THE EFFECT OF BENZEDRINE (β-PHENYLISOPROPYLAMINE SULPHATE) AND PAREDRINE (ρ-HYDROXY-α-METHYL-PHENYLETHYLAMINE HYDROBROMIDE) ON THE CIRCULATION, METABOLISM AND RESPIRATION IN NORMAL MAN [1]

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Since benzedrine enjoys wide clinical usage and has definite pressor properties, an evaluation of the effects of its administration on the cardiovascular dynamics is of theoretical and practical interest. Data are available on changes in pulse rate and blood pressure following the administration of benzedrine in man (1, 2); satisfactory studies of changes in cardiac output in man have not, however, been published. It was therefore decided to measure the cardiac output before and after the administration of benzedrine in man; since changes in circulation are intimately related to changes in metabolism and respiratory dynamics, simultaneous studies of the latter were also made.

The marked psychic stimulating effect of benzedrine negates the use of that drug primarily as a pressor substance. Paredrine, closely related to benzedrine chemically, has no stimulating effect on the cerebral cortex but is a potent pressor substance (3). Accordingly, the effects of its administration on metabolism, respiration and circulation were also studied.

The actions of both of these drugs were compared with the effects of the administration of epinephrine, the prototype of the "sympathomimetic" amines.

MATERIAL AND METHODS

Fifteen subjects ranging in age from 13 to 52 years were used in the present study; 11 were males. No clinical evidence of abnormality of the cardiovascular or respiratory system was present in 14 subjects; 1 subject (Case 13) had partial heart block due to coronary artery sclerosis, but no evidence of congestive failure.

All measurements were made with the patient in the post-absorptive state, under basal conditions, in the semi-recumbent position. The minute volume output of the heart was measured by the method of Starr and Gamble (4), the respiratory rate, respiratory minute volume, tidal air, alveolar carbon dioxide content, respiratory quotient and basal metabolic rate being measured at the same time. The velocity of blood flow was estimated from the arm-to-tongue circulation time, according to the method of Winternitz, Deutsch and Brüll (5). Measurements of arterial blood pressure were made by the auscultatory method with a mercury manometer and a standard arm cuff. Pulse and respiration were counted for 30-second periods, every 2 to 4 minutes.

Because of the large number of measurements made on each subject, it was considered desirable to perform all the studies made without the drug on one day and those after the administration of various drugs on other days; it was felt that the effects of increasing restlessness and hunger associated with the performance of protracted experiments might lead to erroneous results. The patients were in the post-absorptive state and rested until the pulse rate and blood pressure, as measured at 5-minute intervals, established themselves at constant low levels. The drug to be studied was then administered by mouth or by intramuscular injection. The changes in pulse rate and blood pressure were again measured every 5 minutes until maximal changes occurred. At this point the other studies were begun. Measurements of cardiac and respiratory dynamics were made following the administration of the various drugs only when definite pressor effects were noted, unless the doses used were so small that no pressor effects occurred. In such cases measurements were made at arbitrary intervals after giving the drug. Usually the studies on the effects of drugs were made on successive days after the control measurements. In 2 instances (Cases 4 and 5), however, where the possible cumulative effects of the drug were studied, measurements were made several days after the control studies.

The venous pressure normally may vary as much as 2 or 3 cm. of water from day to day. Since this might be the extent of the change, if any, in this measurement as the result of the administration of a drug, a series of experiments was performed during which measurements of only pulse rate, arterial pressure, and venous pressure were made on the same day immediately before, during and after the administration of a given drug. These are reported in another place.

