A Critical Evaluation of the Hypotensive Action of Hydralazine, Hexamethonium, Tetraethylammonium and Dibenzyline Salts in Human and Experimental Hypertension

By Alvin P. Shapiro, M.D., and Arthur Grollman, Ph.D., M.D.

The effects of hydralazine and hexamethonium salts on blood pressure and related functions have been studied in a series of ambulatory and hospitalized hypertensive patients as well as in experimentally induced hypertension (rats and dogs). Comparative observations have also been made on the effects of tetraethylammonium chloride and Dibenzyline, a congener of dibenzylohexedrolyamine (Dibenamine). Critical evaluation of the data indicates that the effectiveness of hydralazine and hexamethonium salts, when used either alone or in combination, is not significantly greater in long term administration than that of previously existing regimens in the treatment of hypertensive vascular disease.

THE TREATMENT of hypertension by specific drug therapy has received renewed impetus with the introduction of potent sympatholytic agents. These have been advocated as a means of lowering the arterial blood pressure for prolonged periods of time, with consequent amelioration of the hypertensive vascular disease.1-4 However, the level of the blood pressure in hypertensive patients varies considerably during the natural history of the disease and is influenced by a variety of nonspecific factors,5-9 including changes in the psychodynamics of the individual's personality and the impact of the doctor-patient relationship.9,10 Moreover, the level of blood pressure, per se, is often an inadequate guide to the severity and progression of the vascular complications.7-8 These considerations emphasize the difficulty in establishing the ultimate value of hypotensive agents. Because of their widespread use and potential dangers,11 a critical study of their effects was undertaken which incorporated certain principles minimizing the aforementioned difficulties.

METHODS AND MATERIALS

Three groups of patients were studied: (1) 10 outpatients with mild to moderately severe essential hypertension from the Hypertension Clinic of Parkland Hospital who were treated with hydralazine chloride (Apresoline); (2) 12 hospitalized patients with hypertensive disease of varying severity treated with hexamethonium bromide and/or hydralazine chloride; (3) 13 hospitalized hypertensive patients given intravenous injections of the drugs under study to evaluate their immediate effects. The clinical findings for the patients in each of the three groups are summarized in tables 1 through 3 respectively.

The 10 outpatients were seen by one investigator who determined all the blood pressures. Hydralazine and a placebo were alternated in such a manner as to be entirely unknown to either patient or investigator. The daily dose was divided into three or four portions per day and office visits, at one or two-week intervals, were scheduled two or three hours after the last dose. An average of five blood pressure determinations at one-minute intervals, with the patient reclining, and an average of two determinations, with the patient standing, were recorded at each visit. Because of the nature of the study, the patients received considerably more attention by the physician than they had in their previous routine clinic visits. One patient died during the study and one discontinued therapy; the remaining eight were on drug or placebo for a total of 13 to 32 weeks.

In the hospitalized patients, drug-placebo alternation was known to the investigator, but not to the trained ward personnel who determined the blood pressures. Moreover, in the early phase of the study, even the fact that such alternation was contemplated was unknown to these individuals. Hexamethonium bromide and hydralazine chloride in combination was given to eight patients, hydral-
lazine alone to three, and hexamethonium alone to one. Hydralazine* was administered orally at 6 a.m., 12:00 Noon, and 6:00 p.m.; hexamethonium* intramuscularly at 9:00 a.m. and 9:00 p.m., with a 3:00 p.m. dose added later in most patients. One patient received both medications simultaneously at four hour intervals from 6:00 a.m. to 10:00 p.m. Each medication was started separately and carried either to the point of maximum effect or to the development of side-effects before the other was added. Further increments to one or both were then given if apparent diminution of the hypotensive action of the drugs developed. Placebos were substituted in a random manner, before, during, or after specific therapy. The blood pressures were recorded at regular intervals, with the patient reclining, from three to eight times per day and a daily average then determined. It has been our experience that variations in the “resting blood pressure”11 from day to day are no less than those seen spontaneously during any given day; consequently, the daily average represents a reliable estimation of the day to day variation.

