Effect of phenoxybenzamine on cardiovascular and plasma catecholamine responses to clonidine

To determine whether the alpha-adrenergic antagonist phenoxybenzamine would alter cardiovascular or plasma catecholamine response to the alpha-adrenergic agonist clonidine, six patients with pheochromocytomas and eight with labile hypertension were studied. Clonidine, 0.3 mg, was given with and without 48 hr pretreatment with 30 mg/day phenoxybenzamine. The response to 10 mg diazepam was also observed in seven of the subjects who had labile hypertension. In the hypertensive patients, clonidine alone induced a fall in supine blood pressure from 137 ± 21/91 ± 14 to 109 ± 18/76 ± 17 mm Hg and, with phenoxybenzamine, clonidine reduced blood pressure from 141 ± 22/89 ± 10 to 107 ± 21/72 ± 11 mm Hg. Plasma norepinephrine fell from 179 ± 60 to 107 ± 79 pg/ml without phenoxybenzamine and from 229 ± 159 to 95 ± 46 pg/ml with phenoxybenzamine in hypertensive subjects. Responses with phenoxybenzamine did not differ from those without phenoxybenzamine and diazepam induced no cardiovascular or plasma catecholamine changes. Clonidine did not lower plasma catecholamines in patients with a pheochromocytoma in the presence or in the absence of phenoxybenzamine. Blood pressure tended to decline after clonidine in pheochromocytoma patients not taking phenoxybenzamine, but it was not reduced by clonidine when these patients were taking phenoxybenzamine. Phenoxybenzamine does not inhibit reduction in blood pressure and plasma catecholamines induced by clonidine in patients with essential hypertension or interfere with the clonidine suppression test in patients with pheochromocytomas.

Andrew Zweifler, M.D., Milton Gross, M.D., and James Sisson, M.D. *Ann Arbor, Mich.*
Divisions of Hypertension and Nuclear Medicine and Department of Internal Medicine, University of Michigan Medical School

Clonidine is an imidazoline derivative that is widely used as an antihypertensive drug. It lowers blood pressure and heart rate by stimulating postsynaptic alpha-adrenergic receptors in the central nervous system.[9, 15] Clonidine also decreases plasma norepinephrine after short- and long-term administration; an absence of this response has been reported recently to be diagnostic of a pheochromocytoma.[1] Despite the fact that, in animals, the hypotensive action of clonidine is blocked by a range of alpha-antagonists,[8, 18] there has been little systematic investigation of the effect of alpha-blockers on the action of clonidine in man. Infusion of phentolamine has been reported to increase plasma norepinephrine concentration in normal subjects

Supported in part by grants from the National Institutes of Health to the Clinical Research Center, University of Michigan Medical School (5-M01-RR-42) and the Division of Hypertension (HL 21893), and the Nuclear Medicine Research Fund.

Received for publication May 17, 1982.

Accepted for publication Sept. 13, 1982.

Reprint requests to: Andrew J. Zweifler, M.D., Division of Hypertension, Box 48, R6669 Kresge Medical Research Building, University of Michigan Medical Center, Ann Arbor, MI 48109.

0009-9236/83/020156+07$00.70/0

Table I. *Recumbent plasma catecholamines and blood pressure in patients*

Diagnosis	*Norepinephrine (pg/ml)*	*Epinephrine (pg/ml)*	*BP (mm Hg)*
Hypertensive	119	21	150/110
	208	20	154/98
	152	26	114/80
	105	34	150/85
	176	22	135/100
	247	58	150/90
	247	57	96/64
	230	47	144/100
Pheochromocytoma	1347	28	140/90
	589*	324*	104/66*
	7188	1427	160/90
	1097	54	138/90
	2339	96	153/108
	2251	—	152/90

*Taking phenoxybenzamine, 20 mg/day.

taking clonidine,[12] but there has been no study of the effect of phenoxybenzamine on any of the responses to clonidine in man. We have recorded blood pressure, heart rate, and plasma catecholamine changes induced by clonidine with and without phenoxybenzamine pretreatment in 14 patients (six with pheochromocytomas and eight with labile hypertension). We also observed the response to diazepam in seven patients in the latter category.

Materials and methods

Subjects. Our subjects were eight patients with labile hypertension suspected of having a pheochromocytoma, but found to have normal rates of urinary catecholamine excretion and normal plasma catecholamine concentrations, and six with pheochromocytomas that were ultimately removed surgically. The eight who proved not to have a catecholamine-secreting tumor were selected for study because of a history of intermittent or unusually variable hypertension and associated symptoms such as headache, flushing, sweating, and palpitations. Baseline blood pressure and plasma catecholamine levels are recorded in Table I.