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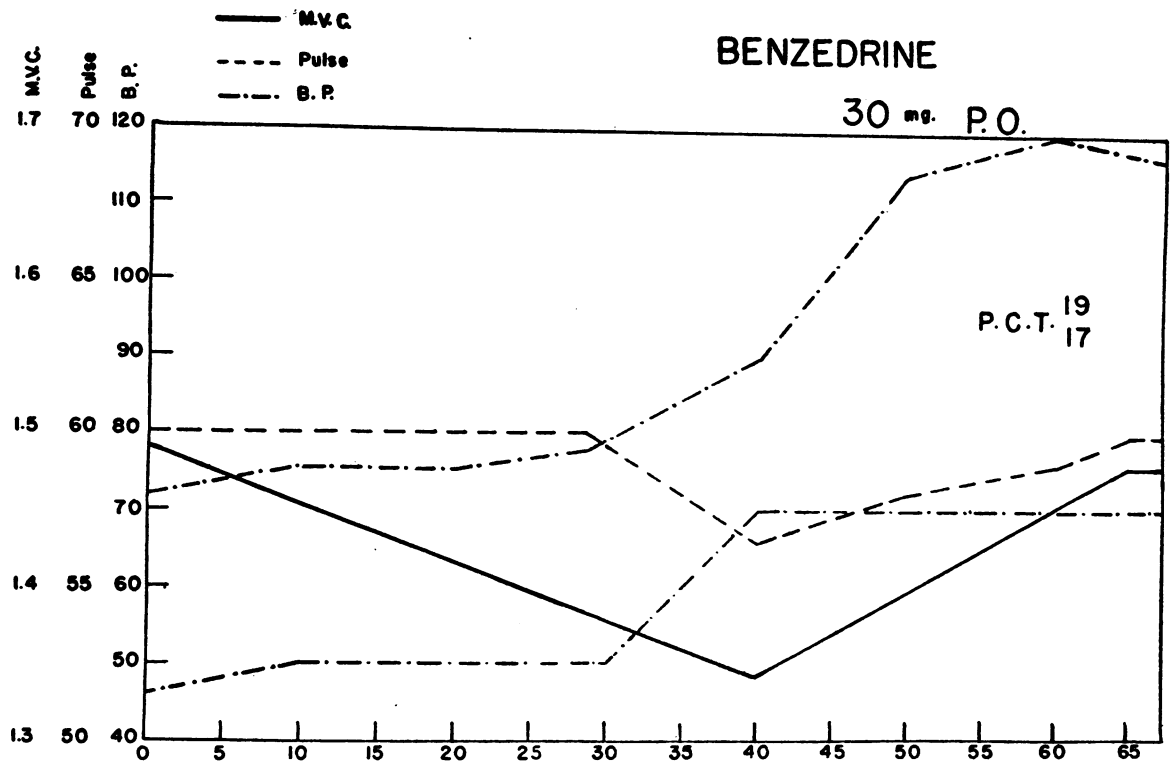

FIG. 1. TRANSITORY EARLY DECREASE IN PULSE RATE AND CARDIAC OUTPUT FOLLOWING THE ADMINISTRATION OF BENZEDRINE (CASE 6)

OBSERVATIONS

Cardiac output. Benzedrine in doses of 10 to 30 mgm. by mouth (Cases 1 to 7, 10, 11, 12) and 10 mgm. intramuscularly (Case 8) caused no increase in cardiac output. Paredrine in doses of 30 to 70 mgm. by mouth (Cases 11, 12, 13) and 15 to 20 mgm. intramuscularly (Cases 14 and 15) likewise caused no increase in cardiac output. These findings are in contrast to those noted after the administration of 1 mgm. of epinephrine subcutaneously (Cases 10 and 11); a striking increase in cardiac output occurred after the injection of this drug.

In 2 instances (Cases 6 and 12) an initial decrease in cardiac output occurred after giving paredrine or benzedrine, with normal readings being found a short time later in 1 case (Case 6) (Figure 1).

Velocity of blood flow. Acceleration of the circulation time did not occur after the administration of benzedrine or paredrine (Cases 1 to 8, 10, 11, 12, 13, 15). In 1 instance (Case 12) paredrine caused a slight slowing of the circulation time. The injection of adrenalin caused a marked increase in the velocity of blood flow (Cases 10 and 11).

Arterial blood pressure. Increases in blood pressure of less than 10 mm. were not considered significant. Benzedrine in 10 mgm. doses by mouth (Cases 1 to 5) caused a significant rise in blood pressure in only 1 instance (Case 2), but with the same dose given intramuscularly (Cases 8 and 9), or with larger doses by mouth (Cases 6, 7, 10, 11, 12), a definite pressor response was noted. The systolic blood pressure rose more than the diastolic in every instance in which a change occurred, so that the pulse pressure increased. The administration of paredrine (Cases 11 to 15) resulted in similar changes; paredrine is apparently a somewhat more potent pressor drug than benzedrine.

