favor that inter-
pretation. Ketanserin is a selective S2-serotoninergic antagonist with additional α1-adrenergic block-
ing properties. In humans, it has a terminal half-life of 12 to 25 hours and is eliminated predominantly
by the liver. The hemodynamic profile of ketanserin is that of a vasodilator drug with actions on both
resistance and capacitance vessels. On short-term intravenous administration, it lowers blood pres-
sure in hypertensive patients with minimal reflex changes in cardiovascular function. When given
orally long term to hypertensive patients, ketanserin causes a sustained reduction in arterial blood
pressure, comparable to that obtained with either α-adrenergic blockers or diuretics. Several studies
have shown a greater efficacy in older (> 60 years of age) than in younger patients independent of
starting pressure. Side effects mainly consist of dizziness, somnolence, and dry mouth, but they are
usually not severe. The mechanism underlying the antihypertensive effect of ketanserin is unclear. It
cannot be attributed to either S2-serotoninergic or α1-adrenergic blockade alone, but an interaction
between the two effects appears to be required. (Hypertension 11: 111-133, 1988)

KEY WORDS ketanserin • serotonin • hypertension • claudication • Raynaud’s phenomenon

SEROTONIN (5-hydroxytryptamine; 5-HT) is a
vasoactive amine originally isolated from clot-
ted blood; it is present in high concentrations in
the intestinal tract.1-3 It can modify the function of
many tissues by interacting with serotoninergic recep-
tors on their cell membranes. The pharmacological
properties of serotoninergic receptors vary (Table 1).
Two major subclasses (5HT1- or S1-receptors, and

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5HT₁ or S₂ receptors) have been identified using radioligand binding techniques in brain tissues. Other subtypes of serotoninergic receptors exist in peripheral tissues. The S₂-serotoninergic receptor is present in vascular smooth muscle, platelets, adrenal cortex, and bronchi. S₁-serotoninergic binding sites are also present in the frontal cortex. The signal transducing system coupled to the human platelet S₂-serotoninergic receptor is mediated through inositol phospholipid metabolism.

Circulating serotonin originates from the enterochromaffin cells in the intestine, which synthesize and release it into the portal circulation. Nearly all the serotonin released is inactivated by the liver or by pulmonary endothelial cells, the remaining part is taken up and stored by the platelets, so that very little, if any, free serotonin is present in the plasma. If serotonin causes vasoconstriction by a peripheral action, it probably only does so following local release from platelets at sites of vascular injury or under artificial circumstances, such as during cardiopulmonary bypass, once released from the platelets, serotonin exerts a positive feedback, inducing further aggregation, by activating S₂-serotoninergic receptors on the thrombocytes.

Although serotonin has numerous vascular effects, so far it has no well-defined role in the etiology of cardiovascular diseases, except possibly migraine and carcinoid syndrome. It has long been suspected as being involved in the pathogenesis of hypertension, but even then its role remains elusive. In particular, a role for serotonin in maintaining the elevated peripheral vascular resistance, characteristic of hypertension, has not been explored.

Ketanserin (3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]-ethyl]-2,4(1H,3H)-quinazolinedione; Figure 1) is a selective S₂-serotoninergic receptor antagonist. Unlike most other serotoninergic antagonists, it has no partial agonist activity. In addition to its serotoninergic antagonist properties, it inhibits α₁-adrenergic receptors. During its initial clinical evaluation, ketanserin appeared to possess antihypertensive properties and, perhaps, improve symptoms in patients with intermittent claudication and Raynaud's phenomenon, raising the possibility of a role for serotonin in these diseases.

This article summarizes the data available on the use of ketanserin in hypertension and vascular disease, as reviewed by the members of the Steering Committee for the Study of Ketanserin in Hypertension. It also reviews the evidence for the role of serotonin in the pathogenesis of these diseases.

### Pharmacokinetics of Ketanserin

Ketanserin has a terminal half-life of 12 to 20 hours after a single dose, an apparent volume of distribution of 200 to 450 L, and a total plasma clearance of 400 to 600 ml/min. Its oral bioavailability is in the order of 50%. Ketanserin is eliminated predominantly by the liver, and less than 1% is cleared by the kidneys. The rate of elimination of ketanserin is determined by hepatic blood flow, intrinsic hepatic clearance, and the binding to plasma proteins. The major metabolite, ketanserin-ol, which is approximately 1000 times less biologically active than ketanserin, has a slightly longer half-life than the parent drug. Its oxidation back to the active compound determines the terminal half-life of ketanserin, which during long-term administration is 25 hours. At therapeutic doses the plasma concentration of ketanserin ranges between 15 and 140 ng/ml within a dosing interval of 12 hours. No clear relationship between plasma concentration and the antihypertensive effect of ketanserin has been found.

The oral bioavailability of ketanserin is slightly higher in the elderly (>65 years of age), although this does not fully explain the greater efficacy.
of the drug in elderly subjects. The oral bioavailability of ketanserin is also higher in patients with advanced liver disease (J.P. Benhamou, personal communication, 1985). In patients with renal failure, the half-life of ketanserin is prolonged because of accumulation of the metabolite ketanserin-ol and reversion of it to ketanserin (J. Heykants, personal communication, 1987). Doses should be smaller in patients with advanced liver disease and in patients with renal failure.

Pharmacokinetic studies have failed to show interactions between ketanserin and digoxin, propranolol, metoprolol, and cimetidine.

**Hemodynamics**

**Short-term Administration**

The hemodynamic effects of a single intravenous dose of ketanserin (10 mg) have been studied in healthy volunteers and in patients at rest and during exercise. In resting healthy volunteers, ketanserin caused no significant changes in arterial blood pressure in two of four placebo-controlled studies and caused a small, transient but significant decrease in arterial blood pressure in two others. Ketanserin significantly attenuated the increase of arterial blood pressure and heart rate following strenuous dynamic exercise in healthy volunteers.