In the studies of acute effects, hydralazine chloride, hexamethonium bromide and/or tetraethylammonium chloride (TEAC) and in three patients Dibenzyline (SKF 688A), were administered on consecutive days, in the order indicated in table 3. Five readings at one-minute intervals were determined with the patient reclining. The drug was then administered intravenously by direct injection, except on two occasions when Dibenzyline was administered as a constant infusion. Measurements of blood pressure were continued at one-half to one-minute intervals until the peak action of the drug had passed and the blood pressure had stabilized. The percentage fall in diastolic pressure was calculated from the lowest point reached by the diastolic blood pressure and the average of the five initial determinations. Usually the systolic blood pressure was also at its lowest at this time.

The studies on experimental hypertension were carried out on rats and dogs rendered hypertensive by the application of a figure-of-eight ligature to one kidney with removal of the contralateral organ.12 The experimental procedures were identical to those used in previous studies in this laboratory.14, 15 The blood pressures were determined on trained unanesthetized animals by the method of Kersten and co-workers16 in the rats, and by puncture of the femoral artery and direct reading on a mercury manometer in the dogs.17 In the rats, the drugs were administered by intraperitoneal injection or orally by admixture with the animals’ food; in the dogs, the drugs were injected intravenously or intramuscularly or fed by enclosing the medication within a bolus of meat.

* Several patients had intravenous test doses of both agents prior to therapy, and one was treated with intravenous hydralazine for five days.

RESULTS

A. Clinical Observations on the Human

1. Outpatients Treated with Hydralazine Chloride. The results obtained in each patient are summarized in table 1; representative protocols are illustrated in figure 1. In none of the patients did the blood pressure decrease significantly during periods on the drug. The alternating periods of drug and placebo revealed that elevations and declines in blood pressure were essentially unrelated to which preparation was being administered. In only one patient (M. E., fig. 1) were the blood pressures consistently lower during drug therapy, but the difference, as indicated in table 1, when all placebo and drug periods are averaged, amounts to only 9/8 mm. Hg. Among the entire group, the largest systolic difference was 13 mm. Hg in patient E. L.; the largest diastolic difference was 8 mm. Hg in patient M. E.

Pulse rates were consistently higher during the periods on drug therapy, ranging from 1 to 19 per minute (average, 6.4). Significant postural hypotension was not noted.

The gradual fall of the blood pressure during the early weeks of the experiment and in several instances throughout the course of observation was quite striking (patients M. F. and D. H., fig. 1). Comparison of the blood pressures on first visits with those on the last week of therapy indicated that these overall declines were usually of greater magnitude than those attributable to the drug (table 1).

All patients improved symptomatically during the course of the study, irrespective of whether placebo or drug was being administered. They “felt better” and expressed a relief of headaches, weakness, and fatigue. Even patient R. S., who had a duodenal ulcer in addition to severe hypertension and who died with rapidly progressive renal failure following the development of pyloric stenosis, had reported improvement prior to this terminal event.

The drug produced side effects which limited further increase in dosage in 8 of the 10 patients. These consisted chiefly of throbbing, pounding headaches, during which the patients felt flushed, frequently nauseated, and occasionally vomited. The maximum tolerated dose varied
DRUG THERAPY IN HYPERTENSION

from 75 to 350 mg. per day. Development of side effects was independent of the effect on the blood pressure. In at least two instances (patient D. R., on April 18, and patient M. F., on June 5, fig. 1) such symptoms appeared during the administration of placebo.

2. Hospitalized Patients. The clinical findings on admission of these 12 patients are presented...
in table 2. Because of the variations in dosage and the different responses noted among patients in this group, the results are presented individually rather than in tabular form. Representative cases are illustrated in figures 2 through 5.

1. R. M. See figure 2.

2. P. D. entered the hospital in the terminal stage of malignant hypertension with progressive hyponatremia and hyperkalemia. Blood pressure declined from 232/135 to 222/100 mm. Hg coincident with five days of therapy with oral hydralazine in a dosage of 300 mg. per day. He did not improve and died during treatment.