The injection of epinephrine (Cases 10 and 11) resulted in a significant rise in systolic blood pressure but the diastolic blood pressure fell in 1 case (Case 11) and did not change in the other (Case 10).

TABLE I

The effects of benzedrine, paredrine and epinephrine on the circulation, metabolism and respiration in normal man

Case	Oxygen consumption	Basal metabolic rate	Respiratory quotient	Alveolar carbon dioxide concentration	Respiratory rate	Respiratory minute volume	Vital capacity	Cardiac output	Cardiac output per 100 cc. oxygen consumed	Pulse rate	Circulation time	Systolic blood pressure	Diastolic blood pressure	Remarks
	cc. per minute	*per cent*		*per cent*	*per minute*	*liters per minute*	*liters*	*liters per minute*	*liters*	*per minute*	*seconds*	*mm. Hg*	*mm. Hg*	
1	248	+ 5	0.82		15	5.8	2.48	3.70	1.49	63	17	126	78	Basal
	238	+ 1	0.80	5.1	14	5.1	2.50	3.37	1.42	63	18	120	84	¾ hour after Benzedrine 10 mgm. p.o.
2	258	+16	0.81		14	6.5	2.53	5.81	2.25	98	12	140	100	Basal
	249	+10	0.82		14	6.2	2.52	5.55	2.28	99	14	152	110	2 hours after Benzedrine 10 mgm. p.o.
3	255	− 4	0.81	5.1	13	5.7	4.64	3.87	1.53	74	13	124	82	Basal
	245	− 5	0.81		12	5.6	4.58	3.95	1.62	75	14	124	84	3 hours after Benzedrine 10 mgm. p.o.
4	167	− 7	0.80	5.3	15	3.9	1.90	2.93	1.77	65	13	108	80	Basal
	157	−12	0.79	5.5	12	2.9	1.80	2.93	1.87	83	12	108	84	Benzedrine 10 mgm. p.o. t.i.d. for 2 days 3 hours after last dose
5	223	± 0	0.80		14	6.4	3.80	4.17	1.87	76	15	104	80	Basal
	226	− 2	0.79	5.7	10	4.3	3 90	4.20	1.85	71	16	104	74	Benzedrine 10 mgm. p.o. t.i.d. for 7 days 1 hour after last dose
6	301	+ 9		5.2	15	6.0	2.60	5.66	1.88	80	14	128	82	Basal
	310	+12		5.2	14	6.2	3.20	6.00	1.93	85	13	140	96	1¾ hours after Benzedrine 30 mgm. p.o.
7	285	− 3	0.83		14	8.5	5.45	4.43	1.56	68	12	114	68	Basal
	297	± 0	0.80		14	7.8	5.62	4.64	1.56	71	13	150	96	3½ hours after Benzedrine 30 mgm. p.o.
8	242	− 4	0.80	5.0	12	6.3	3.20	4.86	2.01	80	12	106	68	Basal
	257	+ 1	0.78	5.1	13	5.7	3.20	5.14	2.04	93	11	132	80	1 hour after Benzedrine 10 mgm. i.m.
9	247	+ 6	0.86	5.5	11	5.7	3.20			78		106	60	Basal
	242	+ 3	0.82	5.7	8	4.8	3.30			78		120	70	1 hour after Benzedrine 10 mgm. i.m.
10	219	− 7	0.80	5.2	13	4.9	4.10	4.27	1.95	55	13	104	60	Basal
	222	− 6	0.83	5.3	14	5.1	4.50	4.57	2.06	59	15	154	78	1 hour after Benzedrine 30 mgm. p.o.
	266	+14	0.83	5.2	15	6.4	4.20	6.53	2.46	96	9	138	50	½ hour after Epinephrine 1 mgm. s.c.
11	227	+ 1	0.79		16	5.9	2.85	3.37	1.49	58	19	80	60	Basal
	265	+19	0.81		16	6.8	2.90	3.87	1.46	59	17	132	90	1½ hours after Benzedrine 30 mgm. p.o.
	289	+28	0.79		16	7.2	3.00	5.33	1.85	82	12	106	60	½ hour after Epinephrine 1 mgm. s.c.
	260	+16	0.81		16	6.5	2.80	3.66	1.39	48	20	180	90	1 hour after Paredrine 50 mgm. p.o.
12	257	+ 2	0.83	5.7	13	5.6	4.20	4.22	1.64	60	18	116	66	Basal
	298	+19	0.80	4.5	18	8.5	4.10	4.74	1.59	52	18	164	90	1 hour after Benzedrine 30 mgm. p.o.
	256	+ 2	0.80	5.5	14	5.7	4.10	3.56	1.39	46	22	160	86	1¼ hours after Paredrine 30 mgm. p.o.
13	171	−13	0.81	5.4	11	4.0	1.60	3.24	1.91	40	20	112	50	Basal
	184	− 8	0.80	5.4	14	4.0	1.60	3.24	1.79	38	19	208	78	1 hour after Paredrine 70 mgm. p.o.
14	263	+ 9	0.80	5.7	8	4.6	5.20	5.02	1.91	63	13	120	70	Basal
	251	+ 4	0.80	5.7	9	4.8	5.30	4.81	1.92	63	12	180	88	½ hour after Paredrine 15 mgm. i.m.
15	256	− 2	0.84	5.2	13	6.1	5.10	5.14	2.01	54		112	74	Basal
	265	+ 1	0.81	5.2	14	6.4	5.10	4.82	1.82	48		132	86	½ hour after Paredrine 20 mgm. i.m.

