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Effect of Dibenamine on Blood Pressure in Normotensive and Hypertensive Subjects.

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Experimental evidence in animals showing that the sympathetic nervous system plays an important part in the mediation of reflex elevation of blood pressure has been presented by several authors.[1,2,3] In hypertensive patients, lowering of the blood pressure has been induced temporarily by means of spinal[4] or continuous caudal[5] anesthesia, and for longer duration by extensive dorsolumbar sympathectomy.[6,7,8] These facts are considered generally to support the theory that a neurogenic factor plays a primary role in the genesis of hypertension.

The clinical evaluation of this neurogenic factor has proven to be difficult. The available tests for determining the presence and degree of the neurogenic element are not satisfactory because they are non-specific or the drugs employed act too diffusely. Indeed, amytal is a central nervous system depressor, spinal and continuous caudal anesthesia block both autonomic and somatic functions, tetraethyl ammonium hydrochloride affects both sympathetic and parasympathetic ganglia[9] and depresses the resting blood pressure of both normotensive and hypertensive subjects.[10,11] The value of the results thus obtained is questionable.

A drug having a relatively prolonged effect and capable of blocking specifically sympathetic impulses would meet the requirements for a desired test. Dibenamine, a new sympatholytic agent, appears to possess these pharmacologic properties.

In order to investigate the role of the neurogenic factor in hypertension, a study of the effect of dibenamine on the blood pressure in normotensive and hypertensive subjects was undertaken.

Methods and Material. Dibenamine (N, N - dibenzyl - β - chloroethylamine - hydrochloride) is a new synthetic autonomic blocking agent. Structurally it is related to the nitrogen mustards. Functionally it is a highly specific sympatholytic and adrenolytic drug.[12,13] The dibenamine* used in this investigation was supplied in ampules as a 5% sterile solution in 50% alcohol, acidified for stability. It was administered by the intravenous route. An infusion of a solution of 0.9% sodium chloride or of 5% glucose was first started. When this was flowing freely, the desired amount of dibenamine was added to the flask containing 300 to 500 cc of the saline or glucose solution and mixed thoroughly. The single dosage used averaged 5 mg per

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3 Grimson, K. S., Kernodle, C. E., Jr., and Hill, H. C., *J. A. M. A.*, 1944, **126**, 218.

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8 Smithwick, R. H., *Arch. Surg.*, 1944, **49**, 180.

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10 Birchall, R., Taylor, R. D., Lowenstein, B. E., and Page, I. H., *Am. J. Med. Sc.*, 1947, **213**, 572.

11 Haimovici, H., unpublished data.

* Dibenamine was supplied by the Givaudan-Delawanna, Inc., Delawanna, N. J., through the courtesy of Dr. W. Gump.

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13 Haimovici, H., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 486.

kg of body weight. The total single dosage, regardless of weight, never exceeded 500 mg in our present study. The infusion was given in most cases over a total period of 60 to 75 minutes. At the completion of the dibenamine administration, the vein through which it was given was flushed with 100 to 150 cc of normal saline or glucose solution. (We found this procedure necessary for preventing local phlebothrombosis, which otherwise frequently followed dibenamine infusion in the early stage of this investigation).

The effects of this drug were studied 69 times in 38 subjects (18 normotensive and 20 hypertensive). Among the latter, 14 were suffering from essential hypertension and 6 from systolic hypertension associated with arteriosclerotic cardiovascular disease.

Arterial blood pressure was measured in the arm by the standard auscultatory method. The measurements were made in the supine, sitting and standing positions. The blood pressure (B. P.) and the pulse rate (P. R.) readings were taken at frequent intervals before, during and after the infusion. In most instances the observations were carried out over a period of 24 to 72 hours. All subjects were hospitalized patients, whose blood pressure was recorded over a period of a few days or weeks before the present tests were undertaken. In addition, the study of B. P. changes preceding and following dibenamine administration was done under standard, basal conditions. After the infusion the patients were kept in bed for about 12 to 24 hours.

Results. A. Effect of dibenamine on the blood pressure in the supine position.

1. Thirty tests were performed in 18 *normotensive* subjects (Table I). The average pre-injection B.P. was 124/73, the average post-injection B.P. was 122/69, with an average change of –2/–4. The range of variations in the post-injection B.P. was between +30 and –40 for the systolic and between +20 and –24 for the diastolic.