In patients with essential hypertension, ketanserin caused a fall in systolic and diastolic blood pressures, with a small and transient rise in heart rate and cardiac output. Therefore, the decrease in arterial pressure is due mainly to a decrease in total peripheral resistance (Figure 2). There was a rise in renal blood flow and a small but nonsignificant increase in glomerular filtration rate. A fall in blood pressure in response to head-up tilting occurred after ketanserin treatment, but the increase in heart rate was not affected by the drug. The relationship between the changes in blood pressure and heart rate caused by phenylephrine was not altered by ketanserin, suggesting that it does not affect the sensitivity of the baroreceptor reflex control of heart rate in the short term.

Normotensive men given a single oral dose of ketanserin in doses that variously did and did not lower blood pressure (i.e., 40 and 120 mg, respectively) showed no alteration of baroreceptor reflex sensitivity during either activation or deactivation. The lack of reflex tachycardia in response to hypotension was thought possibly to be due to an α-adrenergic-blockade-mediated sympathetic inhibition.

In 11 patients with portal hypertension, ketanserin caused a small but significant decrease of mean arterial pressure. Cardiac index and systemic vascular resistance were also reduced, but the changes did not reach conventional levels of statistical significance. Wedged hepatic venous pressure and the hepatic venous pressure gradient decreased significantly, whereas hepatic blood flow was unchanged. The reduction of mean arterial pressure correlated with the severity of cirrhosis, as estimated by Pugh's score.

In patients with cardiac failure and in patients undergoing major surgical procedures, the intravenous administration of ketanserin reduced arterial, right atrial, pulmonary artery, and pulmonary capillary wedge pressures and systemic and pulmonary vascular resistances; cardiac index and stroke work index were increased, but heart rate was not affected. Myocardial oxygen consumption decreased, as judged from the triple index (heart rate × systolic blood pressure × left atrial pressure). In contrast to sodium nitroprusside, ketanserin did not impair the physiological shunt in the lung (i.e., the percentage of flow exiting the lungs with the same oxygen content as pulmonary arterial blood), indicating that capillary perfusion is maintained. It improved peripheral circulation, as as-
sessed by plethysmography and by pulse-wave amplitude, and renal function, as assessed by diuresis and glomerular filtration.

In patients with acute respiratory failure, ketanserin also reduced cardiac preload and afterload, improved the physiological shunt fraction, and reduced hypoxia, provided it was given within 24 hours after onset of the insult. In patients with severe pulmonary hypertension, the predominant short-term effect of ketanserin was systemic rather than pulmonary vasodilatation.

In diabetic patients and in patients with peripheral vascular diseases, the intravenous or intra-arterial administration of ketanserin (10 mg) increased blood flow, blood pressure, and skin temperature in the diseased limbs, despite a reduction of systemic blood pressure. Capillary blood flow increased, to judge from capillaroscopy or laser Doppler capillary perfusion monitoring. In healthy volunteers, ketanserin caused a rise in venous oxygen tension and a reduction in venous carbon dioxide tension at rest but not after exercise.

Long-term Treatment

There have been several studies of systemic hemodynamics in resting and exercising patients with essential hypertension. In all studies, arterial blood pressure decreased. The other findings are not uniform. In one series, 13 patients were investigated before and after 9 months of treatment with an average daily dose of 108 mg. Heart rate and cardiac output were slightly reduced. Vascular resistance fell at rest and during exercise in three patients. Overall no marked changes were seen. In a placebo-controlled study by Fagard et al., 10 patients with resistant hypertension were given 120 mg of ketanserin daily for 6 weeks. Both at rest and during exercise, systemic vascular resistance fell by 14%, heart rate fell by 5%, and stroke volume and cardiac output increased. In a third study, 10 patients received 120 mg of ketanserin daily for 1 month. Total vascular resistance and renal vascular resistance decreased; however, renal plasma flow and glomerular filtration rate were unchanged by ketanserin. A decrease in peripheral vascular resistance in patients with essential hypertension was demonstrated using strain-gauge plethysmography.

Long-term oral treatment with ketanserin attenuated the increase in heart rate and in systolic blood pressure in response to isometric and dynamic exercise. It significantly augmented the ejection fraction, but not the peak ejection rate in response to dynamic exercise, suggesting an improvement of left ventricular performance during exercise. Exercise capacity was unchanged.

In summary, therefore, the hemodynamic profile of ketanserin is that of a vasodilator drug with actions on both resistance and capacitance vessels. The antihypertensive effect is probably due to a reduction in total peripheral vascular resistance. Heart rate increases transiently after intravenous injection, but it decreases by 4 beats/min, on average, during long-term oral treatment. Exercise capacity and renal function are preserved in spite of the decrease in arterial blood pressure.

Therapeutic Efficacy

Ketanserin has been studied clinically in over 18,000 patients (Table 2).

Acute Antihypertensive Effect

In patients with essential hypertension, a single intravenous (10 mg) or oral (40 mg) dose of ketanserin significantly reduced arterial blood pressure. After intravenous treatment, systolic and diastolic blood pressures decreased within the first minute and reached minimal values after about 5 minutes. The return to baseline levels varied, sometimes occurring within minutes, sometimes taking several hours. The antihypertensive effect could be maintained by means of a continuous intravenous infusion. The decrease in systolic and diastolic blood pressures averaged 14% at the time of maximal effect. Older patients (>60 years of age) had a greater acute antihypertensive effect that was unrelated to sex, weight, or baseline blood pressure. Heart rate increased within the first minute of the injection, reached maximal values at 10 minutes (with an average increase of 5 beats/min), and returned to baseline values after 1 hour.

Wenting et al. reported that the blood pressure response to ketanserin was blunted by pretreatment with prazosin and was not affected by pretreatment with furosemide. Murphy et al. reported that, of 11 patients with severe hypertension not responding to high doses of prazosin, seven responded when ketanserin was added to the treatment regimen.

The Use of Intravenously Administered Ketanserin to Lower Blood Pressure in Patients with Hypertensive Emergencies of Different Etiologies

Severe Uncontrolled Hypertension

Four studies were performed in 100 patients (Table 3). In a first study, 10 patients with resistant hypertension were given 120 mg of ketanserin daily for 6 weeks. Both at rest and during exercise, systemic vascular resistance fell by 14%, heart rate fell by 5%, and stroke volume and cardiac output increased.

