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Comparison of Hypotensive Action of Sodium Azide in Normotensive and Hypertensive Patients.* (20770)

M. M. BLACK, B. W. ZWEIFACH, AND F. D. SPEER.

From the Department of Pathology and Clinical Pathology, New York Medical College, Flower Fifth Avenue Hospital, and Department of Biology, Washington Square College, New York University, New York.

In the course of investigations on the effects of various inhibitors on human cancer patients (1), it was noted in cases with co-existent hypertension that the acute administration of sodium azide caused a temporary lowering of the blood pressure toward normotensive levels. In contrast, comparable doses of azide produced no appreciable change in the blood pressure of normotensive individuals. These incidental observations led to a more extended study of the hypotensive effect of sodium azide in both man and experimental animals. A review of the literature indicated that Graham(2) had made an intensive study of the pharmacological effects of sodium azide. However, he made no mention of its effect on hypertensive patients. Page and Olmsted(3), as an incidental finding in studies on vascular reactivity, mentioned the greater susceptibility of dogs with either renal or neurogenic hypertension to the acute hypotensive effects of sodium azide.

* This investigation was supported by a grant from the Leukemia Research Foundation.

In view of the finding that sodium azide, a known metabolic inhibitor(4), produced a more pronounced lowering of blood pressure in hypertensives than in normotensives, it appeared of direct interest to use sodium azide as a tool for investigating hypertensive disease in man and experimental animals. Furthermore, the possibility was entertained that repeated administration of azide to hypertensives might so alter tissue metabolism as to result in a sustained lowering of the blood pressure. Although the drug is usually considered to be highly toxic, it should be noted that the lethal range (10 mg/kg subcut.)(5) is far in excess of the oral dosage required to produce a fall in blood pressure (.01-.02 mg/kg).

Materials and methods. A comparison was made between the effects of sodium azide in normotensive and hypertensive individuals. Included in the normotensive series are normal healthy controls (students, laboratory personnel), as well as patients suffering from diverse types of cancer. The patients with

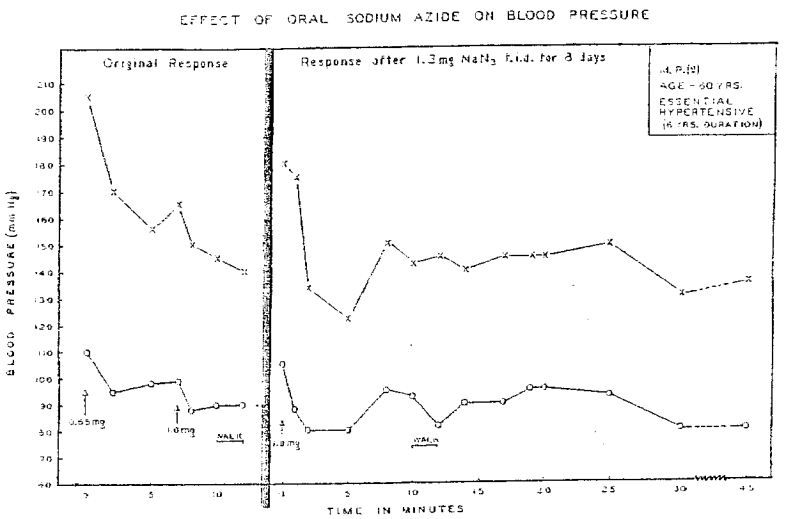

FIG. 1. Acute hypotensive action of sodium azide (oral) on blood pressure of hypertensive patient M. R. Blood pressure recorded in sitting position 205/110. Effect on B.P. with first administration of drug, as indicated in graph on left hand side of figure, remained at this level for 15 min. before returning to the original hypertensive level. Following continued treatment with azide for 3 days, the acute hypotensive effect persisted for more than 45 min., especially noticeable in diastolic pressure readings.

