SPECIAL ARTICLE

Treatment of Hypertensive Disease

By N. N. Savitzki, M.D., and V. P. Nikitin

Of the variety of pathologic conditions involving abnormally high blood pressure, one is of outstanding importance—essential hypertension. According to current views, the principal pathogenetic mechanism responsible for elevation of blood pressure is assumed to be a generalized arteriolar spasm, with a resulting rise of peripheral resistance to the outflow of blood. It has been proved by our investigations, however, that such a concept is far from being universally acceptable.

Not infrequently, the elevation of blood pressure is due to a disturbance of coordination between functions of various links of the cardiovascular system. We have ample evidence that an inadequate response of arterioles (insufficient dilatation) to increasing cardiac output, rather than arteriolar spasm, may be the direct cause of blood pressure elevation. In the treatment of patients with hypertensive disease, the use of potent vasodilating drugs proves to be of minor importance, success depending on a judicious combination of various therapeutic measures aimed at the restitution of normal cardiovascular function. Treatment should include a set of procedures, attacking the causative factors of the disease. The course of the process, as well as the patient’s individuality are to be taken into consideration in selecting a suitable combination of therapeutic agents. Thus, it is well known that there may be wide variations in the sensitivity of individual patients to hypotensive agents having central, ganglionic blocking, adrenolytic, or myotropic activities. It would therefore be a mistake to recommend a “unified” method of treatment, suitable in any case of hypertensive disease.

There do exist, however, important general conditions, that are essential for efficient prophylaxis and treatment of hypertension. Among these may be mentioned the organization on a nationwide scale of outpatient services responsible for the management of patients (termed dispensary system), treatment in overnight or daytime sanatoria attached to factories or institutions, availability of sanatoria and health resorts, and creation of favorable occupational and living conditions.1-4

In this communication no attempt is made to give a general review of current methods of treatment for hypertensive disease. Only some data are discussed on which information seems to be scarce outside our country.

Prolongation of natural sleep has been used extensively as a means of restoring disturbed function of neurohumoral controlling systems. Experience supports our opinion that favorable effects are not attained by high dosage of sedatives, tending to produce signs of intoxication. Besides, it would not conform to the principle of protective inhibition, implying a reduced excitability of nervous cells.

Accordingly, we have been using low doses of barbiturates with a medium duration of activity (Noctal, Nembutal, Medinal, etc.). Barbiturates are generally taken twice daily, before the midday meal and before retiring. In some cases, sedatives should be taken in the morning. In this way, the duration of normal sleep can be prolonged to 12 or 13, occasionally

From the USSR Academy of Medical Sciences, Leningrad, USSR.
as long as 16 hours a day. It has been shown by L. P. Ivanov⁵ that such treatment causes no signs of toxicity and does not affect basal metabolism, nonprotein nitrogen, or blood indican, and prothrombin. Protracted pharmacologic sleep has a beneficial effect upon the general well-being of patients, bringing about alleviation of headaches and of precordial pain. In many cases, the favorable influence of protracted sleep can hardly be attributed to a marked hypertensive effect. It tends to bring about a normal state of higher nervous activity, to improve the blood supply of tissues, and to overcome regional circulatory disorders. A number of different methods of sleep therapy have been suggested; they are reviewed in well-known monographs.¹ ² ⁶ The effectiveness of the method rises, when used in combination with vasodilating agents. These are particularly desirable for patients having frequent regional vascular spasms.

On a suggestion from S. V. Anitchkov,⁷ an original preparation synthesized in the Soviet Union, dibazole (2-benzyl-benzimidazole chloral hydrate)

\[
\begin{array}{c}
\text{C-CH}_2- \\
\text{H}
\end{array}
\]

has been submitted to clinical trials.

