Chapter 8. Antihypertensive Agents

W. Lesley Matier and William T. Comer, Mead Johnson & Company
Evansville, Indiana

Introduction - This review covers advances in the understanding and drug treatment of hypertension during the past year. Diuretics remain the most widely used class of antihypertensives, and the first agent selected for mild hypertensives is usually a diuretic; these agents are discussed in Chapter 7. A new mechanistic approach to treating hypertension with angiotensin converting enzyme inhibitors is covered separately in Chapter 9. The structures of drugs discussed in this chapter are shown or may be found in recent volumes of "Annual Reports in Medicinal Chemistry."

General - The clinical pharmacology[1] of antihypertensive drugs, their use in hypertensive emergencies,[2] and in rational combinations,[3] have been reviewed. In the U.S.A., the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure recommends a stepwise approach to treating hypertension starting with a diuretic.[4] The causes of hemodynamic changes in essential hypertension and their normalization by drug treatment was the topic of a symposium,[5] as was the important role of the sympathetic nervous system in the etiology and maintenance of hypertension.[6] As with renin levels, subgroups of patients with elevated plasma catecholamine levels have now been identified.[7] The vascular damage associated with hypertension may be due to increased synthesis and deposition of collagen in arteries resulting in fibrosis.[8] Vascular damage in hypertensives may also be related to blood velocity;[9] propranolol and clonidine decrease blood velocity and may therefore be preferred over methyldopa and hydralazine which increase blood velocity.

Centrally Acting Antihypertensives - The centrally acting drugs, α-methyldopa and clonidine, continue to be widely used. The action of methyldopa or clonidine is not dependent on patients' renin states although these drugs do lower renin levels.[10,11] A decarboxylase inhibitor failed to block methyldopa's hypotensive action,[12] and its active metabolite, α-methylnorepinephrine, was found more potent than norepinephrine in impairing sympathetic transmission by presynaptic α-receptor stimulation.[13] Methyldopa,[14] but not clonidine,[15] allowed stable blood pressure control when given once daily in high dose.

Clonidine causes physiological changes in patients similar to propranolol, but by an entirely different mechanism. It has been used in place of a β-blocker[16] and in combination with the vasodilator minoxidil.[17] Clonidine has been reported to induce diuresis in hypertensive patients being treated with minoxidil and propranolol.[17]

Studies on the action of clonidine in cats support inhibition of

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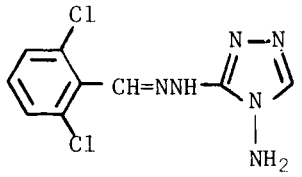
central sympathetic outflow as its major hypotensive mechanism.[18] Similarly, in tetraplegic patients with cervical spinal cord transection, clonidine did not lower blood pressure, indicating that in man, as in animals, intact bulbospinal pathways are needed.[19] Stimulation of peripheral presynaptic α-receptors may contribute to the reduction of catecholamines and blood pressure caused by clonidine,[20] whereas stimulation of postsynaptic α-receptors may account for decreased hypotensive actions of clonidine at higher doses in cats[18] and patients.[21] It has been proposed that these presynaptic α-receptors be classified as α_2 based on the response to various α-agonists. Alpha receptors in the brain mediating hypotensive effects, in the kidney mediating renin release and receptors inhibitory to melanocyte-stimulating hormone, also appear to be α_2; postsynaptic vascular α-receptors, involved in vasoconstrictor responses, are α_1.[22]

The involvement of central histamine receptors in the hypotensive action of clonidine remains uncertain. The action of this drug is antagonized by *i.c.v.* administered metiamide, a specific histamine H_2-antagonist, but the selective histamine H_2-stimulant, dimaprit (4-methylhistamine), raises blood pressure.[23] A histamine metabolite, imidazole acetic acid, exerts a strong, central, hypotensive action antagonized by metiamide and may possibly be an inhibitory neurotransmitter.[24]

Sedation and dry mouth remain the most bothersome side effects associated with clonidine therapy, whereas rebound hypertension is potentially the most dangerous. Reports of hypertensive crises associated with withdrawal of this drug continue to appear.[25,26] The hypertensive response appears to be due to a sudden reversal of the central inhibitory action of clonidine resulting in increased plasma norepinephrine levels.[27] Sedation[28] and paradoxical sleep[29] appear to be mediated by central α_2-receptors and not by histamine H_2-receptors,[30] so separation of sedation from clonidine's antihypertensive effects may not be possible. Both clonidine and methyldopa inhibit conditioned salivation in conscious dogs which is a useful animal model that correlates with the effect in man.[31]



