Clinical application of new antihypertensive drugs

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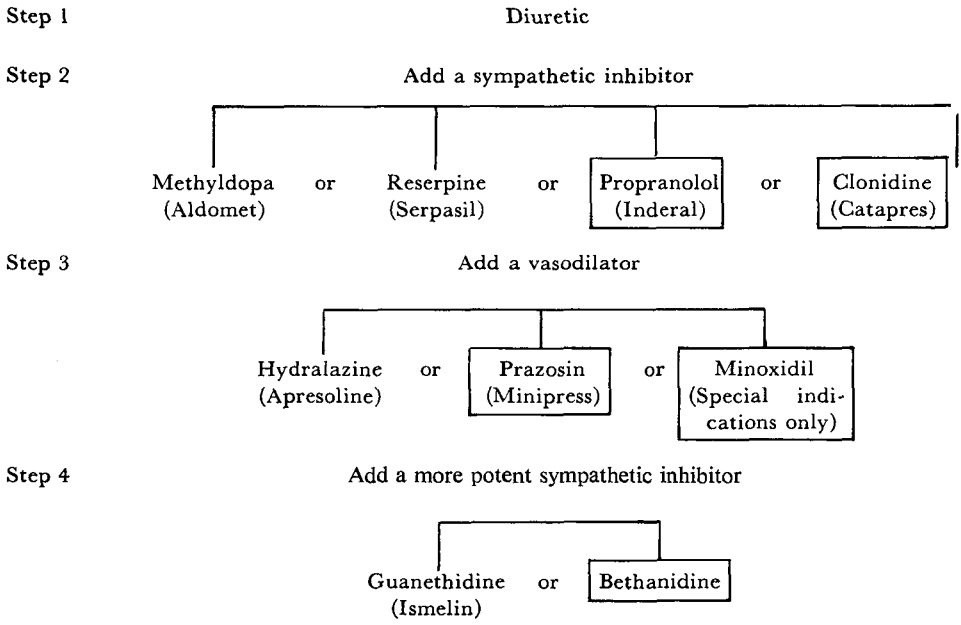
Within the past 2 years several new antihypertensive agents have been introduced for clinical use, and within the next 2 years it is anticipated that several more will be approved by the FDA. It is the purpose of this communication to describe some of these new agents and to indicate how they can be used to best advantage in the management of hypertension.

New sympathetic inhibiting agents

Propranolol (Inderal). The beta blocking agent propranolol which has been approved for managing angina pectoris, cardiac arrhythmias, pheochromocytoma, and idiopathic hypertrophic subaortic stenosis is being widely used for treating hypertension. Official FDA approval of propranolol for treatment of hypertension is expected momentarily.

It is an effective antihypertensive agent, especially when used in conjunction with an oral diuretic and hydralazine (*Table*). The mechanism of its antihypertensive action is not known, although numerous hypotheses have been advanced. It decreases cardiac output by blocking the beta receptors in the heart, but at the same time it increases peripheral resistance by blocking the beta receptors in the arterioles, stimulation of which causes vasodilation. It suppresses renin release by the kidney, but other beta

Table. Role of new therapeutic agents in the ambulatory treatment of hypertension



blocking agents which do not suppress renin activity are equally effective as antihypertensive agents. Furthermore, propranolol does not suppress diuretic induced hyperreninemia, even though it produces an additional antihypertensive effect when added to a diuretic. Direct injection of propranolol into the cerebral ventricles of rabbits results in a prolonged depressor response, suggesting a central action.

Whatever its mechanism of action, and it may not be the same in every case, it has been a valuable addition to the list of antihypertensive drugs. When used with an oral diuretic it is effective in managing mild or moderate hypertension, and the combination of an oral diuretic, propranolol, and hydralazine is one of the most potent antihypertensive regimens available. Propranolol is effective in severe and malignant hypertension and usually causes fewer unpleasant side effects than a regimen containing guanethidine.

Usually the drug is well tolerated and side effects are infrequent. They include nausea, vomiting, light headedness, bizarre mental aberrations, depression, and mild diarrhea or constipation.

Beta blockade can precipitate or aggravate congestive heart failure in patients with preexisting heart disease and can aggravate bronchial asthma and peripheral ischemia in patients who already have a propensity to asthma or who already have chronic occlusive arterial disease. Beta blockade can also mask the warning symptoms of hypoglycemia which are mediated by the beta receptor and can inhibit the release of glycogen in response to hypoglycemia, thus prolonging its duration. For these reasons

propranolol should not be given to insulin dependent, brittle diabetics. It is contraindicated in the presence of second or third degree heart block. The usual starting dose of propranolol for treatment of hypertension is 40 mg twice daily, and this may be increased gradually to as much as 80 mg or even 120 mg four times daily. In Great Britain doses as high as 3 g daily have been used to treat hypertension without any adjunctive agents.

