Serotonin and Serotonin Antagonism in Cardiovascular and Non-Cardiovascular Disease

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Serotonin, or 5-hydroxytryptamine, is a naturally-occurring vasoactive substance found primarily in the brain, enterochromaffin tissue, and blood platelets. It has diffuse cardiophysiologic effects. The multiple effects of serotonin on blood vessels can be explained by the existence of 2 serotonergic receptor subtypes (the S_1 receptor mediates vasodilation, and the S_2 receptor vasoconstriction). Serotonin via the S_2 receptor also augments the actions of several other vasoconstricting substances. Serotonin may be responsible for causing, or at least perpetuating, some forms of systemic hypertension through peripheral and central nervous system (CNS) actions. Ketanserin is a highly selective S_2-serotonergic antagonist with additional α-adrenergic blocking activity, which has been proposed as a therapy for various cardiovascular diseases including hypertension. It has been shown to be more effective than placebo in treating hypertension and comparable in effectiveness to other antihypertensive drugs. Its major side effects relate to the CNS, and prolongation of the electrocardiogram QT interval has been described. Caution must be used when using ketanserin in patients receiving potassium- and magnesium-losing agents, because of the risk of torsades de pointes. Ketanserin has potential utility in the treatment of eclampsia, peripheral vascular disease, carcinoid syndrome, and "shock lung." The drug is not yet approved for clinical use in the United States.

Various circulating substances are involved in blood pressure control in human beings, and among these, the effects of serotonin are now well recognized. Its importance in human hypertension and other cardiovascular disorders was not realized initially, because serotonin antagonism induced by various chemical substances affected blood pressure in conflicting ways.

The recent discovery of serotonin-receptor subtypes has rekindled interest in examining serotonin antagonism as a pharmacologic approach to reducing elevated blood pressure. A subtype selective serotonin blocker, ketanserin (Figure 1), has been proposed as an innovative therapy for systemic hypertension and for other cardiovascular disorders.[1] The drug has now been studied in extensive clinical trials worldwide.

In this article, the cardiovascular effects of serotonin will be reviewed, and the pharmacologic actions and potential therapeutic applications of ketanserin explored.

CARDIOVASCULAR EFFECTS OF SEROTONIN

Serotonin, or 5-hydroxytryptamine (5-HT) (Figure 1), is a naturally-occurring vasoactive substance found primarily in brain, enterochromaffin tissue, and blood platelets. The amine is manufactured mainly in the amine precursor uptake and decarboxylation system (APUD) cells of the gastrointestinal tract,[2] where it is then released into the blood. Intravascularly, blood platelets rapidly bind and store the amine, so that little, if any, exists free in the plasma. Its physiologic effects were described by Page in 1954.[3]

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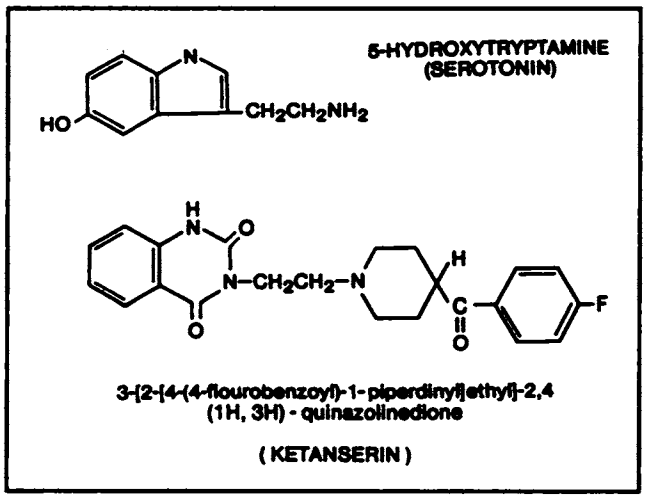

Figure 1. Chemical structures of ketanserin and serotonin.

Physiologic Actions

Serotonin has diverse cardiophysiologic effects (Table I, Figure 2), which led to its designation as an amphibaric molecule.[1] The amine constricts and dilates blood vessels, depending on the vessel site and the condition of its intimal wall. The vascular effects of serotonin are so varied that it can induce different contractile responses in separate segments of the same coronary artery.[4]

These multiple effects on blood vessels can be explained by the well-defined existence of 2 serotonergic receptor subtypes, S_1 and S_2 (Table II). The S_1 receptor mediates the vasodilator activity of serotonin, whereas the S_2 receptor mediates a vasoconstrictive effect. The different vascular responses seen with serotonin in different vascular beds are probably influenced by the distribution of these receptor subtypes.[5]

These receptors are characterized by their radiolabeled binding specificities: {3H}-5-HT specifically labels the S_1 receptors, whereas {3H} spiperone or {3H} ketanserin binds to the S_2 receptors. A third receptor class, 5-HT_3 is identified by its morphine-binding capacity. This receptor was formerly termed the "M" receptor, whereas the S_1 and S_2 receptors were previously indistinguishable and termed "D" receptors for their abilities to bind phenoxybenzamine (dibenzyline). Additionally, recent studies have shown 3 subtypes of the 5-HT_1 receptor called 5-HT_1A, 5-HT_1B, and 5-HT_1C. Evidence also exists for other classes of serotonin receptors, termed 5-HT_3 and 5-HT_4.

Serotonin causes constriction in large arteries and precapillary vessels and causes vasodilation in the arterioles and large veins,[4,6] although numerous exceptions to both exist. Its vasoconstrictive actions are believed to be largely mediated by S_2-serotonergic receptors on platelets and endothelial cells; these effects are substantially attenuated by the serotonin antagonist ketanserin. Serotonin, via the S_2 receptor, amplifies the release and augments the actions of several other vasoconstricting mediators, including histamine, angiotensin II, prostaglandin $F_{2\alpha}$, and norepinephrine.[1,5,7] Additionally, in conjunction with other mediators, it augments platelet aggregation. This, in turn, causes platelet release of more stored serotonin,[8] amplifying its own action.

In vascular diseases, most commonly atherosclerosis and hypertension, the body often develops collateral circulation to augment blood flow to ischemic regions. These collateral vessels are exquisitely sensitive to the vasoconstrictive effects of serotonin.[9,10] Age, atherosclerosis, and hypertension are factors that augment serotonin-induced vasoconstriction.[11] Van Nueten and Janssens showed that serotonin enhanced the vasoconstriction induced by cooling and hypoxia in canine vessels.[7]

Serotonin also exerts a direct influence on the heart and cardiopulmonary circulation. Breuer and his colleagues[12] showed a dose-dependent increase in pulmonary artery pressure, cardiac output, stroke volume, cardiac contractility, and pulmonary vascular resistance after serotonin infusion in the dog; it simultaneously, and in a dose-dependent manner, lowered mean aortic pressure and total peripheral resistance.

Vascular dilation by serotonin is believed to be mediated, in part, by S_1 receptors in the endothelium. Bound serotonin causes release of a relaxation factor originally termed endothelial derived relaxation factor (EDRF) and now identified as nitric oxide (NO), which directly relaxes the vascular smooth muscle cells.[1,8] This observation is substantiated by the finding that vessels devoid of endothelium show increased vasoconstriction in the presence of serotonin.[5] Serotonin also causes the release of other dilator compounds, such as prostaglandin I_1 (PGI_1) and vasoactive intestinal peptide, while inhibiting the release of the vasoconstrictor norepinephrine.[8]

Serotonin in Systemic Hypertension

Peripheral Effects. Serotonin may be responsible for causing, or at least perpetuating, some forms of systemic hypertension. Elderly individuals and hypertensive patients show increased serotonin sensitivity.[1,8] Increased circulating serotonin could cause increased capacitance bed constriction, thereby raising

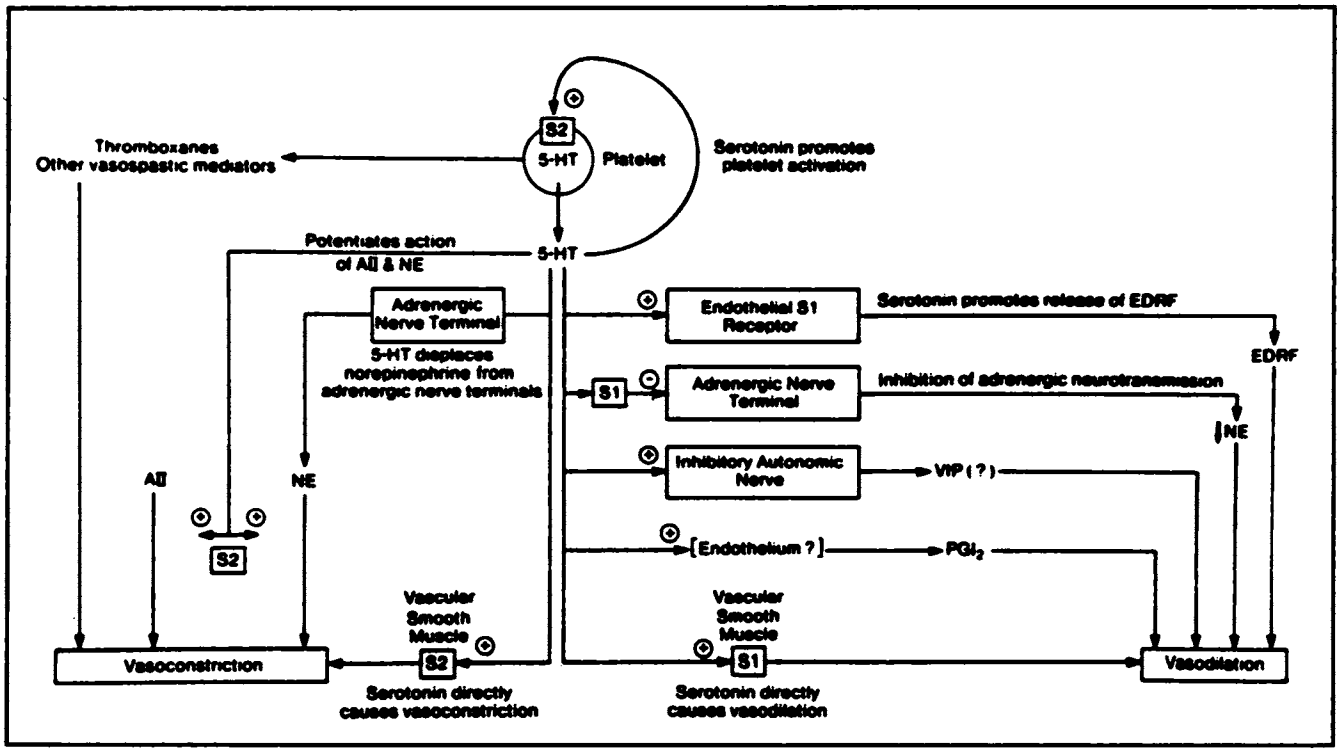

Figure 2. In the vascular bed, the immediate source of serotonin is from activated platelets that release serotonin along with other vasoactive mediators. Serotonin release promotes platelet activation via S_2 receptors on platelets, leading to a positive feedback loop. This released serotonin has contradictory effects. Vasoconstrictor actions: (1) via S_2 receptors, serotonin augments the vasoconstrictor response to norepinephrine (NE) and angiotensin II (AII); (2) serotonin displaces NE from adrenergic nerve terminals, increasing the local concentration of the latter; and (3) serotonin acts directly on S_2 receptors on vascular smooth muscle to promote vasoconstriction. Vasodilator effects: (1) via endothelial S_1 receptors, serotonin promotes release of endothelial-derived relaxing factor (EDRF)/nitric oxide, which acts on smooth muscle to cause vasodilation; (2) serotonin promotes release (and synthesis) of prostacyclin (PGI_2), a potent vasodilator; (3) via S_1 receptors, serotonin inhibits release of NE, thereby inhibiting vasoconstriction; (4) via S_1 receptors, serotonin activates autonomic inhibitory neurons that cause vasodilation, probably via release of vasoactive intestinal peptide (VIP); and (5) serotonin acts directly on S_1 receptors in smooth muscle to cause vasodilation.[41] (with permission).

TABLE I

Physiologic Actions of Serotonin in Humans

1. Vasoconstriction (S_1, S_2)
2. Vasodilation (S_1)
3. Potentiation of other vasoactive mediators (S_2)
4. Increased inotropy
5. Increased chronotrophy
6. Increased gastrointestinal motility
7. Central sleep regulation
8. Increased blood viscosity/decreased red cell deformability
9. Increased stroke volume
10. Increased pulmonary arterial pressure
11. Increased cardiac output

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blood pressure.[13] In diseased and damaged vessels (commonly seen in the elderly and in hypertensive patients in association with atherosclerosis), the degenerating wall elasticity, as well as the increased pressures and blood turbulence, tend to damage the intima. The vessel wall loses its protective endothelial barrier with its S_1 receptors, as well as the EDRF/NO and, with it, much of the dilator activity of serotonin.[6,8] Therefore, the S_2 receptor will be more or less unopposed by the loss of S_1 dilator activity, resulting in augmented constriction. This may explain a decrease in tachyphylaxis seen with serotonin in the vasculature of hypertensive animals.[8] Additionally, damaged intima tends to adsorb platelets, causing increased release of serotonin, thereby perpetuating the cycle.[1]

Hypertensive patients have been shown to exhibit an increase in β-thromboglobulin, suggesting accelerated platelet turnover.[6] In the hypertensive person,

TABLE II

Agonist Actions Mediated by Peripheral Serotonergic Receptor Subtypes

S_1 Receptor	S_2 Receptor
1. Vasodilation	
2. Inhibition of norepinephrine release	1. Vasoconstriction
3. Endothelial-dependent inhibition of vascular smooth muscle activity	2. Facilitation of platelet aggregation
4. Vasoconstriction (in some arterial beds)	3. Augmentation of other vasoconstrictors: prostaglandin $F_{2\text{-}\alpha}$ norepinephrine angiotensin II histamine

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there is both a diminished ability of platelets to bind serotonin and a decreased platelet survival time.[3] Baudouin-Legros and his group showed diminished platelet levels of serotonin in hypertensive individuals.[14] One interpretation would be augmented release, with decreased uptake of serotonin in the presence of increased platelet turnover in those vessels subject to increased blood pressure and turbulence. This would lead to increased serotonin at sites of platelet aggregation.

Another feature in hypertension that tends to enhance the blood pressure elevating effects of serotonin is the impaired clearing of the monoamine by the monoamine oxidase (MAO) system.[6]

Along with its direct vasoactions, serotonin interacts at another site in the hypertensive scheme. It has known aldosterone-stimulating properties in both man and rat,[15] leading to increased sodium and water retention, and possibly elevating blood pressure by this mechanism.

