New Cardiovascular Drugs 1987

Editor

Alexander Scriabine, M.D.

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Preface

The fifth volume of the series *New Cardiovascular Drugs* consists of 12 chapters covering pharmacology, pharmacokinetics, metabolism, toxicology, and clinical use of new drugs for therapy of cardiovascular diseases. Six chapters deal with new antihypertensive drugs. The contributors are industrial and academic scientists from the United States, Federal Republic of Germany, Switzerland, Belgium, and Japan.

The emphasis on antihypertensive drugs reflects intensive activity in this field. In addition to β-adrenoceptor antagonists, vasodilators, calcium channel antagonists, and converting enzyme inhibitors, drugs with possibly novel mechanisms of antihypertensive action, e.g., ketanserin, are described in this volume. All these drugs are in advanced stages of development.

Drugs with novel mechanisms of action were discovered not only for the treatment of hypertension but also for the treatment of other cardiovascular diseases. A cardiac stimulant (DPI 201–106) described in this volume is of conceivable usefulness in the therapy of heart failure; it is thought to have Na^+ channel agonistic action as well as an ability to sensitize contractile proteins to calcium. An antihypoxic drug, idebenone, appears to be effective in patients with cerebrovascular diseases without any significant effect on cerebral blood flow. Its effects include acceleration of ATP formation in the hypoxic tissue and inhibition of lipid peroxidation.

The series *New Cardiovascular Drugs* is now widely known among cardiovascular pharmacologists and clinical investigators. It is highly useful for all scientists involved in drug development.

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Ketanserin

Jan M. Van Nueten, Paul A. J. Janssen, Jan Symoens, Walter J. Janssens, Jozef Heykants, Fred De Clerck, Josée E. Leysen, Herman Vancauteren, and *Paul M. Vanhoutte

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Serotonin has multiple actions on the cardiovascular system (197). In the vasculature it causes either constriction or dilatation (45,260). The constrictor effects are due mainly to a direct action of the monoamine on vascular smooth muscle cells or to amplification of the effects of other endogenous vasoconstrictors. They are mediated mainly by S_2-($5HT_2$)-serotonergic receptors, which also mediate the platelet aggregation induced by the monoamine. The vasodilator component of the action of serotonin can be ascribed mainly to the release of a vasodilator substance from the endothelium or to inhibition of adrenergic neurotransmission; these effects are mediated by serotonergic receptors, which share pharmacological characteristics with S_1-($5HT_1$)-binding sites in the brain (260). Until recently drugs exhibiting selective antagonism of S_2-serotonergic receptors were not available. The antagonists available possessed partial agonistic properties or also inhibited effects of serotonin not linked to S_2-serotonergic receptors (e.g., vasodilatation). Ketanserin, 3-[2-[4-(*p*-fluorobenzoyl)piperidino]ethyl]-2,4(1H,3H)-quinazolinedione (Fig. 1), is the first specific S_2-serotonergic blocking agent devoid of partial agonistic properties (see references in 132). Ketanserin lowers blood pressure in hypertensive patients. Its mechanism of action as an antihypertensive agent is complex. This chapter summarizes the pharmacology, clinical experience, pharmacokinetics, and toxicity of ketanserin.

RECEPTOR BINDING PROFILE

Radioligand binding studies (using brain tissue homogenates and radioactively labeled serotonergic agonists and antagonists) have detected different types of serotonergic binding sites. The early classification distinguished $5HT_1$ (5-hydroxytryptamine$_1$; also named S_1-serotonergic) sites labeled by ^{3}H-serotonin in membrane preparations of various brain areas, and $5HT_2$ (S_2-serotonergic) sites