Clonidine (Catapres). Clonidine was approved by the FDA for clinical use in 1974. It is an imidazoline derivative which appears to act almost entirely centrally to suppress the sympathetic nervous system. In large doses intravenously it produces a pressor response, apparently by direct stimulation of the peripheral alpha adrenergic receptor. Stimulation of alpha receptors in the brain may explain its depressor effect.

It should be administered in conjunction with an oral diuretic for management of mild to moderate hypertension which has not responded adequately to the diuretic alone (*Table*). It is only minimally effective when used by itself, because it encourages sodium and water retention, expanding plasma and extracellular fluid volume which counteract the antihypertensive effect.

Its antihypertensive potency is comparable to that of methyldopa. Adverse effects include drowsiness which is sometimes more severe and persistent than that produced by methyldopa, dryness of the mouth, constipation, fluid retention, and rash. Symptomatic orthostatic hypotension is rarely encountered during therapy with clonidine. Sudden cessation of therapy with clonidine can result in a hypertensive overshoot with symptoms including restlessness, agitation, insomnia, nausea, sweating and chills that resemble a narcotic withdrawal type of reaction. Presumably, this is due to catecholamine release; the symptoms subside and the hypertension can be controlled by reinstituting therapy with clonidine and then withdrawing it more gradually. The usual starting dose of clonidine is 0.1 mg twice daily, and this may be increased gradually to as much as 0.6 mg three or four times daily. Sedation and dryness of the mouth seem to be dose related. Clonidine is available in tablets of 0.1 and 0.2 mg and in combination with the diuretic chlorthalidone (Combipres). Combipres I contains 0.1 mg clonidine and 15 mg chlorthalidone. Combipres II contains 0.2 mg clonidine and 15 mg chlorthalidone.

Bethanidine. This is a potent sympathetic depressant drug which is similar to guanethidine both pharmacologically and chemically. It is not yet available in the United States, although approval is anticipated within the next 2 years. It has been available in other parts of the world including Canada for several years. In Canada it is marketed under the trade name Esbatal in tablets of 10, 25, and 50 mg.

Bethanidine has shorter half-life than guanethidine and therefore it must be given two or three times daily. Usually this is a disadvantage, but in some cases its short duration of action is an advantage because appropriate distribution of the doses may smooth out the diurnal variation of blood pressure that sometimes occurs during therapy with guanethidine, with very low blood pressure in the morn-

ing and uncontrolled hypertension in the late afternoon and evening. A relatively large noontime dose of bethanidine may prevent the late afternoon rise in blood pressure, whereas this cannot be prevented by adjusting the time of administration of guanethidine.

Bethanidine does not cause diarrhea, and this is an advantage for patients who cannot tolerate effective doses of guanethidine because of this side effect. Other side effects of bethanidine are similar to those of guanethidine qualitatively and quantitatively. It has been reported that bethanidine does not deplete norepinephrine from tissue stores as much as guanethidine does.

Like guanethidine, it should be reserved for managing severe hypertension in conjunction with an oral diuretic and methyldopa with or without hydralazine (*Table*).

When prompt reduction of blood pressure is urgent, bethanidine is preferable to guanethidine because its onset of hypotensive action is apparent within 2 or 3 hours, whereas it sometimes takes 2 or 3 days for guanethidine to exert its maximal hypotensive activity.

The usual initial dose of bethanidine is 10 mg two or three times daily, and this dose may be increased gradually until the desired antihypertensive effect is obtained or until side effects preclude further increments. There is no upper limit to dosage. A dose of 50 mg three times daily is not unusual in patients with severe hypertension, but the dose must be increased gradually to these levels.

New vasodilating agents

Diazoxide (Hyperstat). Diazoxide has been available for the management of hypertensive crises for more than 2 years. It is a very potent vasodilating agent which acts primarily to reduce peripheral resistance. Reflexly, it increases cardiac output and heart rate. It is not available for oral use in the United States and probably never will be.