Clonidine response. Patients were admitted to the Clinical Research Center and studied in the fasted state and after at least 30 min of recumbency. Cigarettes, coffee, and tea were not permitted for 24 hr before the experiments. A 19-gauge butterfly needle was introduced into a peripheral vein at 7:30 A.M. and patency of the line was maintained with heparinized saline (15 units/ml). Blood samples were not drawn until at least 30 min after the placement of the venous line. A 0.3-mg dose of clonidine was given orally and blood samples were obtained at −5, 60, 120, 150, and 180 min. This dose was selected after pilot experiments with 0.5 mg (the dose used by Metz et al.[12]) resulted in rather marked somnolence and hypotension in normal subjects. Hossmann et al.[5] had also demonstrated that 0.3 mg clonidine induces substantial cardiovascular and sedative effects. The blood samples were placed into prechilled tubes containing EDTA and glutathione; the tubes were centrifuged promptly and the plasma was then decanted and frozen. Recumbent auscultatory blood pressure and heart rate measurements

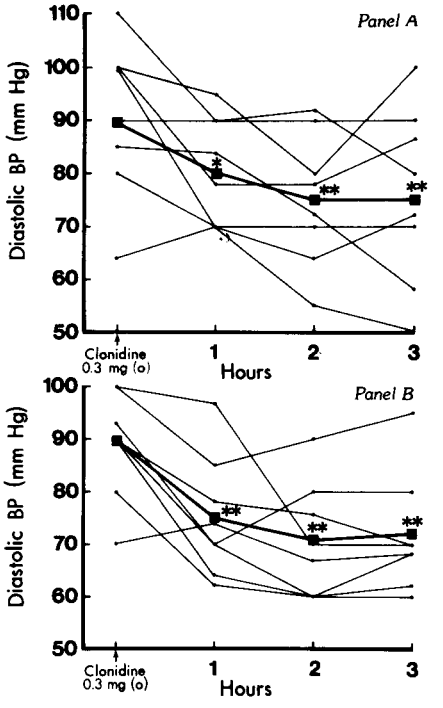

Fig. 1. Change in diastolic blood pressure in eight hypertensive patients and mean change for the group (■—■) after clonidine (0.3 mg orally) with *(panel B)* and without *(panel A)* phenoxybenzamine pretreatment. *P < 0.05; **P < 0.01 vs. time 0.

Table II. *Maximum decrement (±SEM) in plasma norepinephrine, blood pressure, and heart rate during a 3-hr period after short-term clonidine (0.3 mg) and after diazepam (10 mg)*

Parameter	*n*	*Clonidine*	*Diazepam*
Systolic blood pressure (mm Hg)	6	−38.7 ± 21.2†	−5.7 ± 8.6
Diastolic blood pressure (mm Hg)	6	−21.2 ± 16.8*	−0.3 ± 8.3
Heart rate (bpm)	6	−12.3 ± 8.4*	−3.7 ± 6.3
Plasma norepinephrine	7	−35.6 ± 62.4	−7.7 ± 43.2

*P < 0.05; †P < 0.01 vs. time 0.

were obtained at 0, 60, 120, 150, and 180 min by a nurse or one of the investigators.

Clonidine and diazepam. To determine the significance and specificity of the hemodynamic and plasma catecholamine changes after clonidine, seven of the patients with labile hypertension were also studied after oral diazepam (10 mg). Diazepam was chosen rather than an inert placebo in an effort to approximate the hypnotic effect of clonidine. Blood pressure and heart rate were measured at 0, 60, 120, 150, and 180 min in six patients and sequential blood samples for plasma norepinephrine determination were obtained in seven patients. The effect of diazepam was determined 24 hr after the effect of clonidine had been measured.

Effect of phenoxybenzamine on the clonidine response. The clonidine response was observed twice, before and after phenoxybenzamine, in all eight of the patients with labile hypertension and two patients with pheochromocytomas. Three patients with pheochromocytomas were studied without phenoxybenzamine and one was studied twice while taking phenoxybenzamine over a long term. Phenoxybenzamine was given twice a day in a total daily dose of 30 mg for 48 hr before the clonidine test and 10 mg phenoxybenzamine was given the morning of the test.

