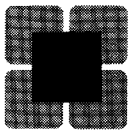

Nontraditional combination pharmacotherapy of hypertension

JAMES M. SUTTON, MD, AND SUSAN P. BAGBY, MD

■ Traditional drug combinations that have additive hypotensive effect include double therapy with a diuretic and any other antihypertensive agent and triple therapy with a diuretic, direct vasodilator, and either a beta blocker or reserpine. Due to the availability of new classes of antihypertensive agents, other combinations of drugs are now increasingly used. The effectiveness of combination therapy for hypertension has been investigated; the results of these studies are reviewed.

□ INDEX TERMS: ANTIHYPERTENSIVE AGENTS; DRUG THERAPY, COMBINATION; DIURETICS; ADRENERGIC BETA RECEPTOR BLOCKADERS; VASODILATOR AGENTS □ CLEVE CLIN J MED 1992; 59:459–468

THE HYPERTENSIVE PATIENT whose blood pressure fails to fall to the target level with a single antihypertensive agent should have another agent substituted (sequential monotherapy) or should receive two or more agents in combination. Traditionally, the two most effective and commonly used drug combinations have been (1) double therapy with a diuretic and almost any other antihypertensive agent and (2) triple therapy with a diuretic, a direct vasodilator, and either a beta blocker or reserpine (sometimes referred to as "standard" triple therapy).[1-4] However, with the availability of new classes of antihypertensive agents, combinations other than these are now increasingly used.

RATIONALE FOR MULTIPLE-AGENT REGIMENS

Antihypertensive agents are categorized by their actions as diuretics, beta blockers, vasodilators (direct vasodilators, alpha-1 blockers, calcium-channel blockers, and angiotensin-converting enzyme [ACE] inhibitors), central adrenergic inhibitors (methyldopa, clonidine, guanabenz, guanfacine), or peripheral adrenergic inhibitors (guanethidine, guanadrel, reserpine). It should not be assumed that combining two agents from different antihypertensive classes will have an additive hypotensive effect, since the response to combination therapy can be reduced by pharmacokinetic or pharmacodynamic interactions. Beta blockers and ACE inhibitors both decrease blood pressure in part via a decrease in angiotensin II; central adrenergic inhibitors and alpha-1 blockers both inhibit the sympathetic nervous system; and central adrenergic inhibitors and ACE inhibitors both affect the sympathetic nervous system (angiotensin II modulates sympathetic nervous system activity).

The effectiveness of combination therapy for hypertension has been investigated in numerous studies. These studies have been limited by factors such as exclusion of patients with complicating medical illnesses, small sample sizes, short "wash-out" and treatment periods, infrequent use of 24-hour blood pressure monitoring, dose ranges too narrow to determine whether a combination is synergistic or merely additive, and a paucity of data on the pharmacology, hemodynamics, and side effects of combination therapy.[5,6] While most of the initial studies were uncontrolled,

From the Division of Nephrology and Hypertension, Arnett Clinic (J.M.S.), Lafayette, Ind, and the Division of Nephrology, Portland Veterans Hospital (S.P.B.), Portland, Ore.

Address reprint requests to J.M.S., the Division of Nephrology and Hypertension, Arnett Clinic, 2600 Greenbush, Lafayette, IN 47904.

TABLE 1
DOUBLE THERAPY COMBINATIONS WITH NO OR MINIMAL ADDITIVE ANTIHYPERTENSIVE EFFECT

Reference	Initial agent, dose/day (mg)	Added agent, dose/day(mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP with monotherapy (mm Hg)	Change in BP with second agent (mm Hg)
12	Clonidine, 0.3	Prazosin, 15	9	UN	4	142/92	+1/+1
9	Clonidine, 0.2–0.4	Propanolol, 160	12	UN	3	156/102	–5/–5
13	Enalapril, 20	Atenolol, 50	16	RAN, DB, CO	4	147/85	–3/–7*
14	Nicardipine, 60	Prazosin, 4	14	UN	1	147/100	+2/0

UN, uncontrolled; RAN, randomized; DB, double-blind; CO, crossover; BP, blood pressure
*Significantly different than monotherapy

TABLE 2
ADDITION OF A SECOND AGENT TO AN ACE INHIBITOR

Reference	ACE inhibitor, dose/day (mg)	Second agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on an ACE inhibitor (mm Hg)	Change in BP with second agent (mm Hg)
29	Enalapril or Captopril, stable dose	Doxazosin, 1–8	56	SB, UN	10	158/101	–15/–17*
30	Captopril, 50–150	Diltiazem (sustained release), 120–360	31	UN	8	146/97	–5/–7*
13	Enalapril, 20	Atenolol, 50	16	RAN, DB, CO	4	147/85	–3/–7*
31	Enalapril, 20	Hydrochlorothiazide, 50	485	RAN, DB, PAR	48	146/94	–18/–10*

SB, single-blind; UN, uncontrolled; RAN, randomized; DB, double-blind; CO, crossover; PAR, parallel; BP, blood pressure
*Significantly different than with an ACE inhibitor alone

recent studies have used either a double-blind crossover or parallel group design.[5]

DOUBLE THERAPY

Beta blocker and central adrenergic inhibitor

Beta blocker and clonidine. The combination of a beta blocker and clonidine has been variously reported to be effective,[7,8] ineffective,[9] or even to elevate blood pressure.[10,11] Two small, prospective, randomized studies investigated this combination; one demonstrated an insignificant hypotensive response (*Table 1*),[9] and the other a slight but significant response.[7] A large retrospective study found this combination to be effective when compared with no antihypertensive therapy, but the combination was not compared with either agent alone.[8] There are anecdotal reports of adverse interactions between these agents: paradoxical hypertension upon the addition of clonidine to a nonselective beta blocker, or vice versa[10,11]; rebound hypertension on withdrawal of clonidine, especially in those also receiving a nonselective beta blocker[15]; and marked bradycardia due to additive chronotropic effects.[16] The poor hypotensive response to this combination may relate to a possible shared central site of antihypertensive action[17] or to an interaction between their peripheral effects (alpha-2 agonist-mediated vasoconstriction and inhibition of beta-2-dependent vasodilation).[18-20]

Other central adrenergic inhibitors. Although combining a beta blocker with clonidine does not appear to be particularly effective, adding a beta blocker to methyldopa further reduced blood pressure in a double-blind crossover study,[21] as did using a beta blocker in conjunction with guanfacine in an uncontrolled postmarketing study.[22] There is one case report of paradoxical hypertension with the use of propranolol and methyldopa.[23]