3. W. A., with grade IV fundi and moderate renal impairment, had a blood pressure on admission of 248/150 mm. Hg; the diastolic pressure fell to levels as low as 113 mm. Hg prior to treatment. With maximum doses of hydralazine (300 mg. per day) continued for six weeks, and a low sodium diet, the diastolic pressure declined to as low as 103 mm. Hg but did not return to previous levels when placebo was substituted for the drug. Renal function and papilledema remained unchanged during therapy, although the patient improved symptomatically. Doses in excess of 300 mg. per day repeatedly induced nausea and vomiting.

4. M. M., with grade IV fundi and severely impaired renal function, was admitted in a comatose state following a convulsion. She regained consciousness following the intravenous injection of hydralazine with a decline in diastolic blood pressure from 170 to 140 mm. Hg. The drug was then given orally in doses up to 800 mg. per day, at which point headaches were induced. Diastolic blood pressure, however, remained at 140 to 150 mm. Hg, was uninfluenced by addition of a low sodium diet, and continued at the same level when placebo was substituted after three weeks of therapy. It did rise to 160 to 170 mm. Hg later in her course when she was transferred to the Metabolic Ward. This was a rather infantile woman, insecure and dependent in her relationships with her physicians and in this new setting, where new and strange demands were made of her, increasing agitation became apparent. This subsided and the blood pressure declined again when the status quo was restored. Retinopathy gradually diminished during her hospitalization, despite only a slight decline in blood pressure.

5. E. F. See figure 3.

6. E. S. See figure 4.

7. E. C., with grade IV fundi but only moderate renal impairment, had a blood pressure of 225/150 mm. Hg on admission; within five days, the diastolic had fallen to a level of 98 mm. Hg while on a low sodium diet. The blood pressure then increased, despite continuation of the diet, to a diastolic level of 130 mm. Hg. With the administration of hexamethonium, the diastolic level ranged from 100 to 120 mm. Hg but this was not decreased further by the addition of hydralazine, nor was it affected by a return to a regular diet. When the drugs were replaced by placebos after five weeks of combined therapy, the blood pressure rose slightly but remained below its initial levels and at the time of discharge had stabilized at 120 to 140 mm. Hg. Hexamethonium produced incapacitating postural hypotension in this patient, while headaches, which were present throughout his hospital stay, were aggravated by hydralazine. The maximum tolerated doses of the drugs were 50 mg. and 450 mg. per day, respectively. Papilledema and retinal hemorrhages gradually subsided during his three month stay in the hospital.

8. D. T. manifested grade IV fundi but good renal function with blood pressure on admission of 220/170 mm. Hg. Diastolic level declined to 120 to 140 mm. Hg during two months of hospitalization during which he received five weeks of combined therapy with hexamethonium and hydralazine in maximum doses of 100 mg. and 250 mg. per day, respectively. Urinary retention and headache prevented further dose increase. However, the diastolic had declined to 140 mm. Hg prior to onset of therapy and persisted at 120 to 140 mm. Hg when placebos were substituted. A low sodium diet while receiving both agents produced no further decrement. Retinal hemorrhages disappeared and papilledema partially

Fig. 2. R. M., with markedly elevated blood pressure on admission, but no evidence of renal or cardiac damage, was treated with hexamethonium bromide (CB) following an 11 day control period. Blood pressure declined markedly, but the drug was discontinued when he coincidentally developed bacillary dysentery (Salmonella pullorum). This responded promptly to antibiotics. No further specific therapy was given; nevertheless, blood pressure continued to decline, reaching normotensive levels.
DRUG THERAPY IN HYPERTENSION

subsided during his hospital stay. Following discharge the blood pressure returned to preadmission levels, despite reinstitution of the combined drug therapy.