Central Effects. Serotonin also aids in central blood pressure regulation. Unlike platelet serotonin manufactured in the APUD cells of the gastrointestinal tract, this serotonin is manufactured locally. Radiolabeling studies in the rat[16] localize serotonergic neurons to specific areas of the brainstem, most of which correspond to the raphe nuclei. Two of these areas, the B7 (dorsal) and B8 (lateral) raphe nuclei of the midbrain and the B3 group in the medulla maintain important functions in central blood pressure control.

The B7–B8 group projects to the preoptic area of the hypothalamus. In the normotensive rat, as little as 20 ng of serotonin injected locally in this area produces significant elevations in blood pressure.[17] This hypertensive response can be antagonized by pretreatment with methysergide or metergoline, nonspecific serotonergic antagonists. Additionally, prior depletion of noradrenergic input to this area produces a hypertensive response that requires the presence of a functioning serotonergic system. This suggests an interaction between these two systems at the hypothalamic level. Finally, the output of this system travels, at least partially, through the sympathetic nervous system, as pretreatment of rats with bretylium tosylate, which depletes catecholamines from post-synaptic nerve terminals, attenuates this pressor response.

The medullary group, B3, can be further subdivided into lateral and midline components. The lateral projects to the intermediolateral cell column of the thoracic spinal cord: the cell bodies of preganglionic sympathetic nerves. Electrical or chemical stimulation of this area is associated with increases in systemic blood pressure and in renal nerve activity.[18] Therefore, these serotonergic neurons may increase sympathetic activity. These neurons may also inhibit vagal depressor responses via a projection to the nucleus of the solitary tract, thereby dampening the baroreceptor reflex arc. Evidence exists that methyldopa and clonidine may act by inhibiting these serotonergic neurons.[17] In contrast, stimulation of the midline group leads to a vasodepressor response.[18]

Which serotonergic subtypes are involved in these pathways needs clarification. Most studies used either nonspecific antagonists such as methysergide or synthesis inhibitors such as parachlorophenylalanine.[17] Preliminary evidence suggests that the S_3 receptors do not contribute to the pressor response from the lateral medullary. It would be of great interest to see if different subtypes are involved in the pressor and depressor responses; peripherally, this is the case.

KETANSERIN AS A PROPOSED THERAPY

Ketanserin (Figure 1) is a highly selective S_2-serotonergic antagonist that has been proposed as a therapy

for various cardiovascular diseases, including hypertension. Its vasoactions are complex, and may include additional α-adrenergic blocking properties.

Ketanserin: Mechanisms of Pharmacologic Action

Blockade of the S_2-serotonergic receptor. The majority of ketanserin's pharmacologic activities are attributed to S_2 serotonin receptor blockade. Many studies have documented ketanserin's blood pressure lowering action through its interference with serotonin vasoconstrictive actions. The drug causes a decrease in peripheral vascular resistance.[10,18] It attenuates the pressor response that serotonin exerts on blood vessels.[10,12,19-21] These studies have been done using rats,[19] dogs,[10] and in human mesenteric,[20] peripheral,[21] pulmonary, and cardiac vessels.[12,22] Ketanserin also inhibited the amplification effects of serotonin on norepinephrine, histamine, angiotensin II, and prostaglandin $F_{2\alpha}$ in the rabbit femoral artery.[10] Van Nueten, working with rabbit coronary and cerebral beds, has shown that ketanserin partially blocks the acute augmented constriction to serotonin that occurs with cooling and hypoxia.[11] It inhibited serotonin-induced constriction in human mesenteric arteries, a state that was not entirely reversed by washing. This finding suggests an irreversible component to ketanserin's actions.[20]

In addition to the serotonin receptors found on endothelium and smooth muscle cells, serotonin receptors are also located on the platelets themselves. It is not surprising to learn that ketanserin also inhibits serotonin interactions at this level. Ketanserin may also antagonize the positive feedback of serotonin on its own release; indirect evidence for this comes from the decreased levels of hydroxyindole acetic acid (HIAA). This agent blocks the contractile response caused by platelets in large arteries.[9] It decreases the maximum aggregation velocity of platelets by serotonin, while decreasing serotonin uptake by the platelets.[23]

Researchers now believe that ketanserin, by blocking the S_2-mediated pressor actions of serotonin, also unmasks unopposed S_1 receptor activity, leading to vasodilation.[7,10,24] Unopposed stimulation of S_1 receptors inhibits the release of catecholamines stimulated from post-synaptic adrenergic nerves.[7,13] This, in turn, would reduce α-adrenergic (constrictor) responses.

In several animal experiments using monkey, rabbit, and dog hindleg arteries, ketanserin blocked serotonin-induced vessel occlusion.[9] These results are interpreted in light of the supersensitivity of collateral vessels to serotonin. Hollenberg feels that the nature of the replication in endothelial cells in collateral vessels may alter or reduce the EDRF and unmask the S_2 constrictor receptors.[9]

More recently, several novel S_2 antagonists have been characterized. MCl-9042, LY 53857, and SR 46349, which are more S_2-specific compounds with negligible α_1-adrenoceptor blockade, exhibit potent antithrombotic activity in various animal models.[25-27] Herbert et al.[26] showed that SR 46349 inhibited both 5-HT and epinephrine-induced rabbit and human platelet aggregation in a dose-dependent manner. For rabbit platelets, SR 46349 was 118 times as potent as ketanserin, whereas for human platelets it was 25 times more potent. SR 46349 was also tested for its ability to affect venous thrombosis under thrombogenic challenge, and a dose-dependent antithrombotic effect was seen. These findings further strengthen the notion that serotonin plays a vital role in platelet aggregation and thrombus formation, and suggest the potential use of serotonergic antagonists in various thrombotic diseases.

Alpha-adrenergic blockade. Not all of ketanserin's pharmacologic effects are explained by serotonin antagonism alone. Studies have uncovered evidence both in favor of and against α-adrenergic blocking actions of ketanserin. The research was done using both short-term and long-term administration of ketanserin in animals and humans. After or before ketanserin administration, drugs that interact with α-adrenergic receptors were given. The data were subsequently interpreted to see if there was an interaction between ketanserin and α-adrenergic antagonist or agonist drugs, which included the α-agonists methoxamine and phenylephrine, and the antagonists prazosin and phentolamine.

Studies using methoxamine seem to support a partial α-blocking action for ketanserin. Ketanserin, when administered for a short term to five healthy patients, blocked a methoxamine-induced depression in heart rate and shifted the blood pressure dose-response curve to the right, thus showing the α-blocking action for ketanserin.[22] However, the reported steady-state levels (88.3 ± 19 ng/mL) were on the high side of those reported in other studies.

In a study with 8 hypertensive patients given 40 mg of ketanserin 3 times a day for 6 weeks, the response to methoxamine was suppressed. It was a nonparallel shift, with the greatest effects occurring at the highest rates of methoxamine infusion.[28] Drug levels were not evaluated.

Studies using phenylephrine have shown a less definite role for an α-blocking effect for ketanserin. Several studies have shown a damping effect of ketanserin on the pressor actions of phenylephrine. Ketanserin infusion in animals caused a clear shift in the

subsequent actions of phenylephrine. In a rat, the degree of ketanserin-induced hypotension was highly correlated with the degree of phenylephrine inhibition.[29] In the rabbit, the ketanserin shift appeared very similar to that caused by prazosin. Gasic et al. showed a similar response after a 10-mg ketanserin infusion in 7 healthy young human men.[30] Ketanserin attenuated a phenylephrine-induced rise in blood pressure, but it had no effect on estimated splanchnic blood flow, indicating a difference in the drug's α-blocking component in systemic and splanchnic vascular beds.[30] Serum levels of ketanserin (256 ± 32 ng/mL) were also much higher in this study than those commonly seen therapeutically.

In one study in which 7 normotensive volunteers received 40 mg of ketanserin twice daily (bid) for 4 days, a shift in the phenylephrine response curve was shown. They found a different effect in the morning and afternoon. The morning effect was greatest, as were the morning ketanserin serum levels. In the morning, the serum levels were 108.4 ± 20 ng/mL compared with the afternoon levels of 33.7 ± 2.2 ng/mL.[31] Another group, using 40 mg of ketanserin 3 times daily (tid) for 6 weeks, showed a decreased phenylephrine response only at the highest rates of phenylephrine infusion.[28]

Other studies have found no modification in the phenylephrine responses after an intravenous 10-mg ketanserin infusion.[24,29] Many of these studies, which used prazosin as a control, showed the well-known α-antagonism of prazosin.[24,32] In one long-term study,[33] hypertensive rats received a dose of 17 mg/kg of ketanserin in their food for 6 weeks with no change in pressor response to phenylephrine (the usual adult human dose is 40 mg bid, therefore the rats received approximately 15 times the adult human dose). At the same time, there was a blunting of the serotonin pressor response.

A more recent study by Naslund et al.[34] supports ketanserin's α-blocking properties. Six patients received either ketanserin or prazosin for four weeks with a similar drop in blood pressure. Each group then received phenylephrine until there was a rise of 20 mm Hg in mean arterial blood pressure. The prazosin group required four times the dose of phenylephrine to raise the blood pressure by the same amount. These data suggest that ketanserin's α-blocking activity makes a minimal contribution to its hypotensive actions.

In a recent study, BalaSubramanian et al.[35] showed in spontaneously hypertensive rats that the mechanisms of ketanserin's antihypertensive effect were different during short-term injection as compared with prolonged infusion. Thirty minutes after short-term intravenous administration of ketanserin, the cardiopressor responses to both the α_1-adrenoceptor agonist, phenylephrine, and 5-HT_2 receptor agonist α-methy-5-HT were inhibited in a dose-dependent manner, suggesting that the combination of α_1 and 5-HT_2 were responsible for the short-term antihypertensive action of ketanserin. In contrast, after long-term administration of ketanserin for 7 days, the response to α-methy-5-HT was significantly attenuated, whereas the response to phenylephrine was maintained, implicating 5-HT_2 blockade, probably through a combination of central and peripheral effects, as the predominant mechanism.

In another study,[36] 8 hypertensive patients received both an intrabrachial artery infusion of serotonin and the α_1-adrenoceptor agonist, methoxamine, after placebo, again at 1 hour after a first oral dose of 20 mg of ketanserin, and again after 1 month of treatment with 20 to 40 mg bid of ketanserin. During placebo, the vascular bed in the forearm showed a biphasic response to serotonin; vasodilation at low dose and vasoconstriction only at highest dose, indicating serotonin may not be considered a universal, endogenous pressor agent. The serotonin or methoxamine-evoked vasoconstriction were not affected by either the short- or long-term administration of ketanserin, indicating that both peripheral S_2 and α_1-adrenergic blockade were unlikely for the antihypertensive action of ketanserin. Moreover, increased venous compliance in the forearm was noted after four weeks of ketanserin treatment, which might partially account for its antihypertensive action through a reduction in cardiac preload.

In contrast to ketanserin's role in blocking the effects of α-agonists, α-adrenergic blockers have been assessed for their ability to block the effects of ketanserin. If ketanserin exerts its primary influence by blocking α-adrenergic receptor sites, then prior administration of prazosin, a strong α-antagonist, should block ketanserin's actions. When prazosin was given before ketanserin infusion, it effectively blocked ketanserin's hypotensive actions.[24] Nelson et al. showed similar results for a similar experiment in sheep.[37]

However, evidence against the α-blocking theory comes from work with phentolamine. When administered before ketanserin in a perfused dog heart, this α-antagonist did not interfere with ketanserin-induced inotropic and chronotropic changes.[38]

Some circumstantial evidence supporting ketanserin's α-blocking properties comes from studies of its sister drug, ritanserin. Ritanserin, *in vitro*, is a potent S_2 antagonist, clearly devoid of any α-adrenergic blocking activity. However, this molecule does not have antihypertensive effects *in vivo*. When given to the spontaneous hypertensive rat for eight weeks, it

did not reduce blood pressure or affect heart rate at rest or after jet air stress induction.[19] There was also no change in subsequent response to prazosin.

A trial in humans by Hosie et al.[39] was equally disappointing. In this trial, a single oral dose of ritanserin showed no significant effect on blood pressure in doses sufficient to induce measurable alterations in psychological function. Ketanserin, however, produced significant changes in blood pressure in these same patients.

Strong support proving that α-antagonism is not essential for ketanserin to bring down blood pressure comes from studying individuals with autonomic nervous system failure. In these patients, α-blockade (through drugs such as prazosin) has no effect on blood pressure. Yet, ketanserin can produce hypotensive actions in these people.[24]

Merely showing that ketanserin manifests α-blocking activity does not prove a primary pharmacologic mechanism for the drug of blocking α-receptors. As noted earlier, serotonin, through the S_2 receptor, enhances α-activity.[6] Thus, ketanserin will show α-adrenergic attenuation through serotonergic mechanisms, whether or not it directly blocks α-receptors.

More research is needed to clarify the relative contributions of serotonin and adrenergic blockade to clearly define ketanserin's mechanism of action.

Central Nervous System Actions. As previously discussed, serotonin may play a role in central nervous system (CNS) blood pressure regulation. The absence of reflex tachycardia with ketanserin strongly points to an additional pharmacologic action beyond that of pure peripheral vasodilation.[34,40] Ketanserin's adverse reaction profile suggests that it does penetrate the blood-brain barrier.[41,42] Furthermore, Reimann et al.[42] have shown ketanserin to cause electroencephalographic slowing similar to that of clonidine (a central α_2 agonist). How ketanserin affects central receptors in blood pressure regulation, and whether conventional doses of ketanserin produce sufficient CNS concentrations to produce a blood pressure lowering effect, remain to be determined.

Van Zwieten et al.[43] did selective infusion of ketanserin into cat vertebral and femoral arteries. They showed a more rapid and profound reduction of blood pressure with the former; this response was not altered by pretreatment with either corynanthine (α_1 antagonist) or rauwolscine (α_2 antagonist), thus suggesting a central S_2 receptor component to hypertension regulation. However, pretreatment with atropine attenuated ketanserin's hypotensive activity. This is consistent with the observation that central serotonergic pathways project to the nucleus of the solitary tract to inhibit vagal outflow.