Beta blocker and vasodilator

While the various beta blockers are all equally effective as monotherapy for hypertension, it is not known whether each is equally effective in combination with the various vasodilators.[24-26] Beta blockers without prominent intrinsic sympathomimetic activity (ISA) decrease cardiac output, while those with prominent ISA decrease peripheral resistance.[27] Possibly, when a beta blocker with ISA is added to a vasodilator, the further vasodilation reduces blood pressure less than would the addition of a beta blocker that decreases cardiac output. For example, in hypertension in pregnancy, hydralazine reduced blood pressure in 55% of

TABLE 3
ADDITION OF A SECOND AGENT TO A BETA BLOCKER

Reference	Second agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on a beta-blocker (mm Hg)	Change in BP with second agent (mm Hg)
32	Felodipine, 10-20	51	RAN,DB,PAR	4–8	172/114	–30/–24*†
	Hydrochlorothiazide, 25–50	47		4–8	170/112	–20/–16*
33	Felodipine, up to 40	50	RAN, DB, PAR	6	177/104	–33/–22*‡
	Prazosin, up to 8	50		6	176/103	–15/–13*
34	Hydralazine, up to 200	20	RAN, PAR	12	166/109	–17/–17*
	Prazosin, up to 8	19		12	172/108	–16/–15*
35	Bendrofluazide, 5–10	19	RAN, CO	4–8	191/117	–21/–12*
	Prazosin, 6–15	19		4–8	191/117	–25/–15*
36	Lisinopril, 10–20	297	RAN, DB, PAR, PC	8	160/102	/–3.2§

RAN, randomized; DB, double-blind; PAR, parallel; CO, crossover; PC, placebo-controlled; BP, blood pressure
*Significantly different than with a beta blocker alone
†Significantly different than beta blocker/diuretic
‡Significantly different than beta blocker/prazosin
§Significantly different than beta blocker/placebo

patients, but hydralazine combined with pindolol (prominent ISA activity) was effective in only 59%.[28]

Beta blocker and ACE inhibitor. Although initial uncontrolled studies suggested these two classes of drugs in combination have no additive hypotensive effect (*Tables 1-3*),[37-39] several double-blind, randomized, crossover trials have in fact found a small additive effect.[13,40-42] In a multicenter trial adding 5 mg of lisinopril to the regimen of patients who remained hypertensive on atenolol monotherapy, the combination did not further reduce blood pressure. Adding 10 or 20 mg of lisinopril reduced blood pressure by only 3/3 mm Hg and 7/5 mm Hg, respectively (*Table 3*).[39] Combining a beta blocker and an ACE inhibitor has been reported to be less effective than combining a diuretic and an ACE inhibitor.[13,38] The blunting by a beta blocker of the increase in plasma renin activity induced by an ACE inhibitor may contribute to the hypotensive response to the combination.[40,41] Variations in response may relate to differences in renin status and age.[40,41]

Beta blocker and calcium-channel blocker. Most of the studies with this very effective combination have used a dihydropyridine calcium-channel blocker (eg, nifedipine, nicardipine, isradipine, felodipine, nitrendipine),[32,33,42-47] while several have used either diltiazem (*Table 4*)[47] or verapamil.[51] Multiple double-blind, randomized, controlled studies have found that combining a beta blocker and a dihydropyridine calcium-channel blocker reduces blood pressure more than either agent alone,[42-45] or than a beta blocker with either hydralazine,[45] a diuretic,[32,46] or prazosin[33] (*Tables 3* and *4*). This combination may even be as effective as triple therapy with a beta blocker, hydralazine, and a diuretic.[45] This combination also has an additive effect in the treatment of angina.[52,53]

The efficacy of combining a beta blocker with a calcium-channel blocker is due to their complementary antihypertensive mechanisms and to their pharmacokinetic interactions. Dihydropyridine calcium-channel blockers increase cardiac output, heart rate, and plasma renin activity, while they decrease peripheral resistance; beta blockers have the opposite effects. Pharmacokinetic effects that influence the hypotensive response in combinations of a beta blocker and a calcium-channel blocker include an increase in peak plasma concentrations of propranolol with verapamil, and enhanced bioavailability of propranolol by nifedipine and of metoprolol by verapamil.[54-56]

Adverse cardiovascular reactions to the combination of a beta blocker and a calcium-channel blocker[52,53,56] have been reported primarily in patients with angina, not hypertension alone. Precipitation of congestive heart failure has rarely been reported with combination therapy using a beta blocker and a dihydropyridine calcium-channel blocker or diltiazem, but it has commonly been reported with the combination of a beta blocker and verapamil. Risk factors for congestive heart failure with this therapy include left ventricular systolic dysfunction, use of either agent in high doses or intravenously, and concurrent use of other agents that decrease inotropy. Symptomatic conduction system abnormalities have not been reported with the combination of a beta blocker and a dihydropyridine calcium-channel blocker but have been reported with the combination of a beta blocker

TABLE 4
ADDITION OF A SECOND AGENT TO A CALCIUM-CHANNEL BLOCKER

Reference	Calcium-channel blocker, dose/day (mg)	Second agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on a calcium-channel blocker (mm Hg)	Change in BP with second agent (mm Hg)
48	Nifedipine, 15–40	Doxazosin, 1–8	52	UN	10	158/104	−16/524*
14	Nicardipine, 60	Prazosin, 4	14	UN	1	147/100	+2/0
14	Nicardipine, 60	Clonidine, 0.3	14	UN	1	153/101	−17/−9*
30	Diltiazem (sustained release), 120–360	Captopril, 50–150	29	RAN, DB	8	146/95	−7/−4*
47	Diltiazem (sustained release), 240	Atenolol, 50	15	RAN, DB, CO, PC	4	172/92	−8/−4*
49	Diltiazem (sustained release), 0–360	Hydrochlorothiazide, 0–100	297	FAC, PC	4	152/99	−8/−3*
50	Diltiazem, 120	Nifedipine, 40	11	DB, RAN, PC	1	134/x	−17/x*

UN, uncontrolled; RAN, randomized; DB, double-blind; CO, crossover; PC, placebo-controlled; FAC, factorial; BP, blood pressure
*Significantly different than with a calcium channel blocker alone

and diltiazem (sinus bradycardia or arrest) or verapamil (sinus bradycardia, atrioventricular block, junctional rhythms).