9. C. M. See figure 5.

10. G. W., with grade III fundi and minimal renal impairment had a blood pressure on admission of

When hexamethonium was replaced by placebos after four weeks of combined treatment the diastolic pressure remained at 133 to 159 mm. Hg; when all therapy was discontinued, and the patient continued on placebos, it varied from 142 to 162 mm. These manipulations accordingly produced insignificant changes in blood pressure; the lower levels, which

Fig. 3. E. F. entered the hospital with grade IV fundi accompanied by marked renal impairment. Initially, intravenous test doses of hydralazine (C-9668) produced a marked although transient fall in blood pressure with relief of severe headache. When continued, intravenous hydralazine induced severe headaches and had to be discontinued; nevertheless, blood pressure did not return to the high levels recorded on admission. When hexamethonium (C-6) and hydralazine in combination were administered, the blood pressure declined temporarily, but severe headaches necessitated discontinuance of drug therapy, after which the blood pressure continued to rise. When the drugs were re instituted, the blood pressure again declined; however, renal function deteriorated further as reflected in the rising blood urea nitrogen. After several days of absence from the hospital without therapy, during which time the blood urea nitrogen fell, therapy was reinstituted; the blood pressure declined, but renal failure progressed and the patient expired.

244/162 mm. Hg. Hexamethonium and hydralazine were administered up to a dosage of 100 mg. and 450 mg. per day, respectively, with further increase precluded by the development of postural hypotension. Diastolic blood pressure declined to 136 mm. Hg but then gradually rose to 143 to 154 mm. despite continuation of the maximum tolerated dose.

were achieved early in the course, could not be maintained. A low sodium diet, instituted during several phases of his treatment, had no significant effect. Despite reinstitution of both drugs following discharge from the hospital, the blood pressure returned to its preadmission levels and progressive vascular damage developed.
11. J. B., with severe impairment of renal function and grade II fundi, had a blood pressure on admission of 205/150 mm. Hg. This declined gradually with no specific therapy, reaching 190/118 mm. Hg three weeks after admission. The administration of hexamethonium and hydralazine in doses up to 75 mg. and 450 mg. per day, respectively, induced no further decline in the blood pressure. Coincident with increasing anxiety about problems at home, the blood pressure rose to levels as high as those on admission despite continuation of therapy, and he left the hospital.

For hydralazine there was a slight rise, but neither at this time nor following the discontinuance of placebos did it return to its initial levels.

3. Comparisons of Intravenously Administered Drugs. The pertinent data obtained with intravenous testing are given in table 3. There was no consistent increase in hypotensive effect with increasing doses of hydralazine. In two patients (W. S. and F. M.), who received increasing doses of hexamethonium bromide, one showed a further fall and one showed a slight decrease in effect. Patients tested with tetraethylammonium chloride were given only one injection of either 200 mg. or 400 mg. One patient (W. S.) received graduated doses of Dibenzyline with only a slight hypotensive effect which was not affected by the increase in dose, while two received single doses by infusion, again with only slight effects. The time of maximum fall varied with the

Fig. 4. E. S. with grade IV fundi and severe renal impairment was in congestive heart failure on admission. The latter was controlled with digitoxin and mercurials with a decrease in blood pressure. With hexamethonium and hydralazine therapy, only a transient further decline occurred even when the dose was increased to 250 mg. and 1.0 Gm. per day, respectively, with both agents given simultaneously. Severe constipation was present at this dose level. Papilledema subsided and many of the retinal hemorrhages resolved during his hospital stay, despite the lack of appreciable decline of blood pressure. The effects could not be finally evaluated for he became increasingly resentful of the treatment and left the hospital.

12. D. P. had a fluctuant blood pressure, with diastolic levels ranging from 100 to 130 mm. Hg during the control period, no measurable renal impairment, and grade I fundi. On a combination of hexamethonium and hydralazine in doses of 100 mg. and 150 mg. per day, respectively, the blood pressure declined to normotensive levels although wide daily fluctuations continued and postural hypotension was marked. When hexamethonium was discontinued and placebos substituted after ten days of combined therapy the blood pressure remained unaltered; when placebos were substituted showed a further fall and one showed a slight decrease in effect. Patients tested with tetraethylammonium chloride were given only one injection of either 200 mg. or 400 mg. One patient (W. S.) received graduated doses of Dibenzyline with only a slight hypotensive effect which was not affected by the increase in dose, while two received single doses by infusion, again with only slight effects. The time of maximum fall varied with the
drug administered. With hydralazine, it averaged 19.6 minutes; with hexamethonium, 6.3 minutes; and with tetraethylammonium, 3.5 minutes.