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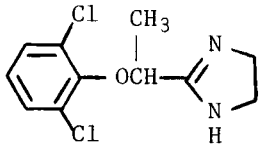
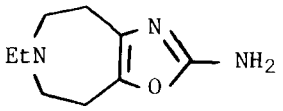


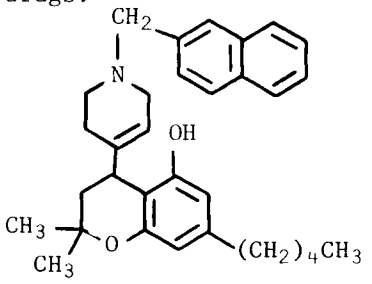
2 lofexidine



3

Several groups have reported QSAR studies of aromatic substituted analogs of clonidine.[32,33] Clonidine-like agents continue to be investigated clinically. Flutonidine,[34] guanabenz,[35] and guanfacine[36] (BS 100-141) are clinically effective agents but are not free of clonidine-type side effects. Tiamenidine, presently in clinical trials in Europe and the U.S., is reported to not cause spontaneous rebound hypertension.[37] Guanabenz[38] and the structurally similar FLA-136[39] (1) reduce norepinephrine turnover in the rat brain. The latter appears to selectively stimulate presynaptic α-receptors without affecting central or peripheral postsynaptic recep-

tors.[40] Lofexidine (2) is a new centrally acting antihypertensive in animals and man.[41] Rebound hypertension may not be a problem with this drug since urinary catecholamine excretion changed very little after its withdrawal. B-HT933 (3) is an interesting new structure showing typical clonidine-like effects in animals.[42] It has been suggested that the centrally acting antihypertensive agent, R28935, inhibits central noradrenergic neurotransmission by blocking central postsynaptic α-receptors in contrast to the stimulation of presynaptic α-receptors by clonidine and related drugs.[39]



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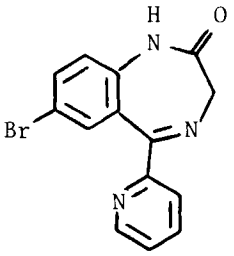
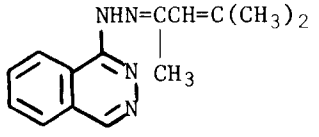


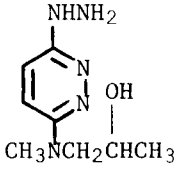
5 bromazepam

The hypotensive and bradycardic effects of Δ^9-tetrahydrocannabinol, a psychoactive constituent of marihuana, is at least partly mediated via activation of central α-receptors.[43] BRL-13776 (4), resulting from structural modification of tetrahydrocannabinols, is antihypertensive in animals, probably as a consequence of central catecholamine depletion.[44] The new benzodiazepine antianxiety agent, bromazepam (5), lowered the blood pressure of a large group of hypertensives without affecting heart rate.[45]

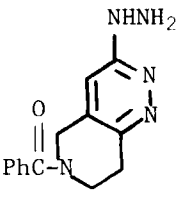
Antihypertensive Vasodilators - The clinical use of hydralazine has been reviewed.[46] It is a valuable drug when combined with β-blockers and diuretics. Its cardiac stimulating actions may be due to direct effect on the myocardium in addition to reflex activation of cardiac sympathetic nerves secondary to a decrease in blood pressure.[47] Alpha blockade enhances hydralazine's hypotensive effect by blocking the vasoconstrictor actions of reflexly released catecholamines whereas propranolol did not cause a synergistic effect.[48] Hydralazine is extensively metabolized in man mainly by N-acetylation and cyclization to triazolo derivatives and by hydrazone formation.[49] Several of these hydrazone metabolites are potent vasodilators but the triazoles are inactive.[50-52] Acetylator phenotype determines the response to hydralazine and other drugs that are extensively acetylated in man.[53] Most of the metabolites from the antihypertensive hydrazone, budralazine (DJ1461, 6), in rats arise from initial formation of hydralazine.[54] Initial clinical experiences with propyldazine[55] (ISF2123, 7) and BQ22-708[56] (8) show them to be effective hypotensives at much lower doses than hydralazine and with the expected side effects of potent vasodilators. Hydralazine, (7) and analogs with free hydrazine groups inhibit diamine oxidases at hypotensive doses.[57]