elevated blood pressures were documented cases of essential hypertension, recorded from 12 months to as long as 10 years. Several patients with renal parenchymatous damage were also studied. Sodium azide was administered orally, except in selected cases where a comparison was made of the response to sublingual and intravenous administration. *Blood pressure* measurements were made by the conventional inflated cuff procedure, with the patient in a sitting position. Several readings were obtained prior to the administration of the drug, after basal conditions had been established. The lowest of 3 blood pressure determinations was taken as the basal pretreatment level. Repeated blood pressure readings rarely differed by more than 15 mm Hg for the systolic values. Determinations were made at 2- to 5-minute intervals following the *acute administration* of sodium azide until the pressure had either returned to its original level, or had stabilized at a new level. Because of the rapidity of the fall in blood pressure, these necessarily represent single readings for each value recorded (Fig. 1). Sodium azide, which is tasteless in aqueous solution, was administered without informing the patient of either the nature of the drug, or the change to be expected. Doses of 0.65 mg and 1.3 mg dissolved in half or quarter of a glass of water were used in the initial experiments. Later it was found that the prescribed dosage in a teaspoon of water was equally effective. In addition to a study of the acute changes produced by sodium azide, the effects of *chronic administration* were observed in a selected group of patients. In this series, the patients were instructed to take the sodium azide orally (0.65-1.3 mg) 3 to 5 times a day.

Results. I. *Acute effects.* Oral administration of sodium azide to hypertensive patients resulted in a rapid fall in blood pressure. In some patients a hypotensive effect was observed as early as 45 to 60 seconds after the drug had been taken. Fig. 1 illustrates the character and the rapidity of the change in blood pressure following several doses of sodium azide. After testing the acute response to azide, the patient, M.R., was placed on a regime of 1.3 mg orally t.i.d. When examined 8 days later, the basal pressure was 180/105. A hypotensive response to the acute administration of azide was again obtained, as depicted in the accompanying graph (Fig. 1). After 36 days, the hypotensive

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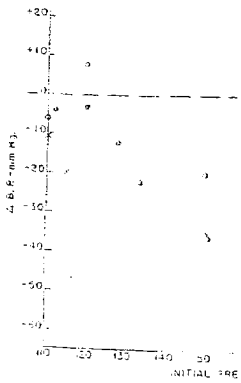

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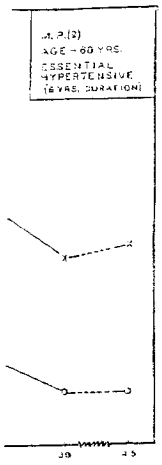

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response to 1.3 mg of azide was even more pronounced than originally. Several features of the response of different patients to sodium azide deserve comment. Although the actual fall in systolic pressure in mm Hg was considerably greater than the change in diastolic pressure, it should be noted that the diastolic pressure more often approached normal values than did the systolic. The fall in blood pressure was not accompanied by any significant change in pulse or respiratory rate. Flushing of the face was not observed. The majority of patients did not develop orthostatic hypotension, even after exercise. It is pertinent to note that exercise during the acute hypotensive phase did not cause any significant elevation in pressure; in fact, most patients exhibited a further lowering of diastolic pressure (5-10 mm Hg). The acute effects of sodium azide, in doses of 0.65 mg and 1.3 mg on the systolic and diastolic pressures of normotensive and hypertensive subjects are summarized in Fig. 2 and 3. The hypotensive action of azide appeared to be more closely related to the height of the initial blood pressure than to the dose level of the drug. In 13 patients whose initial systolic pressures were equal to or greater than 190 mm Hg, the acute drop in pressure averaged 43 mm Hg (range —30 to —65 mm Hg). In contrast, in 9 relatively normotensive individuals, whose systolic pressures were below 140, only a

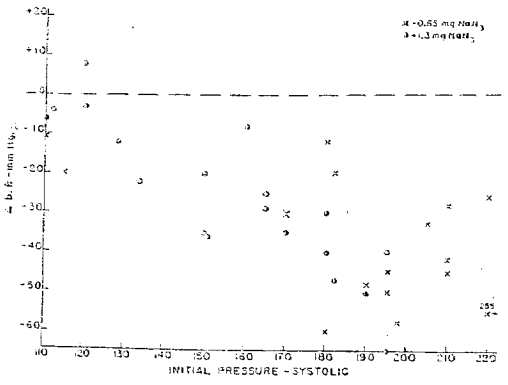

FIG. 2. Acute effect of oral sodium azide on B.P. of 35 patients plotted in relation to original systolic pressures. The change in blood pressure indicated represents maximum fall after administration of the drug. Depressant action of sodium azide was greatest in individuals with highest basal B.P.