Dibazole has a papaverine-like action. It was found to reduce blood pressure on subcutaneous, as well as intravenous, administration to animals following total destruction of the central nervous system. Dibazole was shown to suppress spasm of arterial smooth muscle induced by barium chloride and acetylcholine.⁷ ⁸ Unlike papaverine, dibazole displays definite effects on the central nervous system, even at low doses; and it has been used for the treatment of various paralytic or parietal conditions, as well as for sequellae of cerebral injury.⁹ ¹¹

At present, our experience is based upon records of routine administration of dibazole in 403 patients with hypertensive disease, (241 women, 162 men). Dibazole treatment has been resorted to at various stages of the hypertensive disease. In all of the patients, treatment was preceded by a period of clinical observation. The group included 84 patients with stage I hypertensive disease, 273 with stage II, and 46 with stage III. Dibazole treatment was continued for 12 to 40 days. Intramuscular or subcutaneous injections of 1 ml. of a 2-per cent solution of dibazole were given every day to 330 patients once, or twice in the more serious cases; 3 oral doses, 0.02 to 0.04 Gm. each, were administered to 73 patients. No undesirable effects of dibazole treatment have been noted.

Dibazole treatment was followed by considerable improvement of general condition and reduction of blood pressure in 250 patients. In the other 153, no significant hypertensive effect could be attained, although most of them found their condition had improved, as they were free of severe headaches, tinnitus, and paroxysms of cardiac distress. Dibazole treatment had no effect in 23 patients with hypertensive disease, stage III. Nine of them died: 7 of progressive renal failure and uremia and 2 of cerebral hemorrhage.

The fact that dibazole relieved symptoms of precordial pain in hypertensive patients as well as data, obtained by I. A. Novikova in the laboratory of Professor N. A. Kharauzov,¹² on suppression of experimental atherosclerosis by dibazole, led to a trial of this agent in patients with atherosclerotic cardio sclerosis accompanied by severe anginal pain and in patients with myocardial infarction at the stage known as ‘recovery period.’ Systematic dibazole treatment was found to bring about gradual relief or disappearance of anginal pain. A single injection of dibazole proved ineffective for controlling an acute episode.

Interesting features of circulatory dynamics under the influence of dibazole were revealed in a study by V. I. Kuznetzov et al.¹³ ¹⁴ Detailed data on variations of arterial pressure were available as oscillographic records obtained by means of a special instrument—the mechanocardiograph. Its design provides the possibility of obtaining a high-speed oscillographic record during compression of a blood
vessel. A method for the interpretation of these records has been elaborated.\textsuperscript{15, 16} The tachymetric oscillogram (tachyoscillogram) assumes a very characteristic appearance, deformation of the basal part of the tracing providing a fairly accurate estimate of the level of arterial pressure (fig. 1). The value of minimal pressure (Mn) is indicated as the moment at which the first diastolic notch appears on the lower section of the tracing. Mean dynamic pressure (My) is determined by the appearance of a closure wave (p) in the lower section of the systolic rise. True systolic, or piezometric pressure (Nw), corresponds to the moment of the largest negative oscillation. An abrupt decrease of amplitude of negative deflections and disappearance of pulsation, recorded simultaneously from the radial artery, indicates the level of final or maximal pressure. The difference between maximal and piezometric pressure depends on the magnitude of hemodynamic impact (Mx - Nw), so that the force of impact pressure is readily obtained by subtraction.

In the majority of cases a single 1-ml. injection of a 2-per cent solution of dibazole is followed by a decrease of the maximal and, somewhat less, of the systolic pressure. As a result the magnitude of hemodynamic impact diminishes. Mean and minimal pressures remain almost unaltered, as here oscillations are generally within 5 to 10 mm. Hg (table 1).

In addition to tachyoscillographic investigations, research on various aspects of the activity of dibazole under clinical conditions was based on a number of tests: basal metabolic rate (Krogh), arteriovenous oxygen difference (actylene method), computation of cardiac output (minute volume), specific peripheral resistance (obligate, actual, working value), work of the heart (obligate and actual). Data from a series of examinations by V. I. Kuznetzov\textsuperscript{13} are given as an illustration (table 2).