Curiously, ritanserin infusion did not produce significant changes in blood pressure, despite its known lipophilic nature and probable CNS penetration. Ritanserin, unlike ketanserin, does not displace ^{3}H-spiperone (which labels S_2 receptors) from brainstem S_2 receptors in the rat, and shows somewhat different binding specificities than ketanserin, perhaps suggesting subtypes of 5-HT_2 receptors.[10]

Another explanation for the discrepancy between ketanserin and ritanserin may relate to the former drug's α-blocking properties. Ketanserin may block central α_1 receptors,[10] a property not shared by ritanserin to any significant extent. This is difficult to reconcile, though, because corynanthine antagonism did not alter ketanserin's central hypotensive effects. However, McCall and Harris[40] measured inferior cardiac nerve activity as a gauge of sympathetic outflow in cats treated with prazosin and ketanserin. They found that ketanserin inhibited sympathetic nerve discharge when given alone, but had no additional effect in animals pretreated with prazosin. Additionally, the S_2-specific antagonist, LY 53857, had no effect on sympathetic outflow. This strongly suggests that ketanserin mediates its central effects via α-receptors. Finally, in human brain tissue, {3H} ketanserin shows significant binding to central α_1 receptors in concentrations obtained by current treatment regimens.[44]

Recently, the hypothesis that the absence of reflex tachycardia indicates a central effect of ketanserin has itself been questioned. Berdeaux et al.[45] studied the effect of ketanserin on the baroreceptor reflex in normal individuals. They found that ketanserin, even in doses capable of lowering blood pressure in normotensive individuals, had no effect on baroreceptor sensitivity to either hypotension induced by nitroglycerin or to hypertension induced by phenylephrine. It was the authors' opinion that the absence of reflex tachycardia after ketanserin administration was due to its specificity for peripheral α_1 receptors without significant α_2-blocking activity similar to prazosin.

In summary, ketanserin probably displays some CNS actions, because it does not produce reflex tachycardia in accordance with its hypotensive effects. The mechanism of this central action may be via either α-adrenergic or serotonergic receptors.

Hemodynamic Effects (Table III). Ketanserin has been shown in both short- and long-term treatment studies to lower blood pressure. After intravenous infusion of ketanserin, both systolic and diastolic pressures promptly fall.[22,29,30,46] With long-term use for

TABLE III

Hemodynamic and Metabolic Actions of Ketanserin Treatment in Hypertensive Patients

Function	Acute Therapy	Chronic Therapy
Hemodynamic		
Systemic blood pressure	↓	↓
Peripheral vascular resistance	↓↓	↓
Heart rate	↑*	↔
Cardiac output	↑↔*	↔
Stroke volume	↔	↔
Pulmonary artery pressure	↓↔	↔
Pulmonary wedge pressure	↓↔	↔
Myocardial contractility	↑↔*	↔
Venous capacitance	↑	↑
Metabolic		
Plasma renin activity	↑↔*	↔
Plasma catecholamines	↑*	↔
Plasma aldosterone	↔↓	↔
Urinary Na^+ excretion	↑	↔

*↑ = increase; ↓ = decrease; ↔ = no apparent change; * reflex responses to acute vasodilation with ketanserin.*
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months, no tolerance to the blood pressure lowering effect is seen.[47] Vasodilation appears to be the mechanism by which ketanserin lowers blood pressure[18,22,24,28,29,46–48] in both short- and long-term studies.

As a vasodilator, ketanserin increases regional blood flow to the kidney, gastrointestinal tract, heart, brain, bones, and skin.[24] Coronary blood flow does not appear to be influenced by ketanserin therapy.[22,49] As a consequence of its vasodilator action, ketanserin is associated with modest retention of fluid and weight gain (approximately 1 kg).[24,50,51] The greatest weight gains are seen with the more dramatic hypotensive responses.[52] Because of a hemodilution effect, ketanserin is often found to cause small reductions in blood hematocrit.[53]

Similar to observations made with other vasodilators, ketanserin can cause an increase in heart rate with short-term intravenous administration.[13,46] However, this increase in heart rate is transient, and is not seen with long-term ketanserin treatment.[24,50,54] Furthermore, more recent studies do not show this reflex tachycardia even with intravenous administration.[12,22,24,55,56]

Ketanserin appears to have no effect on cardiac output and its physiologic rise with exercise.[24] Stroke volume is apparently not affected.[12] Right atrial pressure may fall modestly with short-term ketanserin usage, possibly related to venodilator actions.[24,32] Pulmonary capillary wedge pressure may fall (probably owing to reduced afterload) or remain at pretreatment levels.[24,28,29,57,58]

Ketanserin has no apparent direct effect on myocardial contractility[22,48,59]; however, there may be an inotropic effect due to reflex sympathetic tone.[17,38,60] The drug can lower pulmonary artery pressure for a short term,[24,29,47] but with long-term treatment no change in pulmonary artery pressure is seen.[24,28]

Essentially, ketanserin behaves as a peripheral vasodilator with little or no direct effect on the heart.

Electrophysiologic Actions. One potentially adverse effect of ketanserin is prolongation of the ECG QT_c interval. Saman et al.[59] noted prolongation of action potentials consistent with class III antiarrhythmic activity in a rat heart model.

Kamiya et al.,[61] looking into the short- and long-term effects of ketanserin on the electrophysiologic properties of rabbit myocardium, noted that ketanserin behaves on the short term as both a class I and mild class III antiarrhythmic drug. With long-term use, it displays primarily class III actions, showing prolongation of repolarization and an increase in action potential duration. It delays conduction and prolongs refractiveness by both time- and voltage-dependent mechanisms. The study concluded that ketanserin has potential for both suppression and aggravation of cardiac arrhythmias.

Zaza et al.[62] showed an increase in action potential duration in canine Purkinje fibers and myocardium. They showed QT_c prolongation and class III antiarrhythmic effects. In addition, ketanserin facilitated torsade de pointes during epicardial aconitine administration. However, they concluded that ketanserin alone was unlikely to cause torsade de pointes, as it did not increase arrhythmogenicity in absence of other factors, such as hypokalemia.

The initial clinical trials did not show any adverse electrocardiogram (ECG) effects. However, Cameron et al.[63] recently reported a 4 to 10% increase in the QT_c interval in 3 separate studies involving 81 patients. They did not find other ECG abnormalities. A modest but significant effect on the QT_c interval was shown by Nademanee et al.[64] after intravenous ketanserin in 10 patients referred for electrophysiologic study. They noted no effect on His-Purkinje conduction time or ECG QRS duration (type Ia activity). Decreases in atrioventricular nodal conduction time, sinus node recovery time, and the atrial refractory period, consistent with a reflex increase in catecholamines, were also seen.[64] The minor degree of QT_c prolongation seen was not considered clinically significant.

In keeping with these observations, Zehender et al.[65,66] specifically examined QT_c prolongation after 4 weeks of ketanserin administration in 221 patients. They noted an average increase from 400 to 418 milliseconds, with a 30% incidence of QT_c prolongation greater than 30 milliseconds. Twenty-four–hour Holter monitoring failed to reveal a correlation between the amount of prolongation and an increase or decrease in ventricular arrhythmias.

Prolonged QT_c interval carries a risk of subsequent torsade de pointes. Thus far, studies have not shown increased arrhythmia-related deaths from ketanserin. Aldariz et al.[67] reported one case of presumed ketanserin-induced torsades (this patient did have underlying second-degree heart block before initiating therapy). They also noted increased QT_c (5–30%) in 5 of 6 patients treated orally with ketanserin for hypertension.

More recently, evidence from the Prevention of Atherosclerotic Complications (PACK) trial[68] implicates ketanserin's QT_c prolongation as a factor in patient mortality. This study prospectively observed a cohort of patients with intermittent claudication. The study was designed to examine the possibility that ketanserin protects against vascular morbidity. However, the group receiving ketanserin experienced a significant mortality excess that correlated with QT_c prolongation. When the data were analyzed more closely, it became apparent that the mortality was highest in the group receiving non–potassium-sparing diuretics. In summary, ketanserin's adverse arrhythmogenicity, though probably not significant when the drug is used as monotherapy, may potentially manifest itself when the drug is combined with diuretics. Hypokalemia is known to predispose to torsade de pointes. Although there was no documentation of torsade de pointes, the possibility that ketanserin combined with hypokalemia leads to torsade, and sudden death, cannot be overlooked.

Hemorheologic and Antiplatelet Properties of Ketanserin

Blood Viscosity. Ketanserin may increase organ perfusion because of favorable rheologic effects. Several investigators have shown reduced blood viscosity with the drug.[69,70] The drug may increase red blood cell deformability,[57] an opposite effect from serotonin, allowing for better flow through constricted blood vessels.

Many of these favorable hemorheologic effects could also be explained through fluid retention and hemodilution. De Clerck et al.,[71] studying aged dogs, found that when they adjusted for the effects of hemodilution by concentrating the red cells and resuspending them in equal volumes of autologous platelet-poor plasma, ketanserin lost its effect on viscosity.

Platelets. Ketanserin affects platelet aggregation in response to a variety of mediators, with both short- and long-term treatment. It generally inhibits aggregation, but not all studies show the same effect. De Clerck and Xhonneux, looking at 6 patients, did not show an effect of ketanserin on collagen-induced platelet aggregation, either short-term (after 90 minutes) or long-term (1 week of 40 mg bid).[72] However, two other groups showed a prolongation in collagen-induced aggregation time in patients treated for six weeks[53] with ketanserin.

De Clerck and Xhonneux[72] and Zannad et al.[69] showed no effect of short-term ketanserin therapy on adenosine diphosphate (ADP) induced platelet aggregation. De Clerck and Xhonneux[72] also showed no long-term effect. However, other studies found a retardation of ADP-induced aggregation after long-term ketanserin administration of six weeks[53] and one month.[70]

Several researchers showed a decrease in serotonin-induced platelet aggregation after both short- and long-term ketanserin treatment in patients with either peripheral vascular disease or recent myocardial infarction.[5,23,53,69,71,73] Ichikawa's group showed this in canine coronary vessels.[49] A hypersensitive platelet response to serotonin aggregation after the seventh day on ketanserin has been described; this effect was corrected by giving an additional dose of ketanserin.[73] This hypersensitivity suggests an upregulation of serotonin platelet receptors.

Epinephrine-[69] and collagen-induced[53,73] platelet aggregability are also reduced with ketanserin treatment.

Metabolic Actions of Ketanserin (Table III)

Renin Angiotensin System. Ketanserin affects the renin-angiotensin-aldosterone (RAA) axis, sodium metabolism, and plasma catecholamines, which may influence its pharmacologic effects. Various investigators have examined the effects of both serotonin and ketanserin on control of renal blood flow and the RAA axis, and not surprisingly, with different findings. Wenting et al.[46] administered a 10-mg dose of ketanserin intravenously to 12 patients with hypertension, and measured renal plasma flow and glomerular filtration rate (GFR) by clearance of ^{131}I-hippuran and I-thalamate, respectively. They found a decrease in renal vascular resistance but no major change in effective renal plasma flow or GFR. Renin concentration, initially low, rose significantly. Another study[24] also examined the effect of infused ket-

anserin in hypertensive patients and found an increase in renal blood flow, also with no change in GFR. This study too showed an increase in serum renin levels. Two long-term studies showed no change in renal perfusion[24] or GFR.

Another study looked at the long-term effects of ketanserin after three weeks of therapy,[24] and showed a reduction in plasma renin. Two additional studies, one long-term[23] and one short-term[74] found no significant effects on renin concentration.

Over the long term, ketanserin may decrease angiotensin levels.[21] However, Zabludowski et al.[74] found no such change after short-term administration. Likewise, Woittiez et al.[75] saw no effect after eight weeks of therapy.

Investigators reported no effect of ketanserin on circulating levels of aldosterone after short-term[15,24,46] and long-term[23,24] administration. One study used intravenous ketanserin infusion in patients with primary hyperaldosteronism[15] whereas the others involved subjects with essential hypertension. However, deLeeuw and Birkenhager reported that in the long term, ketanserin lowers plasma aldosterone levels.[21] Ketanserin, when given before serotonin, blocked the latter drug's ability to effect aldosterone augmentation. Ketanserin also inhibits the aldosterone release by potassium, angiotensin, and to some extent, adrenocorticotropic hormone (ACTH). Perhaps ketanserin may act at the zona glomerulosa to suppress serotonin or angiotensin II receptors.[76]

Clearly, much more work is needed to determine the role of serotonin, and thus, ketanserin in influencing the RAA system.

Sodium Metabolism. In some forms of essential hypertension, there is a tendency for the body to retain sodium, and an increase in sodium content has been seen in the red blood cells of hypertensive individuals.[57] According to De Cree et al.,[57] ketanserin given orally for one week lowered the intracellular sodium concentration of red blood cells. Lijnen and coworkers[77] made similar observations. These investigators showed a decrease in intracellular sodium, but not potassium content, after one week of ketanserin therapy. They could not show a short-term change in the cell content of sodium, lithium, or potassium, though there was a short-term decrease in ouabain-sensitive ^{86}Rb uptake. After 6 weeks of ketanserin therapy, Wing and associates[78] showed a 24-hour increase in urinary sodium and a decrease in potassium excretion. Lijnen et al.[77] believe that serotonin has an effect that is inhibited by ketanserin in the adenosine triphosphate (ATP) Na/K co-transport regulation of ion transport across cell membranes. Ketanserin may also interfere with the production of angiotensin II, leading to a decrease in aldosterone, and thereby, a decrease in the sodium/potassium exchange at the distal convoluted tubule of the kidney. There is also an additional aldosterone-suppressing effect, as mentioned.

Catecholamine Release. Serotonin can cause a displacement of norepinephrine from post-synaptic nerve terminals. Several investigators have shown that ketanserin can mimic this action in both patients with hypertension and congestive heart failure.[24,46,64]

Several studies have shown that with short-term ketanserin treatment, patients show an increase in heart rate mediated by a reflex increase in catecholamines.[3,38] With long-term therapy, however, the heart rate decreases toward pretreatment values and the catecholamine discharge dissipates.[50,54]

In the exercising patient, ketanserin does not appear to blunt increases in catecholamine levels or exercise performance.[21,24] Ketanserin has also been reported not to blunt exercise-induced increases in heart rate, blood pressure, or norepinephrine levels.[54] However, ketanserin does appear to depress the pressor response to isometric exercise, which is highly dependent on sympathetic tone.[54]

Pharmacokinetics of Ketanserin

Ketanserin lends itself to a simple oral dosing regimen. The drug is completely absorbed by the gastrointestinal tract.[79] However, the liver exerts a considerable first-pass metabolic effect to give ketanserin an oral bioavailability of approximately 50 to 60%.[80] Its volume of distribution, as measured by Hedner et al.[79] and Amery et al.,[80] is 6.73 ± 1.06 and 7.5 L/kg respectively. Amery also determined that 94% of the drug is protein-bound in the plasma.[80] When the molecule is given intravenously, it follows a tri-exponential decay pattern; when delivered orally, it follows a bi-exponential pattern.[79] Most is metabolized in the liver.[3] The liver enzymes either oxidize the molecule to 6-hydroxy ketanserin, or reduce it to ketanserinol.[79,80] Therefore, patients with kidney failure require no reduction in dosage. There are no active metabolites. Hedner and his associates found two distinctive patterns for the body's elimination of ketanserin.[79] After a single oral dose, the half-life was approximately 9 hours. After long-term therapy of one week to establish the steady-state conditions, they found the half-life to be 24.7 ± 2.6 hours. They suggest that ketanserin might be effective as a once-daily regimen.