Noncardiovascular side effects of the combination of a beta blocker and a calcium-channel blocker are usually not limiting. Combining a beta blocker with diltiazem has the fewest noncardiovascular side effects (at least in the treatment of angina).[52,53,57] The combination of a beta blocker and a dihydropyridine calcium-channel blocker may be better tolerated than dihydropyridine alone, due to inhibition of the latter's vasodilatory side effects (eg, flushing, headache).[42,43]

Beta blocker and alpha-1 blocker. Combining a beta blocker with prazosin was as effective as combining a beta blocker with hydralazine[34,58] or a diuretic,[35] but was less effective than combining a beta blocker with felodipine[33] (*Table 3*). Beta blockade may augment the first-dose hypotensive response to prazosin.[59] The ability of alpha-1 blockers to reduce lipids has also been seen when used with a beta blocker: adding terazosin to atenolol reduced low-density lipoprotein and very-low-density lipoprotein cholesterol by 5.7% when compared with atenolol with placebo.[60]

Central adrenergic inhibitor and vasodilator

Alpha-1 blocker. The combination of a central adrenergic inhibitor and an alpha-1 blocker has been demonstrated to be ineffective in animal studies and short-term controlled human studies (*Table 1*).[9,12,61-63] Studies suggesting the contrary have all been uncontrolled, and in many cases subjects were also receiving other antihypertensive agents.[22,64-66] The poor hypotensive response to this combination may relate to a failure of alpha-1 blockade to further inhibit the adrenergic nervous system if sympathetic outflow is already reduced by a central alpha-2 agonist, and vice versa.[67]

Calcium-channel blocker. No controlled studies of dual therapy with a central adrenergic inhibitor and a calcium-channel blocker have been performed in humans. In uncontrolled studies, adding methyldopa, clonidine, or guanfacine to a calcium-channel blocker further reduced blood pressure (*Table 4*).[14,22,68-70] On the other hand, a calcium-channel blocker inhibited the hypotensive response to guanabenz in the conscious spontaneously hypertensive rat[71] and to guanabenz or clonidine in the anesthetized rat or cat.[72] Such inhibition could be explained if the hypotensive action of central adrenergic inhibitors (at least in these animals) were mediated through an increase in intracellular calcium. Such an increase mediates their peripheral vasoconstrictive effect.

ACE inhibitor. No studies have examined the use of a central adrenergic inhibitor with an ACE inhibitor in the chronic therapy of hypertension. In single-dose studies in man, the addition of clonidine to captopril further reduced blood pressure.[73] Captopril also reversed the rebound hypertension that developed with discontinuation of clonidine.[74] The response to this combination may be affected by angiotensin II's enhancement of the sympathetic nervous system at both central and peripheral sites.[75]

Two vasodilators

Calcium-channel blocker and ACE inhibitor. This combination, also effective when used in triple therapy with a diuretic,[76] significantly reduces blood pressure compared with either agent alone[30,77-81] and may be

TABLE 5
ADDITION OF A THIRD AGENT TO A BETA BLOCKER AND A DIURETIC

Reference	Added agent, dose/day (mg)	No. of patients	Study conditions	Duration (weeks)	Supine BP on beta blocker-diuretic (mm Hg)	Change in BP with third agent (mm Hg)
97	Hydralazine, 50–200	28	RAN, PAR, PC	12	155/107	–22/–15*
	Prazosin, 1–20	29		12	169/103	–37/–19*
	Minoxidil, 5–20	10		12	159/98	–22/–14*
	Methyldopa, 25–2000	18		12	159/103	–36/–16*
	Placebo	26		12	158/102	–10/–6
98	Nifedipine (sustained release), 40–80	19	RAN, DB, CO	9	146/96	–27/–16†‡
	Hydralazine, 50–200	19		9	146/96	–17/–15†
99	Prazosin, 8–16	23	RAN, OB, CO	8	178/114	–25/–15†
	Hydralazine, 100–200	23		8	178/114	–24/–16†
100	Nifedipine (sustained release), 20–40	19	RAN, SR, CO	8	164/109	–27/–19†
	Captopril, 50–100	19		8	165/108	–23/–20†

RAN, randomized; PAR, parallel; PC, placebo-controlled; DB, double-blind; CO, crossover; OB, observer-blind; SR, slow-release; BP, blood pressure
*Significantly different than beta blocker/diuretic/placebo
†Significantly different than beta blocker/diuretic
‡Significantly different than beta blocker/diuretic/hydralazine

even more effective than the combination of a beta blocker, hydralazine, and a diuretic.[80] These trials include a double-blind, randomized, crossover trial with nicardipine and enalapril[79] and a large, randomized, parallel study with diltiazem and captopril (*Tables 2* and *4*).[30] Either verapamil, isradipine, or nitrendipine was as effective with captopril as was a diuretic,[80,81] with a direct correlation (r=0.88) between the hypotensive response to a calcium-channel blocker used with either captopril or a diuretic.[80]

Combining a calcium-channel blocker and an ACE inhibitor also has an additive effect in reducing diabetic proteinuria.[82] An ACE inhibitor may prevent the reflex tachycardia[77,78,83,84] and ankle edema that can accompany dihydropyridine use.[77,78]

Calcium-channel blocker and alpha-1 blocker. Prazosin further reduced blood pressure when added to verapamil in a randomized, single-blind, parallel study,[85] as did doxazosin when added to nifedipine in an uncontrolled study (*Table 4*).[48] Prazosin may potentiate nifedipine's tendency to cause first-dose hypotension.[86,87] Potentiation of the first-dose response to an alpha-1 blocker by a calcium-channel blocker has not been examined, but it should be anticipated. The hypotensive response to verapamil and prazosin may relate to verapamil increasing prazosin's bioavailability and peak plasma concentration.[85]

The hypotensive response to the combination of a calcium-channel blocker and an alpha-1 blocker may depend on which calcium-channel blocker is used.[14,88,89] In uncontrolled studies, adding prazosin to nicardipine did not further decrease blood pressure (*Table 1*).[14] Pedrinelli et al found that nicardipine, but not verapamil, inhibited the forearm vascular response to exogenous norepinephrine in humans, suggesting that alpha-1 antagonism contributed to the hypotensive response to nicardipine.[89] If alpha-1 blockade is a significant component of a calcium-channel blocker's hypotensive action, that agent would not be very effective in combination with an alpha-1 blocker.