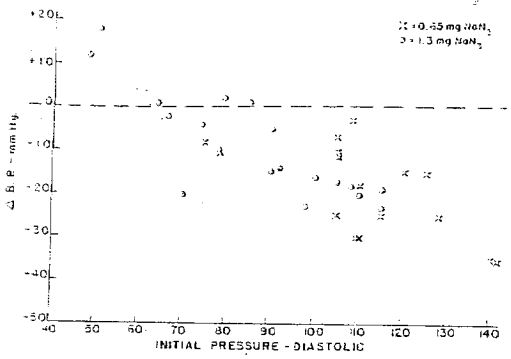

FIG. 3. Acute effect of sodium azide on B.P. of 35 patients (as in Fig. 2) plotted in relation to original diastolic pressures. Hypotensive action most pronounced in patients with highest initial values.

minor effect on the blood pressure occurred—a mean value of —4 mm Hg (range +12 to —22 mm Hg). A similar relationship was also observed with regard to the effect of azide on the diastolic pressure. No apparent refractoriness to the drug developed with repeated administration, comparable and even greater falls in blood pressure being elicited when the azide was administered acutely as many as ten to twelve times to the same patients at intervals of several days to several weeks. Several patients were studied repetitively for the acute effects of sodium azide for periods in excess of one year.

II. *Chronic effects.* Observations have also been made on a group of 39 patients who received sodium azide over periods varying from 5 days to more than 2 years. Of this group, 9 served as normotensive controls (diastolic pressures less than 90 mm Hg), while the remaining 30 had varying degrees of systolic and diastolic hypertension. Neither the diet nor physical activity was restricted during the study. The administration of as much as 1.3 mg of sodium azide 3 times daily for ten days to normotensive individuals had no sustained effect on the blood pressure. The effects of sodium azide on 30 hypertensives are indicated in Table I. The blood pressure values represent the reproducible reading (at least 3 to 4 times) obtained under standard basal conditions in the sitting position after the patient had been allowed to rest for 5 minutes. Blood pressure was routinely recorded from 4 to 12 hours after the last dose of azide had been taken. The response of these patients

TABLE I. Effect of Sodium Azide on Blood Pressure of Hypertensives.

Patient	Azide: Dose (mg)	Azide: Duration (days)	Blood pressure: Pre-treatment	Blood pressure: Post-treatment Acute	Blood pressure: Post-treatment Chronic	Remarks
O. D.	1.3, q.d.	5	270/140	200/110	187/112	Discontinued because of severe epistaxis
N. P.	1.3, t.i.d.	7	205/110	140/ 90	180/105	
E. F.	.7, q.d.	7	176/108	176/108	162/ 95	
G. F.	.4, t.i.d.	7	186/ 90	140/ 80	155/ 88	
M. R.	1.3, "	10	205/110	145/ 90	195/ 95	
P. S.	.65, q.d.	10	220/140	--	165/140	B.P. varied during day; renal parenchymatous damage
C. M.	1.3, by i.v. inj., q.d.	10	150/ 90	115/ 75	115/ 75	
F. G.	1.3, *idem.*	10	165/116	140/ 92	130/ 95	
G. C.	.65, t.i.d.	10	195/108	155/ 85	140/ 90	
D. E.	1.0, "	14	210/140	161/ 85	155/ 76	
L. W.	.65, "	15	210/120	182/110	178/100	
E. L.	1.3, "	17	215/135	142/102	210/130	Renal parenchymatous damage
J. S.	.65, "	18	210/130	158/105	175/105	
S. W.	1.3, "	21	250/105	205/ 95	250/105	Advanced arteriosclerosis
B. A.	.3, q.d.	21	186/104	115/ 68	120/ 80	B.P. remained normal 7 wk post-treatment
G. H.	1.3, t.i.d.	21	200/120	160/110	160/100	Previously treated with apresoline unsuccessfully
A. I.	.65, "	21	160/112	145/ 75	145/ 85	
H. S.	.65, "	21	210/110	160/ 90	160/ 90	B.P. remained normal for 14 days post-treatment
B. C.	.65, "	30	195/110	140/110	135/ 95	
G. S.	.65, "	30	180/110	140/ 90	140/ 90	B.P. remained at low level for several weeks after drug
M. K.	1.3, "	30	260/105	200/ 80	260/100	
H. K.	.5, "	30	182/100	135/ 84	145/ 95	Sympathectomy 7 yr previous
V. G.	.5, "	60	170/115	140/ 90	150/ 95	
A. S.	1.3, "	60	230/128	195/ 95	234/110	
M. W.	.65, "	90	198/110	144/ 92	160/ 90	
F. R.	.65, "	250	195/110	150/ 85	125/ 80	Off medication 2 mo—B.P. unchanged
F. S.	.65, "	275	175/110	145/ 90	130/ 90	
R. K.	1.3, "	365	200/120	125/ 88	155/100	
E. M.	1.3, "	1.5 yr	220/125	190/100	175/ 90	B.P. remained at low level for 4 mo after drug withdrawal
B. M.	.65, "	2.5 yr	180/100	120/ 70	160/105	3 yr postsympathectomy—showed increased sensitivity to azide, 0.3 mg drops B.P. to 70/40