6 budralazine



7 propyldazine



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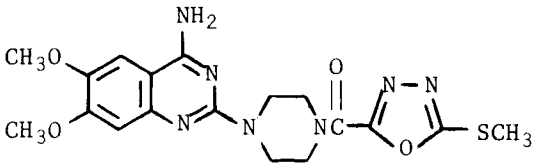
The pharmacology and clinical use of prazosin has been thoroughly reviewed[58-60] and discussed in symposia.[61,62] Many clinical studies confirm its hypotensive actions. As the sole therapy, it was found as effective as methyldopa[63] but less than hydrochlorothiazide.[64] It does not alter renal function, cardiac output, or plasma renin, but it may cause fluid retention[65] and has shown better efficacy in combination with thiazide diuretics.[66,67] The major use for this drug may be in combination with a diuretic and β-blocker in place of hydralazine. The incidence of first-dose fainting and dizziness is quite high in some studies[68,69] and is more pronounced in patients on a low sodium diet.[70] Animal studies show prazosin to be a selective α-blocker with little direct vascular relaxant action.[71,72] It blocks only postsynaptic vascular α-receptors leaving presynaptic α-receptors operational for feedback inhibition of sympathetic neurotransmitter release.[73,74] Both types of α-receptors may be present in postsynaptic tissue.[75] Prazosin is metabolized mainly by O-demethylation and glucuronide formation[76] to weakly active derivatives.[77] The prazosin analog, trimazosin, was found as active as methyldopa in mild hypertensives[78] and first reports on two new analogs, BL-5111A[79] (9) and E 643[80] (10), have appeared.



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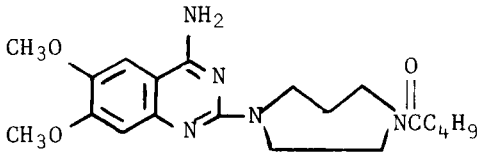

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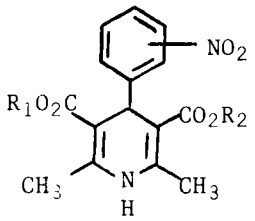
More reports have appeared on the efficacy of minoxidil in combination with a β-blocker and diuretic in treating severe hypertension resistant to standard drugs.[81,82] It may induce anginal attacks in patients with coronary artery disease[83] but concern that it may cause pulmonary hypertension seems unwarranted.[84,85] Diazoxide is an excellent drug for hypertensive crises.[86] This compound and analogs block vasoconstriction in isolated aortic rings from hypertensive rats much more than normotensive rats.[87] The clinically effective[88] vasodilator, guancydine, blocks vasoconstriction due to angiotensin II but has no effect on renin secretion.[89] Dihydropyridines, such as nifedipine (11), YC-93[90,91] (12), and niludipine (13) show potent vasodilating actions. Nifedipine was found effective for hypertensive emergencies but not for mild hypertension.[92,93]



11: $R_1=R_2=CH_3$ (2-NO_2)

12: $R_1=CH_3$, $R_2=PhCH_2N(CH_3)(CH_2)_2$ (3-NO_2)

13: $R_1=R_2=CH_3(CH_2)_2O(CH_2)_2$ (2-NO_2)

Beta-Adrenergic Blocking Agents - In the U.S.A., FDA approval for β-blockers other than propranolol has been delayed because of the possible carcinogenicity of these agents.[94,95] Metoprolol and at least six other β-blockers have completed the required two-year carcinogenicity testing and may now be used in long-term clinical trials. However, tolamolol, bunolol, and possibly timolol caused an increased incidence of tumors in

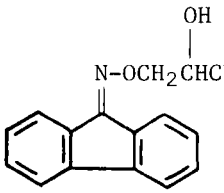
animals, and tolamolol has been withdrawn from U.S. clinical trials.[95]

The growing importance of β-blockers in the treatment of hypertension is indicated by the proliferation of publications on this subject as well as the marked increase in propranolol use. Reviews and symposia proceedings have appeared on the use of atenolol,[96] pindolol, [97] and metoprolol[98] in hypertension. β-blockers are recommended as first choice drugs[99,100] or as the "step 2" drugs of choice after diuretics.[101] A Veteran's Administration study of propranolol in a large group of mild hypertensives found that it normalized the blood pressure in about half the patients and was more effective in combination with a diuretic and with hydralazine.[102] Other β-blockers compare well with propranolol or methyldopa for treating hypertension. However, β-blockers with intrinsic sympathomimetic activity (i.s.a.) may be less effective at high doses than those without i.s.a. since they show a flat dose-response curve for blocking exercise-induced tachycardia at higher doses.[103]