Diazoxide is a benzothiadiazine derivative that, unlike its diuretic cogeners, actually has sodium retaining properties. After a single, rapid intravenous injection of 300 mg it promptly reduces blood pressure, usually to normal levels. If the entire dose is not given rapidly (within 15 to 20 seconds) avid binding by plasma protein will neutralize the antihypertensive effect of the drug. The hypotensive effect of a single dose usually persists for 6 to 18 hours or longer.

In some patients, usually diabetics, it can cause significant but temporary hyperglycemia and for this reason determinations of blood glucose should be made daily while it is being used.

Diazoxide is an effective agent in the management of most hypertensive crises. It is particularly indicated when prompt reduction of blood pressure is desirable. Although hypotension is uncommon after intravenous administration of diazoxide, another drug is preferable in those hypertensive emergencies associated with coronary or cerebral vascular insufficiency when prompt and drastic reduction of blood pressure might unfavorably alter myocardial or cerebral hemodynamics. It is especially indicated for managing hypertensive encephalopathy, malignant hypertension, and eclampsia. Because it increases cardiac output, it is not suitable for managing hypertension associated with acute dissecting aortic aneurysm.

Diazoxide is available in 20 ml ampules containing 15 mg of diazoxide per milliliter. The usual dose is 300 mg given rapidly, intravenously as a bolus injection. The dose can be repeated within 20 minutes if necessary. Sometimes, in resistant hypertension, 600 mg may be given as a bolus injection. Concomitant administration of furosemide will prevent fluid retention and enhance the antihypertensive response to diazoxide and prolong its effect.

Sodium nitroprusside (Nipride). Sodium nitroprusside has been used to manage hypertensive crises for more than 20 years, but it has been prepared commercially only in the past year.

Although chemically unrelated to diazoxide, sodium nitroprusside also reduces blood pressure promptly by a direct effect to relax vascular smooth muscle. Unlike diazoxide, it must be given as a continuous intravenous infusion, because its hypotensive effect is so evanescent that blood pressure quickly rises to hypertensive levels within 2 minutes after the infusion has been stopped. Sodium nitroprusside is consistently and reliably effective, even when hypertension is resistant to other agents, and it would be the drug of choice in the management of most hypertensive crises if its administration did not require close and constant supervision by trained personnel. Because of its transient hypotensive effect, it is safer than diazoxide to use in the management of crises in which prolonged hypotension might be detrimental, such as acute coronary insufficiency, cerebrovascular insufficiency, and intracranial bleeding.

Untoward effects produced by therapy with sodium nitroprusside include sweating, muscular twitching, nausea, anxiety, and apprehension associated with rapid reduction in blood pressure—all promptly relieved by decreasing the rate of infusion or stopping it for a short period. The nitroprusside ion is converted in the body to thiocyanate and, occasionally, acute thiocyanate intoxication, manifested by psychosis and delirium, results from prolonged (usually more than 3 days) administration of sodium nitroprusside, especially when renal failure is present. If large doses are required for more than 72 hours, daily determinations of blood thiocyanate levels should be made and therapy must be withdrawn whenever the concentration exceeds 12 mg/100 ml.

Although sodium nitroprusside is the most potent of the vasodilators, it is the only one which does not incite a reflex increase in cardiac output. It does, however, increase pulse rate as do other vasodilating agents. The best explanation for these observations is that, unlike the other vasodilators, sodium nitroprusside reduces venous return by relaxing the capacitance vessels. It has been demonstrated that sodium nitroprusside greatly improves left ventricular performance in patients with refractory heart failure even when hypertension is minimal. It is the agent of choice in treating hypertensive crises associated with left ventricular failure.

Within 30 seconds after starting an infusion (usually 20 micro drops per minute of a solution containing 100 mg/liter) the blood pressure begins to fall and may drop to hypotensive levels within 30 seconds. Careful titration of the rate of infusion is necessary to control blood pressure adequately, and for this reason patients must be observed closely in an intensive care unit. By expert titration, the blood pressure can be maintained at any desired level.

Sodium nitroprusside is available as Nipride in lyophilized powder, 50 mg/ampule.

Minoxidil. Minoxidil is a piperidinopyrimidine derivative which is being investigated but not commercially available. It is unrelated chemically to other vasodilating agents. It is anticipated that it will be made available soon for limited indications, specifically for azotemic patients whose hypertension is life-threatening and resistant to conventional agents. It is the most potent of the vasodilators for oral administration.