THERAPEUTIC EXPERIENCES IN HYPERTENSION

A vast clinical experience has now been accumulated with ketanserin as an antihypertensive agent.[3,48,51,70,81–83] For the most part, the drug has been shown to be effective in reducing diastolic blood pressure with less impressive efficacy in treatment of systolic blood pressure.[48,84] The reported clinical research experiences with ketanserin are described below.

Intravenous Studies

In an early trial, De Cree et al.[13] gave 10 mg of intravenous ketanserin to 23 patients with mild hypertension. They saw a mean decrease in blood pressure from baseline values of 185 ± 5/99 ± 3 mm Hg to 152 ± 5/82 ± 3 mm Hg with no associated increase in heart rate. Wenting et al.[46] noted a similar blood pressure lowering effect with intravenous ketanserin in 12 patients, with the effect sustained for 2 hours after dosing. During hemodynamic monitoring, these authors concluded that ketanserin's main mode of action was by lowering peripheral vascular resistance. Similar results were seen by Zabludowski et al.[74]

Placebo-Controlled Oral Treatment Studies

Most clinical trials show a beneficial effect of ketanserin used either as monotherapy[24,53] or in combination with β-blockers or diuretics.[51,78,85] The results of these studies are summarized in Table 4.

Studies also provide evidence that ketanserin has its greatest antihypertensive efficacy in the elderly, where serotonin stimulation of the S_2-serotonergic receptors may be more important.[3,13,86–89] The degree of change seen in both systolic and diastolic blood pressures appears to be directly related to the level of pretreatment blood pressure and patient age.[90]

Comparative Studies

Beta-Adrenergic Blockers. Palermo et al.[91] compared ketanserin (40 mg bid) with metoprolol (100 mg bid) in a 3-month study of 40 patients. These investigators reported that 68% of patients showed a blood pressure reduction with ketanserin and 50% achieved a normal blood pressure value. In contrast, 50% of patients responded to metoprolol and only 30% normalized. Milei et al.[92] studied the 2 drugs in 24 patients for 3 months, and concluded that ketanserin might have a greater efficacy advantage, as did Hedner et al.[86] in a similar comparative study.

Ferrara et al.[48] described a discrepancy between reduction in diastolic blood pressure with ketanserin and its apparent lesser effect on systolic blood pressure in a comparison study with metoprolol. Ketanserin showed no significant effect in reducing systolic blood pressure, though diastolic blood pressure was normalized in 87% of the patients studied. Metoprolol showed significant effects on both systolic and diastolic blood pressures, and a greater reduction in heart rate. During exercise testing, metoprolol blunted the increments in heart rate and systolic and diastolic blood pressures, whereas ketanserin mainly affected diastolic blood pressure. They corroborated these findings in a second study.[84]

Ketanserin has also been compared with other β-blockers, including propranolol, atenolol, and pindolol. Staessen et al.[90] conducted a large-scale comparison of 40 mg bid of ketanserin and 80 mg bid of propranolol in 331 hypertensive patients. In their interim report, they noted that at two months, systolic blood pressure was significantly lower on propranolol than on ketanserin. At three months, however, the difference was not statistically significant. Similarly, for diastolic blood pressure, there was a statistically significant difference ($P < .05$) in favor of propranolol at one month, but thereafter a similar reduction in both treatment groups. This is consistent with the findings of Milei et al.[92] who noted a delayed maximal effectiveness of ketanserin. Additionally, it suggests a greater effectiveness of ketanserin on diastolic blood pressure as opposed to systolic blood pressure, as noted by Ferrara et al.[48] Of interest is that a significant association between change in body weight and the change in both systolic and diastolic blood pressures with ketanserin was noted. Greater increases in body weight were associated with smaller decreases in blood pressure. With respect to side effects, both drugs were generally similar. However, after three months of active treatment, patients with multiple complaints were represented in a greater proportion in the ketanserin than in the propranolol group. Additionally, xerostomia was noted only with ketanserin, and this difference was statistically significant at one month.

In a placebo run-in, double-blind, randomized comparison study, our group showed that propranolol, in doses of 40 to 80 mg bid, was significantly more effective than ketanserin 20 to 40 mg bid, in reducing systolic and diastolic blood pressures in patients with systemic hypertension.[93] The lack of an antihypertensive effect with ketanserin was seen despite achieving ketanserin blood levels in the previously documented therapeutic range.[93]

When comparing pindolol 5 mg bid with ketanserin 40 mg bid in a 17-patient crossover trial, both

TABLE IV

Placebo-Controlled Studies of Oral Ketanserin in Hypertension

Study	Dose	Duration	Position	Starting Blood Pressure	Ending Blood Pressure
Cameron & Ramsaey[51]	20–40 mg BID	7 weeks	Supine K	170.1/105.3	160.0*/96.2*
			Supine P	170.3/107.4	ND
			Standing K	160.4/106.9	143.9*/95.6*
			Standing P	163.4/108.9	ND
Wing et al[78]	40 mg TID	6 weeks crossover	Supine K	ND	145*/84**
			Supine P	ND	152/88
			Standing K	ND	143*/89***
			Standing P	ND	152/95
Woittiez et al[73]	40 mg BID	8 weeks	Supine K	168 ± 5/107 ± 3	158 ± 5**/98 ± 2*
			Supine P	same pool	164 ± 6/104 ± 3
			Standing K	160 ± 5/158 ± 5	154 ± 4/104 ± 2*
			Standing P	same pool	158 ± 5/112 ± 3
Fagard et al[18]	40 mg BID	6 weeks crossover	Supine K	ND	142 ± 12*/77 ± 2*
			Supine P	ND	150 ± 6/84 ± 4
Amery et al[53]	40 mg BID	6 weeks crossover	Supine K	ND	153 ± 3*/97 ± 2***
			Supine P	ND	159 ± 3/104 ± 2
			Standing K	ND	155 ± 3**/106 ± 2*
			Standing P	ND	160 ± 4/114 ± 3

*BID = twice daily; TID = three times daily; K = ketanserin; P = placebo; ND = no data; * = P < .01, ** = P < .05; *** = P < .001. Adapted with permission.*[41]

drugs reduced blood pressure, with no reduction in heart rate seen.[94]

When once-daily atenolol (100 mg) was compared with ketanserin (20–40 mg bid) in a small parallel study of hypertensive patients, both drugs were effective. The 40-mg ketanserin daily dose provided no advantage over the 20-mg dose.[23]

In summary, the comparative effects of ketanserin to β-blockers in hypertensive patients show a mixed picture. Studies tend to support a comparable diastolic blood pressure lowering effect with the two drugs, a greater effect on systolic blood pressure with β-blockers, and a greater effect in reducing heart rate with β-blockers.

Alpha-Adrenergic Blockers. Ketanserin has been compared with prazosin in multiple clinical studies. Stokes et al.[95] did a crossover trial comparing 2 mg prazosin to 40 mg ketanserin in 15 patients. Comparable blood pressure lowering effects were seen. Rosenthal et al.[96] compared increasing doses of prazosin (up to 3 mg bid) with ketanserin (20 or 40 mg bid) and noted similar blood pressure lowering effects with the 2 drugs. The maximal effect of ketanserin was achieved at the 20-mg bid dose level.

Hydrochlorothiazide. Only one study reports on a comparative experience with hydrochlorothiazide versus ketanserin.[86] Both drugs were shown to be equally effective for a three-month treatment period. Sixty-five percent of patients responded to ketanserin 40 mg bid, and 68% to the diuretic.

Nifedipine. Hannedouche et al.[97] compared ketanserin with slow-release nifedipine in a multicenter trial in patients older than 50 years of age. If a patient's blood pressure failed to normalize, they received a diuretic. Forty-seven out of 53 (89%) patients who tolerated nifedipine, normalized on nifedipine monotherapy, whereas only 37 of 52 (71%) ketanserin patients did so. Nifedipine patients showed an increase in heart rate not seen with ketanserin. Ketanserin and the calcium antagonists show increased efficacy in the elderly, accounting for the high overall response rate. However, examination of the data showed that 3 of 4 centers reported 100% overall response (mono or combination therapy), an unprecedented finding. As the authors point out, the single-blind nature of the study (i.e., ketanserin and nifedipine tablets were not identical) may have altered the results.

Angiotensin-converting Enzyme Inhibitors. Malatino and colleagues[98] compared ketanserin with enalapril

in a 3-month placebo run-in, active control, double-blind, randomized, parallel design, comparative trial in 30 patients, 50 years of age and older. Both drugs were effective in reducing blood pressure and were equally well tolerated.

Methyldopa. Zin et al.[99] compared ketanserin with methyldopa in an international multicenter trial in patients over 50 years of age. As with prazosin, comparisons with methyldopa relate to physiologic perspectives. Just as ketanserin's similarities to prazosin suggest α-adrenergic activity, so too ketanserin's physiologic similarities to methyldopa suggest central antihypertensive activity. As discussed earlier, a portion of methyldopa's action may be on central serotonergic neurons that regulate sympathetic outflow.[16] Zin et al.[99] found that more ketanserin patients normalized their blood pressure than methyldopa patients (75% versus 49%).

Combination Therapy. Several studies show ketanserin to be effective in combination with either β-blockers, angiotensin-converting enzyme inhibitors, or diuretics. Cameron and Ramsay,[51] in a placebo-controlled trial of ketanserin that included 14 patients already on atenolol (n = 7) or bendrofluazide (n =7), noted no difference between the 2 when combined with ketanserin.

Wing et al.[78] conducted a similar trial with 17 patients, 13 of whom were on pre-existing therapy. Although, for the group as a whole, there was a significant decrease in blood pressure, the only significant individual changes occurred in those patients already on therapy. (The observed absence of ketanserin's hypotensive effect may be owing to the small size of the monotherapy group.) This suggests ketanserin to be more effective in combination.

Beretta-Piccoli et al.[100] saw similar results when they compared the efficacy of 20 to 40 mg bid of ketanserin with placebo in 3 patient groups: 68 patients on monotherapy, 30 on atenolol, and 26 on hydrochlorothiazide 50 mg/amiloride 5 mg. Almost equal efficacy was seen in all 3 treatment groups, with normalization rates of 49%, 50%, and 56%, respectively, after 12 weeks. However, a greater percentage of patients required the higher dose of ketanserin in the monotherapy group (69% versus 47% and 44%). Older patients (>60 years) showed higher efficacy in all 3 groups, with the most profound change seen in diuretic combination (59%, 57%, and 67%, respectively). No significant effects were seen in the placebo group.

In contrast, our group, in the blinded study described previously,[93] could not show a significant additional blood pressure lowering effect when ketanserin was added to propranolol in hypertensive patients measured in the sitting position. Conversely, the addition of propranolol to ketanserin was associated with an additional blood pressure lowering effect, suggesting again that ketanserin used twice daily may not be effective as an antihypertensive drug.[93]

None of these trials specifically compared the effect of the combination in placebo-controlled fashion. Hedner and Persson[50] conducted the first placebo-controlled combination trial. Ten male patients on β-blockers (5 on metoprolol, 4 on propranolol, 1 on pindolol) whose diastolic blood pressures were between 95 and 115 mm Hg, were randomized to 40 mg bid of ketanserin or placebo in a crossover trial. After 4 weeks, ketanserin reduced the blood pressure by $19 \pm 3.6/12 \pm 1.2$ in the supine position, and $14 \pm 4.5/13 \pm 2.0$ in the standing position.

In a randomized, double-blind study, the antihypertensive efficacy of the combination of ketanserin (40 mg bid) and captopril (50 mg bid) was compared with ketanserin or captopril monotherapies in 12 patients with uncomplicated moderate systemic hypertension.[101] These patients received each treatment for one month. Both ketanserin and captopril monotherapies significantly reduced blood pressure compared with placebo, whereas the combination had an even greater blood pressure lowering effect, indicating an additive antihypertensive effect of these two drugs.

The combination of ketanserin with thiazide has been studied very extensively. Ferrara et al.[102] compared 20 mg of ketanserin plus 25 mg of hydrochlorothiazide with 40 mg of ketanserin plus 12.5 mg of hydrochlorothiazide in a once-daily dose. They found both regimens effective in controlling diastolic blood pressure, but only the former group displayed a significant effect on systolic blood pressure. The former dosing showed adequate control for 24 hours, whereas the latter group maintained its hypotensive effects for only 8 hours. One problem with this study is that these patients may not have been refractory to hydrochlorothiazide monotherapy. Thiazide monotherapy may easily account for these results.

In a separate study, Ferrara et al.[103] compared the antihypertensive efficacy of 40 mg of ketanserin used alone with 25 mg of hydrochlorothiazide, and the combination of 40 mg of ketanserin with 12.5 mg of hydrochlorothiazide in 20 patients with mild to moderate hypertension. They found that ketanserin induced a significant fall in systolic and diastolic pressures for up to eight hours, whereas thiazide failed to cause any change in pressure. The combination, when first used, caused significant reductions in both systolic and diastolic blood pressures for up to 10

hours. After 6 weeks of long-term treatment with the combination, an additional fall in blood pressure was noted; however, adequate control of blood pressure was maintained only for up to 8 hours, suggesting that this combination, given once daily, is not sufficient to normalize blood pressure on a long-term basis.

Leary et al.[104] noted equal efficacy of ketanserin monotherapy (40 mg once daily) and the ketanserin-hydrochlorothiazide (40 mg + 25 mg once daily) combination in 21 patients after 12 weeks. However, they noted that the patients receiving combination therapy showed more rapid reduction of blood pressure early in treatment, though after 12 weeks both combination and ketanserin monotherapy showed similar reductions. Previous studies found once-daily ketanserin effective in lowering blood pressure, although it showed an inferior degree of control for 24 hours.

In summary, ketanserin seems to be very useful in combination with other drugs. The diuretic-ketanserin combination seems to be uniquely suited to elderly patients. Additionally, ketanserin monotherapy has been associated with an increase in weight that, according to some studies, negatively correlates with efficacy. The addition of a diuretic to ketanserin may counteract this weight gain and may allow for once-daily dosage as opposed to the more conventional two or three times daily regimen. However, as noted above, the diuretic-ketanserin combination may have adverse electrophysiologic effects that may be of concern.