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<table>
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<tr>
<th>Indication</th>
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<th>Oral</th>
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<tr>
<td>Peripheral vascular disease</td>
<td>592</td>
<td>1,433</td>
</tr>
<tr>
<td>PACK study</td>
<td>—</td>
<td>1,942</td>
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<tr>
<td>Clinical pharmacology</td>
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<td>751</td>
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<td>1,300</td>
</tr>
<tr>
<td>Total</td>
<td>6,370</td>
<td>12,313</td>
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PACK = Prevention of atherosclerotic complications with ketanserin.

*On September 20, 1985, the Ministry of Public Health granted authorization to Janssen Netherlands to distribute ketanserin tablets and ampuls for all indications claimed in their registration dossier (International Registration File indications) for patients who did not adequately respond to commercially available antihypertensive drugs. This restricted release, granted in very rare cases, was based on the fact that a registration dossier had been submitted and that ketanserin is irreplaceable in its therapeutic class.
tension were given ketanserin intravenously at doses of 10 mg/min to a maximum of 30 mg until diastolic blood pressure decreased below 90 mm Hg, followed by a continuous infusion at 10 mg/hr for 2 hours. The reduction in diastolic blood pressure was usually achieved in the third minute of administration (20 mg ketanserin) and lasted for the entire 24-hour period. Side effects were not reported.

In a second study, 115 20 patients with uncontrolled primary or secondary hypertension, including 14 with renal hypertension, received a 5-mg intravenous bolus of ketanserin every minute up to a maximum of 30 mg, followed by an intravenous infusion at 4 to 20 mg/hr for 6 hours. In the 16 patients who responded to treatment with a diastolic blood pressure decrease of more than 15 mm Hg within 5 minutes, blood pressure remained satisfactorily controlled over the 6-hour ketanserin infusion. Four patients reported dizziness (1 severe), and one reported dry mouth. The four treatment failures reached the maximum bolus dose (30 mg) without symptoms.

In a third study, 117 eight of 20 patients with severe uncontrolled hypertension received an intravenous injection of 5 mg of ketanserin every 4 minutes up to a maximum of 50 mg (mean, 38 mg) and the other 12 patients received ketanserin (10 mg every 5 minutes up to a maximum of 30 mg; mean, 28 mg) and placebo in a crossover fashion. Only 11 of the 20 patients reached the target diastolic blood pressure (<100 mm Hg), and some patients failed to respond at all. It was not possible to predict which patients would respond to ketanserin and to what extent. In 18 of the 20 patients, sedation or somnolence were found to be the prominent side effects.

In a fourth study, 118 50 patients with essential hypertension with a hypertensive emergency received a single intravenous or intramuscular injection of 5 or 10 mg of ketanserin. One hour after injection, the average blood pressures were reduced by 10 to 19% systolic and by 18 to 19% diastolic. No side effects were observed when the drug was administered intramuscularly. After intravenous injection, three patients complained of mild somnolence and two of dizziness.

Ketanserin (5 mg injected in 2 minutes) did not control blood pressure in four patients with renal artery stenosis or in four subjects with renal hypertension. 92

To summarize these data, intravenous ketanserin clearly does not always reduce blood pressure adequately in patients with uncontrolled hypertension, and side effects increase as increasing doses are given. For these reasons, ketanserin is not suitable for routine use in hypertensive emergencies.

### Intraoperative and Postoperative Hypertension

Ketanserin has been shown to control hypertensive episodes, probably caused by serotonin release, during and after major operations, including coronary artery bypass. The usual dose was 10 mg intravenously, often followed by a continuous infusion at a rate of 2 to 4 mg/hr. 82, 85, 68, 69, 113, 119–127
Hypertensive Crisis in Carcinoid Syndrome

Surgery for carcinoid syndrome is commonly associated with an increase in free plasma serotonin levels, which may cause sharp rises in blood pressure. Ketanserin controlled a hypertensive crisis in three patients with carcinoid syndrome undergoing a major operation. In three other patients, ketanserin was given prophylactically and no hypertension occurred, suggesting that hypertensive crises may have been prevented. One of these patients was unresponsive to sodium nitroprusside, trimetaphan, and diazoxide therapy.

Hypertensive Crisis During Preeclampsia or Eclampsia

Two placebo-controlled studies were performed in a total of 50 postpartum, preeclamptic patients. Ketanserin (10–20 mg i.v.) effectively controlled systolic and diastolic blood pressures in virtually all patients with minimal side effects. The decrease in blood pressure could be maintained by a continuous infusion of ketanserin. Intravenous ketanserin administration also controlled blood pressure in 17 severely preeclamptic patients during labor. The treatment reduced to normal the frequency of uterine contractions. Eleven patients complained of dizziness and sleepiness, but no other adverse maternal or fetal effects were seen.

Hypertensive Crisis During Cerebrovascular Disease

A single intravenous injection of 5 mg of ketanserin in four patients with transient ischemic attack or cerebrovascular accident and presumably consequent hypertension reduced the hypertensive reaction for up to 40 minutes, and the antihypertensive effect could be maintained by a continuous infusion. However, in view of the findings of Jennings and Opie, in which central nervous system side effects of sedation and somnolence followed large doses, the intravenous use of ketanserin may be better avoided in patients suspected of having cerebrovascular accidents or ischemia.

Chronic Antihypertensive Effect

Dose

Data from controlled dose-finding studies in which either the dose per intake or the number of doses per day varied have been summarized by Breckenridge. At 20, 40, and 60 mg or more per intake, ketanserin reduced blood pressure significantly more than did placebo. The initial dose is 20 mg twice daily, increased if necessary to 40 mg twice daily. Increasing the dose beyond this level induces little if any additional fall in blood pressure and increases the risk of side effects.