fell into 3 categories: (1) Five cases showed only minimal changes in blood pressure after chronic administration. (2) In 10 patients the blood pressure showed a significant fall with azide, but the diastolic pressure remained above 100 mm Hg. (3) In the remaining 15 hypertensive patients, both the systolic and the diastolic pressure was maintained at near normotensive levels throughout the period of medication. Treatment with azide brought about a fall in blood pressure to normotensive levels which persisted for periods ranging from 14 days to 2 months, in 5 of the patients after the drug had been withdrawn. In these 5 cases some doubt may be entertained as to the validity of the blood pressure lowering effects of the sodium azide *per se*. It should be emphasized that all 5 cases had well-documented histories of persistent hypertension for periods of at least 2 years. Also it should be noted that at the onset of treatment, all these hypertensives exhibited a typical blood pressure response to the acute administration of sodium azide. The more common occurrence (22 out of 26) was a gradual return of the blood pressure within 1 to 3 days to hypertensive levels after withdrawal of the drug. During the period of sodium azide treatment, a majority of patients showed a definite improvement in their subjective symp-

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toms, especially as regards headache, chest pains, and general mental outlook.

III. *Toxicity.* Three patients have been taking sodium azide daily for more than one year without evidence of damage to organs, such as the kidney, heart, liver on the basis of routine clinical studies. Kidney function was not impaired as evidenced by the quality and quantity of urine output, blood urea N and NPN. In contrast to the reported effects with hexathonium(6,7), there was no evidence of a change in bowel habits or urinary function. An occasional patient complained of a transient sensation of pounding in the head shortly after taking the drug. In 20 of the patients, continued treatment with sodium azide was followed by an increased sensitivity to the drug, necessitating a reduction in the daily dosage from 0.5 to 0.25 mg t.i.d.

IV. *Mode of administration.* Because of the unusual rapidity with which the decline in blood pressure developed following oral azide, studies were carried out with several different methods of administration. Sodium azide was administered intravenously as an infusion of 5% glucose solution containing 3.0 γ/ml of the drug. It was found that an infusion rate of 10 γ per ten minutes sufficed to lower and to maintain the blood pressure of a hypertensive patient from a level of 190/110 to 150/85 mm Hg for a period of several hours. Sublingual administration was introduced on the premise that this route might provide a more ready absorption of azide into the blood stream than oral *per se*. Tests performed on 3 hypertensives indicated that three drops containing a total of 0.1 mg by sublingual route were as effective as 0.65 mg orally.

V. *Animal experiments.* Experiments were carried out on normotensive and hypertensive rats (renal) in an attempt to clarify the mechanism of action of sodium azide. Several pertinent observations warrant discussion at this time. As in man, azide lowered the blood pressure of renal hypertensive rats from a level of 180-200 mm Hg (mean pressure by direct cannulation) to 120-130 mm Hg. As little as 0.1 mg of azide (150-180 g, body weight) was sufficient to produce a fall in blood pressure of 30 to 45 minutes duration in animals made hypertensive three months previous by either a figure-of-eight loop on the kidney or by partial ligation of the renal artery. The intravenous administration of comparable doses of azide to normotensive rats, either acutely or by slow infusion, had no effect on blood pressure. In contrast to other hypotensive drugs, azide, administered to rats which had been subjected to hemorrhage until a blood pressure of 40 mm Hg was achieved, produced no deleterious effect on either the blood pressure or the peripheral circulation as visualized in the mesentery. Sodium azide (.01-.5 mg), applied to the surface of the mesentery, had no direct dilating action on the constricted blood vessels in the terminal vascular bed of rats subjected to hemorrhage.