Severity of the disease did not furnish any criteria by which the action of an individual drug or of a given dose could be predicted, nor did a consistent pattern of response emerge which might be related to the type of hypertensive mechanism. For example, in patients M. M. and D. H. a marked response to 20 mg. of hydralazine occurred (60 per cent and 38

---

**Table 2.**—Clinical Status on Admission of Twelve Hospitalized Patients Treated with Hydralazine and Hexamethonium

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Race/Sex</th>
<th>Admission Blood Pressure (mm. Hg)</th>
<th>Fundi (Keith-Wagener)</th>
<th>Albuminuria</th>
<th>Blood Urea Nitrogen (mg.%)</th>
<th>Urine Concentration Test</th>
<th>Total PSP Excretion in 1 hour (per cent)</th>
<th>ECG*</th>
<th>Cardiac Silhouette (+ indicates enlargement)</th>
<th>Congestive Failure (0 to 3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. M.</td>
<td>43</td>
<td>W M</td>
<td>215/155</td>
<td>II</td>
<td>0</td>
<td>15</td>
<td>1.022</td>
<td>60</td>
<td>N</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P. D.</td>
<td>49</td>
<td>N M</td>
<td>232/130</td>
<td>IV</td>
<td>3+</td>
<td>184</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>LVP</td>
<td>3+</td>
</tr>
<tr>
<td>W. A.</td>
<td>56</td>
<td>W M</td>
<td>248/130</td>
<td>IV</td>
<td>trace</td>
<td>20</td>
<td>1.014</td>
<td>39</td>
<td>LVP</td>
<td>+</td>
<td>1+</td>
</tr>
<tr>
<td>M. M.</td>
<td>46</td>
<td>N F</td>
<td>260/170</td>
<td>IV</td>
<td>3+</td>
<td>28</td>
<td>1.015</td>
<td>30</td>
<td>LVP</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>E. F.</td>
<td>34</td>
<td>N M</td>
<td>280/180</td>
<td>IV</td>
<td>4+</td>
<td>34</td>
<td>—</td>
<td>5</td>
<td>LVP</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>E. S.</td>
<td>36</td>
<td>N M</td>
<td>245/155</td>
<td>IV</td>
<td>4+</td>
<td>24</td>
<td>1.010</td>
<td>20</td>
<td>LVP</td>
<td>+</td>
<td>3+</td>
</tr>
<tr>
<td>E. C.</td>
<td>58</td>
<td>W M</td>
<td>228/150</td>
<td>IV</td>
<td>1+</td>
<td>11</td>
<td>1.014</td>
<td>58</td>
<td>LVP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D. T.</td>
<td>34</td>
<td>W M</td>
<td>212/170</td>
<td>IV</td>
<td>trace</td>
<td>13</td>
<td>1.026</td>
<td>70</td>
<td>N</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. M.</td>
<td>52</td>
<td>N F</td>
<td>240/140</td>
<td>II</td>
<td>0</td>
<td>14</td>
<td>1.018</td>
<td>25</td>
<td>LVP</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>G. W.</td>
<td>39</td>
<td>N M</td>
<td>243/162</td>
<td>III</td>
<td>1+</td>
<td>13</td>
<td>1.020</td>
<td>58</td>
<td>LVP</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J. B.</td>
<td>43</td>
<td>N M</td>
<td>205/130</td>
<td>II</td>
<td>trace</td>
<td>20</td>
<td>1.010</td>
<td>25</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D. P.</td>
<td>33</td>
<td>W M</td>
<td>210/130</td>
<td>I</td>
<td>0</td>
<td>11</td>
<td>1.026</td>
<td>76</td>
<td>N</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* N = Normal; LVP = Left Ventricular Preponderance.
per cent fall in diastolic pressure, respectively); yet quite different responses to 10 mg. of hexamethonium (0 per cent and 47 per cent, respectively) were elicited.