Long-Term Hypertension Control

The studies described above examined the antihypertensive effects of ketanserin for up to three months. However, in some trials, ketanserin was continued as an open-label drug or compared with an active control drug for up to one year in double-blind studies. Most studies have reported continued antihypertensive efficacy of ketanserin after initial responses were seen,[91,105] and in some instances, a greater effect over time.[92] In one study, the initial effectiveness of ketanserin was lost over time (12 months), despite increasing doses of ketanserin.[70]

Use in Severe Hypertension

Jennings and Opie[106] used intravenous ketanserin to treat eight patients with severe hypertension in their dose-response study. They found that 4 of 8 patients responded favorably to repeated 5-mg boluses, 2 responded partially, and 2 not at all. The mean response time was approximately 30 minutes. Three patients responded within 2 minutes of the first bolus, whereas 3 responded only after 50 to 70 minutes. All eight patients studied described symptoms of fatigue of varying degrees. In a double-blind comparison by the same investigators of ketanserin and placebo in severe hypertension, using 10-mg intravenous boluses in 12 patients, a mean ketanserin dose of 28 mg was required to control blood pressure (diastolic pressure < 100 mm Hg). Side effects were frequent, with dizziness and somnolence seen in almost all patients. The antihypertensive effect was only transient, and the investigators concluded that ketanserin would be inferior to other blood pressure lowering regimens in treating hypertensive urgencies and emergencies.

In contrast, Murphy and associates[107] showed a good blood pressure lowering response to intravenous ketanserin in severely hypertensive patients. The effects of therapy were maintained for more than 6 hours using a 4 to 20 mg/hr drug infusion, and the response rate compared favorably with those of clonidine, diazoxide, and labetalol. Also, few side effects were seen.

Milei et al.[56] confirmed Murphy's positive results. Milei's group compared the intravenous and intramuscular routes of administration in patients with essential hypertension (supine diastolic blood pressure > 110 mm Hg). The dose (5 or 10 mg) and route of administration (intramuscular versus intravenous) depended on symptomatology (headache, dizziness, blurred vision, vomiting, confusion, and somnolence). The more hypertensive patients tended to have more symptoms. Five and 10 mg by both routes of administration provided excellent responses within 60 minutes. The intravenous infusion of 10 mg led to more rapid responses (92% response rate after 10 minutes). Intramuscular injection produced no side effects, whereas 5 of 31 patients complained of dizziness or somnolence after intravenous administration. The hypotensive response persisted up to two hours. The authors concluded that ketanserin would be a useful agent in managing severe hypertension.

No simple explanation accounts for the differing results of these trials. Although the patients in the Jennings/Opie trial[106] all had essential hypertension; compared with only 4 of 20 in Murphy's group,[107] all 4 of these patients responded reasonably well. Additionally, Milei's patients all had essential hypertension and they responded well. Therefore, ketanserin should be a suitable agent for severe hypertension in either the intramuscular or intravascular route, depending on symptom severity.

Hyperaldosteronism. Intravenous ketanserin has

been used to treat patients with hyperaldosteronism; and good blood pressure control was seen.[15] The mechanism of action of ketanserin in this setting is unknown, because aldosterone levels were not lowered. Ketanserin may not provide any advantage in this condition over other antihypertensive regimens.

Preeclampsia. Astrom and Samelius[1] in 1957 first suggested a role for serotonin in the etiology of preeclampsia when they saw its potent vasoconstrictive action in human placental tissue. Abnormal platelet studies and decreased platelet serotonin concentration[17] provided the rationale for using a serotonin antagonist to treat pregnancy-induced hypertension.

In animal models, Furuhashi et al.[108] showed that ketanserin significantly reduced placental blood flow in both spontaneously hypertensive and normotensive rats. After ketanserin treatment, the placental and fetal weights of normotensive rats decreased significantly in a dose-dependent manner, whereas the hypertensive group showed no significant changes in either placental or fetal weight. Two studies have been conducted on the postpartum treatment of preeclampsia.

Weiner et al.,[109] in a double-blind crossover trial, found that a ketanserin infusion reduced blood pressure from an average of 167/105 to 126/71 versus 157/98 to 150/91 for placebo. Overall, 18 of 20 patients reached the therapeutic goal of diastolic blood pressure less than 95 mm Hg. When comparing pure preeclampsia (not associated with chronic or essential hypertension) with superimposed preeclampsia, they showed a significantly greater absolute change and percentage change in the former group: 10 of 11 achieved normalization for age (diastolic blood pressure 60 to 70 mm Hg) versus 3 of 9 in the latter group. This greater absolute response occurred despite lower starting blood pressures (higher blood pressures usually respond more dramatically to medication). This suggests that ketanserin has some specificity for preeclampsia, as serotonin may be a significant mediator of it.

A slightly different study by Montenegro et al.[110] in 30 postpartum preeclamptic patients grouped the subjects by severity. After adjusting for the effects of placebo, ketanserin worked more effectively in mild than in severe preeclampsia. They concluded that although ketanserin is effective in preeclampsia, serotonin is not a factor in its severity. One difficulty with this conclusion is that the authors made no distinction between pure preeclampsia and superimposed preeclampsia. They clearly attempted to include mainly the pure form, as 73% of the patients were primiparous, and the mean age was 21.5 years (reducing the likelihood of having chronic hypertension). However, this is an imperfect exclusion criteria. As suggested by Weiner et al.,[109] ketanserin may be less effective in cases of superimposed preeclampsia, and this may explain, in part, its decreased effectiveness in those cases of severe preeclamptic hypertension.

Postpartum studies address only the maternal aspects of the condition. The fetoplacental insufficiency of preeclampsia also jeopardizes the fetus. Conventional vasodilator therapy may compromise the fetus by reducing the pressure head on the already damaged placental vessels. Because serotonin causes potent placental vasoconstriction, researchers hoped that ketanserin would block this action, improving placental blood flow.

Hulme and Odendaal[111] conducted an open trial of intravenous ketanserin in 16 patients with severe preeclampsia during labor, and saw beneficial reductions of maternal blood pressure. They found no changes in long-term fetal heart rate variability or fetal acceleration patterns. Four patients showed an improvement in variable decelerations concurrent with decreased uterine activity. These results suggested that at least for the short term, ketanserin could reduce maternal blood pressure without compromising placental blood flow, because the rate of accelerations did not change. Additionally, ketanserin may improve placental circulation by inhibiting uterine contractions. This could potentially cause an adverse effect on the progression of labor (not seen in this small study). The study's conclusions must be interpreted cautiously, because the patients simultaneously received nonstandard doses of meperidine, oxytocin, and magnesium sulfate, whose effects on blood pressure and uterine contractility were not accounted for.

Preliminary data on oral ketanserin use in ambulatory patients during the third trimester has been reported by Voto et al.[112] In comparison with methyldopa (10 patients in each group), they saw significant improvement in blood pressure in both groups. In this small sample they recorded less favorable outcomes for the ketanserin group in terms of Apgar scores and morbidity; they saw one incidence of neonatal death in the ketanserin group. Further studies are certainly needed. It would also be useful to have results of fetal monitoring to show a lack of detrimental fetal effects.

In conclusion, intravenous ketanserin appears to be a safe and effective therapy for postpartum preeclampsia, at least in its mild forms. It holds promise as peripartum therapy, in both intravenous and oral formulations, because it does not appear to compromise placental flow; however, further studies are

needed to confirm its safety, particularly in the oral formulation.

Clinical Use in Hypertension

Dosing Regimen. Varying dosing regimens have been proposed for ketanserin in the treatment of systemic hypertension. Doses ranging from 20 mg once daily to 60 mg tid have been employed with varying results. A 60-mg tid dose has been associated with intolerable side effects, including orthostatic hypotension, dizziness, and fatigue.[105]

In studies using 20-mg and 40-mg formulations, effective blood levels are achieved with a better side effect profile.[53,105] The most commonly used dosing plan in the majority of clinical trials was 40 mg bid. Although 40 mg once daily was examined, it probably cannot provide the same 24-hour blood pressure control.[81] Some evidence is mounting that a three times daily ketanserin dosing regimen would be optimal.[113] In practice, one can often avoid side effects with ketanserin by initiating treatment with 20 mg bid for several days, and then increasing the dose to 40 mg bid.

Ketanserin has a relatively flat dose-response curve within the 20 to 40 mg bid dosing range, and almost no additional effect when 60 mg bid is used.[86] There is no direct relationship between steady-state levels of ketanserin in the blood and the reduction in blood pressure.[81,105] A relationship has been seen between blood pressure reduction and peak serum levels of ketanserin. The greatest hypotensive effect and the highest side effect frequency are seen one to two hours after oral ingestion when serum levels are highest.[78,81,114] Ketanserin may lend itself to use in a sustained-release delivery system, which could provide once-daily dosing and, perhaps, fewer side effects.

Aliberti et al.[115] more recently compared the short-term antihypertensive effect of a dose of 20 mg of ketanserin after sublingual and oral route. They showed that a significantly higher and more rapid hypotensive effect was obtained after sublingual administration. This could be explained by more rapid absorption; the ketanserin plasma levels rise more rapidly with sublingual than with oral administration.

Side effects (Table V). An ideal antihypertensive drug should provide a low side effect profile. The side effect profile of ketanserin may relate, in part, to its serotonergic blocking actions.

With high doses of ketanserin (180–200 mg daily), orthostatic hypotension and fatigue are common problems that lead to poor patient compliance.[70,105] At lower doses (average 40 mg bid), the drug is better tolerated but an incidence of fatigue and sedation varying from 5 to 60% has been described.[23,50,54,78,81,90,92] Sedation is seen relatively early with ketanserin use and rarely leads to treatment discontinuation. This problem may be avoided by starting at lower dosing levels of ketanserin (20 mg bid) and titrating upward after several days.

TABLE V

Side Effects Reported with Ketanserin in Clinical Trials

1. Postural hypotension and dizziness (probably dose related)
2. Sleep disturbances and anxiety (may be related to central serotonergic activity)
3. Fatigue
4. Sedation
5. Xerostomia (infrequent)
6. Headache (infrequent)
7. Nasal stuffiness (infrequent)
8. Constipation and diarrhea (rare)

Reproduced with permission.[41]

Other commonly seen side effects with ketanserin include xerostomia,[50,90,95,107] headache,[81,90,106] and nasal stuffiness. Rarely, constipation and diarrhea are reported. Mild increases in weight,[57] reductions in hematocrit,[24,53] and 24-hour sodium and creatinine clearance are seen, but no more than with other vasodilators.[70] Lipids and lipoproteins are probably not affected by the drug.

In the largest trial reported to date (1,011 patients) by DeMartini et al.,[83] an overall side effect incidence of 24% was noted. Most of these were not dangerous, and they noted a dropout rate of only 1.38% due to side effects.

The side effect incidence with ketanserin does appear favorable when compared with placebo or other antihypertensive medications.[23,47,51,86,93,96,97,99] Rarely were side effects a reason for patient dropouts with ketanserin in these trials. Qualitatively, ketanserin is associated with more sleep disturbances and anxiety, whereas β-blockers are associated with more complaints of depression and headache. Both β-blockers and ketanserin share fatigue as a common complaint.

Summary—Role of Ketanserin and Serotonin Blockade in Antihypertensive Treatment

Serotonin and abnormal serotonergic receptor activity may play a role in hypertension development in some patients, especially the elderly. Ketanserin, a

TABLE VI

Other Cardiovascular Uses of Ketanserin

1) Peripheral vascular disease
   a) Intermittent claudication
   b) Raynaud's phenomenon (related to scleroderma)
2) Coronary artery disease
   a) Angina pectoris
   b) Coronary spasm
   c) Prevention of restenosis following balloon angioplasty
3) Congestive heart failure
4) Pulmonary embolism
5) Primary pulmonary hypertension

selective S_2-serotonergic blocker, is an effective antihypertensive drug. Its mechanism of action still is not clearly defined, and α_1-adrenergic blocking actions and/or CNS activity may also be important. The drug does compare favorably with other antihypertensive drug regimens; however, its greatest effect may be on diastolic blood pressure rather than systolic blood pressure. Its side effect profile consists of CNS reactions, which may be avoided by using lower doses at the onset of therapy and titrating slowly to achieve a desired blood pressure effect. Also, it must be used with caution in patients taking potassium- and magnesium-losing diuretics.

Overall, the drug does not provide major advantages over other antihypertensive drug classes. There may be special subgroups (elderly) where ketanserin may have an advantage, but this needs to be clearly established.

OTHER CARDIOVASCULAR APPLICATIONS OF KETANSERIN

Ketanserin has been used for a wide spectrum of vascular and cardiac disorders with varied success (Table VI).

Peripheral Vascular Disease

Intermittent Claudication. The pharmacologic approach to intermittent claudication addresses the pathophysiology of the condition from two perspectives. Drug therapy aims to either increase vascular diameter, thereby decreasing flow impedance (conventional vasodilator treatment), or increase red blood cell deformability, thereby decreasing blood viscosity (pentoxifylline). Ketanserin acts uniquely through both mechanisms. Additionally, serotonin may be important in mediating collateral vessel contraction.[116]

Unfortunately, clinical results are contradictory. De Cree et al.[117] conducted the first placebo-controlled study in 20 patients (11 ketanserin, 9 placebo) with typical unilateral leg claudication reproduced during exercise testing. Patients received 20 mg tid of ketanserin for 2 months and 40 mg tid thereafter. After three months of therapy, there was no improvement in measured flow in the claudicant leg with ketanserin, compared with a placebo group decline. They saw no improvement in the reactive hyperemia profile, or thigh/arm blood pressure ratios measured by plethysmography. Claudication distance progressively improved from the first month onward.

Bounameaux et al.[118] repeated De Cree's work in a two-center study. Additionally, after three months they gave both groups placebo for two months. Surprisingly, only the placebo group improved the pain-free and maximum claudication distance (31% and 30%, respectively). The researchers saw no changes in either ketanserin or placebo group ankle/arm pressure ratios or flow parameters, despite adequate ketanserin blood levels and measurable inhibition of serotonin-induced platelet aggregation.

The contradictory findings of these studies may be explained. De Cree et al.[119] noted that in comparing Doppler velocimetry and plethysmography, they showed an improvement with ketanserin only using plethysmography. They theorized that ketanserin dilated collateral blood vessels. Plethysmography measures total limb flow, whereas Doppler velocimetry measures only single vessel flow. Bounameaux et al.[118] only report data obtained by Doppler measurement. In a subsequent study by Bounameaux et al.[120] using a third measurement, thallium scintigraphy, it was found that in 10 patients given 10 mg of intravenous ketanserin, no significant change in intraextremity ratios occurred. This finding showed no improvement in blood flow in the claudicant limb, supporting their earlier findings.