Cardioselective β-blockers, such as metoprolol and atenolol, and drugs with i.s.a. such as pindolol,[104] are less likely to cause bronchospasm than non-selective agents such as propranolol, but all these drugs may cause bronchoconstriction at higher doses in asthmatics and are contraindicated.[105] Surprisingly, *d*-propranolol increases airway resistance in rats and guinea pigs as much as *dl*-propranolol suggesting that β-blockade is not the only factor responsible for the bronchoconstriction.[106] The effect of β-blockers on blood lipids remains controversial, and any advantage for β_1 or non-selective drugs is uncertain.[107] The β_1-selective drugs may be safer in diabetic patients.[108] Of concern with all β-blockers is their potential to cause the oculomucocutaneous syndrome associated with practolol, but such an effect has not so far been seen with β-blockers other than practolol.[109]

Most β-blockers, with the exception of sotalol[110] and nadolol, have relatively short plasma half-lives.[5] However, several of these drugs[5,97,111] are effective on a once-daily schedule since their hypotensive action in man lasts for many hours after their disappearance from plasma.

How β-blockers lower blood pressure is still unclear. Various central actions of some β-blockers have been demonstrated, but there is little direct evidence that centrally mediated blood pressure lowering occurs in man.[112] Some of the central effects may be mediated by blockade of serotonin uptake.[113] The inhibition of renin secretion by these drugs continues to attract many investigators. However, except in a small number of patients with renin-dependent forms of hypertension, renin lowering does not seem to be the major factor in the hypotensive response.[114] Sotalol decreases norepinephrine release from sympathetic nerve endings by its action on presynaptic β-receptors,[20] but the physiological significance of this action remains uncertain. A new hypothesis concerning the mechanism of β-blockers in hypertension stresses the importance of blocking vascular β_2-receptors thereby allowing adenyl cyclase to regain responsiveness to physiological vasodilators such as histamine and PGE_2.[115] In agreement with this concept, indomethacin, a PG-synthesis inhibitor, blocks the hypotensive action of β-blockers in rabbits and in patients.[116]



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The recognized ability of β-blockers to acutely decrease cardiac output and chronically decrease peripheral resistance are still important contributing mechanisms to their lowering of blood pressure. In fact, several of these mechanisms may simultaneously contribute to the hemodynamic profile of β-blockers, and β-adrenergic blockade itself remains the single pharmacologic parameter most predictive of clinical usefulness in lowering blood pressure.

Two new agents, 14[117] (IPS-339) and 15,[118] are selective β_2-receptor blockers. The oxime ether, 14, is an extremely potent β_2-blocker *in vitro* (β_2/β_1=155) and *in vivo*; however, it raised blood pressure in normotensive and hypertensive rats.[119]

In addition to the 18 β-blockers already marketed somewhere in the world,[120] as well as those in advanced clinical trials, new agents continue to be developed. Preclinical pharmacology on the cardioselective agent, bevantolol[121] (16), and the non-selective, bufurolol[122] (17), has appeared. Mepindolol (2-methylpindolol) is even more potent than pindolol but has less inotropic effect on the heart.[123] Carazolol (18) is more potent than 15 well-known β-blockers and has a high therapeutic index.[124] Structural requirements for cardioselectivity in ureido and acylamino analogs of atenolol and practolol have been clarified.[125,126] In *N*-oxyalkyl compounds of the tolamolol type, the oxygen of the N substituent appears to play a major role in determining selectivity.[127]

Ar-X-CH(OH)CH_2NH-R

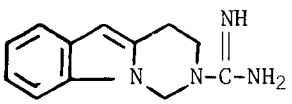
	Ar	X	R
15	4-benzimidazolyl	OCH_2	i-Pr
16	3-methylphenyl	OCH_2	3,4-dimethoxyphenethyl
17	2-[7-ethylbenzofuranyl]	--	t-Bu
18	4-carbazolyl	OCH_2	i-Pr
19	4-hydroxy-3-[NH_2CO]phenyl	--	1-methyl-3-phenylpropyl
20	4-[4-CF_3-imidazolyl]phenyl	OCH_2	t-Bu
21	5-benzodioxolyl	--	t-Bu/i-Pr
22	3,4-dihydroxyphenyl	OCH_2	t-Bu
23	3-HO-4-CH_3SO_2NH-phenyl	OCH_2	t-Bu