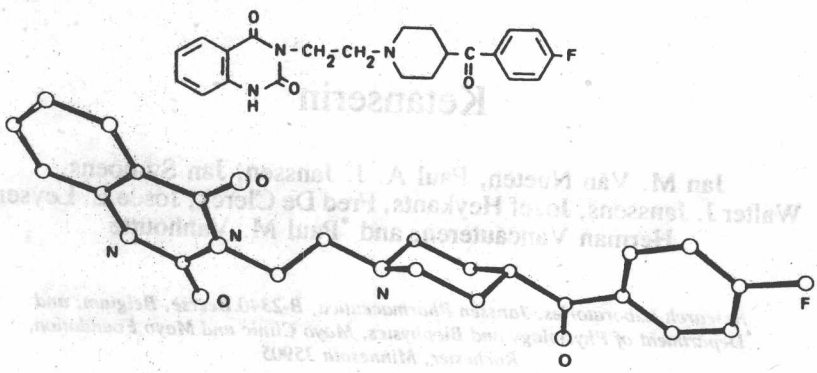

FIG. 1. Chemical structure of ketanserin.

labeled by ^{3}H-spiperone in frontal cortex tissue (12,148,150,201). $5HT_1$ sites have been subclassified as $5HT_{1A}$, $5HT_{1B}$, and $5HT_{1C}$ subtypes based on the observation of biphasic inhibition curves with certain drugs or selective displacement in particular brain areas. Spiperone, 8-OH dipropylaminotetraline (80HDPAT), and spiroxatrine distinguish $5HT_{1A}$ subtypes (177,189,200), and ^{3}H-8-OH dipropylaminotetraline selectively labels the $5HT_{1A}$ sites (100). [^{125}I]Iodocyanopindolol (a β-adrenergic blocking agent) labels $5HT_{1B}$ sites when binding to β-adrenoreceptors is precluded (121). Mesulergine selectively inhibits the labeling of $5HT_{1C}$ sites by ^{3}H-serotonin in the choroid plexus (198). In the latter tissue, similar sites are labeled by ^{3}H-mesulergine (122) and by ^{125}I-lysergic acid diethylamine (297). Various pharmacological and physiological effects have been attributed to $5HT_1$ receptor subtypes, e.g., components of the serotonergic syndrome in rodents (243), inhibition of serotonin and norepinephrine release from nerve endings (79), constriction of cerebral vascular smooth muscle (203), and production of cerebrospinal fluid (297). However, the physiological role of $5HT_1$ receptors remains to be established firmly because of the paucity of selective agonists and antagonists acting at $5HT_1$ binding sites (157,183,243,274).

S_2-serotonergic sites can be labeled with various serotonergic antagonists, to which ^{3}H-ketanserin was the first selective ligand (153). Using this ligand S_2-serotonergic receptor sites were labeled on membrane preparations of various brain areas of several mammalian species including humans and on the spinal cord and platelets of the cat (153–155,224). ^{3}H-ketanserin also labels solubilized S_2-serotonergic receptor sites (129,295), and it is a suitable ligand for *in vivo* labeling of S_2-serotonergic receptor sites (144). Other ligands such as ^{3}H-spiperone (148), ^{3}H-mianserin (202), ^{3}H-LSD (11), ^{125}I-LSD (107) are less selective (157). Known serotonergic antagonists, belonging to several chemical classes, display high binding affinity (in the nanomolar range) for S_2-serotonergic receptor sites, whereas serotonin

itself and serotonergic agonists have binding affinities in the micromolar range (157).

By correlating the *in vitro* measured binding affinities of drugs with their potency to antagonize pharmacological effects, S_2-serotonergic sites were linked to several central and peripheral roles. In the central nervous system, S_2-serotonergic sites mediate behavioral excitation induced by serotonergic agonists in rodents (tremor and clonic seizures induced by tryptamine, head twitches induced by mescaline and 5-hydroxytryptophan) and discriminative stimulus effects elicited by serotonergic agonists (LSD, quipazine); a role in mood disorders is also possible (157). Peripheral effects of serotonin mediated by S_2-serotonergic receptors are vaso- and bronchoconstriction and platelet aggregation (51,150,153,154,156,265, 267,270). In human platelets the phosphoinositide turnover forms part of the signal-transducing system coupled to S_2-serotonergic receptor sites (43,44). The second messengers involved include inositol trisphosphate (which has a role in mobilization of intracellular Ca) and diacylglycerol (which activates protein kinase C) (14).