Plasma norepinephrine and epinephrine were determined by radioenzymatic assay.[14] Student's paired was used for within-group analysis and the unpaired test was used for comparison of groups.

Results

Clonidine versus diazepam. Patients became drowsy within an hour of receiving either medication and usually slept lightly through the remainder of the experiment. Substantial and significant reductions in blood pressure and heart rate were noted after clonidine, but not after diazepam (Table II). Plasma norepinephrine concentrations also declined more after clonidine, but this change was not significant.

Effect of phenoxybenzamine on the clonidine response

Blood pressure and heart rate

LABILE HYPERTENSION. Blood pressure fell below control levels 1 hr after clonidine and had not recovered at 3 hr (Table III). Baseline blood pressure and the hypotensive response to clonidine was no different after phenoxybenzamine (Table III; Fig. 1), although the percent fall in pressure tended to be somewhat greater (Fig. 2). Heart rate was below baseline 2 and 3 hr after clonidine. If anything, this effect was intensified by phenoxybenzamine (Fig. 3).

PHEOCHROMOCYTOMA. Although blood pressure tended to decline after clonidine, this effect was significant at only one observation point (Table III). There were no significant heart rate changes. After phenoxybenzamine the baseline blood pressure was not significantly lower and clonidine did not alter blood pressure or heart rate.

Plasma catecholamines

LABILE HYPERTENSION. Plasma norepinephrine declined progressively after clonidine, but the response became a significant one only 3 hr after the drug was taken (Table IV). Plasma norepinephrine appeared to fall more rapidly after phenoxybenzamine, but percent reduction of norepinephrine was similar on both occasions (Fig. 4). Clonidine had no effect on plasma epinephrine concentration with or without phenoxybenzamine.

PHEOCHROMOCYTOMA. Plasma catecholamine concentrations appeared to increase after clonidine, but not significantly so. Clonidine

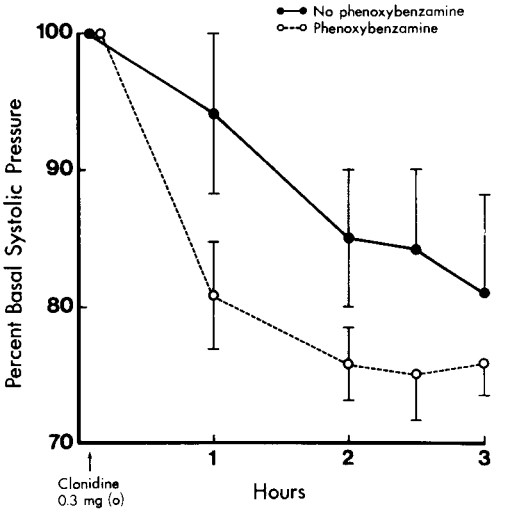

Fig. 2. Percent reduction in systolic blood pressure (±SEM) in eight hypertensive patients given 0.3 mg clonidine with and without phenoxybenzamine pretreatment.

during phenoxybenzamine therapy had similar effects (Table IV).

Discussion

Our data demonstrate that phenoxybenzamine does not inhibit the decrease in blood pressure, heart rate, and plasma norepinephrine concentration induced by clonidine. There is, in fact, a suggestion that phenoxybenzamine potentiates these effects. This finding is in apparent conflict with the results of Metz et al.,[12] who reported that infusion of the alpha-adrenergic–receptor blocker phentolamine reversed the reduction of plasma norepinephrine in normal subjects receiving clonidine. The two studies were designed quite differently, however, and the subjects are dissimilar. This may explain the discrepancy, but a review of the pharmacology of clonidine, phenoxybenzamine, and phentolamine allows another explanation. Clonidine is an alpha-adrenergic agonist that has a special affinity for $alpha_2$-receptors, but also occupies $alpha_1$-receptors. It enters the brain readily and lowers blood pressure primarily by inhibiting sympathetic outflow from the central nervous system[9]; however, a peripheral action may also be important, particularly in relation to its effect on heart rate.[10]

Phentolamine is an alpha-adrenergic antagonist that blocks $alpha_1$-receptors only slightly more than $alpha_2$-receptors[2] and it does not have notable central nervous system effects.[19] Phenoxybenzamine, on the other hand, is an alpha-adrenergic antagonist that has quantitatively different effects on $alpha_1$- and $alpha_2$-receptors. In the perfused cat spleen, Dubocovich and Langer[3] observed phenoxybenzamine to be 30 times as potent in blocking $alpha_1$ than $alpha_2$ responses during nerve stimulation. Moreover, epinephrine-induced aggregation of human blood platelets, which is almost certainly subserved by an $alpha_2$-receptor, is blocked by phentolamine and not by phenoxybenzamine.[6] Phenoxybenzamine enters the central nervous system,[11] but has not been observed to inhibit the central nervous system effects of clonidine in animals.[7, 16]