Alpha-1 blocker and ACE inhibitor. In an uncontrolled study adding doxazosin to an ACE inhibitor further decreased blood pressure (*Table 2*).[29] A higher likelihood of first-dose hypotension with an alpha-1 blocker has been reported in patients already receiving an ACE inhibitor.[90] The response to this combination may be influenced by angiotensin II modulation of the functional activity of alpha-1 adrenoreceptors.[91]

Two calcium-channel blockers. Several small series of patients with angina who received the combination of a dihydropyridine calcium-channel blocker and either verapamil or diltiazem found an additive hypotensive and antianginal effect. The additive hypotensive response is consistent with the quite different chemical structures and binding sites of these agents (*Table 4*).[50,92,93] Diltiazem increases nifedipine blood levels.[50,92] Side effects of a dihydropyridine and either diltiazem or verapamil may be more common than with either agent alone.[92]

Peripheral adrenergic inhibitor with a beta blocker or central adrenergic inhibitor

Reserpine, guanethidine, and guanadrel are rarely used due to a high incidence of side effects, especially

TABLE 6
EFFICACY OF COMBINATION ANTIHYPERTENSIVE DRUG THERAPY

Additive hypotensive effect clearly documented
Diuretic + any other antihypertensive agent
Diuretic + direct vasodilator + beta blocker or reserpine
Beta blocker + alpha-1 blocker
Beta blocker + calcium-channel blocker
Calcium-channel blocker + ACE inhibitor
Additive hypotensive effect shown in preliminary studies
Central adrenergic inhibitor + ACE inhibitor
Central adrenergic inhibitor + calcium-channel blocker
Alpha-1 blocker + ACE inhibitor
Alpha-1 blocker + calcium-channel blocker
Disputed additive hypotensive response
Alpha-1 blocker + central adrenergic inhibitor
Beta blocker + central adrenergic inhibitor
Beta blocker + ACE inhibitor

orthostasis. Guanethidine exerted an additive hypotensive effect in a small controlled study with a beta blocker[94] and an uncontrolled study with methyldopa.[95] These combinations were also effective with a diuretic, as was the combination of guanadrel, propranolol, and a diuretic.[96]

TRIPLE THERAPY

Vasodilator, beta blocker, and diuretic

In uncontrolled studies the combination of an ACE inhibitor, a beta blocker, and a diuretic has been effective, probably more so than the combination of hydralazine, a beta blocker, and a diuretic (*Table* 5).[38,100,101] In the largest study, giving captopril to 201 patients with diastolic blood pressures greater than 95 mm Hg who were already taking a beta blocker and a diuretic reduced the blood pressure below 95 mm Hg in 59% (captopril 25 mg bid) and 56% (captopril 50 mg bid) of subjects.[101] However, most of the hypotensive response to this combination appears to be due to the ACE inhibitor and diuretic, there being little or no further hypotensive response with the addition of a beta blocker to these two agents.[36,38]

When added to a beta blocker and a diuretic, a dihydropyridine calcium-channel blocker reduced blood pressure further than hydralazine (*Table* 5)[98,100,102,103] and as much as minoxidil.[104]

The hypotensive response to 1 mg of prazosin was equal to that of 12.5 to 20 mg of hydralazine when combined with a beta blocker and a diuretic (*Table* 5).[99,102] Increasing prazosin dosage above 8 mg/day did not further reduce blood pressure.

Adding a nitroglycerin patch to a beta blocker and a diuretic in a double-blind, randomized, crossover trial significantly decreased systolic blood pressure, especially in patients with the highest systolic pressures.[105]

Central adrenergic inhibitor, beta blocker, diuretic

In two double-blind, crossover studies, combining methyldopa (750 mg/day) with atenolol (150 mg/day) and a diuretic reduced blood pressure significantly more than combinations of either methyldopa or atenolol with a diuretic.[106,107]

Relative effectiveness

Several studies have investigated which agent is the most effective in combination with a beta blocker and a diuretic.[97,100,103,104,108,109] In the largest study, McAreavey et al compared the hypotensive response to placebo, methyldopa, hydralazine, minoxidil, prazosin, or labetalol (substituted for prazosin and a beta blocker) when these were added to a beta blocker and a diuretic (*Table* 5).[97] Each produced a significant further reduction in blood pressure, but only 9% to 25% of patients reached a level of 140/95 mm Hg. Similar incomplete responses have been noted by others.[97,99,102,110] In uncontrolled studies, supine diastolic blood pressure of 95 mm Hg was attained in 70% of 201 patients on adding captopril,[101] and in 81% of 19 patients on adding sustained-release nifedipine.[100]

Side effects of adding a third agent to a beta blocker and a diuretic were best documented by McAreavey et al.[97] The agents investigated can be ranked in order of decreasing patient acceptability: placebo, hydralazine, prazosin, methyldopa, minoxidil, and labetalol (however, up to 3.2 g/day of labetalol was used).

Central adrenergic inhibitor, vasodilator, diuretic

Central adrenergic inhibitors can mitigate the reflex tachycardia and loss of blood pressure control that occurs with the combination of a direct vasodilator and a diuretic.[111-113] In 18 patients taking hydralazine and a diuretic who were studied in a randomized, parallel fashion, clonidine was as effective as propranolol in reducing blood pressure and preventing reflex tachycardia.[113]

The combination of methyldopa, enalapril, and a diuretic was as effective as that of a beta blocker, hydralazine, and a diuretic in a randomized, double-blind, parallel group, multicenter study of 120 patients. Only 3.4% of patients withdrew from the methyldopa regimen vs 10% from the other regimen. With methyldopa there was also a lower incidence of hypokalemia (enalapril blunts the kaliuretic effect of diuretics).[114]

QUADRUPLE THERAPY

In uncontrolled studies of quadruple therapy, adding clonidine,[115] methyldopa,[116] guanethidine,[116] prazosin,[115-117] captopril,[118] or nitrendipine[119] to the combination of a direct vasodilator, beta blocker, and diuretic further decreases blood pressure.