Twenty-four-hour blood pressure monitoring in patients taking 40 mg twice daily showed a consistent reduction of systolic and diastolic blood pressures throughout the period, with preservation of the diurnal variation. Although the terminal half-life of ketanserin is 25 hours, there is inconclusive evidence that once-daily dosing can control blood pressure over 24 hours. Most studies have used twice-daily doses.
Combination Therapy

Ketanserin (40 mg twice daily), but not placebo, reduced blood pressure in patients with essential hypertension when added to a β-adrenergic receptor blocker or a diuretic regimen to which the patients were not responding adequately.\(^{43, 147, 152, 184-186}\) Similarly, in patients responding poorly to ketanserin therapy alone, the combination with a β-adrenergic receptor blocker or a diuretic significantly lowered blood pressure.\(^{166, 167, 187, 188}\) The decreases in blood pressure during combination treatment were greatest when the initial blood pressures were highest.\(^{189}\) In hypertensive blacks, once-daily treatment with 40 mg of ketanserin plus 25 mg of hydrochlorothiazide reduced blood pressure (particularly systolic) faster than did once-daily treatment with 40 mg of ketanserin alone. Both drug regimens were effective over the 24-hour period.\(^{146}\) Ferrara et al.\(^{190}\) reported that once-daily treatment with 20 mg of ketanserin plus 25 mg of hydrochlorothiazide reduced blood pressure over 24 hours and was slightly more effective, particularly on systolic blood pressure, than once-daily treatment with 40 mg of ketanserin plus 12.5 mg of hydrochlorothiazide.

As monotherapy, ketanserin had a greater blood pressure-lowering effect in patients over 60 years of age (systolic and diastolic blood pressure). This effect was independent of the height of the pretreatment blood pressure. This greater efficacy in older patients has also been observed when ketanserin treatment was combined with atenolol or with hydrochlorothiazide plus amiloride treatment.\(^{177}\)

In conclusion, ketanserin is useful in association with β-blockers and diuretics. The combined effects seem to be additive rather than synergistic.

Peripheral Vascular Disease

Intermittent Claudication

The effect of ketanserin on intermittent claudication was assessed in 12 placebo-controlled parallel group studies\(^{191-193}\) and reviewed by Clement and Duprez.\(^{194}\) After 3 to 6 months of treatment, walking distance increased significantly with ketanserin in seven centers and with placebo in two centers. More patients experienced a doubling of walking distance with ketanserin than with placebo (25 vs 13%) treatment, and fewer patients deteriorated with ketanserin treatment than with placebo (23 vs 32%) treatment; this difference in response rate was significant. In a subgroup of 55 hypertensive patients in whom systolic blood pressure was measured in both legs, the ankle/arm blood pressure ratio rose significantly (+ 8%) in the more affected leg during ketanserin therapy despite a significant fall in systemic blood pressure. In the placebo group (\(n = 45\)), neither systemic nor leg pressures changed significantly.\(^{195}\)

Raynaud's Phenomenon

In healthy volunteers, ketanserin treatment prevented or attenuated the decrease of digital blood flow, accelerated the recovery of digital temperature and digital blood flow after cold challenge,\(^{92, 197}\) and increased resting calf blood flow.\(^{92}\) In patients with Raynaud's phenomenon, ketanserin treatment attenuated but did not prevent cold-induced vasoconstriction.
bo-controlled studies, the daily number of attacks, their duration, and severity were on average halved during ketanserin treatment compared with placebo.

Symptomatic relief has been reported during ketanserin treatment in patients with primary or secondary Raynaud’s phenomenon. In placebo-controlled studies, the daily number of attacks, in the fingers, is reduced. Some of this improvement may be the result of a reduction in the frequency and severity of the attacks, but the mechanism is not fully understood. In placebo-controlled studies, the daily number of attacks, their duration, and severity were on average halved during ketanserin treatment compared with placebo treatment. The responses varied between studies, and some showed no effect at all.
Other Effects

Cardiac Electrophysiology

Ketanserin treatment prolonged the action potential duration in ventricular muscle of the rabbit, with a depressant effect on conduction.212, 213 The overall cellular electrophysiological effects are consistent with a weak Class III antiarrhythmic action, although there may be species differences.214 In healthy volunteers215 and in patients,216-218 ketanserin treatment slightly prolonged the QTc interval, but this effect was not observed in other, larger studies.157, 219 A blinded analysis of the available electrocardiograms from various studies showed QTc prolongation in 48 of 162 patients. Overall, the increase averaged 16 msec.220 In an electrophysiological study in 10 patients with a history of cardiac arrhythmias, there was no change in the ventricular effective refractory period after a single intravenous injection of 10 mg of ketanserin, although the QTc interval was significantly prolonged by an average of 14 msec, consistent with the in vitro effects of the drug.221

Hormonal Changes

Renin-Angiotensin System

The activity of the renin-angiotensin system is only slightly affected by treatment with ketanserin. After intravenous administration, modest and inconsistent increases in plasma renin and angiotensin II have been observed in recumbent volunteers and in patients with essential hypertension or heart failure.48-50, 55, 60, 115 In healthy, sitting volunteers, ketanserin treatment produced an increase in plasma renin and angiotensin II, both at rest and during exercise, but a decrease in plasma aldosterone during exercise.49 Ketanserin increased the plasma levels of aldosterone and renin both under basal conditions and in response to metoclopramide222 but did not influence 5-hydroxytryptophan-induced aldosterone secretion.223 In patients with primary aldosteronism, a transient decrease in plasma aldosterone and a concomitant decrease of plasma cortisol without a change in plasma renin have been claimed.224 More prolonged oral administration of ketanserin, in both volunteers and patients with hypertension, did not affect plasma renin, plasma angiotensin II, plasma aldosterone, or renal aldosterone excretion.162, 164, 177, 315 By contrast, three other studies reported that in essential hypertension ketanserin treatment produced a reduction in plasma renin and angiotensin II with101 or without100, 103 a concomitant decrease of plasma aldosterone. In normal volunteers, treatment with ketanserin for 3 days caused no change in basal levels of renin, angiotensin II, or aldosterone, and there was no change in the aldosterone response to administered angiotensin II.216, 225