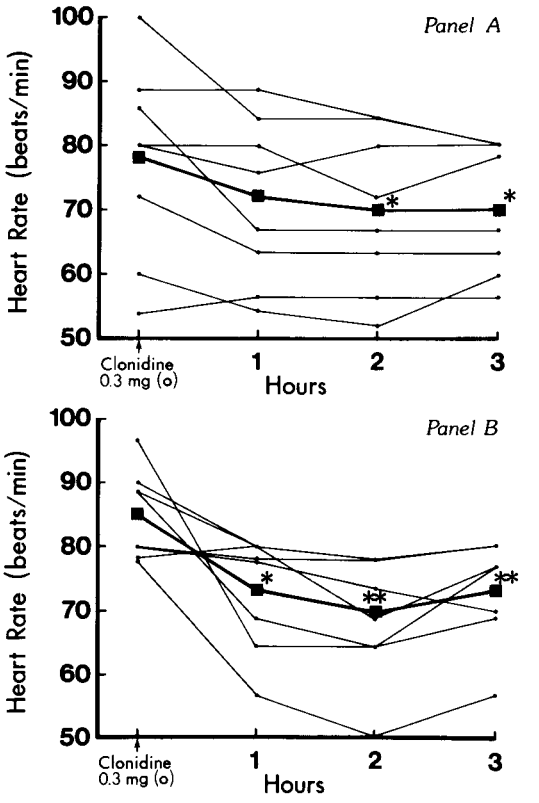

Fig. 3. Change in heart rate in eight hypertensive patients and mean change for the group (■—■) after clonidine (0.3 mg orally) with *(panel B)* and without *(panel A)* phenoxybenzamine pretreatment. *P < 0.05 and **P < 0.01 vs. time 0.

Table III. *Effect of clonidine on blood pressure and heart rate in patients taking and not taking phenoxybenzamine*

	Hours after clonidine								
	0			*1*			*2*		
	SBP	*DBP*	*HR*	*SBP*	*DBP*	*HR*	*SBP*	*DBP*	*HR*
Hypertensive (n = 8)									
Clonidine	137	91	78	127	81*	71	115†	75†	70*
	(21)	(14)	(15)	(22)	(10)	(13)	(20)	(12)	(12)
Clonidine and phenoxybenzamine	141	89	85	115	75†	73*	106	71†	69†
	(22)	(10)	(7)	(18)	(11)	(9)	(19)	(10)	(10)
Pheochromocytoma									
Clonidine (n = 5)	149	94	80	134	88	76	134	84†	76
	(9)	(8)	(13)	(16)	(12)	(14)	(23)	(11)	(15)
Clonidine and phenoxybenzamine	115	74	73	111	78	74	110	79	74
(n = 3)	(17)	(8)	(5)	(7)	(14)	(3)	(11)	(15)	(4)

SBP = systolic blood pressure in mm Hg (±SD); DBP = diastolic blood pressure in mm Hg (±SD); HR = heart rate in bpm (±SD).
*P < 0.05; †P < 0.01 vs. time 0.

Table IV. *Effect of clonidine on plasma catecholamines in patients taking and not taking phenoxybenzamine pretreatment*

	Hours after clonidine									
	0		*1*		*2*		*2.5*		*3*	
	NE	*E*	*NE*	*E*	*NE*	*E*	*NE*	*E*	*NE*	*E*
Hypertensives (n = 8)										
Clonidine	179	38	151	41	141	44	124	33	107*	39
	(60)	(16)	(55)	(17)	(86)	(26)	(85)	(13)	(79)	(33)
Clonidine and phenoxybenzamine	229	52	182	45	112*	37	124	34	95*	31
	(159)	(27)	(146)	(32)	(51)	(20)	(74)	(27)	(46)	(13)
Pheochromocytoma										
Clonidine (n = 5)	2844	401	4102	326	3843	315	5728	248	2172	249
	(2489)	(684)	(2871)	(556)	(2231)	(527)	(5338)	(365)	(1115)	(348)
Clonidine and phenoxybenzamine (n = 3)	1610	246	2484	191	2720	281	3332	199	2886	228
	(1297)	(194)	(3439)	(128)	(4340)	(215)	(3820)	(107)	(4301)	(150)

NE = plasma norepinephrine in pg/ml (±SD); E = plasma epinephrine in pg/ml (±SD).
*P < 0.05 vs. time 0.