SIDE EFFECTS OF NONTRADITIONAL ANTIHYPERTENSIVE PHARMACOTHERAPY

Side effects due to combination therapy have been poorly characterized. Most of the studies on combination drug therapy have been performed with small groups of patients, and most side effects occur in a minority of patients. For these reasons, statistically significant differences in the incidence of side effects between monotherapy and combination therapy have rarely been shown. Side effects have been investigated primarily by eliciting patient complaints at office visits, as opposed to the more sensitive method of a patient questionnaire.[2]

Combinations reported to have an incidence of side effects that is no worse or even less than monotherapy include: (1) a dihydropyridine calcium-channel blocker with either a beta blocker[42,43] or an ACE inhibitor[77,78,83,84] (lower incidence of side effects than with the dihydropyridine alone); and (2) prazosin with either hydralazine[99] or a beta blocker (lower incidence of lipid effects than with a beta blocker alone).[60]

CONCLUSION

On reviewing the data on the use of two antihypertensive agents from different classes in combination (but not including a diuretic), most such combinations have an additive hypotensive response (*Table* 6). None have been shown to decrease mortality like some of the more traditional combinations. Many of these nontraditional combinations have been studied only preliminarily. Side effects of most of these combinations have been poorly characterized.

REFERENCES

1. Zacest R, Gilmore E, Koch-Weser J. Treatment of essential hypertension with combined vasodilatation and beta-adrenergic blockade. N Engl J Med 1972; **286:**618–622.
2. Dollery CT. Pharmacologic basis for combination therapy of hypertension. Annu Rev Pharmacol Toxicol 1977; **17:**311–323.
3. Simpson FO. Combination therapy in hypertension. Drugs 1980; **20:**69–73.
4. Weber MA, Drayer JIM. Single agent and combination therapy of essential hypertension. Am Heart J 1984; **108:**311–315.
5. Sever PS, Poulter NR, Bulpitt CS. Double-blind crossover vs. parallel groups in hypertension. Am Heart J 1989; **117:**735–740.
6. Freestone S, Silas JH, Ramsay LE. Sample sizes for short term trials of antihypertensive drugs. Br J Clin Pharmacol 1982; **14:**265–268.
7. Weber MA, Drayer JIM, Laragh JH. The effects of clonidine and propranolol separately and in combination on blood pressure and plasma renin activity in essential hypertension. J Clin Pharmacol 1978; **18:**233–240.
8. Vanholder R, Lamiere N, Ringoir S. Long term experience with the combination of clonidine and beta-adrenoreceptor blocking agents in hypertension. Eur J Clin Pharmacol 1985; **28:**125–130.
9. Lilja M, Jounela AJ, Juustila H, Mattila MJ. Interaction of clonidine and beta blockers. Acta Med Scand 1980; **207:**173–176.
10. Saarimaa H. Combination of clonidine and sotalol in hypertension. Br Med J 1976; **1:**810.
11. Warren SE, Ebert E, Swerdlin AH, Steinberg S, Stone R. Clonidine and propranolol—paradoxical hypertension. Arch Intern Med 1973; **139:**253.
12. Hubbell FA, Weber MH, Drayer JIM, Rose DE. Combined central and peripheral sympathetic blockade: absence of additive antihypertensive effects. Am J Med Sci 1983; **285:**18–26.
13. Wing LMH, Chalmers JP, West MJ, et al. Enalapril and atenolol in essential hypertension: attenuation of hypotensive effects in combination. Clin Exp Hypertens [A] 1988; **10:**119–133.
14. Kanniainen E, Lilja M, Juustila H, Pasanen A, Jounela AJ. Nicardipine in combination with other antihypertensive drugs: calcium antagonist and prazosin have no additive antihypertensive effect. Cor Vasa 1990; **32:**126–133.
15. Jonkman FAM, van Zwieten PA. Aggravation of the severity of clonidine withdrawal syndrome in conscious rats by beta-2 adrenoreceptor antagonists. Drugs 1990; **40 Suppl 4:**45–47.
16. Byrd BB, Collins HW, Primm RK. Risk factors for severe bradycardia during oral clonidine therapy for hypertension. Arch Intern Med 1988; **148:**729–733.
17. Reis DJ, Ruggiero DA, Morrison SF. The C1 area of the rostral ventrolateral medulla oblongata. A critical brainstem region for control of resting and reflex integration of pressure. Am J Hypertens 1989; **2:**363S–367S.
18. Wing LMH, Reid JL, Davies DS, Dargie HJ, Dollery CT. Apparent resistance to the hypotensive effect of clonidine. Br Med J 1977; **1(6054):**136–137.
19. Drayer JIM, Keim JH, Weber MA, Case DB, Laragh JH. Unexpected pressor response to propranolol in essential hypertension: an interaction between renin, aldosterone, and sympathetic activity. Am J Med 1976; **60:**897–903.
20. Birkenhager WH, DeLeeuw PW. Adrenergic vasoconstriction as a cause of inadequate hypotensive response to beta-adrenergic blockade. Hypertension 1983; **5 (III Suppl):**III31–III35.
21. Petrie JC, Galloway DB, Jeffers TA, et al. Methyldopa and propranolol or practolol in moderate hypertension. Br Med J 1976; **2:**137–139.
22. Board AW, Perry VP, Shepperson BE, Nyman CE, Carchman SH. A postmarketing evaluation of guanfacine hydrochloride in mild to moderate hypertension. Clin Ther 1988; **10:**761–773.
23. Nies AS, Shand DG. Hypertensive response to propranolol in a patient treated with methyldopa—a proposed mechanism. Clin Pharmacol Ther 1973; **14:**823–826.
24. Floras JS, Hassan MO, Jones JV, Sleight P. Cardio-selective and nonselective beta-adrenoreceptor blocking drugs in hypertension: a comparison of their effect on blood pressure during mental and physical activity. J Am Coll Cardiol 1985; **6:**186–195.
25. Wallin JD, Shah SV. Beta-adrenergic blocking agents in the treatment of hypertension. Choices based on pharmacologic properties and patient characteristics. Arch Intern Med 1987; **147:**654–658.

