

The Effect of "Sympatholytic" Drugs on the Cardiovascular Responses to Epinephrine and Norepinephrine in Man

By EDWARD D. FREIS, M.D., J. CALVIN MACKEY, M.D., AND WILLIAM F. OLIVER, M.D.

Under controlled conditions the effects of various "sympatholytic" agents on the cardiovascular responses to epinephrine and norepinephrine were compared in man. The dosages of the sympatholytic drugs administered approximated those usually employed clinically. Such basic data are given for the following agents: Dibenamine, the imidazoline derivatives [Priscoline and Regitine (C-7537)], the dihydrogenated alkaloids of ergot (D.H.K. and C.C.K.), L-hydrazinophthalazine (C-5968), tetraethylammonium, and hexamethonium (C6).

IN RECENT years a variety of agents have been introduced which inhibit the motor activities of the sympathetic nervous system. Determination of the mode of action of such drugs has not been clarified completely especially in man. According to Nickerson¹ "adrenergic blockade" refers only to compounds which specifically inhibit the responses of effector cells to both epinephrine and sympathetic nervous impulses. Thus, adrenergic blocking agents such as Dibenamine should be differentiated from drugs which inhibit transmission through the sympathetic nervous system either in the ganglia, such as tetraethylammonium² or the central nervous system, such as pentaquine,³ but do not block the pressor effects of epinephrine.

The present investigation was designed to determine under controlled conditions the effects of the various "sympatholytic" drugs on the pressor responses to an excess of circulating epinephrine in man. In addition, it seemed of interest to test the effectiveness of such drugs in inhibiting the hypertension associated with

an excess of circulating norepinephrine. This substance has assumed greater importance since it has been found in mammalian chromaffin tissues⁴ and in human pheochromocytomas⁵ and since the hypertension produced by norepinephrine in man resembles essential hypertension in many respects.⁶ Finally, a systematic study in which various drugs are tested under identical conditions in doses customarily used clinically seemed worthwhile in order to supply basic data as to the comparative value of these compounds as adrenergic blocking agents in man.

MATERIALS AND METHODS

The subjects were young or middle-aged adult men admitted to the wards of the Veterans Administration Hospital, Washington, D. C. All were convalescing from nonfebrile illnesses at the time of testing and none exhibited cardiovascular abnormalities.

Commercial epinephrine in a concentration of 1 μ g. per cc. in saline and norepinephrine in a concentration of 1.5 μ g. per cc. were infused intravenously. The rate of infusion was controlled by an adjustable clamp and calibrated Murphy drip bulb. With the patient reclining in the supine position an infusion of isotonic saline was introduced through an antecubital vein. The needle used in this infusion was connected to a three way stopcock to permit introduction of the norepinephrine and epinephrine solutions as well as the blocking agents studied without disturbing the patient. The arterial pressure was measured in the opposite arm with an arm cuff and mercury manometer while the heart rate was counted at the wrist.

In the control period, after the arterial pressure

From the Medical Service, Veterans Administration Hospital, Washington, D. C.

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The norepinephrine used in this study was generously supplied by Ciba Pharmaceutical Products, Summit, New Jersey.

and heart rate had become stabilized, the epinephrine solution was introduced through the three way stopcock and the rate of infusion regulated by adjusting the clamp of the Murphy drip. The responses of arterial pressure and heart rate were measured at both low and high infusion rates of epinephrine. Following these control determinations using epinephrine, the three way stopcock was turned so that saline was again infused. After the arterial pressure and heart rate had returned to basal values the norepinephrine infusion was connected and the responses to this agent measured at low and high infusion rates. It should be noted that the dose ranges of both epinephrine and norepinephrine were considerably lower in these studies on human subjects than the dosages of such substances usually employed in investigations in animals.

Following the control determinations the particular blocking agent under study was given through the intravenous tubing of the saline infusion following which epinephrine and norepinephrine again were infused at the same rates as had been administered during the control period. An exception to this procedure was used in testing the adrenergic blocking action of benzodioxane. Because of its fleeting action, this drug was given during the infusions of epinephrine and the dose was repeated again during the infusion of norepinephrine.