Serotonergic antagonists distinguish to various extents between the serotonergic binding site subtypes (Table 1). In addition to the actual ability of a drug to differentiate between binding site subtypes related to a particular neurotransmitter, the specificity of a drug is determined by the binding profile, which comprises its binding affinity for various neurotransmitter receptor sites (148). Table 2 summarizes the receptor binding profile of ketanserin and other reference serotonergic antagonists; it describes the affinities of these drugs for H_1-histaminergic, α_1- and α_2-adrenergic, D_2-dopaminergic, and cholinergic muscarinic receptor sites.

The data in Tables 1 and 2 reveal that ketanserin is selective and specific for

TABLE 1. *Binding affinities of drugs for serotonin receptor binding sites*

	K_i values (nM)			
Drug	$5HT_{1A}$[a] ^{3}H-80HDPAT rat cortex[b] hippocampus[a]	$5HT_{1B}$[b] ^{125}I-CYP rat cortex	$5HT_{1C}$[b] ^{3}H-mesulergine pig choroid plexus	$5HT_2$[b,c] ^{3}H-ketanserin rat frontal cortex
Ketanserin	1,900[b]	1,900[b]	98[b]	0.39[c]
Pizotifen	1,770[a]	na	na	0.28[c]
Cyproheptadine	790[a]	na	na	0.44[c]
Mianserin	1,150[b]	4,680[b]	10[b]	1.4[c]
Cinanserin	1,100[a]	10,000[b]	200[b]	2.0[c]
Metitepine	72[b]	50[b]	28[b]	0.39[c]
Spiperone	42[b]	4,790[b]	1,150[b]	0.53[c]
Metergoline	6.0[b]	25[b]	0.5[b]	0.28[c]
Methysergide	57[a]	na	na	0.94[c]
Mesulergine	275[b]	1,320[b]	1.6[b]	3.8[b]
Iodocyanopindolol	4.0[b]	0.32[b]	9,770[b]	na

[a] Data from ref. 100.
[b] Data from ref. 122.
[c] Data from ref. 153.
na not available.

TABLE 2. *Binding affinities of drugs for various neurotransmitter receptor sites*

Drug	K_i values (nM)				
	Histamine-H_1 ^{3}H-pyrilamine guinea pig cerebellum	Adrenergic-α_1 ^{3}H-WB4101 rat forebrain	Adrenergic-α_2 ^{3}H-clonidine rat cortex	Dopamine-D_2 ^{3}H-haloperidol rat striatum	Cholinergic muscarinic ^{3}H-dexetimide rat striatum
Ketanserin	10	10	>10,000	220	>10,000
Pizotifen	1.9	120	480	99	23
Cyproheptadine	2.7	100	790	31	19
Mianserin	2.9	82	60	620	>10,000
Cinanserin	1,200	1,200	>10,000	1,600	>10,000
Metitepine	4.9	0.47	48	4.0	>10,000
Spiperone	>10,000	10	>10,000	0.16	>10,000
Metergoline	1,100	38	380	23	>10,000
Methysergide	>10,000	2,300	2,600	200	>10,000

Data from ref. 151.

S_2-serotonergic receptor sites. The drug has a binding affinity for S_2-serotonergic sites in the nanomolar range; a similar potency is found when the S_2-serotonergic binding sites are labeled in various tissues using different labeled ligands (3,21, 24,31,80,96,108,130,133,149,151,154,179,199,203,224,284). Ketanserin is selective because it distinguishes between S_2- and S_1-serotonergic binding site subtypes with a potency difference larger than 250-fold. By contrast, the ergot derivatives, e.g., metergoline, methysergide, and mesulergine, differentiate poorly between the various serotonergic binding sites. Ketanserin is specific because it has a higher binding affinity (at least 25-fold) for S_2-serotonergic sites than for H_1-histaminergic and α_1-adrenergic receptor sites. Cinanserin also can be considered selective for S_2-serotonergic sites. However, other known serotonergic antagonists, e.g., cyproheptadine, pizotifen, and mianserin, bind with equal affinity to S_2-serotonergic and H_1-histaminergic sites. Metitepine potently binds to several receptor sites, and spiperone displays its highest binding affinity for D_2-dopaminergic sites.