Pulse rate. The administration of benzedrine caused increases in pulse rate ranging from 4 to 18 beats per minute in 4 experiments (Cases 4, 6, 8, 10) and a decrease of 8 beats per minute in 1 (Case 12), and 5 beats in another (Case 5). There was no relationship between the dose of the drug given and the change in heart rate. In 2 additional instances (Cases 6 and 9) transitory slowing of the pulse rate occurred soon after benzedrine was given. Paredrine caused a de-

crease in heart rate of 6 to 10 beats in 3 cases (Cases 11, 12, 15), and no change in the other 2. Epinephrine increased the heart rate markedly in both instances in which it was given.

Basal metabolic rate. Neither benzedrine nor paredrine affected the basal metabolic rate except in Cases 11 and 12; in both instances the rises in metabolic rate were associated with restlessness. Epinephrine, on the other hand, increased the metabolic rate significantly (Cases 10 and 11). None of the drugs affected the respiratory quotient.

Respiratory dynamics. None of the drugs influenced the respiratory dynamics except in those experiments in which the metabolism was raised; in these instances the respiratory minute volumes increased (Cases 10, 11, 12). The vital capacity did not change.

DISCUSSION

Benzedrine, when given in the doses usually employed clinically for its psychic stimulating effect, *i.e.,* 5 to 10 mgm. by mouth, exerts little or no pressor effect. In larger doses, however, it causes a definite increase in systolic and diastolic blood pressures. In doses up to 30 mgm. given by mouth and 10 mgm. intramuscularly, it causes no increase in cardiac output or velocity of blood flow, although the pulse may be increased significantly in some cases. The findings with respect to the output of the heart become even more uniform if these values are related to changes in metabolism. The results of the studies on cardiac output here reported differ from those recorded by Berggren and Söderberg (6) in 2 subjects. These authors concluded that benzedrine increases the cardiac output. Their results, however, are so variable from experiment to experiment, and their control values so abnormal as to suggest some grave technical error in their measurements of the cardiac output. Their findings were not controlled by measurements of the circulation time. The uniformity of the results here reported with respect to cardiac output and circulation time after the administration of benzedrine, and their striking differences from the effects of epinephrine in the same subjects lead us to conclude that benzedrine does not increase the output of the heart. In occasional instances, such as Case 6 (Figure 1), an initial reduction in cardiac output may be detected. This is associated with the initial slowing of the pulse detected in this and other experiments and is probably due to a reflex initiated by the rise in blood pressure and effected through the vagus nerve. This effect is transitory, however, the cardiac output soon returning to its normal level. The action of benzedrine in causing a reflex stimulation of the vagus nerve may be of importance in precipitating the collapse which occasionally occurs after the administration of overdoses of that drug.