RESULTS

Effect of Epinephrine and Norepinephrine Alone

At low infusion rates (below 0.10 μg . per Kg. per minute), epinephrine frequently resulted in a decrease rather than an increase in the mean [(systolic + diastolic)/2] arterial pressure. This was due primarily to a reduction in diastolic blood pressure although systolic pressure frequently was depressed as well. As the mean pressure fell, the cardiac rate increased. With higher infusion rates of epinephrine (0.10 microgram per Kg. per minute or above) the mean arterial pressure usually rose. This elevation was due to the fact that the percentage increase in systolic pressure was greater than the percentage decrease in diastolic pressure. However, there was considerable variation in response among different patients, some exhibiting very little depressor response, while others showed depressor responses exclusively even at the high infusion rates. Following cessation of the epinephrine infusion, the cardiovascular responses disappeared rather slowly over a period of 2 to 10 minutes.

In contrast, the responses to norepinephrine were uniform in all patients. Immediately following infusion of an effective dose (0.1 to 0.2 microgram per Kg. per minute) both the systolic and diastolic pressure rose and the heart rate decreased. These cardiovascular responses disappeared in one to three minutes after the infusion was discontinued.

Effects of Dibenamine

Dibenamine was administered to 4 subjects in doses of 170 to 360 mg. (2.3 to 6 mg. per Kg.). In every case the pressor responses to epinephrine were reversed even with doses of epinephrine as high as 0.5 microgram per Kg. per minute (table 1). The hypertension that resulted from the infusion of norepinephrine was 90 to 100 per cent abolished. In 2 subjects complete abolition occurred at low rates of norepinephrine infusion but not at high infusion rates. Nevertheless, marked inhibition of the norepinephrine hypertension occurred even at high infusion rates (0.5 to 1.0 μg . per Kg. per minute of norepinephrine).

Dibenamine tended to exaggerate the tachycardia which accompanied the infusion of epinephrine, while in 3 of the 4 cases it completely abolished the bradycardia that occurred during norepinephrine infusion.

Effect of Benzodioxane

Benzodioxane was administered to 3 subjects in doses of 10 to 20 mg. during the infusions of epinephrine and norepinephrine. Two subjects received 10 mg. intravenously during the infusion of epinephrine. No significant inhibition of the pressor response occurred although there was an increased tachycardia in one of the cases. These 2 subjects received an additional 10 mg. of benzodioxane during the norepinephrine infusion. Thirty-one and 54 per cent inhibition of the norepinephrine hypertension resulted. However, this inhibition was quite fleeting, lasting only one to two minutes.

The third subject (W. S.) received 20 mg. of benzodioxane during the infusion of epinephrine with resulting "reversal" which was of less extent and of much briefer duration (four minutes) than was observed in the subjects who received Dibenamine. An additional dose of 20