As a rule, administration of dibazole was followed by an increase of the arteriovenous difference, while oxygen consumption per unit time was not altered. The increase of the arteriovenous difference may be assumed to be due to dilatation of capillaries and opening of additional canals. The latter results in a reduced velocity of blood flow through tissues and increases oxygen consumption. The diminished cardiac output (minute volume), without any significant reduction of the stroke volume should be considered as an adjustment, tending to relieve the strain of the heart's work. Computation of the actual work performed by the left ventricle provides convincing evidence of the relief afforded to the heart muscle by an injection of dibazole (table 3).

Thus, the favorable therapeutic effect of dibazole is mainly determined by its capacity to relieve the heart muscle, to raise oxygen
consumption by tissues, and to abolish regional spasms. These data provide some explanation for the benefit derived by patients with frequently recurring paroxysms of stenocardia from systematic dibazol injections.

Alterations of circulatory dynamics, similar to those due to dibazol, were found to follow subcutaneous administration of phenatin (1 ml. of a 5 per cent solution). Phenatin, a product of condensation of amphetamine and nicotinic acid, stimulates the central nervous system, but in contradistinction to amphetamine, it has a hypotensive effect.

Data on the treatment of hypertensive disease with ganglionic-blocking agents ("Pendiomid"— diethylenetriamine; hexamethonium salts; Nanophyrum and others)* as well as Rauwolfia serpentina alkaloids, may be omitted due to space limitations; considering the number of available publications, research on this aspect seems to be widely known.

A judiciously planned diet is highly important for the success of therapy in hypertensive disease. The benefit of a salt-free diet has long been established by clinical practice.\textsuperscript{17, 18} Dysfunction of the pituitary-adrenal system in hypertensive disease often results in enhanced mineralo-corticoid activity with retention of sodium and chloride in tissues and extracellular fluid and depletion of potassium ions. Naturally, a number of special rations has been suggested for compensating disturbances of mineral metabolism in hypertension. Kempner’s rice diet seems to be the more widely known. It should be noted, however, that such a diet is tolerated with difficulty due to its monotony and poor taste, many patients refusing to submit to this treatment.

We have been using a so-called "potassium diet" since 1955. It contains vegetables, fruits, sugar, melted butter, sour cream, saltless bread, peas, beans, oatmeal, rice, and jam, providing a total of 2,329 to 2,313 calories. The amount of sodium in the ration is 0.334 to 0.664 Gm.; of potassium 4.462 to 3.774 Gm.; the Na:K ratio being 1:10 or 1:6. The potas-

*1 ml. of 2% dibazol.

Mn, minimum pressure; My, mean dynamic pressure; Nw, piezometric pressure; Mx, final or maximal pressure; S, impact pressure (Mx–Nw).

The results of clinical trials have proved this diet to be an effective therapeutic method in hypertensive disease. Its use is indicated, along with various hypotensive agents, in the treatment of patients with persistent elevation of blood pressure (fig. 2).

It should be noted that in occasional cases the hypotensive effect of the potassium diet proves to be much greater than that of continuous administration of such undoubtedly potent agents as the Rauwolfia alkaloids (fig. 3). Favorable results have been obtained in the treatment of hypertensive disease by other authors using diets based on closely related principles.\textsuperscript{18, 19}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
Patient, age in years & Time (min.) after Dibazol* & Mn & My & Nw & Mx & S \\
\hline
S., 36 & Control & 115 & 140 & 175 & 210 & 35 \\
& 10 & 118 & 145 & 180 & 202 & 22 \\
& 20 & 110 & 150 & 185 & 200 & 15 \\
& 30 & 110 & 150 & 180 & 195 & 15 \\
& 40 & 110 & 145 & 180 & 205 & 25 \\
\hline
Sh, 30 & Control & 105 & 122 & 140 & 165 & 25 \\
& 10 & 105 & 122 & 145 & 165 & 20 \\
& 20 & 100 & 125 & 140 & 160 & 20 \\
& 30 & 100 & 120 & 140 & 155 & 15 \\
& 40 & 100 & 120 & 140 & 155 & 15 \\
\hline
D., 71 & Control & 93 & 100 & 155 & 192 & 37 \\
& 10 & 90 & 100 & 150 & 175 & 25 \\
& 20 & 70 & 95 & 137 & 162 & 25 \\
& 30 & 75 & 94 & 140 & 160 & 20 \\
& 40 & 75 & 94 & 140 & 160 & 20 \\
\hline
P., 45 & Control & 130 & 150 & 195 & 240 & 45 \\
& 10 & 120 & 150 & 195 & 240 & 45 \\
& 20 & 110 & 145 & 195 & 230 & 35 \\
& 30 & 110 & 140 & 195 & 220 & 25 \\
& 40 & 105 & 140 & 182 & 195 & 13 \\
\hline
\end{tabular}
\caption{Effects of Dibazol on Tachyoscillogram in Four Patients}
\end{table}