Adrenergic System

The effects of ketanserin on catecholamines have usually been observed, both at rest and during exercise.48-50, 54, 55, 60, 115 During long-term oral treatment in volunteers and in patients with hypertension, resting plasma norepinephrine or epinephrine levels remained unchanged,107, 142, 144, 177, 215 decreased,101 or increased.100 Also during long-term treatment, the increase in plasma norepinephrine caused by sympathetically stimulated stimulation was blunted by ketanserin treatment when the stimulus was weak (noise or isometric exercise) but not when it was strong (tilt or dynamic exercise).101, 107, 226

Other Hormones

Ketanserin treatment had no effect on the basal release of pituitary hormones (prolactin, growth hormone, luteinizing hormone, adrenocorticotropic hormone, vasopressin), on thyroid function and, on plasma cortisol levels.178, 222, 223, 227-229 Ketanserin treatment reduced plasma prolactin levels in patients with functional but not with puerperal prolactinemia.228, 231, 232 It also reduced the serum prolactin and adrenocorticotropic hormone but not the cortisol response to insulin-induced hypoglycemia.230

Volume and Weight Changes

Changes in body weight during long-term treatment with ketanserin vary: Some authors report increases100, 102, 144, 152, 154, 160, 175 and others, no change.99, 101, 142, 150, 167, 233 Although in one study approximately 100 mmol of sodium was retained in the first week of treatment,220 Omvik and Lund-Johansen99 found that on average there were no significant changes in either plasma volume or extracellular fluid volume. However, sodium retention may limit the magnitude of the fall in blood pressure, since blood pressure fell more in patients who had a fall in extracellular fluid than in those who had no change or a rise in extracellular fluid.

Effects on Renal Function

During short-term and long-term treatment with ketanserin in patients with essential hypertension, renal blood flow and glomerular filtration rate were unchanged in spite of a reduction in blood pressure and renal vascular resistance.41, 51, 84, 101-103, 149 Creatinine clearance was unchanged in one study144 and slightly decreased in two.198, 254 Sodium excretion remained constant in three studies,103, 144, 229 increased significantly in one,159 and decreased in another.200 A marked diuretic and saluretic activity of ketanserin treatment was observed in normal subjects undergoing diuresis after loading with water or mannitol, without significant modifications of renal blood flow or glomerular filtration rate. These findings suggest that ketanserin interferes with the transport of ions at the tubular level.235

Blood Physiology and Chemistry

Hematology and Biochemistry

The limited published data on the hematological and biochemical effects of ketanserin do not reveal clinically relevant changes. A reanalysis of the individual hematological and biochemical assessments in
600 patients treated with ketanserin monotherapy for 3 months reveals the following small but significant changes: a decrease in hemoglobin (-0.7%), hematocrit (-2.3%), white blood cell count (-2.1%), calcium (-0.8%), and total cholesterol (-1.7%) and an increase in creatinine (+3.8%), all within normal limits. The rise in serum creatinine was not accompanied by a rise in urea and uric acid. No proteinuria attributed to ketanserin treatment has been reported.

Carbohydrate Metabolism

Ketanserin treatment did not change fasting glucose levels.232 233 The effect of long-term treatment with ketanserin on glucose tolerance has not been reported.

Lipid Metabolism

A few studies have investigated the effects of ketanserin treatment on serum lipids. Several studies report no changes in serum cholesterol or serum triglycerides132 144 157 158 232 or no change in total serum cholesterol but a significant reduction in serum triglycerides.108 On the other hand, retrospective analyses in 50 and in 18 nonfasting hypertensive patients who received ketanserin (40 mg twice daily) monotherapy for 3 months and for 1 year, respectively, indicated a fall in total cholesterol and low density lipoproteins and a rise in high density lipoproteins. In the patients who, in a double-blind parallel group, received propranolol, no significant changes were seen at 3 months while total cholesterol and high density lipoprotein cholesterol increased and low density lipoprotein cholesterol remained unchanged at 1 year237 238 In another study, 37 hypertensive patients were treated in double-blind parallel groups for 3 months in monotherapy. Serum cholesterol decreased significantly with ketanserin (40 mg twice daily) treatment, whereas with metoprolol (100 mg twice daily) treatment the high density protein level decreased significantly.161

Platelets

Studies in humans demonstrate that short-term as well as long-term treatment with ketanserin inhibits ex vivo platelet aggregation and the release reaction induced by serotonin. It also reduces the platelet aggregability of platelets to serotonin has been reported.232 Ketanserin treatment reduces platelet aggregating plasma levels of 0-thromboglobulin.240 245 Platelet aggregation induced by nonserotoninergic agents (e.g., epinephrine, ADP) is not affected by ketanserin treatment.232 243 246 247 This effect of ketanserin was more pronounced in platelet-rich than in platelet-poor plasma.248 The whole-blood viscosity and the clogging of white blood cells decreased with ketanserin treatment.247 In patients with essential hypertension, the elevated sodium content of the red blood cells decreased after treatment with ketanserin.249 No changes were found in the ouabain-sensitive Rb+ uptake or Na+ efflux.250

Complaints and Adverse Events

Complaints

A slow intravenous injection of a therapeutic dose (10 mg) of ketanserin is usually well tolerated in healthy volunteers and in patients with essential hypertension. Transient hypotension may occur in some elderly, sodium-depleted, or postoperative patients. Drowsiness and sleepiness are frequent after administration of higher doses (28-38 mg).111 without an additional fall in blood pressure. After a single 10-mg intravenous dose of ketanserin in seven healthy volunteers, mild sedation was demonstrated by means of psychometric performance tests as well as electroencephalographic recordings.259