Table 3.—The Effect of Intravenous Hydrallazine, Hexamethonium, and Tetraethylammonium Salts and Dibenzyline Chloride on the Blood Pressure of Hypertensive Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Diagnosis*</th>
<th>Blood Pressure on Admission mm. Hg</th>
<th>Percentage Fall in Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hydrallazine Chloride (mg.)</td>
<td>Hexamethonium Bromide (mg.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 15 20 25 30 5 10 15 20 200 400 5 10 15</td>
<td></td>
</tr>
<tr>
<td>E. F.</td>
<td>M. H.</td>
<td>280/180</td>
<td>11.2 25.2 29.4 17.0 37.0</td>
</tr>
<tr>
<td>M. M.</td>
<td>M. H.</td>
<td>260/170</td>
<td>18.5 18.0 60.0f 0.0 5.0</td>
</tr>
<tr>
<td>W. S.</td>
<td>M. H.</td>
<td>220/156</td>
<td>10.3 30.1 6.5 10.4 8.1 5.7 6.6</td>
</tr>
<tr>
<td>O. H.</td>
<td>B. E. H.</td>
<td>184/114</td>
<td>38.1 47.4 15.3</td>
</tr>
<tr>
<td>P. D.</td>
<td>M. H.</td>
<td>232/130</td>
<td>12.0 18.0 4.3</td>
</tr>
<tr>
<td>E. B.</td>
<td>B. E. H.</td>
<td>230/134</td>
<td>25.4 44.4 13.5</td>
</tr>
<tr>
<td>J. B.</td>
<td>B. E. H.</td>
<td>205/150</td>
<td>7.2 13.4 16.2 3.2 4.0</td>
</tr>
<tr>
<td>F. M.</td>
<td>M. H.</td>
<td>222/156</td>
<td>17.9 16.3 20.2</td>
</tr>
<tr>
<td>A. M.</td>
<td>B. E. H.</td>
<td>160/120</td>
<td>8.3 17.4</td>
</tr>
<tr>
<td>T. T.</td>
<td>B. E. H.</td>
<td>202/120</td>
<td>8.3 15.8 24.8 14.5 30.7</td>
</tr>
<tr>
<td>E. S.</td>
<td>M. H.</td>
<td>220/150</td>
<td>17.3 19.2 20.0</td>
</tr>
<tr>
<td>G. W.</td>
<td>M. H.</td>
<td>238/135</td>
<td>2.9</td>
</tr>
<tr>
<td>M. S.</td>
<td>M. H.</td>
<td>242/142</td>
<td>14.9 11.7 25.0</td>
</tr>
</tbody>
</table>

* B. E. H.: Benign Essential Hypertension; M. H.: Malignant Hypertension
† First dose administered in this patient
‡ E. F. received 25 mg. and M. M. 35 mg. by I. V. infusion in 5% D/W over a 2½ hour period.

Fig. 6. The effect of the oral administration of hexamethonium chloride (O—O), hexamethonium bromide (■■), and hydralazine chloride (□—□) in doses of 100 mg. per kilogram of body weight and of Dibenzyline (●●●) in doses of 50 mg. per kilogram of body weight, on the average blood pressure of groups of six rats. The drugs were administered with the animals’ food for four successive days (0 to 3 inclusive as indicated). More prolonged periods of medication resulted in death of the animals.

B. The Effects on the Blood Pressure in Experimental Hypertension

1. The Rat. Preliminary observations using doses (based on relative surface area) comparable to those used in the human indicated that none of the drugs under study exerted any detectable lowering of the blood pressure when administered either parenterally or orally. Only in excessive doses, beyond that toleratted by the human, were declines in blood pressure noted, and under these conditions some of the animals died.