Another problem in comparing these two studies is the different responses of the two control groups to placebo. In neither trial did the placebo group remain stable. If a training effect is to be assumed, as presumably occurred in the trial by Bounameaux et al.,[118] then in De Cree's trial[117] the lack of clinical improvement and the deterioration in the placebo group biases the data in favor of ketanserin.

Cameron et al.[121] confirmed the negative findings with ketanserin in 21 patients (12 placebo, 9 ketanserin 40–60 mg bid). They showed a small nonsignificant improvement with placebo but not with ketanserin. Their study actually favored the ketanserin group because this group showed a shorter mean claudication time at baseline. The placebo

group analysis showed shorter baseline claudication time to be associated with a greater degree of improvement during the course of the study.

More recently, Walden et al.[122] conducted a 12-month, double-blind, placebo-controlled study in 35 patients with intermittent claudication (18 placebo, 17 ketanserin) started at 20 mg tid for 1 month, then increased to 40 mg tid. They too showed that there were no significant differences in claudication distance between the ketanserin and placebo groups. Also, the hemodynamic measurements reflected no significant differences between these two groups.

To resolve these contradictions, Thulesius et al.[123] conducted a placebo-controlled multicenter trial in 179 patients. They treated patients with ketanserin 40 mg tid for 6 months. On average, the ketanserin group, compared with placebo, improved their pain-free walking distance (65 versus 42%); however, this was not statistically significant. They defined a positive response to be a doubling in pain-free distance. Using this definition, they found that 28% responded to ketanserin versus 15% to placebo ($P = .02$). Subjectively, however, they saw no difference between patient groups. Despite a decrease in systemic blood pressure, the ankle/arm pressures did not change in either group. The study serendipitously discovered a higher incidence of serious cardiovascular complications (myocardial infarction, unstable angina, transient ischemic attacks, cerebral hemorrhage, and short-term deterioration of peripheral vascular disease) in the placebo group.

Janicek et al.[124] showed that serotonin may play an important role in the development of ischemia in some patients with peripheral vascular disease. In their study, low dose ketanserin (3–30 μg/kg) was given intra-arterially to 23 patients with advanced peripheral vascular disease at the time of diagnostic arteriography. An additional seven patients received placebo. They evaluated the angiographic response by coded reading (−1–+3) and by computer-assisted measurement of arterial segments in pelvis, thigh, knee, and lower leg regions. None of the patients in the placebo groups showed vasodilation, whereas 13 of 23 (57%) ketanserin-treated patients showed unequivocal vasodilation primarily at the level of collateral vessels. When vasodilation was evident in one anatomic region, another ketanserin-responsive anatomic area, assessed separately, would be identified in the same patient. Moreover, vasodilation of the geniculate artery, which generally serves as an important collateral to the calf, correlated positively with increased calf blood flow. It was also noted that in response to ketanserin, the smaller collateral arteries dilated much more readily than larger arteries. These findings supported those of animal models; supersensitivity of the limb collaterals to serotonin after occlusion has been shown in the cat, rat, dog, and rabbit, and ketanserin reversed the response to serotonin.[125]

Clement and Duprez[126] conducted a pooled analysis of the above studies and included one unpublished placebo-controlled trial. Both the placebo and ketanserin groups showed improvement in treadmill walking distance (65 versus 25%, nonsignificant [NS]). Fewer ketanserin patients deteriorated with a higher percentage of "responders" in the ketanserin group. Most importantly, they found a reduced frequency of intercurrent cardiovascular events in the ketanserin group. These results led to the Prevention of Atherosclerotic Complications With Ketanserin (PACK) trial.[68] The study randomized in double-blind fashion 3,899 patients with intermittent claudication to receive either placebo or ketanserin (20 mg tid for 1 month followed by 40 mg tid). The study was designed to examine the incidence of primary cardiovascular events (myocardial infarction, stroke, amputation, vascular death) and secondary events (possible myocardial infarction, angina, transient ischemic attacks, deep vein thrombosis, pulmonary emboli, hypertension, renal failure) during one year of treatment. However, some ketanserin patients were prematurely discontinued owing to concerns of an excess number of deaths. The ketanserin group had a mortality rate higher than that of the placebo group. This difference was attributed to the previously unknown combined actions of ketanserin and potassium-losing diuretics. Five months after the trial onset, all patients with QT_c intervals greater than 500 milliseconds were discontinued; after 9 months all patients taking diuretics were withdrawn.

When the results were further analyzed, the ketanserin group was divided based on whether the patient was on a potassium-losing diuretic. In those ketanserin patients taking potassium-losing diuretics, the mortality rate was twice that of the placebo group. In those ketanserin patients not receiving potassium-losing diuretics, mortality was moderately reduced compared with placebo. (As previously discussed, both hypokalemia and ketanserin can increase the QT_c interval, predisposing to torsade de pointes.) The report noted a 23% reduction in the number of study endpoints for those ketanserin patients not on potassium-losing diuretics. Obviously, the results of retrospective subgroup analysis must be viewed with caution. However, these results show enough promise to warrant further study with ketanserin. Future research must avoid the combination of ketanserin with other medications known to prolong the QT_c interval.

The role of ketanserin in treating intermittent claudication remains undefined. Although some patients respond, we cannot identify them before therapy. However, ketanserin may have a role in preventing cardiovascular complications in these patients.

Raynaud's phenomenon and systemic sclerosis. Despite extensive research, the pathophysiology of Raynaud's phenomenon remains a mystery, although several theories do exist.[127] Because of serotonin's known vasoconstrictive properties and a heightened sensitivity to serotonin found in patients with systemic sclerosis, ketanserin seems to be a reasonable choice to treat this vasoconstrictive disease.[128]

Klimiuk's group[129] showed decreased levels of serotonin concentration in CREST patients compared with normal subjects. Ketanserin normalized platelet serotonin concentration, suggesting platelet activation in this disorder. A double-blind trial[130] of 24 patients with systemic sclerosis given either ketanserin or placebo failed to show improvement in either functional or objective clinical signs. However, the physicians gave better global ratings to the ketanserin patients.

In a placebo-controlled crossover experiment, Baart de la Faille et al.[131] induced Raynaud's phenomenon in 15 patients by lowering room temperature, then gave them either ketanserin or placebo. They found that ketanserin improved the blue skin color and increased digital skin temperature.

Seibold and Terregino[132] using plethysmographic techniques, immersed the hands of four women with primary Raynaud's phenomenon in ice water while they administered either ketanserin or placebo, and found that ketanserin did not improve cold intolerance. Ketanserin did, however, improve digital flow parameters when given during the cold immersion. They concluded that ketanserin relieves, but does not prevent, Raynaud's phenomenon. They argued that serotonin may mediate, but not initiate, these episodes of vasoconstriction.

In a study examining both intravenous and prolonged oral ketanserin treatment, Lagerkvist and Linderholm[133] also found intravenous ketanserin to improve finger blood flow parameters in four arsenic workers with Raynaud's phenomenon. They then administered ketanserin in a placebo-controlled, randomized, crossover model for four weeks to 17 people, and found no subjective or objective improvement (skin temperature or finger systolic pressure).

A double-blind international study[134] observed 222 patients in 10 countries for 3 months. They noted a 34% reduction in the frequency of Raynaud's attacks for ketanserin versus 18% for placebo. Global evaluation by both patients and physicians showed subjective improvements, though finger blood studies failed to show objective improvements.

More recently, Arosio et al.[135] gave oral ketanserin 40 mg bid to 12 patients with stable Raynaud's phenomenon for 15 days. They showed that ketanserin reduced the number and duration of ischemic attacks and caused their spontaneous reversal, as indicated by the daily recordings of the patients during treatment. During the ketanserin treatment period, spontaneous onset was noted in 17% of patients as compared with 37% during washout, whereas reversal was spontaneous in 92% as compared with 25% during washout. Moreover, post-treatment thermometric data revealed a significant increase in basal temperatures on all fingers, in temperature after cooling, and in temperature after thermal recovery as compared with the washout period.

Brouwer et al.[128] attempted to determine the relative contributions of the 5-HT_2–serotonergic and α_1-adrenergic antagonistic properties to the role of ketanserin in Raynaud's phenomenon. Ketanserin was given intravenously to 11 patients with primary Raynaud's phenomenon during reflex digital vasoconstriction induced by moderate body cooling. Ketanserin normalized digital skin temperature and digital blood flow as measured by plethysmography and Doppler flowmetry. Pretreatment with the α-adrenoceptor antagonists prazosin and phentolamine failed to abolish the vasodilatory effect of ketanserin, ruling out a sympatholytic effect of ketanserin on the digital vascular bed. The authors concluded that 5-HT_2 receptor is present in the digital vasculature and its activation probably plays a role in cold-induced digital vasoconstriction in patients with Raynaud's phenomenon.

In contrast, Marasini et al.[136] showed the lack of correlation between the extent of vasodilation and 5-HT_2–platelet receptor inhibition in 18 patients with Raynaud's phenomenon after long-term oral ketanserin (20 mg tid for 1 month). Because the vasodilatory and platelet inhibitory effects of ketanserin are mediated by the same serotonin receptors, the author inferred that α_1-adrenoceptor antagonistic property of ketanserin may be involved instead of S_2 receptor blockade.

Using platelet aggregation tests as a standard of measuring the efficacy of ketanserin in treating Raynaud's phenomenon, Marasini et al.[137] assessed the serotonin-induced platelet aggregation in 10 patients with Raynaud's phenomenon during treatment with oral ketanserin. They found that platelet aggregation was completely inhibited in all patients 90 minutes

after the first dose of 40 mg of ketanserin. However, only 1 patient showed complete inhibition of aggregation 12 to 14 hours after the last dose of ketanserin on the 31st day of treatment. Only 3 patients reported a 50% reduction in the frequency of the attacks per day. With an additional dose of 40 mg, complete inhibition of aggregation was seen again in all patients. The authors speculated that more frequent dosing might be required to achieve more effective blockade of serotonin in this disorder.

In summary, intravenous ketanserin may ameliorate, but not prevent, Raynaud's attacks. It may prove useful for severe attacks requiring hospitalization. Long-term oral ketanserin shows some tendency to reduce the symptoms in Raynaud's disorders. Future evaluation should focus on a quick-acting oral form of ketanserin to alleviate vasospastic attacks after they begin.

Coronary Artery Disease

Angina Pectoris. Conceptually, ketanserin should reduce the signs and symptoms of ischemic heart disease by favorably influencing the myocardial oxygen supply-demand relationship (much like calcium-channel antagonists). Ketanserin's afterload reducing actions should decrease demand, and its beneficial effects on coronary artery diameter should increase supply.

Unlike verapamil, ketanserin does not depress inotropic function, and according to Saman et al.[59] it may actually improve contractility. In contrast to nifedipine, oral ketanserin does not cause tachycardia. Walker et al.[138] showed a small but significant drop in cardiac oxygen consumption after ketanserin infusion during paced tachycardia in 10 patients undergoing diagnostic catheterization for chest pain. However, they found no changes in cardiac lactate extraction, questioning the significance of the change in oxygen consumption.

Cameron and Ramsay[139] conducted a crossover trial of single doses of 20 to 40 mg of oral ketanserin versus placebo in 10 patients with stable angina refractory to β-adrenergic blockade. Ketanserin did not change the exercise time-to-angina during a six-hour period. They found no change in heart rate, and only a nonsignificant drop in the rate-pressure product. The authors concluded that at least in this single dose study, ketanserin has no beneficial effect in patients with angina.

Coronary Spasm. The syndrome of coronary spasm may be induced by prostacyclin deficiency, local release of thromboxane A_2, hyperactivity of the peripheral nervous system, and other mediators.[140] Evidence has suggested that serotonin accumulation at sites of endothelial vascular injury and coronary artery stenosis may contribute to or cause myocardial ischemia through a vasoconstricting effect. In canine studies, infused serotonin specifically causes epicardial coronary spasm, accounting for the ECG findings of the Prinzmetal syndrome. Also, serotonin released from activated platelets would explain vasospasm in sites of preexisting arteriosclerotic narrowing and plaque rupture. In the canine model, it has been shown that serotonin concentration is increased 18 to 30 times at the site of a coronary artery stenosis when cyclic coronary artery flow reductions occur. Activation of the S_2 receptor has been implicated as mediating this event, because ketanserin usually abolishes or significantly attenuates the frequency of cyclic flow reductions. However, some investigators using a similar experimental model have reported conflicting results. One group showed that during dynamic coronary stenosis, preadministration of ketanserin failed to abolish coronary flow reduction, whereas preadministration of methysergide, a nonselective serotonin antagonist, did block this serotonin action.[49] A more recent study in baboons showed that ketanserin had no effect on regional myocardial blood flow in the ischemic areas and normal areas immediately and one week after left anterior descending artery ligation.[141]

Despite this sound theoretical base, clinical findings with ketanserin do not support 5-HT_2 involvement in coronary spasm. Freedman et al.[142] found no change in the dose of ergonovine required to produce ischemia in seven patients during ketanserin administration. At the same time, ketanserin blocked serotonin-induced constriction in the hand veins of these patients.

In vitro studies using human epicardial coronary arteries have suggested that serotonin receptor profiles in vessel segments from ischemic heart disease patients are different from those in undiseased vessels. In undiseased vessels α-methyl-5-HT, a selective agonist at 5-HT_2 receptors, produced contraction similar to 5-HT, whereas GR 43175, a selective 5-HT_1–like receptor agonist, produced contractions that achieved only 30% of maximum response to 5-HT. In contrast, in diseased vessels, the response to 5-HT_2 receptor agonist was significantly reduced, though the 5-HT_1–like receptor mediated response was maintained.[143] The possibility that serotonin may cause vasospasm by its action on 5-HT_1–like receptors may offer an explanation for the failure of ketanserin to block serotonin-induced coronary vasospasm in animal models.