TABLE 1

Pt.	Wt. Kg.	Arterial Pressure mm. Hg	Heart Rate/min.	Control						After Drug											
				Epinephrine			Norepinephrine			Drug	Dose mg.	Epinephrine					Norepinephrine				
				Dose Mg./Kg./min.	Change M.A.P.* %	Change Heart Rate %	Dose Mg./Kg./min.	Change M.A.P.* %	Change Heart Rate %			Dose Mg./Kg./min.	Change M.A.P.* %	Reversal	Change Heart Rate %	Dose Mg./Kg./min.	Change M.A.P.* %	Inhibition† %	Change Heart Rate %		
S. T.	76	114/76	82	0.10	+20	+16	0.12	+20	-20	Dibenamine	170	0.10	-7	+	+66	0.13	+2	90	-10		
L. B.	84	120/80	92	0.10	+8	+13	0.10	+20	-18	"	350	0.10	-16	+	+8	0.15	0	100	0		
				0.13	+13	+17	0.25	+33	-22			0.13	-16	+	+13	0.25	+3	91	0		
A. S.	59	118/70	70	0.07	-4	+9	0.23	+31	-26	"	350	0.085	-10	+	+53	0.23	+3	90	0		
				0.10	-6	+54															
W. S.	61	110/70	68	0.23	+8	+23	0.15	+11	-20	"	360	0.26	-15	+	+6	0.37	0	100	0		
				0.33	+16	+5	0.18	+17	-20			0.50	-14	+	+24	0.68	+8	0	0		
																1.01	+13		0		
W.	61	110/80	70	0.20	+11	+31	0.35	+29	-9	Benzodioxane	10 + 10	0.20	+14	-	+31	0.20	+20	31	-5		
C. W.	69	110/70.	70	0.09	+9	+13	0.15	+24	-10	"	10 + 10	0.09	+5	0	+39	0.15	+11	54	0		
W. S.	61	120/80	70	0.15	+3	+29	0.10	+8	-23	"	+20	0.15	-5	+	+48	0.10	+2	75	-5		
W.	61	110/80	70	0.08	+10	+28	0.22	+19	-6	C6	50	0.08	+14	-	0	0.22	+20	0	-10		
R. B.	65	118/78	72	0.16	-17	+5	0.20	+9	-5	C6	35	0.16	0	-	+13	0.20	+52		-12		
T. W.	61	130/80	100	0.10	0	+24	0.18	+14	-4	C6	50	0.10	+7	-	+16	0.18	+28		-8		
C. W.	69	110/70	70	0.09	+9	+14	0.15	+14	-14	TEA	400	0.09	+12	-	-32	0.15	+31		-18		
J. L.	64	100/68	68	0.14	-3	+30	0.15	+14	-18	TEA	350	0.14	+6	-	+5	0.15	+26	0	-23		
A. C.	80	118/72	64	0.08	+2	+31	0.26	+17	-22	Priscoline	25	0.08	-6	+	+30	0.26	+7	60	-18		
C. T.	70	125/70	80	0.07	-6	+15	0.17	+14	-19	Priscoline	25	0.07	-16	+	+35	0.17	+19	0	-7		
											125					0.17	+7	50	-10		
A. T.	65	125/74	60	0.09	0	+33				C-7337	25	0.09	-8	+	+65						
							0.09	+17	-20	"	50					0.09	+4	76	+4		
							0.14	+22	-20	"	50					0.14	+16	27	-7		
W. H.	57	112/80	60	0.10	+7	+17	0.20	+15	-13	"	25	0.10	-5	+	+22	0.20	+7	53	-16		
							0.45	+27	-23							0.45	+12	56	-16		
S. P.	64	130/95	68	0.18	-1	+30	0.15	+12	-14	"	50	0.18	-11	+	+42	0.15	+4	75	0		
				0.24	+6	+28	0.23	+25	-24			0.24	-11	+	+42	0.23	+6	76	0		
												0.34	-23	+	+89	0.52	+11	?	-8		
W. W.	48	105/60	68	0.12	+33	+37	0.28	+51	-24	C-5968	18	0.12	+12	-	+40	0.28	+45	12	-4		
R. W.	80	140/80	72	0.23	+6	+11	0.31	+22	-22	"	25	0.23	+14	-	+11	0.32	+12	45	-5		
F. R.	94	120/88	76	0.11	-3	+40	0.16	+22	-16	"	30	0.11	+7	-	+14	0.16	+16	36	-4		
																0.32	-31		-4		
J. S.	91	108/70	84	0.05	-8	+14	0.09	+24	-14	D.H.K.	0.5					0.09	+25	0	-14		
				0.10	-9	+19	0.26	+41	-24			0.10	-11	-	+18	0.26	+37	10	-23		
				0.20	+9	+24						0.20	+10	-	+22						
E. W.	60	102/62	76	0.25	+41	+10	0.13	+20	-11	C.C.K.	0.3	0.25	+87	-	-5	0.13	+23	0	-23		
							0.40	+53	-31							0.40	+58	0	-40		

* M.A.P. = "Mean" Arterial Pressure = $\frac{\text{Systolic} + \text{Diastolic}}{2}$

† % Inhibition = $\frac{\text{Control B.P. Change} - \text{After Drug B.P. Change}}{\text{Control B.P. Change}}$

mg. of benzodioxane was also administered during the infusion of a minimal pressor dose of norepinephrine (0.1 microgram per Kg. per minute) with a resulting 75 per cent inhibition of the hypertensive response. The duration of the inhibiting effect was only two minutes. It is of interest that one week previously the same patient had received Dibenamine in a dose of 6 mg. per Kg. (table 1). Following Dibenamine the norepinephrine pressor response was completely abolished even with infusion rates of norepinephrine which were four times greater than those used during the benzodioxane experiments.