26. Eggertsen R, Hansson L. Vasodilators in hypertension—a review with special emphasis on the combined use of vasodilators and beta-adrenoreceptor blockers. Int J Clin Pharmacol Ther Toxicol 1985; **23:**411–423.
27. Man in t'Veld AJ. Effect of beta blockers on vascular resistance in systemic hypertension. Am J Cardiol 1987; **59:**21F–25F.
28. Rosenfeld J, Bott-Kanner G, Boner G, et al. Treatment of hypertension during pregnancy with hydralazine monotherapy or combined therapy with hydralazine and pindolol. Eur J Obstet Gynecol Reprod Biol 1986; **22:**197–204.
29. Englert RG, Mauersberger H. A single-blind study of doxazosin in the treatment of essential hypertension when added to nonresponders to angiotensin-converting enzyme inhibitor therapy. Am Heart J 1988; **116:**1826–1832.
30. Wolfson P, Abernathy D, Dipette DJ, Zusman R. Diltiazem and captopril alone and in combination for the treatment of moderate systemic hypertension. Am J Cardiol 1988; **62:**103G–108G.
31. Vidt DV (for the Multicenter Study Group). A controlled multiclinic study to compare the antihypertensive effects of MK-421, hydrochlorothiazide, and MK-421 combined with hydrochlorothiazide in patients with mild to moderate essential hypertension. J Hypertens 1984; **2 Suppl 2:**81–88.
32. Borgmastars H, Forsen B, Tuomilehto J. Felodipine vs. hydrochlorothiazide as an addition to a beta-blocker in the treatment of hypertension. Drugs 1987; **34 Suppl 3:**136–138.
33. Jackson B, Morgan TO, Gibson J, Anderson A. Felodipine vs. prazosin as an addition to a beta-blocker in the treatment of essential hypertension. The Australian Multicenter Study. Drugs 1987; **34 Suppl 3:**109–119.
34. Malmberg L, Fagerberg SE, Frithz G. Peripheral vasodilation in the treatment of hypertension. Prazosin compared with hydralazine in patients not responding to beta-blockade. Acta Med Scand 1982; **665 Suppl:**121–124.
35. Marshall AJ, Pocock J, Barritt DW, Heaton ST. Evaluation of beta blockade, bendrofluazide, and prazosin in severe hypertension. Lancet 1977; **1:**271–274.
36. Drayer JIM, Weber MA, Lipson JD, Megaffin BB. Differential effects of diuresis and beta-adrenoreceptor blockade during angiotensin converting enzyme inhibition in patients with severe hypertension. J Clin Pharmacol 1982; **22:**179–186.
37. Swedish Lisinopril Study Group. Lisinopril combined with atenolol in the treatment of hypertension. J Cardiovasc Pharmacol 1991; **18:**457–461.
38. MacGregor GA, Markandu ND, Smith SJ, Sagnella GA. Captopril: contrasting effects of adding hydrochlorothiazide, propranolol, or nifedipine. J Cardiovasc Pharmacol 1985; **7:**S82–S87.
39. Huang CM, del Greco F, Quintanilla A, Molteni A. Comparison of antihypertensive effects of propranolol and captopril in essential hypertension. JAMA 1981; **245:**478–482.
40. Hansson L. Beta blockers with ACE inhibitors—a logical combination? J Hum Hypertens 1989; **3:**97–100.
41. Pickering TG. The use of converting enzyme inhibitors in combination with other antihypertensive agents. Am J Hypertens 1991; **4:**73S–78S.
42. Anderton JL, Vallance BD, Stanley NN, Crowe PF, Mittra B, Perks WH. Atenolol and sustained-release nifedipine alone and in combination in hypertension. A double-blind, crossover, randomized trial. Drugs 1988; **35 Suppl 4:**22–26.
43. Maclean D, Mitchell ET, Coulson RR, Fitzsimons TJ, McDevitt DG. Atenolol-nifedipine combinations compared to atenolol alone in hypertension: efficacy and tolerability. Br J Clin Pharmacol 1988; **25:**425–431.
44. Nifedipine-Atenolol Study Review Committee. Nifedipine and atenolol singly and combined for treatment of essential hypertension: comparative multicenter study in general practice in the United Kingdom. Br Med J 1988; **296:**468–473.
45. Morgan TO. A review of the antihypertensive effects of felodipine alone or in combination. J Cardiovasc Pharmacol 1989; **15(4 Suppl):**S76–S84.
46. Groom P, Simpson RJ, Singh B, Ward DE, Peers E, Richardson PDI. A double-blind comparison of felodipine and hydrochlorothiazide added to metoprolol to control hypertension. Eur J Clin Pharmacol 1988; **34:**21–24.
47. Tonkin AL, Wing LMH, Russell AE, et al. Diltiazem and atenolol in essential hypertension: additivity of effects of blood pressure and cardiac conduction with combination therapy. J Hypertens 1990; **8:**1015–1019.
48. Lindner UK, von Manteuffel G-E, Stafunsky M. The addition of doxazosin to the treatment of hypertensive patients not responsive to nifedipine. Am Heart J 1988; **116:**1814–1820.
49. Burris JD, Weir MR, Oparil S, Weber M, Cady WJ, Stewart WH. An assessment of diltiazem and hydrochlorothiazide in hypertension. Application of factorial trial design in multicenter clinical trial of combination therapy. JAMA 1990; **263:**1507–1512.
50. Toyosaki N, Toyo-Oka T, Natsume T, et al. Combination therapy with diltiazem and nifedipine in patients with effort angina. Circulation 1988; **77:**1370–1375.
51. MacInnes GT, Findlay IN, Murray G, Cleland JGF, Dargie HJ. Cardiovascular responses to verapamil and propranolol in hypertensive patients. J Hypertens 1985; **3(3 Suppl):**S219–S221.
52. Packer M. Combined beta-adrenergic and calcium entry blockade in the treatment of angina pectoris. N Engl J Med 1989; **320:**709–718.
53. Strauss WE, Parisi AF. Combined use of calcium channel and beta adrenergic blockers for the treatment of chronic stable angina. Ann Intern Med 1988; **109:**570–581.
54. Vinceneux P, Canal M, Domart Y, et al. Pharmacokinetic and pharmacodynamic interactions between nifedipine and propranolol or betaxolol. Int J Clin Pharmacol Ther Toxicol 1986; **24:**153–158.
55. Keech AC, Harper RW, Harrison PM, Pitt A, McLean AJ. Pharmacokinetic interaction between oral metoprolol and verapamil for angina pectoris. Am J Cardiol 1986; **58:**551–552.
56. Carruthers SG, Freeman DJ, Bailey DG. Synergistic adverse hemodynamic interaction between oral verapamil and propranolol. Clin Pharmacol Ther 1989; **46:**469–477.
57. Johnston DL, Lesoway R, Humen DP, Kostuk WJ. Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine, and diltiazem in exertional angina pectoris: a placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985; **55:**680–687.
58. Jones JV, Steiner JM. Double-blind crossover comparison of hydralazine and prazosin in hypertensive subjects on beta-adrenoreceptor blocking agent (atenolol). Br J Clin Pharmacol 1980; **10:**531–533.
59. Elliot HL, Mclean K, Sumner DJ, Meredith PA, Reid JL. Immediate cardiovascular responses to oral prazosin—effects of concurrent beta blockers. Clin Pharmacol Ther 1981; **29:**303–309.
60. Holtzman JL, Kaihlanen PM, Rider A, Lewis AJ, Spindler JS, Oberlin JA. Concomitant administration of terazosin and atenolol for the treatment of essential hypertension. Arch Intern Med 1988; **148:**539–543.
61. Oates HF, Stoker LM, Stokes GS. Interactions between prazosin, clonidine and direct vasodilators in the anesthetized rat. Clin Exp Pharmacol Physiol 1978; **5:**85–89.
62. Cavero I, Lefevre F, Roach AG. Differential effects of prazosin on the pre and post synaptic alpha-adrenoreceptors in the rat and dog. Br J Pharmacol 1977; **61:**469–474.
63. Van Zwieten PA, Lam E, Timmermans PBMWM. The interaction between prazosin and clonidine. Clin Sci 1978; **55:**259s–261s.
64. Andrejak M, Fievet P, Makdassi R, et al. Lack of antagonism in the antihypertensive effects of clonidine and prazosin in man. Clin Sci 1981; **61:**453s–455s.
65. Kochar MS, Zeller JR, Itskovitz HD. Prazosin in hypertension with and without methyldopa. Clin Pharmacol Ther 1979; **25:**143–148.
66. Kuokkanen K, Mattila MJ. Antihypertensive effect of prazosin in combination with methyldopa, clonidine or propranolol. Ann Clin Res 1979; **11:**18–24.
67. Drayer JIM, Weber MA. Antihypertensive agents which inhibit sympathetic activity: potentially adverse effects of combination treatment. Am Heart J 1982; **104:**660–665.
68. Guazzi MD, Fiorentini C, Olivari MT, Bartorelli A, Necchi G, Polese A.