Similarly, in 5 experiments paredrine caused striking elevation of the blood pressure with no increase in cardiac output. These findings are in agreement with those reported by Stead and Kunkel (7) in 2 subjects following the administration of a methyl derivative of paredrine. In 1 instance (Case 12) a decrease in cardiac output and slowing of circulation time due to the action of the vagal reflex were detected. Although 2 other subjects exhibited marked slowing of the pulse, no change in cardiac output was found. It is possible that when the cardiac output is decreased through the action of the vagal reflex, the venous pressure increases and acts to increase the output of the heart to its former level.

The action of benzedrine and paredrine on the normal cardiovascular system differs in several ways from that of epinephrine. The latter causes marked tachycardia, increase in cardiac output and acceleration of circulation time with only moderate transitory elevation of systolic blood pressure and no rise or even a fall in diastolic blood pressure. The observations on the effects of adrenalin recorded here are similar to those previously reported by other authors (8, 9, 10). Benzedrine and paredrine, on the other hand, cause considerable increases in systolic and diastolic blood pressure with no increase in cardiac output or velocity of blood flow. Epinephrine tends to precipitate ventricular arrhythmias; neither paredrine nor benzedrine has been observed to do this.

The increase in pulse pressure which occurs after the administration of benzedrine and paredrine in man does not indicate an increase in cardiac output. The concept that cardiac output parallels pulse pressure, which is widely held, probably dates back to the work of Hürthle (11). However, as long ago as 1904, Erlanger and

Hooker (12) pointed out that, theoretically, when blood pressure is elevated, the pulse pressure should increase even though the systolic output remains constant; vasoconstriction should cause an increase in pulse pressure. The observations of Katz and Wiggers (13) on intact animals have shown that increasing the peripheral resistance raises the blood pressure and increases pulse pressure without changing the cardiac output significantly. Even in the heart-lung preparation, where vasomotor influences are absent, there is no necessary relation between systolic output and pulse pressure (14).

The effect of the administration of benzedrine on basal metabolism has been studied by others (6, 15, 16, 17) with divergent results. In the experiments here reported, benzedrine caused no change in basal metabolism, in spite of the definite psychic stimulation usually observed, unless the subject became restless. It is clear that the administration of benzedrine in the doses usually employed for clinical purposes places no burden on the cardiovascular system, either directly or by raising the metabolic rate.

The prolonged pressor action of benzedrine and paredrine should be of value in clinical conditions associated with fall in blood pressure, except that the marked psychic stimulation caused by benzedrine negates the use of that drug. Paredrine, having no such action, is the drug of choice in such conditions. Favorable results of its use in orthostatic hypotension (18) and spinal anesthesia (19) have been reported. In addition, it has been found, in this clinic, to restore the blood pressure to normal in Addison's disease and in shock due to coronary thrombosis. It has also been found a useful adjunct in the treatment of the peripheral vasomotor collapse of hemorrhage, pulmonary embolism, and surgical shock; results in the collapse associated with overwhelming infection have not been satisfactory. It must be borne in mind that the effects of paredrine on the cardiovascular dynamics in all of the above-mentioned clinical conditions are not necessarily the same as those observed in this investigation on subjects with normal circulations. Accordingly, the widespread use of paredrine in these conditions should await further studies.

SUMMARY AND CONCLUSIONS

1. The effects of benzedrine and paredrine given in doses of 10 to 70 mgm. on the metabolism, respiration and circulation were studied in 15 subjects with normal cardiovascular systems. The drugs were given by mouth or intramuscularly. In 2 cases the effect of these drugs was compared to that of epinephrine.

2. Benzedrine and paredrine in doses of 20 mgm. or more caused a marked rise in systolic and diastolic blood pressures in normal man. The cardiac output, pulmonary circulation time, vital capacity, basal metabolic rate, and respiratory dynamics were not changed.

3. In several instances transitory slowing of the pulse occurred at the onset of the rise in arterial pressure due apparently to a vagal reflex. In some such cases a transitory slight decrease in cardiac output was also detected.