Effect of the Imidazoline Derivatives, Prisoline and C-7337

Two subjects received 25 to 125 mg. of. Prisoline while 3 others received 25 to 50 mg. of C-7337. All doses were given intravenously. The effects of both drugs were essentially similar. In all cases epinephrine reversal occurred even at relatively high infusion rates (case S. P., table 1). The tachycardia that resulted from epinephrine infusion was exaggerated. However, in contrast to the results obtained with Dibenamine, the imidazoline compounds only partially inhibited (0 to 76 per cent; average 60 per cent inhibition) the pressor response to norepinephrine.

Effect of Tetraethylammonium (TEA) and Hexamethonium (C6)

Since both of these drugs inhibit transmission through autonomic ganglia they are considered together. It was more convenient to study the effects of ganglionic blocking agents using C6 since this drug has a longer duration of action than TEA.⁷ Three subjects received 35 to 50 mg. of C6 intravenously. In all of these cases the pressor effects of both epinephrine and norepinephrine were intensified (table 1). The results were similar in 2 subjects who received 350 and 400 mg. respectively of TEA intravenously.

Effect of L-Hydrazinophthalazine

Three subjects were given L-hydrazinophthalazine (C-5968) in doses of 18 to 30 mg. (0.31 to 0.37 mg. per Kg. body weight) intra-

venously. A fall in arterial pressure occurred in one case and an increase in heart rate developed in 2 cases approximately 15 minutes after the drug was administered. Twenty minutes after C-5968 was given the responses to epinephrine and norepinephrine were tested.

No consistent effects were observed in regard to the epinephrine response. In one instance there was slight inhibition of the epinephrine pressor response and in 2 cases there was slight potentiation. The degree of tachycardia was uninfluenced in 2 cases and slightly inhibited in the other. The pressor response to norepinephrine, however, was moderately reduced in all instances (12 to 45 per cent inhibition). In addition, there was almost complete abolition of the bradycardia accompanying the norepinephrine induced hypertension. This marked inhibition of heart rate occurred despite elevation of mean arterial pressure as high as 30 to 45 per cent above the basal values.

Effect of the Dihydrogenated Alkaloids of Ergot

Previous studies⁸ utilizing the same technics have demonstrated that the dihydrogenated alkaloids of ergot were very weak adrenolytic agents in the dosages customarily used in man. For the sake of completeness, however, and to test the effects of these drugs on the cardiovascular responses to norepinephrine, 2 patients were studied before and after the intravenous administration of the dihydrogenated alkaloids. One case was given 0.5 mg. of dihydroergokryptine while the other received 0.3 mg. of the combined dihydrogenated alkaloids (C. C. K.). In neither instance was significant inhibition of the cardiovascular responses to either epinephrine or norepinephrine observed.

DISCUSSION

The effects of the various "sympatholytic" drugs on the pressor response to epinephrine appear to be similar in both man and animals. Thus, in animals, epinephrine reversal has been demonstrated after Dibenamine,⁹ Prisoline,¹⁰ C-7337¹¹ and benzodioxane. In addition, inhibition of epinephrine induced hypertension has been demonstrated in man after Dibenamine,¹² Prisoline¹³ and benzodioxane.¹⁴ However, it was apparent from this study that the

epinephrine reversal produced by therapeutic doses of Dibenamine, Priscoline and C-7337 was more complete and lasting than that produced by similar doses of benzodioxane. The fleeting adrenolytic effect of benzodioxane has been noted previously by Prunty and Swan.¹⁵

In contrast, the effects of these agents on the hypertension resulting from norepinephrine has not been extensively investigated. In the present study Dibenamine produced the most complete inhibition of norepinephrine hypertension while Priscoline and C-7337 produced only partial inhibition. Benzodioxane also produced partial blockade, but, as with epinephrine, its action was fleeting, lasting less than two minutes.