Phenoxybenzamine would therefore not be expected to inhibit the response to clonidine in man, since clonidine's cardiovascular and hormonal effects are due to stimulation of alpha$_2$-receptors that phenoxybenzamine does not antagonize or can only block when present in high concentration. A recent investigation in patients with essential hypertension demonstrated that phenoxybenzamine in the dose range used in our study did not increase plasma norepinephrine concentration in recumbency, although it did reduce upright blood pressure.[13] Blockade of alpha$_2$-receptors should elevate plasma norepinephrine concentration. Apparently the dose of phenoxybenzamine that is clinically acceptable antagonizes alpha$_1$-receptors but has no substantial effect on alpha$_2$-receptors and therefore is not capable of blocking the action of clonidine.

The situation is not so clear in the case of

Hours after clonidine					
2.5			*3*		
SBP	*DBP*	*HR*	*SBP*	*DBP*	*HR*
113*	79*	74	109†	76†	70*
(25)	(14)	(18)	(18)	(17)	(10)
105	72†	71*	107	72†	73†
(19)	(12)	(11)	(21)	(11)	(8)
126	84	72	129	86	76
(20)	(16)	(10)	(14)	(16)	(7)
115	77	73	111	76	74
(13)	(14)	(8)	(10)	(11)	(2)

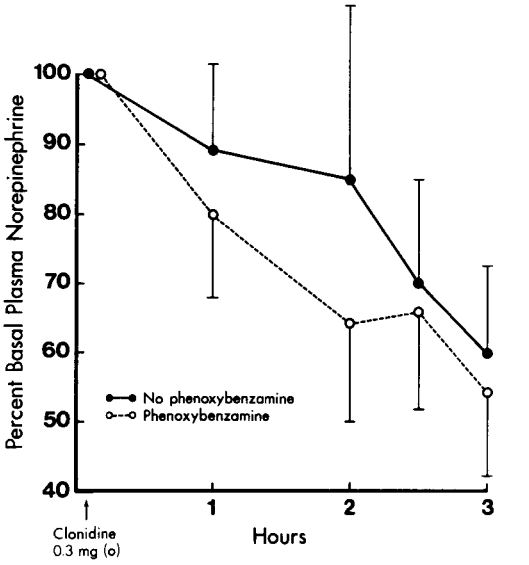

Fig. 4. Percent reduction in plasma norepinephrine concentration (±SEM) in eight hypertensive patients given 0.3 mg clonidine with and without phenoxybenzamine pretreatment.

phentolamine since, although more balanced than phenoxybenzamine in its antagonism of alpha$_1$- and alpha$_2$-receptors, it is relatively less effective in penetrating the central nervous system. Perhaps phentolamine blocks only the peripheral action of clonidine, particularly when administered over a short term. This might explain the failure of blood pressure to rise while plasma norepinephrine increased to control levels when Metz et al.[12] infused phentolamine into clonidine-treated normal subjects.

Our major finding is that clonidine may be given to patients taking phenoxybenzamine without loss of clonidine's effects. This may have both diagnostic and therapeutic implications. The clonidine suppression test has been recently reported to be of value in the diagnosis of pheochromocytoma in patients with moderate elevations of plasma norepinephrine concentration.[1] Plasma catecholamines are not lowered by clonidine in patients with sporadic pheochromocytoma. We have, in fact, observed a tendency for plasma catecholamines to rise in response to clonidine in patients with pheochromocytomas. This may be a reaction to blood pressure decline, which is modest, but it may also result from blockade of alpha$_2$-receptors by clonidine, which is known to act as an alpha$_2$-antagonist in the presence of high concentrations of catecholamines.[17] Our data reveal that pretreatment with phenoxybenzamine does not alter the pattern of change in plasma norepinephrine concentration after clonidine dosing in patients with pheochromocytomas. Patients suspected of having such tumors and being treated with phenoxybenzamine need not have the drug discontinued to undergo the clonidine suppression test.