Some patients report lightheadedness, lack of concentration, or drowsiness 1 to 2 hours after the initial oral doses of ketanserin. These side effects, which are dose-dependent, usually disappear within a few days. During long-term oral therapy in placebo-controlled trials (dosage, 20 to 40 mg b.i.d. or t.i.d.) and in response to a nonleading question (e.g., "Did the tablets upset you in any way?"), somnolence was present slightly more often with ketanserin treatment (6.8 vs 3.8%; p = 0.41), whereas headache was more common with placebo treatment (9.0 vs 3.7%; p = 0.08).138 In a psychopharmacology study in 24 elderly patients with essential hypertension, treatment with ketanserin (40 mg twice daily for 5 weeks) caused a slight reduction of vigilance, without electroencephalographic changes and without impairment of visuomotor coordination; momentary well-being expressed on a mood scale was significantly better with ketanserin treatment than with placebo treatment.260 In studies comparing ketanserin (40 mg b.i.d.) treatment with that of other antihypertensive agents, the incidence of complaints and the dropout rate for side effects was similar between ketanserin and the reference drugs (see Tables 4 and 5). During combination treatment with 8-blocking agents or with diuretics, side effects were not more prominent than during ketanserin monotherapy.139 In a few early studies using higher doses (60 mg or more per intake), side effects, predominantly drowsiness, fatigue, dizziness, and head-
ache, were common, without an additional fall in blood pressure. Thus, single doses of ketanserin larger than 40 mg are generally not recommended. 99 108-139

Severe Adverse Events

A systematic screen in the 1636 patients with essential hypertension for whom individual case record forms were available indicated that the incidence of severe events was not higher with ketanserin than with placebo treatment (Table 6). 236 However, eight cases of reversible ventricular tachycardia, five of the torsade de points type, were reported in the approximately 18,000 patients (see Table 2) treated so far with ketanserin. All eight cases had other factors possibly contributing to the development of the arrhythmia (Table 7). As with other drugs that prolong QTc interval, ketanserin should be used with caution in patients with severe bradycardia (e.g., second- or third-degree heart block) or in combination with drugs that affect repolarization (e.g., antiarrhythmics of Classes la, 1c, and III). Potassium loss should be prevented. If diuretics are given, a potassium-sparing diuretic should be added. 220

Mode of Action

The relative contributions of the $S_2$-serotoninergic and $\alpha_1$-adrenergic antagonistic properties (and perhaps other mechanisms) to the hypotensive effect of ketanserin during long-term oral treatment remain poorly understood. 225 261-263 Although most attention has been focused on the possible peripheral actions of ketanserin, an effect on the central nervous system cannot be discounted on present evidence. Furthermore, with regard to the relative importance of blockade of $S_2$-serotoninergic and $\alpha_1$-adrenergic receptors in peripheral resistance vessels, the possibility should be considered that these receptors overlap on the cell surface, sharing binding sites. 264 265

Central Actions

Much of the work pertaining to the central effects of ketanserin has been obtained in experimental animals and may be of doubtful relevance to humans. Alteration of cerebral serotonin levels in laboratory animals has variable effects on vascular tone, with the results in rats often being opposite to those obtained in cats and dogs. 266 In humans, the sedation and sleepiness observed after high intravenous doses of ketanserin 113 and the transient sedation and alterations in the electroencephalogram following oral administration indicate that the drug reaches the brain. 259 260 Experiments in the dog 267 and the cat 268 also suggest that a centrally mediated inhibition of sympathetic nerve activity contributes to the hypotensive action of ketanserin. Furthermore, a single dose of ketanserin reduces sympathetic nerve activity in rats 9 and cats. 266 All of these findings suggest that ketanserin may lower blood pressure by a central mechanism. However, injection of ketanserin into the cerebral ventricle of the rat did not lower blood pressure. 270 The sensitivity of the baroreceptors and the stress-induced cardiovascular reactivity are not changed during long-term treatment with ketanserin in the rat. 271 In humans, there is only scanty evidence that ketanserin treatment may blunt reflex increases in sympathetic outflow 101, 102; it did not reduce the levels of circulating catecholamines, which would be expected if it suppressed the central adrenergic system. 144 Ritanserin, which penetrates the brain more readily than ketanserin, 272 273 does not lower blood pressure when given intravenously. 112

Peripheral Vascular Effects

Evidence in Favor of $S_2$-Serotoninergic Blockade

In vitro, ketanserin inhibits the serotonin-induced contraction of human digital, saphenous, pulmonary, cerebral, mesenteric, gastric, colonic, and umbilical arteries and veins. 274-282 Ketanserin also partially inhibited cerebrospinal fluid-induced contractions of human cerebral arteries 283 and platelet-induced contractions of human digital arteries 284 in vitro. Intra-arterial infusion of ketanserin (50 ng/kg/min) prevented the vasoconstriction induced by intra-arterial infusion of serotonin in the forearm of seven healthy volunteers, but it did not influence the initial vasodilatation caused by serotonin. 285 Similar dose-dependent effects were obtained when serotonin and ketanserin were injected into finger veins of 25 healthy volunteers. 286 These observations indicate $S_2$-serotoninergic receptor blockade in vivo.

Long-term and short-term treatment with ketanserin

TABLE 6. Severe Adverse Events per 100 Patient-years in Patients with Essential Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 130)</th>
<th>Ketanserin (n = 430)</th>
<th>$\beta$-blocker (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular event</td>
<td>18</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>CVA</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>12</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>&lt;0.5</td>
<td>0</td>
</tr>
<tr>
<td>Extrasystoles</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>&lt;0.5</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Depression</td>
<td>6</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Amnesia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vision disturbances</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0</td>
<td>&lt;0.5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>26</td>
<td>34</td>
</tr>
</tbody>
</table>

Values are number of events per 100 patient-years, rounded to the nearest unit. n = patient-years; CVA = cardiovascular accident.
caused inhibition of the response of human platelets to serotonin but not to other aggregatory agents (e.g., ADP or epinephrine); this also demonstrates blockade of $S_2$-serotoninergic receptors in humans.*177239 "24 '24324 *

Evidence Against $S_2$-Serotoninergic Blockade

Single doses of another $S_2$-serotoninergic antagonist, ritanserin, at doses that have no effects on $\alpha_1$-adrenergic receptors, had no significant effect on blood pressure; in the same study, however, single doses of ketanserin significantly lowered blood pressure.112 These observations argue against $S_2$-serotoninergic blockade alone as the explanation for the antihypertensive effect of ketanserin.