Short and long term efficacy of a calcium antagonistic agent (nifedipine) combined with methyldopa in the treatment of severe hypertension. Circulation 1980; **61**:913–919.
69. Spritzer N, Spritzer TS, Rodrigues R. Treatment of resistant hypertension; 3 years of follow up with the combination of verapamil and methyldopa. J Cardiovasc Pharmacol 1989; **13(4 Suppl)**:S65–S67.
70. Mitrovic V, Patyna W, Bruchhausen V, Hüting J, Schlepper M. Interactions of clonidine and nifedipine in moderately severe hypertensive patients. J Clin Pharmacol; **31**:549–555.
71. Lappe RW, Saslow BA, Wendt RL. Effects of nifedipine on the hypotensive actions of alpha-2 agonists in conscious spontaneously hypertensive rats. J Cardiovasc Pharmacol 1984; **6**:S748–S752.
72. Timmermans PBMWM, de Jonge A, van Meel JCA, Mathy MJ, van Zwieten PA. Influence of nifedipine on functional responses in vivo initiated at alpha-2 adrenoreceptors. J Cardiovasc Pharmacol 1983; **4**:1–11.
73. Ribeiro A, Mulinari R, Gavras I, Kohlman O, Ramos O, Gavras H. Sequential elimination of pressor mechanisms in severe hypertension in humans. Hypertension 1986; **8(I Suppl)**:I169–I173.
74. Hauger-Klevene JH. Treatment of clonidine rebound syndrome with sublingual captopril. N Engl J Med 1986; **314**:181–182.
75. Ball SG. The sympathetic nervous system and converting enzyme inhibition. J Cardiovasc Pharmacol 1989; **13(3 Suppl)**:S17–S21.
76. Mimram A, Ribstein J. Effect of chronic nifedipine in patients inadequately controlled by CEI and a diuretic. J Cardiovasc Pharmacol 1985; **7**:S92–S95.
77. White WB, Viadero JJ, Lane TJ, Podesla S. Effects of combination therapy with captopril and nifedipine in severe or resistant hypertension. Clin Pharmacol Ther 1986; **39**:43–48.
78. Guazzi MD, Decesare N, Galli C, et al. Calcium channel blockade with nifedipine and angiotensin converting enzyme inhibition with captopril in the therapy of patients with severe primary hypertension. Circulation 1984; **70**:279–284.
79. Donnelly R, Elliot HL, Reid JL. Nicardipine combined with enalapril in patients with essential hypertension. Br J Clin Pharmacol 1986; **22**:283S–287S.
80. Brouwer RML, Bolli P, Erne P, Conen D, Kiowski W, Buhler FR. Antihypertensive treatment using calcium antagonists in combination with captopril rather than diuretics. J Cardiovasc Pharmacol 1985; **7**:S88–S91.
81. Eggertsen R, Svensson A, Dahlof B, Hansson L. Additive effect of isradipine in combination with captopril in hypertensive patients. Am J Med 1989; **86 Suppl 4A**:124–126.
82. Bakris GL. Renal effects of calcium antagonists in diabetes mellitus: an overview of studies in animal models and in humans. Am J Hypertens 1991; **7**:487S–493S.
83. Bellet M, Sassano P, Guyenne T, Corvol P, Menard J. Converting enzyme inhibition buffers the counter regulatory response to acute administration of nicardipine. Br J Clin Pharmacol 1987; **24**:465–472.
84. Stornello M, Di Rao G, Iachello M, et al. Hemodynamic and humoral interactions between captopril and nifedipine. Hypertension 1983; **5(III Suppl)**:III154–III156.
85. Elliot HL, Meredith PA, Campbell L, Reid JL. The combination of prazosin and verapamil in the treatment of essential hypertension. Clin Pharmacol Ther 1988; **43**:554–560.
86. Jee LD, Opie LH. Acute hypotensive response to nifedipine added to prazosin in treatment of hypertension. Br Med J 1983; **287**:1314.
87. Sluiter HE, Huysmans FTM, Thien TA, Koene RAP. The influence of alpha-1 adrenergic blockade on the acute antihypertensive effect of nifedipine. Eur J Clin Pharmacol 1985; **29**:263–267.
88. Abernathy DR, Winterbottom LM. Forearm vascular alpha-1 adrenergic blockade by verapamil. Clin Pharmacol Ther 1990; **47**:755–759.
89. Pedrinelli R, Taddei S, Salvetti A. Calcium entry blockade and alpha adrenergic vascular reactivity in human beings: differences between nicardipine and verapamil. Clin Pharmacol Ther 1989; **45**:285–290.
90. Baba T, Tomiyama T, Takebe K. Enhancement by an ACE inhibitor of first-dose hypotension caused by an alpha-1 blocker. N Engl J Med 1990; **322**:1237.
91. Marwood J, Tierney G, Stokes G. Interactions between enalaprilat and doxazosin at rat tail artery alpha-1 adrenoreceptors. J Cardiovasc Pharmacol 1991; **17**:1–7.
92. Frishman W, Charlap S, Kimmel B, et al. Diltiazem, nifedipine, and their combination in patients with stable angina pectoris: effects on angina, exercise tolerance, and the ambulatory electrocardiographic ST segment. Circulation 1988; **77**:774–786.
93. Kiowski W, Erne P, Linder L, Buhler FR. Arterial vasodilator effects of the dihydropyridine calcium antagonist amlodipine alone and in combination with verapamil in systemic hypertension. Am J Cardiol 1990; **66**:1469–1472.
94. Pearson RM, Bending MR, Bulpitt CJ, et al. Trial of combination of guanethidine and oxprenolol in hypertension. Br Med J 1976; **1**:933–936.
95. Leonard JW, Gifford RW, Humphrey DC. Treatment of hypertension with methyldopa alone or combined with diuretics and/or guanethidine. Am Heart J 1965; **69**:610–618.
96. Gore RD. Safety and efficacy of a three-drug regimen for the treatment of hypertension: hydrochlorothiazide, propranolol, and guanadrel. Clin Ther 1983; **6**:86–92.
97. McAreavey D, Ramsay LE, Latham L, et al. Third Drug Trial: comparative study of hypertensive agents added to treatment when blood pressure remains uncontrolled by a beta blocker plus thiazide diuretics. Br Med J 1984; **288**:106–111.
98. Myers MG, Leenen FHH, Burns R, Frankel D. Nifedipine tablet vs hydralazine in patients with persisting hypertension who received combined diuretic and beta blocker therapy. Clin Pharmacol Ther 1986; **39**:409–413.
99. Vandenburg MJ, Sharman VL, Wright P, Drew PJ, Barnes JN. Hydralazine and prazosin in the treatment of hypertension. Br J Clin Pharmacol 1983; **16**:537–542.
100. Potter JF, Beevers DG. Comparison of nifedipine and captopril as third line antihypertensive agents in hypertensive patients with beta blocker and diuretic therapy. J Clin Pharmacol 1987; **27**:410–414.
101. Muiesen G, Alicandri C, Agabiti-Rosei E, et al. A multicenter trial of low dose captopril administered twice daily in patients with essential hypertension unresponsive to a diuretic and a beta-blocker. J Clin Hypertens 1987; **3**:144–152.
102. Ramsay LE, Parnell L, Waller PC. Comparison of nifedipine, prazosin and hydralazine in the treatment of hypertensive patients uncontrolled by a thiazide diuretic plus a beta-blocker. Postgrad Med J 1987; **63**:99–103.
103. Co-operative Study Group. Felodipine vs hydralazine: a controlled trial as third line therapy in hypertension. Br J Clin Pharmacol 1986; **21**:621–626.
104. Muir AL, Wathen CG. The use of felodipine in the treatment of severe hypertension. Drugs 1987; **34 Suppl 3**:120–124.
105. Simon G, Wittig VJ, Cohn JN. Transdermal nitroglycerin as a step 3 antihypertensive drug. Clin Pharmacol Ther 1986; **40**:42–45.
106. Wilson C, Scott ME, Abdel-Mohsen A. Atenolol and methyldopa in the treatment of hypertension. Postgrad Med J 1977; **53 Suppl 3**:123–127.
107. Webster J, Jeffers TA, Galloway DB, Petrie JC, Barker NP. Atenolol, methyldopa and chlorthalidone in moderate hypertension. Br Med J 1977; **1**:76–78.
108. Ramsay LE. Diuretic and beta blocker in hypertension—then what? J R Coll Physicians Lond 1980; **14**:249–253.
109. Conway J. Third-line therapy. A cautionary note. Clin Exp Hypertens [A] 1985; **7**:1339–1346.
110. Beilen LJ, Bulpitt CJ, Coles EC, et al. Long term antihypertensive drug treatment and blood pressure control in three hospital hypertension clinics. Br Heart J 1980; **43**:74–79.
111. Mulvill-Wilson J, Gaffney FA, Neal WW, Graham RM, Pettinger WA, Blomquist CG. Single and combined therapy for systemic hypertension with propranolol, hydralazine, and hydrochlorothiazide: hemodynamic and neuroendocrine mechanisms of action. Am J Cardiol 1985; **56**:315–320.
112. Velasco M, Urbina-Quintana A, Morillo J, Vizcarrondo H, Ramirez A, Hernandez-Pieretti O. Systemic and cardiac hemodynamic inter