It seems remarkable that benzodioxane which has such fleeting and relatively weak adrenolytic effects should be so reliable in predicting the presence of pheochromocytoma.¹⁴ The results of this investigation suggest that a small dose of 15 to 20 mg. of Priscoline or C-7337 might be as reliable or perhaps more reliable than benzodioxane since such small doses of the imidazolines seldom produce significant reduction of basal arterial pressure; yet they would be expected to have a hypotensive effect in the presence of an excess of circulating epinephrine.

As has been observed in animal experiments ganglionic blocking agents such as TEA and C6 exaggerated rather than suppressed the hypertensive effects of both epinephrine and norepinephrine. It appears^{16, 17} that this intensified response is due to blockade of the cardiovascular "moderator" reflexes of the autonomic nervous system, especially those reflex arcs originating in the carotid sinus and aortic arch.

Although the number of cases studied was small, there seemed to be a consistent quantitative difference in the action of Dibenamine as compared with the imidazoline compounds, Priscoline and C-7337. Although all of these agents produced epinephrine reversal, there was more complete inhibition of the effects of norepinephrine following Dibenamine than following the imidazolines. These results apparently were not due to dosage differences since the degree of norepinephrine blockade was greater after minimal effective doses of Dibenamine

than after relatively large doses of Priscoline and C-7337. These data suggest, therefore, that Dibenamine is an active blocking agent for both epinephrine and norepinephrine whereas the imidazoline compounds, while qualitatively similar, are potent blocking agents for epinephrine but are less active against norepinephrine. In this regard it may be of interest that in animals the dosages of Priscoline and C-7337 required to produce epinephrine reversal are far less than the amount required to block sympathetic nerve stimulation,¹¹ whereas with Dibenamine this difference in dosage is less.¹

The action of L-hydrazinophthalazine (C-5968) differs from that of any of the other agents. In animals given larger doses than those used clinically in man the drug moderates but does not block epinephrine and norepinephrine hypertension nor does it produce epinephrine reversal.¹⁸⁻²⁰ In the present study there appeared to be slight inhibition of the norepinephrine but not the epinephrine pressor response. However, the most striking observation was the marked inhibition of the bradycardia induced by norepinephrine. The significance of this observation is not clear; since the bradycardia probably is reflex in nature, it may be that C-5968 interrupts the reflex arc at an unknown point.

The present study demonstrates the difficulty in classifying autonomic blocking agents according to a simple schema. The concept of central, ganglionic and peripheral blocking agents is a useful but crude approximation. Thus, Dibenamine, the imidazolines and L-hydrozinophthalazine all appear to exhibit distinctive differences in their ability to inhibit the cardiovascular effects of epinephrine and norepinephrine. This suggests that each of these drugs may act at different points in the chain of reactions involved in the activation of effector cells.

SUMMARY

The effects of various "sympatholytic" drugs on the pressor responses to epinephrine and norepinephrine were investigated under controlled conditions in man. The dosages used approximated those customarily employed clinically.

1. Following Dibenamine there was "reversal" of the pressor response to epinephrine and complete or nearly complete abolition of the pressor response to norepinephrine.

2. The imidazolines (Priscoline and C-7337) also produced epinephrine reversal but only partially inhibited the hypertension induced by norepinephrine.

3. Benzodioxane irregularly produced epinephrine reversal and only partially inhibited the pressor response to norepinephrine. The adrenolytic effect was of fleeting duration.

4. L-hydrazinophthalazine failed to affect epinephrine responses, slightly inhibited the norepinephrine pressor response and almost completely blocked the bradycardia induced by norepinephrine.

5. Ganglionic blocking agents such as tetraethyl ammonium and hexamethonium intensified the pressor effects of both epinephrine and norepinephrine.

6. Clinical doses of the alkaloids of ergot had little or no inhibiting affect of epinephrine and norepinephrine pressor responses.

7. Although, in general, agents which inhibit or reverse epinephrine hypertension also modify the norepinephrine pressor response, there appear to be quantitative differences in the degree of inhibition obtained with different agents.

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