It is especially effective in managing severe hypertension in patients with renal failure and has practically eliminated the need for bilateral nephrectomy to control hypertension in this situation. Like hydralazine, it causes reflex tachycardia and increase in cardiac output as well as fluid retention, and for this reason it should be used with a sympathetic inhibiting agent (usually propranolol) and an oral diuretic (furosemide when renal failure is present) (*Table*).

Minoxidil causes facial hirsutism which is particularly distressing to women. Its prolonged use is associated with an unusual hemorrhagic degenerative lesion in the right atrium of dogs, the exact significance of which is unknown. Endocardial lesions in the right atrium have also been found at postmortem examinations in two patients. For this reason its use has been restricted to management of refractory hypertension in patients with renal failure.

Minoxidil is available for clinical investigation only in tablets of 1, 5, and 10 mg. The usual maintenance dose is 10 or 15 mg twice daily.

Prazosin (Minipress). Prazosin is a quinazoline derivative which reduces peripheral resistance by direct action on the arterioles. FDA approval of this drug is anticipated soon. Pharmacologically, it behaves as if it has both direct vasodilating and alpha adrenergic blocking properties. The alpha blockade takes place at a site distal to the conventional alpha receptor where phentolamine and dibenzyline act. The reflex increase in cardiac rate and output incited by prazosin seems to be less than that caused by hydralazine or minoxidil and, therefore, inclusion of a sympathetic depressant in the regimen is not always necessary. It does cause fluid retention, and hence it should be used with an oral diuretic in the management of mild or moderate hypertension. It could be used as an alternative to one of the sympathetic inhibiting drugs in step two of the *Table*. Its role in combination with a sympathetic inhibiting agent has not been fully explored, but it is entirely likely that it would also serve as an alternative in step three of the *Table*.

Adverse effects include headache, palpitation, drowsiness and dizziness. Orthostatic hypotension rarely occurs. There have been reports of sudden collapse and loss of consciousness 30 to 90 minutes after the initial dose of prazosin. It is estimated that this unexplained reaction occurs in at least 1% of patients. Prazosin is usually well tolerated but is of only modest hypotensive potency, comparable to that of methyldopa, reserpine, and clonidine. It will be available in 2 and 5 mg tablets.

New antihypertensive drugs on the horizon

Under investigation at the present time are compounds which specifically

inhibit the effect of angiotensin II. Compound SQ20881 inhibits the enzyme that converts inactive angiotensin I to vasoactive angiotensin II and saralasin (P-113, 1-sar-8-ala-angiotensin II) is a specific antagonist of angiotensin II. These agents have been useful in identifying hypertension that is angiotensin dependent, since they have no depressor effect in patients who do not have increased plasma angiotensin II. They are important research tools and may prove to be helpful in selecting patients with renovascular hypertension who will respond to surgical treatment. They may be beneficial in managing acute hypertensive crises due to increased angiotensin, but because they have to be given parenterally they have no role in chronic antihypertensive therapy.

Prostaglandin A_1 is a potent peripheral vasodilator which has been shown to reduce blood pressure and increase renal blood flow when given intravenously. It is under investigation for treatment of hypertensive crisis.

The ideal antihypertensive agent

None of these agents, effective though they are, would qualify as the ideal drug for managing hypertension. The search goes on. The immediate need is for a long-acting orally effective vasodilator and a long-acting beta blocker that could be combined with a long-acting diuretic in a single tablet to improve compliance with antihypertensive regimens.

Hydralazine and propranolol, although effective, have short durations of action and therefore must be given several times daily. Poor compliance with regimens is a major obstacle to adequate control of hypertension, and anything that will minimize the number of tablets and frequency of dosage will certainly improve compliance. One tablet per day would be ideal therapy.

In addition to its long duration of action, the ideal antipressor regimen should not only specifically correct the hemodynamic abnormalities identified for each patient, but also should be consistently and persistently effective in reducing blood pressure and be relatively nontoxic, free of unpleasant side effects, and inexpensive.

Dissatisfaction with available antipressor drugs should not deter the physician from employing them to the best of his ability, until more acceptable agents are introduced. Therapeutic nihilism and pessimism have been dispelled by the results of antipressor treatment. The dangers of antihypertensive therapy have been over-emphasized in the past; with few exceptions the adverse effects of drug treatment are more annoying than harmful. Albeit imperfect, empiric, and palliative, antihypertensive drug therapy, when effectively and judiciously administered, prevents or postpones cardiovascular and renal complications and prolongs useful life.

Suggested reading

Propranolol

Bravo EL, Tarazi RC, Dustan HP: β-adrenergic blockade in diuretic-treated patients with essential hypertension. N Engl J Med 292: 66–70, 1975.