McFadden et al.[144] gave intracoronary serotonin to patients with stable angina (n = 9) and variant angina

(n = 5), and to a control group with angiographically normal vessels, and measured the response using quantitative coronary angiography. The control group showed a dose-related biphasic response to the infusion of serotonin: dilation at lower concentration (10^{-7} to 10^{-5} mol/L), but constriction at higher concentration (10^{-4} mol/L). In patients with stable coronary disease, infusion of serotonin caused progressive constriction. Moreover, the atherosclerotic vessels showed an increased sensitivity to the constrictor effects of serotonin compared with the control. In patients with variant angina, the discrete stenotic coronary segments showed occlusive spasm at a dose that dilated normal vessels and caused only slight constriction in vessels from a stable angina group (10^{-5} to 10^{-6} mol/L). In a separate study, McFadden et al.[145] showed that although serotonin (10^{-4} mol/L) caused significant vasoconstriction in both proximal and distal vessel segments from patients with stable angina (n = 8), ketanserin blocked this action only in the proximal vessel segments. In variant angina patients (n = 3), occlusive spasm occurred at the site of previous stenotic segment after administering 10^{-5} mol/L of serotonin in 2 patients and 10^{-6} mol/L in 1 patient. Ketanserin again failed to relieve the vasoactive effect of serotonin in this group. In the control group (n = 7), serotonin caused significant vasoconstriction in distal epicardial vessels that was significantly inhibited by ketanserin. The results from these studies supported the hypothesis that serotonin may cause vasospasm in patients with atherosclerotic coronary artery by activating S_1-like receptors and that the blockade of S_2 receptors alone may not be sufficient to inhibit the vasoactive effects of serotonin. Whether S_2 blockade prevents vasoactive action of serotonin depends on several factors such as presence or absence of a functional endothelium, and the intricate balances of S_1, S_2, and S_1-like receptors in any given vessel segment.

Contrasting McFadden's findings, Golino et al.[146] in a similar study found that serotonin (2.4×10^{-7} to 2.4×10^{-5} mol/L) has vasodilating effect on normal human coronary arteries (control, n = 7) and that ketanserin potentiated the vasodilation. They also showed that in patients with coronary artery disease (n = 7), serotonin caused a dose-dependent vasoconstriction that was completely inhibited by ketanserin. The author hypothesized that serotonin, probably by activation of S_1 receptors and subsequent release of endothelium-derived relaxing factor, causes vasodilation under normal physiologic conditions. Ketanserin potentiates this vasodilation by its S_2 blockade, and thus further unmasks the effect of S_1-receptor activation. They also suggested that because the endothelial cells are probably dysfunctional in patients with coronary artery atherosclerosis, and therefore unable to release an adequate amount of endothelium-derived relaxing factor, the vasoconstricting effect of the S_2 receptor predominates and ketanserin prevents this effect.

Several factors may account for the contradictory findings of these two studies. The highest dosage of serotonin infused by Golino et al.[146] that caused vasodilation was approximately one-quarter that used in McFadden's study.[145] Also, the subject profiles of the control groups in these two studies differ. The control group in Golino's study consisted of women without any clinical evidence of coronary artery disease, whereas McFadden selected patients with atypical chest pain who had at least one conventional risk factor for coronary disease as their control.

In summary, from these studies in animal models and patients, it seems evident that the subtypes of receptors responsible for the response of serotonin in healthy and diseased coronary arteries are different. Serotonin, released as a result of coronary atheromatous plaque disruption and subsequent platelet aggregation, may be one of the key mediators in coronary vasospasm. The elucidation of the mechanism of action of serotonin at different receptor subtypes will assist in the understanding and treatment of myocardial ischemia.

Prevention of Restenosis after Balloon Angioplasty. After percutaneous transluminal angioplasty, the high incidence of coronary artery restenosis remains an important clinical problem. The effects of ketanserin on early (after 24 hours) and late (4–9 months) restenosis was investigated. The investigators found that a 24-hour infusion of intravenous ketanserin after balloon coronary angioplasty could prevent early restenosis, but did not influence the incidence of late restenosis.[147]

Congestive Heart Failure

Recent studies[148] confirm the benefits of vasodilator therapy in congestive heart failure, both on symptoms and survival. Ketanserin should also provide relief.[149] It inhibits the serotonin-mediated augmentation to angiotensin II and catecholamines, both of which are elevated in congestive heart failure. It is a direct vasodilator without causing significant reflex tachycardia, at least in long-term therapy.

As early as 1981, Demoulin et al.[150] treated congestive heart failure patients with ketanserin. They gave a single intravenous bolus to eight patients, and noted an increase in cardiac index and a drop in pulmonary capillary wedge and right atrial pressures. These changes were maximal at 15 minutes and dis-

appeared by 1 hour. The authors hypothesized that congestive heart failure leads to a high serotonin state. The elevated catecholamines cause platelet activation and serotonin release.

Similar responses to intravenous ketanserin were seen by Grobecker et al.[60] His group gave intravenous ketanserin (bolus followed by drip) to 20 patients with class III-IV congestive heart failure, and they saw a drop in total peripheral resistance with an improved stroke volume. The physiologic changes lasted longer than in the previous study, probably owing to the prolonged infusion used.

Majid et al.[55] found similar results in seven patients, noting improvements in mean cardiac output, mean blood pressure, pulmonary capillary wedge and right atrial pressures, and systemic vascular resistance, at rest and with exercise. However, oral ketanserin produced no significant changes. The authors suggest that although this oral regimen usually produces blood levels comparable to those of intravenous administration, this may not be true in these congestive heart failure patients because of decrease bioavailability.

On the contrary, Brune et al.[148] evaluated the hemodynamic effects of oral ketanserin (80 mg daily) for 12 months in 5 patients with coronary artery disease and congestive heart failure (New York Heart Association [NYHA] classes II-III, mean ejection fraction 44%) and found significant reductions in pulmonary wedge pressure and mean arterial pressure both at rest and on exertion. Cardiac output increased slightly and heart rate remained unaltered.

Surprisingly, the investigators noted no change in circulating catecholamines after intravenous ketanserin. (Therapeutic increases in cardiac output in congestive heart failure are usually accompanied by a short-term decrease in the levels of catecholamines). Grobecker and his group[60] saw a brief increase in norepinephrine levels after intravenous ketanserin administration, followed by a fall after two hours. They noted that ketanserin can inhibit the active uptake of catecholamines by human platelets *in vitro* and *in vivo*. Majid et al.[55] do not state at what time after the injection of ketanserin their catecholamine levels were drawn, and this time may have differed from patient to patient. This may account for their findings of no change in circulating catecholamines.

In summary, intravenous ketanserin seems useful as a vasodilator in the short-term treatment of congestive heart failure due to systolic dysfunction. Its long-term efficacy, particularly in the oral form, and compared with other vasodilator treatments, remains to be proven.

Left Ventricular Hypertrophy

Using echocardiographic techniques, ketanserin has been shown to cause regression of left ventricular hypertrophy with preservation of systolic contractile function in hypertensive patients.[151,152] The drug appears to be as effective as β-blockers in causing regression; however, the clinical importance of this action has not yet been determined.[153]

Pulmonary Vascular Disease

Pulmonary Embolism. Pulmonary embolism, a deadly but common disorder, involves more than the physical destruction of an artery. Various humoral mediators released by damaged lung and the clot itself contribute to produce the bronchoconstriction, pulmonary vasospasm, and increase in vascular permeability that lead to pulmonary edema. These responses result in hypoxemia secondary to the four classic mechanisms: ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch, shunt, diffusion defects, and hypoventilation. The release of serotonin from the damaged lung[154,155] and from the activated platelets may play a key part in this scheme.

Huval and coworkers[156] first showed ketanserin's potential role in treating pulmonary emboli. They induced pulmonary emboli in dogs by administered clot and then treated half with a single dose of ketanserin. The group showed improvements in shunt fraction, pulmonary arterial pressure, and pulmonary vascular resistance that persisted for 2.5 hours, with resolution of perfusion defects seen on radionucleotide lung scans in 6 of 7 treated dogs.

These results were confirmed by Thompson et al.[157] in his study of dogs, where he found that much of the hypoxemia and increased pulmonary vascular resistance induced by injected clot could also be duplicated with a serotonin infusion. However, serotonin infusion did not cause pulmonary edema. Pretreatment with intravenous ketanserin attenuated both the hypoxia and increase in pulmonary vascular resistance produced by clot and serotonin infusion. Ketanserin also prevented the postembolic development of pulmonary edema and blocked postembolic platelet sequestration. This study suggests that (1) serotonin appears to be an important mediator in pulmonary embolism; (2) the drop in PaO_2 with serotonin infusion, which did not lead to pulmonary edema, is similar to that seen with clot administration, indicating that pulmonary edema does not appear mechanistically important to causing hypoxemia; and (3) ketanserin antagonizes both direct effects of serotonin (pulmonary hypertension) and

indirect actions of activated platelets (pulmonary edema).

Although the results of Thompson's study[157] appear extraordinarily promising, it must be noted that extremely high doses of ketanserin were used: a bolus of 1 mg/kg followed by a .33 μg/min drip. The equivalent human dose would be a 70-mg bolus, seven times the usual intravenous dose. Breuer et al.,[12] using more conventional doses of ketanserin (and lower serotonin doses) showed only partial antagonism of the increased pulmonary vascular resistance and pulmonary artery pressure induced by serotonin.

Clinical results leave less clear findings than experimental models. Huet et al.[158] did a study of intravenous ketanserin in 10 patients with angiographically-proven pulmonary embolism. They found a mild reduction of pulmonary artery pressure with an 8% drop in pulmonary vascular resistance, accompanied by a 9–mm Hg drop in systemic arterial pressure secondary to systemic vasodilation. Nine of 10 patients increased PaO_2 after ketanserin therapy. However, a rise in venous PO_2 accompanied the rise in PaO_2, suggesting that the changes in PaO_2 may well be due to decreased tissue oxygen extraction instead of improved lung function.

The available clinical data suggest a potential role for ketanserin in the therapy of acute pulmonary embolism as a means to decrease pulmonic pressures. Whether tissue oxygenation, the goal of therapy, improves remains in question. One avenue meriting further exploration is the prophylactic administration of either intravenous or oral ketanserin in patients at risk for pulmonary emboli. If a pulmonary embolus occurs, the on-board ketanserin should attenuate the serotonin-mediated amplification that leads to further lung damage. Perhaps this would be given analogous to heparin or warfarin.

Primary Pulmonary Hypertension. Primary pulmonary hypertension, unlike its systemic counterpart, presents special difficulties in treatment.[159] It is usually progressive, and often refractory to all therapy short of heart-lung transplant.[159] Conventional vasodilator therapy shows no specificity for the pulmonary circulation, and often causes intolerable hypotension that may compromise right ventricular blood supply, worsening right ventricular function. Vasodilator tachyphylaxis usually causes long-term treatment failure, even when early therapy appears successful. Another consideration is that the pulmonary hypertension may not be due to reversible vasoconstriction. A significant contribution may be fixed, and therefore unresponsive to any form of pharmacotherapy.

Unfortunately, ketanserin fared no better than other vasodilators. In one trial of 20 patients by McGoon and Vliestra,[160] 17 of 20 patients showed a decrease in peripheral vascular resistance but only 5 showed a decrease greater than 5 U/m^2. Pulmonary pressure showed no change, but this variable may not be as significant to follow.[159] They noted a small increase in mixed venous oxygenation, possibly due to decreased peripheral utilization. A few patients did show significant reductions in peripheral vascular resistance and pulmonary artery pressure. Vasodilators frequently produce these kinds of idiosyncratic responses, but they do not necessarily indicate good long-term prognosis. Finally, 10 patients on long-term oral therapy showed no increase in survival. Ketanserin, along with a battery of other vasodilators, may be useful in an empiric method to find the right drug for a particular patient.

Pulmonary Hypertension in Systemic Sclerosis. Although the etiology of systemic sclerosis, one cause of secondary pulmonary hypertension, remains obscure, a link to platelets and serotonin has been suggested by Seibold et al.[161] for both the acute vasospasm and the chronic fibrosis.

As in the idiopathic variety of pulmonary hypertension, drug therapy produces poor clinical results. In Seibold's study,[161] 86% (12 of 14) of patients with pulmonary hypertension secondary to systemic sclerosis showed a decrease in pulmonary vascular resistance after intravenous ketanserin. In contrast, three of six patients showed some response to nifedipine, three of five to captopril, and two of four to isosorbide dinitrate. However, the fact that only 36% of the patients showed a concomitant drop in pulmonary arterial pressure suggested that an increase in cardiac output with passive vessel recruitment led to this decrease in peripheral vascular resistance. They concluded that in systemic sclerosis, a predominantly "fixed" obstruction causes the pulmonary hypertension.

Ketanserin showed no specific advantages over other vasodilators in the therapy of either primary pulmonary hypertension or that secondary to systemic sclerosis. However, as with other vasodilators, individual patients will respond dramatically to this drug. According to Packer,[159] even hemodynamically, successful vasodilator therapy does not consistently provide clinical improvement.

Portal Hypertension. The overfill hypothesis postulates that a primary increase in hepatic blood flow leads to elevated portal hypertension. Vorobioff et al.[162] found splanchnic vasodilation critical for the maintenance of elevated pressures in the portal vein

stenotic model. However, reduction in flow by hemorrhage, β-blockade, or nitrate administration does not, in itself, reduce portal pressure to normal.[163]

When various investigators[162,164] increased portal inflow (through saline infusions) in normal rats, they found portal collateral resistance reduced to values significantly lower than those seen in portal hypertensive rats. This suggests that even during the high splanchnic blood flow state, the portal collaterals maintain an inappropriately high resistance. When portal blood flow drops, the collaterals increase their high tone even further, maintaining the elevated pressure. Hence, decreased inflow with conventional agents does not lower portal pressure significantly.

Collateral vessels, as shown by Hollenberg[116] in the rabbit femoral artery system, are exquisitely sensitive to the vasodilator action of ketanserin, suggesting that ketanserin might be a useful agent to treat portal hypertension. Cummings et al.[164] showed that in the portal vein ligated rat model, isolated superior mesenteric veins were threefold more sensitive to the effect of serotonin than controls. Ketanserin attenuated this effect.

Intraportal injection of ketanserin significantly decreased portal pressure and portal flow in experimental rats.[164,165] Portal hypertensive rats showed a reduced cardiac output not seen in controls. The authors theorized that ketanserin reduced cardiac preload, leading to decreased cardiac output and diminished portal flow. In contrast to the situation with nitrates, ketanserin did not cause an increase in portal collateral resistance. The open collaterals maintain a larger decrease in portal pressure. This may be due to a hypersensitivity to 5-HT in collateral vessels exposed to the higher portal pressures antagonized by ketanserin.

Cummings et al.[165] showed that ketanserin's ability to decrease portal pressure is most likely due to its 5-HT_2 rather than its α-blocking properties. Intramesenteric prazosin compared with ketanserin failed to lower portal pressure despite a similar drop in systemic blood pressure. More recently, Matsai et al.[166] showed that ritanserin, a selective 5-HT_2 antagonist without α_1-adrenolytic property, reduced portal pressure without decreasing arterial pressure in long-term bile duct ligated cirrhotic dogs[161] and in CCl_4-induced cirrhotic rats.[167] Using a portal vein ligated rat model, ritanserin was shown to achieve a 20% reduction in portal pressure without any changes in the systemic circulation.[168] Furthermore, the reduction in portal pressure was not due to changes in portal venous flow, which was the same in ritanserin- and placebo-treated animals. These findings supported the hypothesis that the effect of serotonin blockade on portal pressure probably is due to a reduction in portal collateral resistance.