*\begin{flushleft}
A preparation of lower toxicity—"Benzohexoxonium"—is used now in the Soviet Union.
\end{flushleft}
In our opinion failure to obtain any effect from rest and pharmacologic agents is to be regarded as an indication for prescribing the potassium diet, over-nutrition being a relative indication.

Before closing, it should be emphasized, with regret, that a very simple, although fairly effective method—oxygen inhalation—has not become a routine method of treatment in hypertensive disease. Investigations of arterial blood saturation and respiratory activity in patients with hypertensive disease have disclosed slight arterial hypoxemia in half of the cases. Arterial hypoxemia was detected in patients with hypertensive disease, stage I, though it was more pronounced and of more frequent occurrence in stage II. In these cases, the oxygen capacity of hemoglobin was unimpaired and the dissociation curve of oxyhemoglobin was normal. Carbon dioxide tension of arterial blood remained at a normal level, or somewhat lower. Studies of pulmonary ventilation proved its effectiveness to be unimpaired, while alveolar air oxygen tension was normal, or even slightly higher, in these patients. It should be noted that in patients with hypertensive disease, alterations of the respiration quotient, vital capacity, limit and reserve of respiration are by no means rare. The occurrence of arterial hypoxemia at an early stage of hypertensive disease is evidently due to a disturbance of adequate relationship between pulmonary ventilation and circulation. At later stages of the disease, there may be an additional factor—impaired diffusion capacity of respiratory membranes.

In hypertensive disease, oxygen therapy improves the well-being of patients. Pulse and respiration rates are lowered, dyspnea is relieved, and there is a marked hypotensive
TREATMENT OF HYPERTENSIVE DISEASE

Figure 2

Patient B, age 50. Hypertensive disease, stage II. Blood pressure dynamics and chloride elimination on potassium diet.

effect. Inhalation of air with high oxygen content (40 to 50 per cent) at regularly spaced intervals in an oxygen tent has often been found to reduce blood pressure to normal levels for more or less considerable periods.

In conclusion, it is stressed that the aim of therapeutic procedures is to promote restitution of normal functioning of neurohumoral mechanisms and normal tissue metabolism. Wide variations in the responses of patients to hypotensive agents may indicate the variety of pathogenic mechanisms underlying the presenting symptom of the disease, elevated blood pressure.

Summario in Interlingua

Es presentate un revista del tractamento de hypertension essentiel como illo es prattici in le U.R.S.S. Le autor sublinha le necessitate de differentiare le tractamento secundo le idiosyncrasias del patiente individual.

Inter le valide principios general, le effecto benefic es notate que le prolongation del somnio exerce super le hypertension e le stato general del sanitate del patiente hypertensive. Le prolongation del somnio pote esser effectuate sin risco per medios pharmacologic.

Es reportate in detalio le successos clinici obtenite in le U.R.S.S. per medio del recentemente synthesisate droga cognosseite como dibazol (hydrato de 2-benzyl-benzimidazol-choral). Le effecto de dibazol super le dynamica circulatori esseva studiate per medio del mecanocardiographo que provide rapidisse registraziones oscillographic del vasos sanguinee sub compression.

References


Symposium on Coronary Heart Disease
Will Be Continued in the September 1960 Issue
Treatment of Hypertensive Disease
N. N. SAVITZKI and V. P. NIKITIN

Circulation. 1960;22:308-314
doi: 10.1161/01.CIR.22.2.308

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1960 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/22/2/308.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/