The stage has now been reached where any new β-blocker needs a unique characteristic to justify its development. Labetalol (AH 5138, 19), a drug with both α- and β-antagonist actions,[128,129] has been introduced in the U.K. This drug, given *i.v.*, lowers blood pressure by decreasing vascular resistance and cardiac output with very little negative inotropy.[130] Postural hypotension is common after labetalol *i.v.*[131] but not *p.o.*[132] It is useful for hypertensive emergencies[133] and is an effective antihypertensive agent in some patients not well controlled by other β-blockers;[134] it does not induce bronchoconstriction.[135] A similar concept to labetalol has led to the development of an agent that combines β-blocking and direct vasodilating actions in a single molecule.[136] Compound 20 is as potent as hydralazine in lowering blood pressure in SH rats,

it causes cardioselective β-blockade in dogs and increases iliac blood flow in the dog hind limb by a direct vasodilator mechanism. The benzodioxoles[137] (21, R=i-Pr or t-Bu) may have an action in addition to β-blockade since they lower blood pressure in SH rats after single oral doses.

Structural requirements for good β-adrenergic receptor affinity have been determined using "adenyl cyclase coupled" β-receptors on frog erythrocyte membranes labelled with (-)-[^{3}H] alprenolol.[138] These results agree well with SAR's established in whole organ systems and strongly support the existence of the hypothetical β-adrenergic receptors. In membrane systems from rabbit heart, lung, and uterus, the β_1-selectivity of practolol and atenolol compared to propranolol is maintained at the β-receptor-adenyl cyclase level, although to a lesser degree.[139] Although the phenoxypropanolamine structure is usually associated with β-blocking activity, 22 and 23 are potent agonists.[140] Their ability to assume a rigid, bicyclic, hydrogen-bonded conformation may explain the similarity of receptor binding of these agents and phenethanolamines.[140] Surprisingly, 23 shows β_1 selectivity as an agonist.

Peripheral Sympathetic Nerve Inhibitors - The interaction of guanidine antihypertensives with other drugs has been reviewed.[141] New interest has developed in the use of guanethidine in mild hypertension in addition to its traditional use in severe hypertension. It has been found to be more effective than a thiazide diuretic and caused few side effects in mild-moderate hypertension when given in single, daily, low doses.[142] It was superior to bethanidine in a large group of moderate-severe hypertensives.[143] Structural damage to noradrenergic neurones after chronic high doses of guanethidine does not seem to be related to its useful pharmacological actions and is probably unimportant in normal use.[144] The wide variation in the dose of debrisoquin needed to control blood pressure appears due to genetic differences in patients' ability to metabolize it to the 4-hydroxy derivative.[145] Sympathetic blocking drugs should not be used in hypertensive patients particularly prone to exertional hypotension.[146] Several new sympathetic inhibitors including EMD 21192[147] (24) and guanazodine[148] (25) are being tested clinically.



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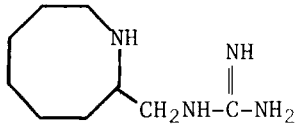
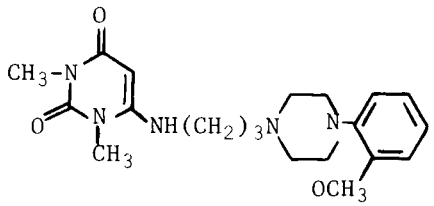


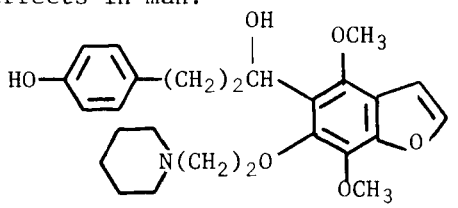
25 guanazodine



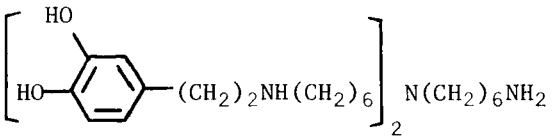
26 urapidil

Miscellaneous Antihypertensives - The recently reported drugs, urapidil[149] (26) and piprofural[150] (27), lower blood pressure by central and complex peripheral effects including α-blockade. The latter drug also has antiarrhythmic properties and inhibits calcium influx into muscle cells. The dopamine derivative, Sandoz 27-403 (28) was identified from a search for a substance that would stimulate vascular dopamine receptors without affecting α- and β-adrenoceptors.[151] It lowers blood pressure in normotensive dogs at 2.5 μg/kg *i.v.*, but not *p.o.*, by dilation of vessels in the mes-

enteric and renal vascular beds without reflex tachycardia. Its hypotensive action is blocked by the dopamine antagonists, haloperidol and ergometrine. Bromocryptine, another dopamine agonist, has antihypertensive effects in man.[152]



27 piprofural



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