Bravo EL, Tarazi RC, Dustan HP, et al: Dissociation between renin and arterial pressure responses to beta-adrenergic blockade in human essential hypertension. Circ Res 36: I-241–I-247, 1975.

Bühler FR, Laragh JH, Baer L, et al: Propranolol inhibition of renin secretion; a specific approach to diagnosis and treatment of renin-dependent hypertensive dis-

eases. N Engl J Med **287:** 1209–1214, 1972.
Stokes GS, Weber MA, Thornell IR: β-Blockers and plasma renin activity in hypertension. Br Med J **1:** 60–62, 1974.
Tarazi, RC, Dustan HP: Beta adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variations. Am J Cardiol **29:** 633–640, 1972.
Zacest R, Gilmore E, Koch-Weser J: Treatment of essential hypertension with combined vasodilatation and beta-adrenergic blockade. N Engl J Med **286:** 617–622, 1972.

Clonidine

Gifford RW Jr: Clonidine in the management of mild hypertension in 22 patients. Cleve Clin Q **36:** 173–182, 1969.
Hansson L, Hunyor SN, Julius S, et al: Blood pressure crisis following withdrawal of clonidine (Catapres, Catapresan), with special reference to arterial and urinary catecholamine levels, and suggestions for acute management. Am Heart J **85:** 605–610, 1973.
Kosman ME: Evaluation of clonidine hydrochloride (Catepres): a new antihypertensive agent. JAMA **233:** 174–176, 1975.
Mroczek WJ, Leibel BA, Finnerty FA Jr: Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic. A double-blind crossover study. Am J Cardiol **29:** 712–717, 1972.

Bethanidine

Gifford RW Jr: Bethanidine sulfate—a new antihypertensive agent. JAMA **193:** 901–905, 1965.

Diazoxide

Miller WE, Gifford RW Jr, Humphrey DC, et al: Management of severe hypertension with intravenous injections of diazoxide. Am J Cardiol **24:** 870–875, 1969.
Mroczek WJ, Davidov M, Gavrilovich L, et al: The value of aggressive therapy in the hypertensive patient with azotemia. Circulation **40:** 893–904, 1969.
Sellers EM, Koch-Weser J: Influence of intravenous injection rate on protein binding and vascular activity of diazoxide. Ann NY Acad Sci **226:** 319–332, 1973.

Sodium nitroprusside

Cohn JN: Vasodilator therapy for heart failure; the influence of impedance on left ventricular performance (Editorial). Circulation **48:** 5–8, 1973.
Gifford RW Jr: Current practices in general medicine. 7. Treatment of hypertensive emergencies including use of sodium nitroprusside. Mayo Clin Proc **34:** 387–394, 1959.
Miller RR, Vismara LA, Zelis R, et al: Clinical use of sodium nitroprusside in chronic ischemic heart disease. Effects on peripheral vascular resistance and venous tone and on ventricular volume, pump and mechanical performance. Circulation **51:** 328–336, 1975.
Palmer RF, Lasseter KC: Sodium nitroprusside. N Engl J Med **292:** 294–297, 1975.

Minoxidil

Gilmore E, Weil J, Chidsey C: Treatment of essential hypertension with a new vasodilator in combination with beta-adrenergic blockade. N Engl J Med **282:** 521–527, 1970.
Limas CJ, Freis ED: Minoxidil in severe hypertension with renal failure. Effect of its addition to conventional antihypertensive drugs. Am J Cardiol **31:** 355–361, 1973.
Pettinger WA, Mitchell HC: Minoxidil—an alternative to nephrectomy for refractory hypertension. N Engl J Med **289:** 167–171, 1973.

Prazosin

Mroczek WJ, Fotiu S. Davidov ME, et al: Prazosin in hypertension; a double-blind evaluation with methyldopa and placebo. Curr Ther Res **16:** 769–777, 1974.
Onesti G, Fernandes MA, Kim KE, et al: Prazosin in the treatment of hypertension (Abstr). Clin Pharmacol Ther **15:** 216, 1974.
Stokes GS, Weber MA: Prazosin: preliminary report and comparative studies with other antihypertensive agents. Br Med J **2:** 298–300, 1974.
Turner AS, Watson O, Peel DS: Clinical experience with prazosin hydrochloride in arterial hypertension. NZ Med J **81:** 240–242, 1975.
Prazosin and sudden collapse. Lancet **1:** 645, 1975.