Discussion. Sodium azide has been found to be more effective in lowering the blood pressure from hypertensive toward normotensive levels than it is in dropping the blood pressure below control levels in normotensive individuals. The blood pressure was lowered in patients with essential hypertension, as well as in several with elevated blood pressure associated with renal parenchymal damage. Comparable hypotensive effects were observed in hypertensive rats treated both acutely and chronically with the drug. Repetitive administration on the drug over periods of 10 days or longer resulted in the appearance of an increased effectiveness in an appreciable percentage of patients tested, manifested by a greater hypotensive effect following equivalent doses and/or progressively more sustained periods of normotensive levels. In the present series it was not possible to predict on the basis of previous clinical history which of the patients would respond best to sodium azide.

In view of the small size of the present series of cases treated with sodium azide, it should be emphasized that its clinical evaluation must await considerable further investigation, especially in terms of the mode of administration and the possible use of other azide derivatives. The necessity remains to rule out all possible toxic effects of long continued administration of sodium azide before routine use in the treatment of hypertension is attempted. Because of its known effects on specific enzyme systems *in vitro*, such as cytochrome oxidase(8), catalase, peroxidase, carbonic anhydrase, and possibly transphos-

phorylation(9), sodium azide provides an interesting metabolic tool to investigate the pathogenesis of hypertension along biochemical lines.

Summary. 1. A comparison was made between the effects of sodium azide in both normotensive and hypertensive patients. Doses of 0.65-1.3 mg, administered orally, had a rapid hypotensive effect which persisted from 10-15 minutes. When given chronically to hypertensives (0.6-1.3 mg 3 to 4 times daily for periods up to 2 years), sodium azide produced a sustained lowering of the blood pressure toward normotensive levels. Repeated administration of the drug results in a greater hypotensive effect following equivalent doses and/or a progressively more sustained period of normotensive blood pressure levels. The observations indicate that a significant difference exists in the relative sensitivity of hypertensive and normotensive individuals to the hypotensive effects of sodium azide. 2. Intravenous injection of the drug to animals subjected to hemorrhage had no dilating effects on the constricted blood vessels in the exteriorized mesentery. Sodium azide (0.5 mg/100 g body wt) lowers the blood pressure of hypertensive rats. The observation that sodium azide in hypertensives rarely lowers the elevated blood pressure below normotensive levels suggests a general non-specific action of the drug on all vascular beds.

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Effect of 17-Vinyltestosterone on the Mammae, Uteri, Thymus, and Adrenal Glands of Spayed Female Mice.[1] (20771)

D. S. FLUX. (Introduced by R. Gaunt.)

From the National Institute for Research in Dairying; University of Reading, England.

17-vinyltestosterone appears to be an interesting steroid in that it shows evidence of androgenic activity (Kochakian(1), Leathem (2)) and also indications of corticoid activity (Lewis, de Majo & Rosemberg)(3) but did not support lactation in adrenalectomized rats in doses up to 2 mg daily (Flux)(9). It is closely related structurally to ethinyl testosterone (pregneninolene, anhydrohydroxy progesterone) which has progesterone-like, oestrogenic and androgenic activities (Emmens & Parkes(4), Chamorro(5-7)). Since androgens and at least one 11-deoxycorticosteroid, 11-deoxycorticosterone acetate (see review by Folley(8)), have been found to promote growth of the mammae in experimental animals, it was decided to investigate the effect of 17-vinyltestosterone on the mammary glands of spayed mice, and in addition to collect data on its effects on body weight, uterus weight and on the weight of the thymus and adrenal glands.

Methods. Female mice of the CHI strain were ovariectomized at 14 days of age and weaned at 21 days. Mice in one group of 6 animals were each subcutaneously implanted with one 100 mg tablet of 17-vinyltestosterone, those in another group were each given four 50 mg tablets and 6 otherwise untreated ovariectomized mice and 6 intact mice were used as controls. The animals were killed at 42 days of age and the uteri and the thymus and adrenal glands were weighed. The uteri were split and blotted to remove any fluid in

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