actions between guanfacine and hydralazine in hypertensive patients. Eur J Clin Pharmacol 1984; **27:**393–396.
113. Mroczek WJ, Davidov ME. A randomized clinical trial of clonidine and propranolol in hypertensive patients receiving a diuretic and a vasodilator. Curr Ther Res 1978; **23:**294–299.
114. Leonetti G, Cuspidi C, Sampieri L, et al. Evaluation of the efficacy and safety of enalapril plus hydrochlorothiazide plus methyldopa vs standard triple therapy in the treatment of moderate to severe hypertension: results from a multicenter study. J Hum Hypertens 1990; **4:**5–11.
115. Mitchell H, Pettinger WA. Clonidine and prazosin in hypernoradrenergic vasodilator-treated and beta blocker-treated patients. Clin Pharmacol Ther 1981; **30:**297–302.
116. Vandenburg MJ, Sharman VL, Drew P, Barnes J, Wright P. Quadruple therapy for resistant hypertension. Br J Clin Pract 1985; **39:**17–19.
117. Heagerty AM, Russell GI, Bing RF, Thurston H, Swales JD. The addition of prazosin to standard triple therapy in the treatment of severe hypertension. Br J Clin Pharmacol 1982; **13:**539–541.
118. Traub YM, Levey BA. Combined treatment with minoxidil and captopril in refractory hypertension. Arch Intern Med 1983; **143:**1142–1144.
119. Hoffler D, Stoepel K. Nitrendipine in hypertension that is difficult to control. J Cardiovasc Pharmacol 1984; **6:**S1060–S1062.