4. The effects of adrenalin in man were quite different from those of benzedrine and paredrine. They consisted in a slight rise in systolic pressure, no change or a fall in diastolic pressure, marked increase in cardiac output, and shortening of the circulation time.

5. Benzedrine in doses ordinarily used clinically, *i.e.,* 5 to 10 mgm., has no significant effect on the cardiovascular dynamics.

6. The prolonged pressor action, with no increase of cardiac output and no psychic stimulating effect, suggests that paredrine may be a useful drug in the treatment of certain types of vascular collapse, especially where stimulation of the myocardium may be undesirable.

BIBLIOGRAPHY

1. Alles, G. A., The comparative physiological actions of dl-β-phenylisopropylamines. I. Pressor effect and toxicity. J. Pharmacol. and Exper. Therap., 1933, **47**, 339.
2. Myerson, A., Loman, J., and Dameshek, W., Physiologic effects of benzedrine and its relationship to other drugs affecting the autonomic nervous system. Am. J. M. Sc., 1936, **192**, 560.
3. Abbott, W. C., and Henry, C. M., Paredrine (β-4-hydroxyphenylisopropylamine). A clinical investigation of a sympathomimetic drug. Am. J. M. Sc., 1937, **193**, 661.
4. Starr, I., Jr., and Gamble, J. C., An improved method for the determination of cardiac output in man by means of ethyl iodide. Am. J. Physiol., 1928, **87**, 450.

5. Winternitz, M., Deutsch, J., and Brüll, Z., Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufszeit mittels Decholininjektion. Med. Klin., 1931, **27**, 986.
6. Berggren, S., and Söderberg L., The effect of phenylisopropylamine (benzedrine) on cardiac output and basal metabolism in man. Skandinav. Arch. f. Physiol., 1938, **79**, 115.
7. Stead, E. A., Jr., and Kunkel, P., Mechanism of the arterial hypertension induced by paredrinol (α-N-dimethyl-ρ-hydroxyphenylethylamine). J. Clin. Invest., 1939, **18**, 439.
8. Field, H., Jr., and Bock, A. V., The action of adrenalin chloride on the circulation in man. J. Clin. Invest., 1924, **1**, 581.
9. von Euler, U., and Liljestrand, G., Die Wirkung des Adrenalins auf das Minutenvolumen des Herzen beim Menschen. Skandinav. Arch. f. Physiol., 1927, **52**, 243.
10. Starr, I., Jr., Gamble, C. J., Margolis, A., Donal, J. S., Jr., Joseph, N., and Eagle, E., A clinical study of the action of 10 commonly used drugs on cardiac output, work, and size; on respiration, on metabolic rate and on the electrocardiogram. J. Clin. Invest., 1937, **16**, 799.
11. Hürthle, K., Ueber eine Methode zur Registrirung des arteriellen Blutdrucks beim Menschen. Deutsche Med. Wchnschr., 1896, **22**, 574.
12. Erlanger, J., and Hooker, D. R., An experimental study of blood-pressure and pulse-pressure in man. Johns Hopkins Hosp. Rep., 1904, **12**, 145.
13. Katz, L. N., and Wiggers, C. J., The influence of high systemic blood pressures on the right ventricle and pulmonary circuit. Am. J. Physiol., 1927, **82**, 91.
14. Skelton, R., On the relation of pulse pressure to the output of the heart. J. Physiol., 1921, **55**, 319.
15. Lagen, J. B., Soley, M. H., and Leake, T. B., Effect of benzedrine sulfate on basal metabolic rate. Proc. Soc. Exp. Biol. and Med., 1936, **35**, 276.
16. Molitch, M., and Poliakoff, S., The effect of benzedrine sulphate on the basal metabolism of children. Arch. Pediat., 1937, **54**, 683.
17. Donley, D. E., Observations on the use of benzedrine in the psychoses. Ohio State Med. J., 1937, **33**, 1229.
18. Korns, H. M., and Randall, W. L., Benzedrine and paredrine in the treatment of orthostatic hypotension, with supplementary case report. Ann. Int. Med., 1938, **12**, 253.
19. Altschule, M. D., and Gilman, S., The use of paredrine to correct the fall in blood pressure during spinal anesthesia. New England J. Med., 1939, **221**, 600.