PHARMACODYNAMICS

Platelets

Direct Effects of Serotonin

Serotonin interacts with blood platelets to produce activation inducing shape change, aggregation, and possibly the release of cellular products (49,51). This activation is due to specific interaction of serotonin with S_2-serotonergic receptors on the platelet membrane (52,53).

Serotonin-induced aggregation of human, dog, cat, or rat platelets is inhibited by ketanserin in a dose-dependent way (Fig. 2) (49,53,176). This inhibition is observed in clinically relevant concentrations (176). The specificity of this inhibition

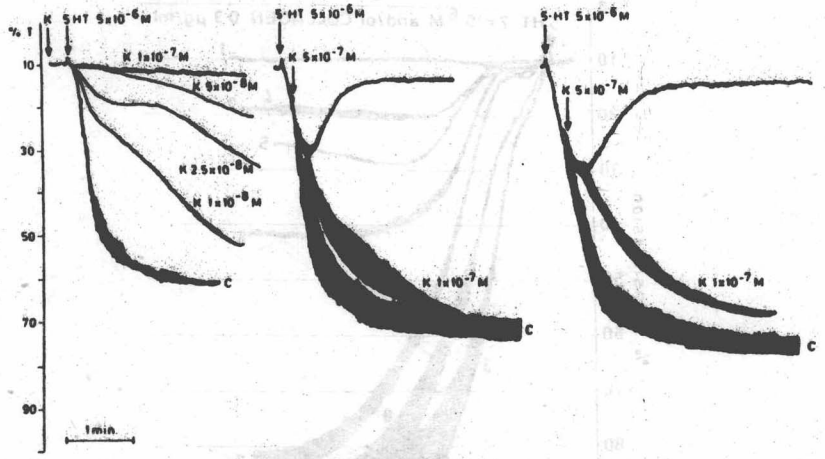

FIG. 2. Determination of serotonin-induced platelet aggregation (measured as an increase of light transmission) in platelet-rich plasma samples of the cat under control (solvent) conditions (C) and its inhibition by ketanserin (K) administered 10 sec before the addition of serotonin (left) and 10 sec (middle) or 20 sec (right) after induction of aggregation. (From ref. 51.)

is demonstrated by the findings that ketanserin does not significantly affect the primary aggregation reaction induced by other aggregating agents such as adenosine diphosphate (ADP), *l*-epinephrine, or thrombin (15,47,53).

Amplifying Effects of Serotonin

Aggregation of platelets leads to release of serotonin and biosynthesis of prostanoids such as thromboxane A_2. The monoamine itself can facilitate further aggregation of platelets in several mammalian species. Although serotonin has a weak aggregating action on normal human platelets, it strongly augments (amplifies) the aggregation of platelets induced by low concentrations of other agonists, including ADP, collagen, epinephrine, and norepinephrine. It also enhances the release reactions. The amplification by serotonin of platelet reactions to other aggregating substances is inhibited *in vitro* and *in vivo* by low concentrations of ketanserin in various species including man (Fig. 3), demonstrating the involvement of S_2-serotonergic receptors (47,99).

Secondary Platelet Recruitment

During the aggregation process induced by various agonists, platelets release a number of mediators including serotonin. The platelet activating and amplifying