2. In *hypertensive* subjects the effect of dibenamine varied with the type of hypertension. The results obtained fall into 3 groups.

a. The first group (Table I) includes those patients with essential hypertension whose B. P. fell to normal or below normal levels. Six out of the 7 subjects in this group had an uncomplicated essential hypertension (benign phase) and one had visceral changes characteristic of the malignant phase of the disease. In the 17 tests performed in this group, the average pre-injection B. P. was 180/112, the average post-injection B. P. was 132/86, with an average change of –48/–26.

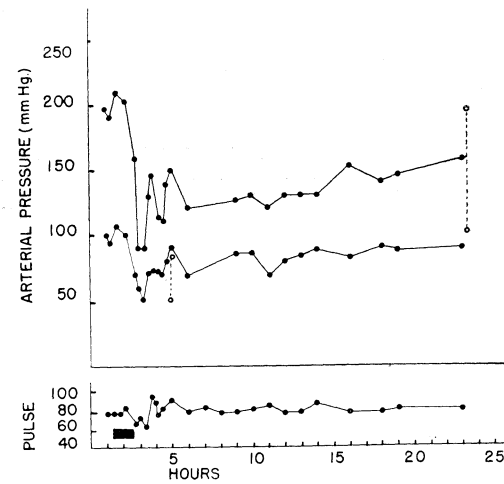

FIG. 1.

Typical effect of dibenamine (■■) on the resting blood pressure and pulse rate in a case of benign essential hypertension. The vertical broken lines represent orthostatic blood pressure changes after one minute in the upright position.

The onset of the depression on the B. P. occurred occasionally during the infusion, but in most instances the fall began at or soon after the conclusion of the drug administration. The maximum fall was recorded usually within 30 to 60 minutes after the onset of the depression. However, in 2 instances a delayed response was seen, and the maximum depression of the B. P. was noted 2½ and 4½ hours respectively after the completion of the dibenamine infusion.

The return of the supine B. P. to the pre-injection level was gradual and took usually from 24 to 72 hours. Fig. 1 illustrates a typical response of a patient with moderately advanced essential hypertension.

The depressor effect of dibenamine was usually more marked after the second and subsequent injections than after the first one,

TABLE I.
Effect of Intravenous Injection of Dibenamine on the "Resting" Blood Pressure and Pulse Rate.

Group of patients	No. of subj.	No. of inj.	Pre-injection		Post-injection		Change in		
			B.P.	P.R.	B.P.	P.R.	Syst.	Diast.	P.R.
1. Normotensive	18	30	124/73 ± 2.2/1.7*	78 ± 2.0	122/69 ± 3.0/1.9	84 ± 2.8	— 2 ± 2.6	— 4 ± 1.5	+6 ± 1.6
2. Essential hypertension (benign phase†)	7	17	180/112 ±5 .7/3.0	82 ± 2.8	132/86 ± 6.8/3.9	86 ± 3.9	—48 ± 3.6	—26 ± 2.5	+4 ± 2.1
3. Essential hypertension (malignant phase)	7	12	231/136 ± 7.6/5.6	100 ± 4.0	204/122 ± 5.2/3.3	102 ± 3.8	—27 ± 4.3	—14 ± 3.2	+2 ± 1.1
4. Systolic hypertension (associated with A.S.C.V.D.)	6	10	177/81 ± 3.8/3.6	82 ± 6.6	170/79 ± 5.9/2.7	83 ± 4.5	— 7 ± 4.8	— 2 ± 2.0	+1 ± 3.5

* Mean ± Standard Deviation of the Mean.
† In this group, which responds to dibenamine, one patient presented visceral manifestations characteristic of the advanced phase of essential hypertension.

if an interval of only 2 to 4 days elapsed between the injections. This was noted even when the B. P. had returned to the pre-injection level during the interval, and might indicate a certain cumulative effect of the drug. Thus the average of the lowest B. P. after repeated dibenamine infusion was 107/75 as compared to 132/86, the average of the B. P. after all the injections.

b. The second group (Table I) includes 7 patients with essential hypertension whose B. P. did not change significantly after the administration of dibenamine. All the patients in this group had clinical manifestations of the malignant phase of essential hypertension (neuroretinitis, impairment of the renal function, E.C.G. changes indicative of myocardial damage, etc.). The effect of dibenamine on the B. P. in this group was either a small depression, no change or even a slight rise over the pre-injection values. When a fall in B. P. did occur, neither the systolic nor the diastolic pressures ever reached a normal level. The average pre-injection B. P. was 231/136, while the average post-injection B. P. was 204/122.

c. The third group of hypertensives includes 6 patients with systolic hypertension and arteriosclerotic cardiovascular disease (Table I). In this group the B. P. exhibited only slight variations, and the average pre-injection and post-injection values were practically the same (177/81 and 170/79).