Evidence in Favor of $\alpha_1$-Adrenergic Receptor Blockade

In normal volunteers, the short-term administration of ketanserin depressed the pressor dose-response curve to methoxamine, indicating blockade of peripheral vascular $\alpha_1$-adrenergic receptors.288 In patients during cardiopulmonary bypass, administration of ketanserin abolished the pressor effect of norepinephrine.289 The administration of ketanserin for 6 weeks to patients with essential hypertension produced a significant reduction in arterial pressure and a moderate depression of the pressor response to high doses of methoxamine.100 A similar shift in the pressor dose-response curve to phenylephrine was seen in hypertensive patients treated for 2 months with ketanserin, 40 mg twice daily.290 Ketanserin administered to normotensive volunteers also caused a significant reduction in arterial blood pressure and a shift to the right of the pressor dose-response curve to phenylephrine; the shift was modest compared with that induced by prazosin.36 291, 292 The blood pressure response to the infusion of angiotensin II189, 293 was unaffected by ketanserin treatment in contrast to the response to phenylephrine. These data suggest that there is a weak but distinct $\alpha_1$-adrenergic blockade in at least some situations, when ketanserin is administered.

Evidence Against $\alpha_1$-Adrenergic Receptor Blockade

Ketanserin administered intravenously caused a decrease in blood pressure in salt-depleted recumbent subjects, a more marked postural fall in blood pressure in both sodium-depleted and sodium-replete normal subjects, and no shift in the pressor dose-response curve to phenylephrine in normal subjects.30 The short-term administration of ketanserin to patients with essential hypertension reduced arterial pressure without altering the blood pressure response to graded infu-
TABLE 7. (Continued)

<table>
<thead>
<tr>
<th>Recent or concomitant therapy</th>
<th>Recent or concomitant disease</th>
<th>Action taken</th>
<th>Outcome</th>
<th>Possible predisposing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nafronyl i.a.</td>
<td></td>
<td>Stop ketanserin; Holter monitor</td>
<td>Recovered</td>
<td>Nafronyl</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Mitral valve disease, mastectomy for cancer</td>
<td>Stop ketanserin; metoprolol, tocainide</td>
<td>Recovered</td>
<td>Preexisting QT prolongation; serum K+ below normal</td>
</tr>
<tr>
<td></td>
<td>Diabetes, gout, 2nd-degree AV block, left anterior hemiblock</td>
<td>Stop ketanserin; Holter monitor; pacemaker</td>
<td>Recovered</td>
<td>2nd-degree AV block; serum K+, 3.5 mmol/L</td>
</tr>
<tr>
<td>Verapamil; HCTZ-K+</td>
<td>Hypertension, minor stroke, angina</td>
<td>Stop ketanserin; electric defibrillation</td>
<td>Recovered</td>
<td>Baseline QT slightly prolonged; serum K+, 2.5 mmol/L; K+-losing diuretic</td>
</tr>
<tr>
<td>Quinidine, warfarin, isosorbide dinitrate, spironolactone, HCTZ</td>
<td>Hypertension; MI, DVT, nephrectomy; amputation of toe, sympathectomy</td>
<td>Stop ketanserin and quinidine; pacemaker</td>
<td>Recovered</td>
<td>Quinidine; diuretics</td>
</tr>
<tr>
<td>Hydroquinidine, gliclazide, HCTZ + amlodize, guanfacine, theophylline</td>
<td>WPW, LBBB, diabetes, hypertension, left ventricular insufficiency</td>
<td>Stop ketanserin and hydroquinidine</td>
<td>Recovered</td>
<td>Quinidine; diuretics</td>
</tr>
<tr>
<td>Digoxin, nitroglycerin, furosemide, spironolactone, pentoxifylline, indomethacin, aspirin</td>
<td>Old MI, coronary bypass</td>
<td>Stop ketanserin</td>
<td>Recovered</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Insulin, pyrissuccideanol dimaleate</td>
<td>Diabetes</td>
<td>Stop ketanserin; lidocaine infusion</td>
<td>Recovered</td>
<td>Baseline QTc = 0.476 sec</td>
</tr>
</tbody>
</table>

sions of phenylephrine.52 In another study in patients with essential hypertension, ketanserin (10 mg i.v.) treatment lowered arterial pressure but did not alter the pressor effect of bolus injections of phenylephrine.52,54 Finally, ketanserin also had a distinct hypertensive action in normotensive patients with autonomic insufficiency caused by an efferent sympathetic lesion, who were unresponsive to phentolamine therapy (Figure 5).54 These studies demonstrate that peripheral α-adrenergic blockade is not essential for the acute antihypertensive action of ketanserin.59

Evidence in Favor of Combined Effects on S2-Serotoninergic and α1-Adrenergic Mechanisms

Van Nueten et al.295 demonstrated that the direct and amplifying contractile effects of serotonin on blood vessels are inhibited by the S2-serotoninergic antagonists ketanserin and ritanserin. In this regard ritanserin was the more potent of the two drugs.

Ketanserin is a competitive antagonist, whereas ritanserin exerts irreversible antagonism. Ketanserin is a moderately active α1-adrenergic antagonist, whereas ritanserin is ineffective in this regard. In spontaneously hypertensive rats (SHR), ketanserin treatment lowered blood pressure, whereas ritanserin treatment did not, indicating that S2-serotoninergic antagonism alone induces no antihypertensive effect in the SHR.296–298 However, ritanserin treatment potentiated the blood pressure–lowering effect of a low dose of prazosin, indicating an interaction between S2-serotoninergic and α1-adrenergic mechanisms.

![Figure 5](http://hyper.ahajournals.org/) Effects of ketanserin (10 mg i.v.) and phenolamine (20 mg i.v.) treatment on arterial blood pressure and heart rate in patients with autonomic insufficiency. Mean values from observations in four patients are shown. Reprinted from Schalkenkamp44 with permission.
The interactions among ketanserin, ritanserin, phenylephrine, and phentolamine were also studied in patients during coronary bypass surgery. Although ritanserin did not modify the pressor effect of phenylephrine, it potentiated the effect of phentolamine in blocking the pressor response to phenylephrine. These data suggest that the antihypertensive effect of ketanserin is probably due to its combined effects on \( S_2 \)-serotonergic and \( \alpha_1 \)-adrenergic mechanisms.