The results with oral administration are summarized in figure 6. It will be noted that on continued administration of these large doses the decline in blood pressure was only moderate and was not sustained.

2. The Dog. Results comparable to those obtained in the rat were also noted when the drugs were injected or administered orally to the hypertensive dog. In general, however, the dog was more reactive and more pronounced decrements in blood pressure were obtained with comparable doses based on the relative surface areas of the two species. Nausea and vomiting, however, were common concomitants of therapy and were observed when the blood pressure declined 30 mm. Hg or more.

The intramuscular injection of tetraethylammonium chloride in doses of 20 mg. per kilogram of body weight resulted in a maximum decline in the mean blood pressure varying from 0 to 30 mm. Hg in different animals with
a return to the pretreatment level within four hours. Administration of Dibenzyline in doses of 20 mg. per kilogram produced essentially the same results. Hydralazine or hexamethonium chlorides injected intramuscularly or intravenously in doses of 2 mg. per kilogram resulted in a decline in mean blood pressure of 10 to 20 mm. Hg. When this dose was increased the decline in pressure was proportionately greater. The effect of giving the two drugs simultaneously resulted in an additive effect but no apparent synergism.

DISCUSSION

The results which have been presented do not indicate any impressive hypotensive effects of hydralazine or hexamethonium, alone or in combination, when administered in a carefully controlled manner. In hospitalized patients, significant declines in blood pressure which did occur during specific therapy persisted when placebos were substituted. Nor did clinical improvement necessarily coincide with the decline in blood pressure. In outpatients, treated with hydralazine alone, the blood pressure often fell significantly during the course of several months of treatment, but alternation of drug with placebo revealed that the drug, per se, had minimal effects.

That these agents have immediate hypotensive effects, especially when given parenterally, is undisputed. On the other hand, the maintenance of hypotensive effects, which others have reported4 and which were often noted in our patients, are not necessarily attributable to the action of drugs. Evaluation of long term administration must take into consideration other factors which will impinge upon the patient and influence the blood pressure.9 Hospitalized hypertensive patients undergoing no specific treatment, for instance, regularly reveal a fall in blood pressure, even when malignant acceleration is present; precisely when such a decline will occur in relationship to the duration of hospitalization cannot be predicted.19 20 These effects of hospitalization are not simply a result of bed rest or relief from physical exertion; as a matter of fact, these patients whenever possible were encouraged to be ambulatory. Entrance into the hospital may constitute an escape from an emotionally stressful situation. A doctor-patient relationship which is reassuring and supportive may be developed; this is particularly true in an experimental study where special attention is given to the patient. These considerations apply equally to individuals treated on an outpatient status, especially when the administration of a new agent is associated with new enthusiasms and positive and supportive attitudes on the part of the physician.9 22

Conversely, stress, including that produced by disturbances in the doctor-patient relationship, may counteract the hypotensive effects of any therapeutic regimen.21 22 Such was apparent in patient J. B. whose family situation required his return to work, making hospitalization intolerable, and in patient M. M. from whom metabolic studies demanded cooperation which taxed her capacity so that hospitalization became threatening. Objections to the rigid regimen of treatment similarly affected the course in other patients both in the outpatient and hospitalized groups.

Side effects occurred frequently and constituted serious deterrents to continued therapy. These included postural hypotension, blurring of vision, urinary retention, and constipation with hexamethonium and headache, nausea, and vomiting with hydralazine. The significance of side effects, however, must also be cautiously evaluated, as evidenced by the appearance of typical “hydralazine headaches” in several instances during administration of placebos. Similarly, relief of symptoms which did not coincide with physical improvement was frequently noted.