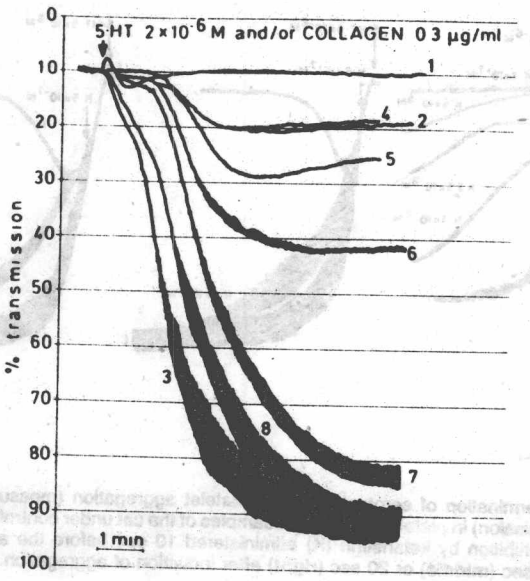

FIG. 3. Platelet aggregation in human platelet-rich plasma. Serotonin amplified the response to a threshold concentration of collagen. This amplification is inhibited with ketanserin: (1) 5HT; (2) collagen (COLL); (3) 5HT + COLL; (4) 5HT + COLL + ketanserin (5×10^{-7} M); (5) 5HT + COLL + ketanserin (1×10^{-7} M); (6) 5HT + COLL + ketanserin (7.5×10^{-8} M); (7) 5HT + COLL + ketanserin (5×10^{-8} M); (8) 5HT + COLL + ketanserin (1×10^{-8} M). (From ref. 47.)

effects of this endogenously released serotonin may stimulate the release reactions and therefore contribute to a secondary platelet recruitment to form an irreversible aggregate. These secondary effects of endogenously released serotonin are prevented by ketanserin (15,54). Through such mechanisms, ketanserin may reduce the platelet release reaction *in vivo*, as evidenced by the reduction of plasma β-thromboglobulin levels in patients with cardiovascular disease treated with the drug (62).

In particular conditions serotonin can behave as a potent platelet agonist by amplifying the effect of other agonists, thereby contributing to the propagation of an irreversible aggregate *in vitro*. By such mechanisms it may contribute to the mechanical obstruction of a blood vessel by a platelet thrombus. This conclusion is substantiated by the observation that ketanserin reduces experimental thrombus formation. Thus in the rat ketanserin reduces the thrombotic obstruction of the carotid artery damaged to thrombogenicity by freezing or electrical stimulation. The drug also prevents thrombus formation in canine coronary arteries damaged by electrical stimulation or a mechanical constrictor (Fig. 4) (25,104,123,218).

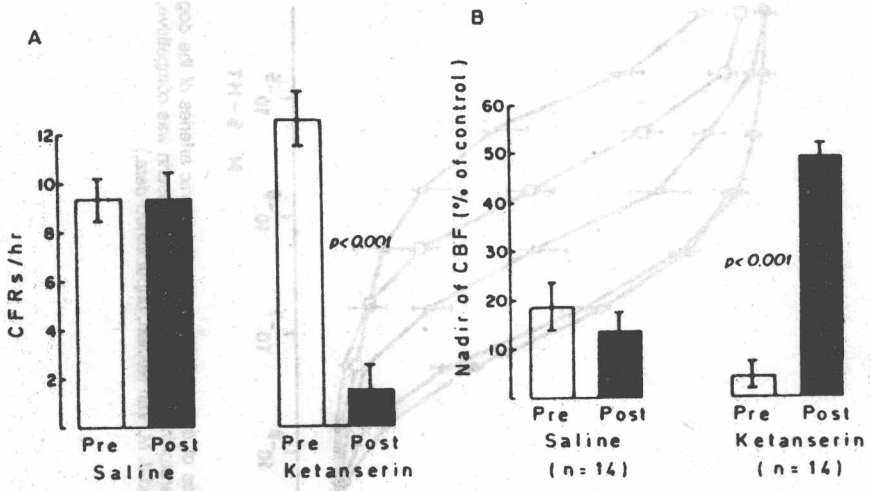

FIG. 4. **A:** The number of cyclic flow reductions per hour (CFRs) due to platelet aggregates in the canine coronary artery damaged by a mechanical constrictor before and after saline, or ketanserin (0.25–0.5 mg/kg i.v.). **B:** The maximum depression, or nadir, of coronary blood flow (CBF) during coronary blood flow reductions was computed by averaging the three lowest values during each 1-hr interval. (From ref. 25.)