**Aldosterone Secretion**

Serotonin is a potent stimulator of the liberation of aldosterone in vitro. Ketanserin has been shown (also in vitro) to inhibit the serotonin-induced release of aldosterone. However, these observations raise the possibility that part of the antihypertensive effect of ketanserin is related to inhibition of the secretion of the mineralocorticoid. However, there is no consistent decrease of plasma aldosterone levels during short-term or long-term treatment with ketanserin (see Hormonal Changes).

**Conclusions**

The mechanism of blood pressure reduction by ketanserin in hypertensive patients remains imperfectly understood. It cannot be attributed to \( S_2 \)-serotonergic blockade alone. It can occur in the absence of evident \( \alpha_1 \)-adrenergic blockade. However, particularly with prolonged therapy, features of \( \alpha_1 \)-adrenergic blockade appear, although there are differences between the pattern of effects caused by ketanserin and by prazosin treatment. Combined effects on \( S_2 \)-serotonergic and \( \alpha_1 \)-adrenergic mechanisms appear to be required. Also, a central modulating action by ketanserin on pressor reflexes cannot be excluded.

**Possible Role of Ketanserin in the Treatment of Hypertension**

The data presented here indicate that ketanserin is an effective and well-tolerated antihypertensive drug. The side effects usually are not severe at doses effective in reducing blood pressure (20 or 40 mg twice daily), although with larger doses side effects become more prominent without any additional lowering of the blood pressure.

As has been stated, the mode of antihypertensive action is not fully established. Although there is considerable evidence that the drug induces some features of \( \alpha_1 \)-adrenergic receptor blockade, this effect is not adequate to explain in full the antihypertensive mechanism, and an action through the \( S_2 \)-serotonergic receptor, either at the peripheral vascular level or within the central nervous system, cannot be excluded.

The evidence for the participation of serotonin in the pathogenesis of hypertension is likewise controversial. There is evidence that pulmonary clearance of serotonin is reduced in SHR, and a selective hypersensitivity to serotonin has been repeatedly reported in vascular tissues in experimental hypertension.

Ketanserin prevents the vasoconstriction evoked by serotonin in isolated kidneys taken from hypertensive rats. The cellular mechanism underlying the increased sensitivity of hypertensive blood vessels to serotonin probably does not involve an increased affinity of serotonergic receptors for the monoamine, since the inhibitory potencies of serotonergic antagonists such as ketanserin and methysergide are comparable in blood vessels from normotensive and hypertensive animals. The most likely explanation for the exaggerated response to activation of serotonergic receptors is a greater mobilization of calcium from intracellular stores. The indirect vasoconstrictor effects of serotonin also are altered in hypertension. This change includes the amplifying and the indirect sympathomimetic effects of serotonin. Furthermore, higher concentrations of the monoamine can evoke endothelium-dependent contractions in SHR, but not in normotensive rats. In addition, the data showing that the constrictor responses to serotonin are exaggerated in blood vessels from aging animals could provide an explanation for the age dependency noted in the therapeutic efficacy of ketanserin. A major and as yet unanswered question is how, in the absence of free serotonin in plasma, serotonin can induce peripheral vasoconstriction. The most likely explanation is that there is reduced endothelial degradation of serotonin, decreased uptake capacity of platelets, and accelerated platelet turnover in hypertensive animals, which could act together to increase the local concentrations of the monoamine at the blood vessel wall, where serotonergic receptors are located (Figure 6), but this remains a hypothesis.

In human hypertension, the evidence for participation of a serotonergic mechanism is scanty. However, the serotonin content in platelets of hypertensive patients is significantly reduced, by approximately 30%, compared with that in normotensive subjects. Long-term treatment with ketanserin (40 mg and 80 mg daily) does not affect the serotonin content of platelets. The uptake of serotonin by platelets from hypertensive patients is reduced; kinetic analysis shows a reduced maximal rate of enzymatic reaction without a significant alteration of the \( K_m \). The release of serotonin from platelets induced by thrombin and other agonists, including serotonin itself, is significantly augmented in hypertension. In severe hypertension, the levels of \( \beta \)-thromboglobulin in the plasma are elevated, suggesting increased release or accelerated platelet turnover (for review, see Reference 313). All changes in platelet behavior occurred to various extents in some but not all hypertensive patients. There is also evidence for an increased responsiveness to serotonin of forearm blood vessels in humans, although this increase is no greater than that observed with other vasoconstrictor agents.

There is evidence that certain neurons, particularly in the medulla and spinal cord, are serotonergic. At present, their possible contribution to the maintenance of vascular tone and their possible participation in a serotonergic pathogenic component in hypertension in either experimental animals or humans are not clear.
Stimulation of some central serotoninergic pathways raises blood pressure, while stimulation of others diminishes blood pressure. 315

Aside from its role as an antihypertensive drug and as a tool for investigation of the role of serotonin in hypertension, the possible effects of ketanserin on the vascular disease process are of great interest. The observation that ketanserin may improve intermittent claudication, while not finally confirmed, implies that the drug may have some action in already diseased vessels that might influence other vascular beds involved in hypertension. A possible mechanism for the involvement of serotonin in peripheral vascular disease can be postulated. Atherosclerotic plaques, in particular if the endothelium is injured, are sites of platelet aggregation. 316, 317 Animal experiments show that atherosclerotic arteries and collateral blood vessels are hypersensitive to serotonin from aggregating platelets; ketanserin inhibits these augmented responses. 318-325 Thus, the release of serotonin could result in the occurrence of spastic constriction of the atherosclerotic arteries; decreases in the diameter of collateral blood vessels could contribute to the perfusion of the tissues. 326, 327, 328 The hemorrheological properties of the blood coming from ischemic tissues would be altered, resulting in an increased viscosity. 329 Ketanserin partly corrects this abnormality, suggesting that serotonin may be involved. 108, 246, 252-254, 328 If the deformability of the blood cells were reduced by serotonin released from aggregating platelets, 323 this would endanger the perfusion of the tissues at the microcirculatory level. The possibility that ketanserin may affect not only blood pressure but also atherosclerosis is of interest.

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