Certain of the difficulties in evaluation imposed by the factors just discussed can be minimized by adequate control measures. The use of placebos, however, is of itself insufficient. As others have pointed out and as this study again emphasizes, their substitution should be unknown both to investigator as well as to subject.25 26 Moreover, parallel observations of the changing life situations and stresses acting on the patient are necessary, as are observations of the doctor-patient, or investigator-subject, relationship, since this represents an
important factor in the patient’s current life situation while under treatment.\(^9\)

The results on experimentally induced hypertension in rats and dogs, in whom a more objective evaluation of the direct effect of drugs on the blood pressure can be obtained, are in accord with our results in patients. Significant declines resulted only with doses much larger than tolerated by man. Such declines were not sustained with continued administration while about a third of the animals died when the treatment was extended beyond three or four consecutive days.

Our results thus indicate that the ultimate hypotensive effects of these agents are only slight or transient, when they are given in doses which can be tolerated. Sustained depressor effects which did occur were usually not attributable to pharmacologic activity, while clinical improvement did not necessarily co-occur with decline in blood pressure. These considerations assume added significance in view of the dangers, particularly of deterioration of renal function, which exist with the indiscriminate use of hypotensive agents.

**Summary**

1. A critical study of the effects of hydralazine and hexamethonium salts was carried out in three groups of hypertensive patients and on rats and dogs with experimental hypertension.

2. Ambulatory patients showed no appreciable change in blood pressure directly attributable to hydralazine. More seriously ill patients treated in the hospital with hydralazine alone or in combination with hexamethonium revealed only infrequent and transient declines in blood pressure directly induced by the drugs in doses which could be tolerated. Such clinical improvement as was elicited did not always correlate with observed depression of the blood pressure.

3. Comparison of the immediate effects of the intravenous administration of these drugs, as well as of Dibenzyline chloride and tetraethylammonium chloride, revealed no consistent or predictable patterns of response.

4. In evaluating the clinical effects of hypotensive agents, the need was emphasized for assessing other factors which are known to influence blood pressure and which cannot be completely eliminated from any study. This pertained particularly to the effects of hospitalization and the doctor–patient relationship.

5. A more objective evaluation of hydralazine, hexamethonium, tetraethylammonium chloride, and Dibenzyline chloride was possible in the rat and dog with experimental hypertension. Here the results in the unanesthetized animal indicated appreciable depressor effects only when used acutely and in dosages several times as great as are tolerated by the human.

**Acknowledgments**

Several of the hospitalized patients were studied at the Veterans Administration Hospital, Dallas, Texas. We wish to express our appreciation to Drs. Seymour Eisenberg and Julian Acker of this institution for their invaluable aid in following these patients. The assistance of Dr. John Archer and Mrs. Marian Metropoulos in the studies at Parkland Hospital is likewise gratefully acknowledged. Generous supplies of hydralazine and placebos were supplied by Dr. F. L. Mohr and Ciba Pharmaceutical Products Inc.; hexamethonium salts were supplied through the courtesy of Dr. D. S. Searle and Broughs, Wellcome & Co.; Dibenzyline was furnished by Dr. R. N. Buckley of Smith, Kline & French Laboratories.

**Sumario Español**

Los efectos de las sales de hydralazine y hexamethonium en la presión arterial y funciones relacionadas han sido estudiados en una serie de pacientes hipertensos ambulatorios y aislados así como también en hipertensión inducida experimentalmente (perros y gatos). Observaciones comparativas también se han hecho sobre los efectos del cloruro de tetraetilamonio y el Dibensyline, congéneres del dibencilocloroetilamina (Dibenamine). Evaluación crítica de los datos indica que la efectividad de las sales de hydralazine y hexamethonium, cuando son usadas aisladamente o en combinación, no es significativamente mayor en el tratamiento por largo tiempo que el de los regímenes previamente existentes en el tratamiento de la enfermedad hipertenso vascular.
REFERENCES


A Critical Evaluation of the Hypotensive Action of Hydralazine, Hexamethonium, Tetraethylammonium and Dibenzyline Salts in Human and Experimental Hypertension

ALVIN P. SHAPIRO and ARTHUR GROLLMAN

Circulation. 1953;8:188-198
doi: 10.1161/01.CIR.8.2.188

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1953 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/8/2/188