Platelet Uptake of Serotonin

Platelets can take up serotonin and store it in intracellular granules. Ketanserin does not inhibit the uptake of serotonin into platelets at concentrations that block their activation by the monoamine (15,47,145,146,221). These findings provide further evidence for the involvement of different serotonergic receptors in serotonin-induced platelet aggregation and uptake of serotonin in platelets (15,19,146). Ketanserin is a potent functional S_2-serotonergic receptor blocker but a weak inhibitor of serotonin uptake.

Vascular Tissues

Direct Vasoconstrictor Effects of Serotonin

In vitro

In most large arteries and veins, serotonin causes contraction by activation of serotonergic receptors in the vascular smooth muscle cells. Usually these vascular contractions are inhibited by ketanserin in a dose-dependent way (Fig. 5).

This antagonism is of the competitive type (pA_2 values from 8.4 to 9.1) in

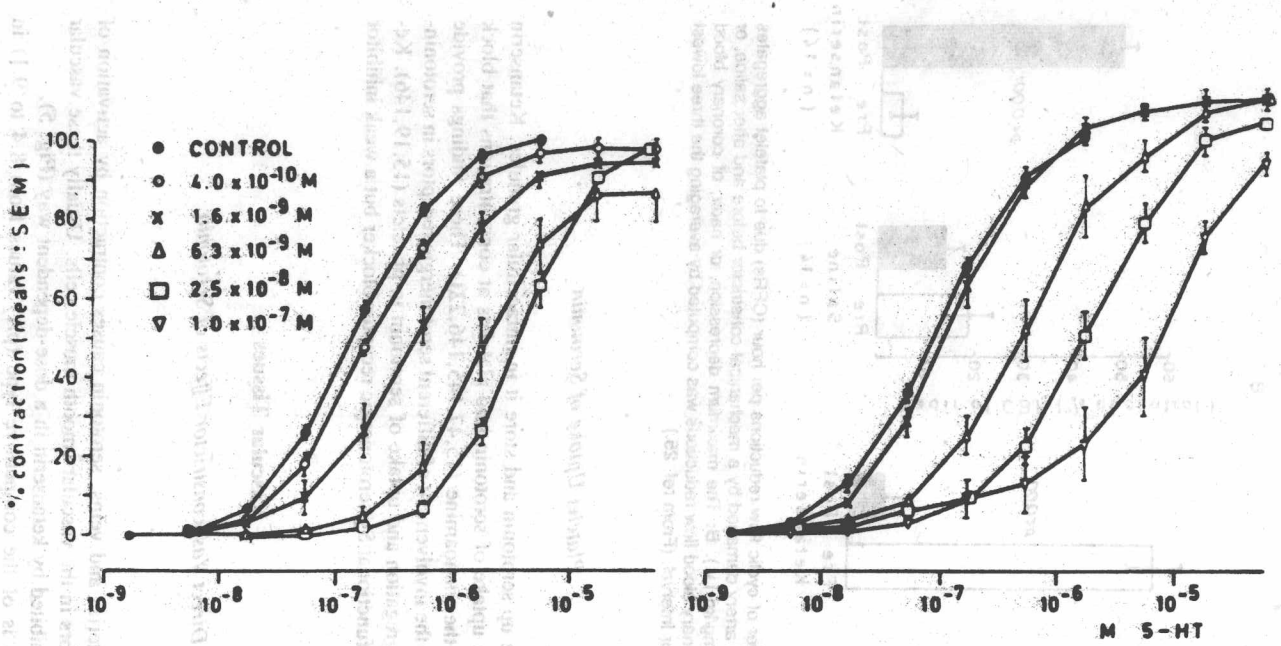

FIG. 5. Cumulative dose-response curves to serotonin (5-HT) on isolated caudal arteries of the rat (left) and gastrosplenic arteries of the dog (right). Ketanserin caused a dose-dependent inhibition of the contraction induced with serotonin. The antagonism by ketanserin was competitive, as indicated by the parallel shift to the right of the dose-response curve. (From ref. 265 and J. M. Van Neuten, *unpublished data.*)