B. Orthostatic changes. In most instances marked postural hypotension, accompanied by marked tachycardia (140 to 160), was seen following the intravenous administration of dibenamine, in both normotensive and hypertensive subjects. The orthostatic changes were present usually at or soon after the completion of the infusion and disappeared 12 to 24 hours thereafter. As a rule postural tachycardia outlasted by about 12 hours postural hypotension.

C. Other effects. The range of variations in the resting pulse rate was between +36 and −20, with an average change of +3. This applied to all groups of patients.

Measurement of skin temperatures of the head and the upper and lower extremities, under control conditions, were recorded in all

cases. Release of the sympathetic tone was apparent first in the head, second in the upper extremities, and last in the lower extremities. Delayed or absent responses were noted in the lower extremities of certain patients.

Observations on these effects and others (pupillary changes, sweat function, pain, etc.) will be reported elsewhere.

D. Side Effects. Side reactions due to the administration of dibenamine were either local or general. Local reactions included phlebothrombosis, which has been mentioned already under methods and materials, and pain in the arm along the vein during the infusion, which was seen in 4 instances. Most general reactions were minor. Dryness of the mouth and congestion of the nose were seen in practically all cases. Drowsiness and transient nausea were common. The major side effects included vomiting in 8 instances, mental confusion and emotional lability in 3 cases, and one case of mental confusion with loss of sphincteric control and deep sleep lasting one hour.

All side effects were transient. A slow, even rate of infusion and confinement to bed of the patient for about 12 hours after the injection, *i. e.* until the orthostatic hypotension could no longer be elicited, appeared important factors in the prevention or reduction of the side effects to a minimum.†

Comments. The administration of dibenamine resulted in a significant reduction of the resting B. P. of subjects with benign or moderately advanced essential hypertension only. These results are at variance with those presented by Hecht and Anderson.[14] Orthostatic hypotension occurred in both normotensive and hypertensive subjects.

There is ample evidence to show that dibenamine is a very potent and highly specific adrenolytic and sympatholytic agent.[12,13] It probably acts directly on the neuro-effector cells, where it blocks the sympathetic impulses or the action of sympathomimetic substances (sympathin E, epinephrine). Thus the B. P. changes induced by dibenamine may be interpreted as being due to the blockade of sympathetic tone.

The lowering to normal levels of the resting blood pressure by dibenamine, in subjects with benign or moderately advanced essential hypertension only, tends to suggest that: 1. a neurogenic element, *i. e.* altered sympathetic tone is present in essential hypertension, and 2. the evaluation of this element by the administration of dibenamine may be of great help in the selection of patients when surgery is contemplated.

Because of its specific sympatholytic action, dibenamine offers a valuable tool for the investigation of the neurogenic component of a variety of vascular conditions. Further study is under way.

Summary. 1. Dibenamine hydrochloride, a new sympatholytic and adrenolytic drug was administered intravenously in the dosage of 5 mg/kg of body weight to normotensive and hypertensive subjects. 2. Reduction to normal or below normal levels in resting arterial blood pressure was observed only in benign or moderately advanced essential hypertension, but not in the malignant phase. Orthostatic hypotension occurred in both normotensive and hypertensive subjects. 3. The depressor effect started at the end of the infusion and lasted 24 to 72 hours. 4. All side reactions were transient, and major side reactions occurred only in a few instances. 5. The role of the neurogenic factor in essential hypertension is discussed. The usefulness of dibenamine in evaluating the neurogenic element is suggested.

† Much care was exercised by keeping the patient in bed during the phase of orthostatic hypotension because of the possible deleterious effect of the latter on the coronary circulation in advanced cardiovascular disease.

[14] Hecht, H. H., and Anderson, R. B., *Am. J. Med.*, 1947, **3**, 3.