The possibility that the combination of clonidine and phenoxybenzamine might be useful in the treatment of hypertension is of therapeutic interest. Occasionally there is a rapid and potentially dangerous rise in blood pressure after discontinuation of clonidine[4] that relates to its rather short duration of action. Phenoxybenzamine, on the other hand, has a prolonged effect. In cases in which clonidine, along with other antihypertensive medication, might be stopped abruptly by accident or by design, the presence of phenoxybenzamine in the therapeutic regimen might be of value, since, long after discontinuation, its residual alpha$_1$-blocking action might protect against "clonidine rebound."

References

1. Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RW: Clonidine suppression test. N Engl J Med **305**:623-626, 1981.
2. Cubeddu LX, Barnes EM, Langer SZ, Weiner N: Release of norepinephrine and dopamine-beta hydroxylase by nerve stimulation. I. Role of

neuronal and extraneuronal uptake and of alpha-presynaptic receptors. J Pharmacol Exp Ther **190:**431-450, 1974.

3. Dubocovich ML, Langer SZ: Negative feedback regulation of noradrenaline release by nerve stimulation in the perfused cat spleen: differences in potency of phenoxybenzamine in blocking pre- and post-synaptic adrenergic receptors. J Physiol **237:**505-519, 1974.
4. Hansson L, Hunyor SN, Julius S, Hoobler SW: 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.
5. Hossmann V, Maling TJB, Hamilton CA, Reid JL, Dollery CT: Sedative and cardiovascular effects of clonidine and nitrazepam. CLIN PHARMACOL THER **28:**167-176, 1980.
6. Hsu CY, Knapp DR, Halushka PV: The effects of alpha-adrenergic agents on human platelet aggregation. J Pharmacol Exp Ther **208:**366-370, 1979.
7. Hunt GE, Atrens DM, Bickeri FT, Paxinos G: Alpha-adrenergic modulation of hypothalamic self-stimulation: effects of phenoxybenzamine, Yohimbine, dexamphetamine and their interactions with clonidine. Eur J Pharmacol **53:**1-8, 1978.
8. Kobinger W: Central alpha-adrenergic systems as targets for hypotensive drugs. Rev Physiol Biochem Pharmacol **81:**40-100, 1978.
9. Kobinger W, Pichler L: Centrally induced reduction in sympathetic tone—A postsynaptic alpha-adrenoreceptor stimulating action of imidazolines. Eur J Pharmacol **40:**311-320, 1976.
10. Langer SZ: The role of alpha- and beta-presynaptic receptors in the regulation of noradrenaline release elicited by nerve stimulation. Clin Sci Mol Med **51**(suppl. 3):423s-426s, 1976.
11. Lerner P, Dendel PS, Major LF: Dopamine-beta-hydroxylase in cerebrospinal fluid and plasma: Effects of alpha-adrenergic agents. Brain Res **189:**183-191, 1980.
12. Metz SA, Halter JB, Porte D, Robertson RP: Suppression of plasma catecholamines and flushing by clonidine in man. J Clin Endocrinol Metab **46:**83-90, 1978.
13. Mulvihill-Wilson J, Graham RM, Pettinger W, Muckleroy C, Anderson S, Gaffney FA, Blomqvist CG: Comparative effects of prazosin and phenoxybenzamine on arterial blood pressure, heart rate, and plasma catecholamines in essential hypertension. J Cardiovasc Pharmacol **1**(suppl.):S1-S7, 1979.
14. Peuler JD, Johnson GA: Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. Life Sci **21:**625-626, 1977.
15. Reid JL, Wing LMH, Mathias CJ, Frankel HL, Neill E: The arterial hypotensive action of clonidine: studies in tetraplegic subjects. CLIN PHARMACOL THER **21:**375-381, 1977.
16. Schmitt H, Schmitt H: Interactions between 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride (ST-155), Catapresan) and alpha-adrenergic blocking drugs. Eur J Pharmacol **9:**7-13, 1970.
17. Schumann HJ, Endoh M: α-Adrenoceptors in the ventricular myocardium: Clonidine, naphazoline and methoxamine as partial α-agonists exerting a competitive dualism in action to phenylephrine. Eur J Pharmacol **36:**412-421, 1976.
18. VanZwieten PA, Lam E, Timmermans PB MWM: The interaction between prazosin and clonidine. Clin Sci Mol Med **55:**259-261, 1978.
19. Weiner N: Drugs that inhibit adrenergic nerves and block adrenergic receptors, *in* Gilman AG, Goodman LS, and Gilman A, editors: The pharmacologic basis of therapeutics, ed. 6. New York, 1980, Macmillan, pp. 176-210.