Pomier-Layrargues et al.[169] further investigated the combined effect of ritanserin and propranolol on portal hypertension in cirrhotic rats. They showed that intravenous injection of ritanserin caused a 19% reduction in portal pressure without altering portal-venous inflow or any other systemic hemodynamics. Furthermore, portal venous resistances were slightly but significantly lowered. The addition of propranolol further enhanced the reduction of portal pressure to 38%. However, the ritanserin-induced decrease of portal venous resistance was not magnified by propranolol. The authors concluded that the simultaneous use of propranolol and ritanserin would result in a cumulative reduction in portal pressure by acting through different hemodynamic mechanisms. β-blockers act mainly by decreasing cardiac output and portal venous flow, and 5-HT_2 antagonists act probably by reducing intrahepatic and/or portocollateral resistances.

These promising results in animals led to attempts to treat cirrhotic patients with ketanserin. Hadengue et al.[170] treated 11 patients with histologically-proven alcoholic cirrhosis and esophageal varices with intravenous ketanserin. They reported a significant decrease in wedged hepatic venous pressure and a decrease in the hepatic venous pressure gradient, indicating a decrease in portal pressure. However, in contrast to the animal studies, they found a significant decrease in azygous blood flow, reflecting a decreased collateral blood flow. They noted an overall decrease in mean arterial pressure correlating with the degree of cirrhosis.

The lack of control or comparison groups makes it difficult to interpret these results. Without knowing the effect of other vasodilators in these patients, it is difficult to determine if these patients showed collateral vessel supersensitivity. Although there was a decrease in collateral flow with ketanserin therapy, we do not know how this decrease would compare with that of other drugs. Other drugs may have caused an even greater decrease in collateral flow, with potentially worse clinical results.

The authors attempted to explain the correlation between hypotensive effect and severity of cirrhosis[170]; they suggest that serotonin supersensitivity in this disease is related to the degree of hepatic failure. A more probable explanation can be found by examining ketanserin metabolism. Because the liver metabolizes almost all of this drug, the augmented hypotensive effects may reflect decreased metabolism and higher ketanserin blood levels. Unfortunately, drug levels were not reported.[170]

Similar results were found in a subsequent study

TABLE VII

Noncardiovascular Uses of Ketanserin

1) Portal hypertension
2) Airway obstruction
3) Acute respiratory failure
4) Carcinoid syndrome
5) Improved bladder contraction (neurogenic bladder)

by Hadengue et al.[171] Ketanserin was added to either verapamil or propranolol to explore beneficial combinations. When ketanserin was added to verapamil or propranolol, it caused a reduction in hepatic wedge pressure, hepatic venous pressure gradient, and azygous blood flow. The study concluded that ketanserin may have a role in patients with portal hypertension unresponsive to propranolol alone.

A long-term study by Vorobioff et al.,[172] in which 16 patients with alcoholic cirrhosis were treated with 40 to 80 mg of ketanserin daily, also showed a decrease in hepatic venous pressure gradient and wedge hepatic venous pressure. There was, however, no evidence of clinical benefit. In addition, the authors noted a high incidence of side effects, particularly hepatic encephalopathy. This was predictable, knowing ketanserin's effect on collateral flow around the liver. As ketanserin is metabolized in the liver, cirrhosis may lead to higher serum levels and more toxic effects. Regrettably, serum levels were not measured.

It seems from animal studies that serotonergic mechanisms may be exploited as a means to reduce portal pressure. In humans, ketanserin did not show the specificity for collateral vessels noted in animal models. Nevertheless, ketanserin may yet prove useful in the treatment of portal hypertension.

NON-CARDIOVASCULAR APPLICATIONS OF KETANSERIN (TABLE VII)

Airways Obstruction

Treatment of airway obstruction, a common and complex disorder, has been attempted with anticholingeric therapy, mast cell stabilization, β-adrenergic stimulation, etc. Research into serotonin's role in the pathogenesis of airway obstruction produces conflicting results. Some *in vitro* animal models show serotonin-induced bronchoconstriction,[16] whereas others show bronchodilation. Although, *in vivo* serotonin provokes no significant response in healthy patients, it does induce bronchospasm in some patients with asthma. Serotonin may work through vagal mechanisms in large airways, because atropine antagonizes this effect. In small airways, it works directly.[17]

Cazzola et al.[173] conducted a double-blind, placebo-controlled, crossover trial of ketanserin in 14 patients with nonasthmatic chronic obstructive pulmonary disease (COPD). After intravenous ketanserin, 7 patients showed an improvement of more than 15% in FEV_1 and 9 showed an increase of at least 20% in $FEF_{50\%}$.

More recently, Cazzola et al.[174] conducted a double-blind, crossover study on the effect of 10 mg of inhaled ketanserin in 8 patients with nonasthmatic COPD, compared with 10 mg of intravenous ketanserin. They showed that nebulized ketanserin induces mild bronchodilation in patients with COPD; however, intravenous ketanserin had more rapid onset of action and sustained a longer bronchodilatory response than inhaled ketanserin. The onset of action of intravenous ketanserin, determined by a 15% increase in the mean FEV_1 over the baseline values, occurred between 5 and 30 minutes. Using the same criteria, the onset of action of nebulized ketanserin occurred between 15 and 60 minutes.

Theoretically, ketanserin should ameliorate COPD. Again, serotonin may promote vagal-mediated bronchoconstriction. Additionally, hypoxia stimulates serotonin release from neuroepithelial bodies in the lungs. This may create a high-serotonin state that would lend itself to ketanserin antagonism.

These studies suggest a possible role for ketanserin in the management of airway obstruction.[173] Future studies should explore this therapy in patients with a significant component of bronchoreversibility.

Acute Respiratory Failure

A complex mix of events involving increased capillary permeability, increased airway resistance, pulmonary hypertension, and hypoxia produce the adult respiratory distress syndrome, or "shock lung." Attempts to lower pulmonary hypertension with conventional vasodilator agents usually fail because of worsening hypoxia; the dilation of vasculature in poorly ventilated lung causes V/Q mismatch. Ketanserin, because it has the propensity to simultaneously dilate the bronchi, should not impair the $\dot{V}/\dot{Q}$ relationship.[58]

Adult respiratory distress syndrome is thought to be a high-serotonin state for several reasons: Injured lung and platelet microthrombi release serotonin. Although more than 90% of serotonin can be cleared by passage through the normal lung, injured pulmonary tissue may not maintain this capability. Addi-

tionally, hypoxia itself may be a stimulus for serotonin release.[17]

Numerous animal studies show ketanserin's beneficial effects in artificially-induced respiratory failure. Clinical results, although limited, show promise. Vincent et al.[154] treated eight patients with acute respiratory failure of varied etiologies. They reported significant decreases in both systemic and pulmonary vascular resistances, as well as in right ventricular stroke work index. However, they found no significant changes in PaO_2, Q_s/Q_t, or PCO_2. More recent work by Rodermaker et al.[58] in six patients with acute respiratory distress syndrome (ARDS) also showed a decrease in pulmonary artery pressure, without altering ventilation/perfusion matching. Ketanserin showed no deleterious effects on gas exchange. This combination of decreased workload without an increase in shunt fraction or decrease in PaO_2 seems unique to ketanserin. The maintained PaO_2 may result from impaired peripheral oxygen utilization.

Vincent's study[154] involved only a few patients with great variability in their physical states: Huval et al.[175] looked only at patients already on ventilatory support. They showed that early in the course of respiratory failure, the platelet count dropped an average of 26,000 across the pulmonary bed. Additionally, they saw a depletion of platelet serotonin compared with both normal platelets and platelets measured later in the disease course. These factors suggest the early presence of a high-serotonin state.

As seen earlier, ketanserin led to a decrease in both systemic and pulmonary arterial pressures; however, the time frames differed—systemic pressure fell within minutes and returned to baseline by 1.5 hours, whereas pulmonary pressure in the patients with early failure remained 10% below normal. The authors suggested that the α-adrenergic blockade mediate the systemic effects, whereas serotonin blockade mediates the pulmonary actions.[175]

Unlike the study by Vincent et al.,[154] the patients with early failure showed an actual decrease in shunt fraction, greatest if ketanserin administration occurred within two days of symptom onset. This may reflect a decrease in serotonin-mediated bronchoconstriction, because they noted a modest decrease in peak inspiratory pressures. Ketanserin showed little benefit later in the course.

In summary, serotonin may be a mediator of some of the physiologic aberrations in adult respiratory distress syndrome, and ketanserin therapy may prove valuable to treat this syndrome.

Carcinoid Syndrome

A carcinoid is a slow-growing malignancy of the argentaffin cells, most commonly found in the gastrointestinal tract. These APUD cells release serotonin, associated with the clinical symptoms of diarrhea and flushing. By blocking the actions of serotonin, investigators hope to alleviate the distressing symptoms of carcinoid syndrome.

Jaffe et al.[176] explored the relationship between serotonin, ketanserin, and two other mediators on the intestinal handling of water and electrolytes. They used dog jejunum as an experimental model for carcinoid syndrome. Infusion of 5-HT increased jejunal bowel motility and Na^+ and water secretion. When they pretreated the dogs with intravenous ketanserin before infusing the 5-HT, ketanserin reduced both the rate and strength of bowel contractions. Ketanserin also reversed serotonin's secretory affect on water and sodium flux. These findings suggest a possible therapeutic role for ketanserin in limiting carcinoid symptoms of diarrhea.

In a study examining the effect of 5-HT_2 receptor blockade on the subjective changes and induced changes in serum levels of 5-HT, Ahlman et al.[177] pretreated carcinoid patients with ketanserin. Subsequently, they gave them a pentagastrin challenge. Pentagastrin leads to a release of serotonin and precipitates carcinoid syndrome in sensitive patients. After pretreatment with ketanserin, they reported decreases in facial flushing and almost complete blockade of gastrointestinal complaints (although they do not explain how they quantified these changes), without affecting the pentagastrin-induced release of serotonin. These findings seem to implicate 5-HT in the development of the carcinoid gastrointestinal symptoms, supporting the conclusions of the preceding study. Because ketanserin did not alter the induced release of serotonin, it seems logical that ketanserin blocked the peripheral effects of serotonin on the bowel.

Gustafsen and colleagues[178] tested ketanserin as a treatment for carcinoid syndrome in a double-blind, placebo-controlled, crossover design study. They gave seven symptomatic patients either placebo or oral ketanserin for one week (all but one patient had received prior ketanserin treatment for two years). The patients reported whether their symptoms were increased, reduced, or unchanged. Ketanserin reduced the incidence and intensity of flushing in five of seven patients. Two of seven patients reported a reduction in diarrhea. Because the study involved a small number of patients familiar with the effects of ketanserin, we must be cautious in our conclusions based on this study. Perhaps the patients knew if they were on active medication because of an alternate effect of ketanserin with which they were familiar (i.e., fatigue, headache). This would tend to invalidate the placebo control.

Ketanserin may prove useful in alleviating some of the symptoms of carcinoid. Experimental evidence seems to support a more significant role of serotonin as a mediator of the gastrointestinal symptoms compared with the facial flushing.[177] One would not expect a vasodilator (such as ketanserin) to be useful as a treatment in a syndrome characterized by blood vessel dilation. We must also remember that carcinoid syndrome is associated with the release of many biologically active products (i.e., histamine, prostaglandins, pancreatic polypeptide, substance P, neurotensin, motilin, gastrin, insulin, parathyroid hormone, glucagon, adrenocorticotropic hormone, calcitonin, and probably others) that may also contribute to carcinoid symptomatology. Serotonin blockade would not be expected to alleviate those conditions not mediated by 5-HT.

Urodynamic Effects of Ketanserin

Besides circulatory applications, ketanserin shows promise in urology because of its effects on the bladder, urethral muscle, and penile detumescence. Scientists first learned of serotonin's ability to increase bladder contractility in the 1950s.[179] Unfortunately, the lack of specific antagonists left this, like the rest of serotonology, a finding devoid of clinical relevance. Ketanserin's synthesis brought new hope for the treatment of unstable bladders.

Delaere et al.[179] studied the effect of intravenous ketanserin in 17 patients with unstable bladders, and surprisingly found no changes in intravesicle volume or mean bladder contraction pressure. Even more unexpectedly, they found that women with normal bladder function experienced a significant increase in maximal urethral flow rate, suggesting decreased urethral pressure. Analysis of urethral pressure profiles showed a highly significant decrease in urethral closure pressure in all women, most pronounced 15 minutes after drug administration. This was accompanied by a decrease in functional urethral length after 5 and 15 minutes. (The men experienced only a slight decrease in urethral pressure, and their urethral lengths were not studied.) These findings suggested there was no significant S_2-related activity in the bladder, and that the effect on urethral muscle was identical to that seen with α-adrenergic blockade.

To clarify serotonin's role in micturition, Klarskov et al.[180] conducted an *in vitro* study of bladder and urethral muscle. Detrusor, trigone, and urethral strips from pigs and humans responded in dose-related fashion to serotonin; the detrusor contracted, whereas the trigonal and urethral segments relaxed. Serotonin probably mediated this action because atropine, ketoprofen, tetrodotoxin, propranolol, hexamethonium, phentolamine, guanethidine, or morphine could not oppose it. Ketanserin, however, even at concentrations high enough to produce complete antagonism with vascular muscle, only produced partial antagonism in this system. Methysergide also produced only partial antagonism. These studies suggest the involvement of receptors other than S_2 to account for serotonin's action on the bladder wall.

Preliminary work by Horby-Peterson et al.[181] reveals that ketanserin may have a role in erectile dysfunction. A group of four patients received an injection of ketanserin, with increases in penile circumference ranging from 12 to 35%. In all four patients, the circumference decreased to initial value 40 minutes after injection. The authors attribute this effect to ketanserin's vasodilator properties.

Ketanserin may prove useful in the treatment of neurogenic bladder by virtue of its α-blocking effect on urethral muscle. It may also have a role in impotence by increasing penile tumescence.

CONCLUSION

Serotonin antagonism may play an important role in future cardiovascular and non-cardiovascular therapy. The drug ketanserin holds the most promise in the treatment of hypertension, congestive heart failure, pulmonary emboli, early adult respiratory distress syndrome, and preeclampsia. Additionally, it may prove to be very valuable in preventing intercurrent cardiovascular events. The results of the PACK study show that caution must be exercised with the use of ketanserin in combination with potassium-losing diuretics.

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