Newer Drugs in the Treatment of Hypertension

II. Use of Hexamethonium in Combination with Hydralazine

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Sixty-one patients exhibiting severe hypertensive vascular disease were treated with hexamethonium in combination with hydralazine for periods up to 22 months. Results, in terms of blood pressure control, were considerably better with combined therapy than with hexamethonium alone regardless of whether hydralazine was added to hexamethonium initially or later. Improvement in retinopathy and in the electrocardiogram was noted. The malignant phase of hypertensive disease was reversed in eight of nine instances. Late systemic reactions to hydralazine occurred in seven patients. One death, attributed to possible hexamethonium poisoning, was observed. Hexamethonium-hydralazine therapy represents a potent combination of drugs for the treatment of severe hypertensive vascular disease.

In a previous study it was demonstrated that hexamethonium, although a potent anticholinergic compound capable of lowering blood pressure for short periods, is not satisfactory as a single drug for the long-term treatment of severe hypertension. While this study was in progress, preliminary clinical investigation of hydralazine (Apresoline) demonstrated this compound to be partially effective in the treatment of hypertension. Hydralazine possesses complex actions which include the neutralization of pressor substances, central vasodepression, weak adrenergic blocking effect, and direct peripheral vasodilatation. The discoveries that it increases renal blood flow and decreases cerebral vascular resistance concomitantly with fall in systemic blood pressure lent considerable interest to this agent. The rise in renal blood flow is associated with increased cardiac output and tachycardia; the latter effects can be prevented by prior administration of hexamethonium. Subsequent clinical investigations have shown, with few exceptions, that hydralazine employed concurrently with hexamethonium is more effective in the treatment of hypertension than either agent used alone.

The present investigation was begun in an effort to study the effects of combined hexamethonium-hydralazine therapy in the long-term treatment of severe hypertension. Its purpose was two-fold: (1) to determine whether the combination of hexamethonium and hydralazine would be more effective than hexamethonium alone in controlling hypertensive disease when hydralazine was added after months of hexamethonium administration, or (b) when administration of the two agents was begun concomitantly; and (2) to evaluate critically the usefulness of combined hexa-
methonium-hydralazine therapy in the long-term management of the
patient exhibiting severe hypertension.

**Material and Methods**

Sixty-one patients with severe, stable or progressive hypertensive vascular disease with an average systolic and diastolic blood pressure of 212/130 were selected for study. Thirty-one of these patients, comprising series I, were individuals already under treatment with hexamethonium alone, and had been treated for periods of 3 to 27 months (average 10 months) before hydralazine was added. Hydralazine was added to hexamethonium in these 31 patients for one of the following reasons: (1) unsatisfactory response to hexamethonium alone in spite of adequate trial; (2) failure to maintain initial good response with continued administration of the drug. Series II consisted of 30 patients who were treated concurrently with hexamethonium and hydralazine from the outset.

In series I, the ages of the 31 patients ranged between 31 and 65 years with an average age of 50 years. There were 24 males and 7 females. According to Palmer's classification of hypertension they may be grouped before treatment was instituted as follows: grade II, 15 patients; grade III, 15 patients; grade IV, 1 patient. One or more serious complications of hypertension had occurred in 13 patients prior to treatment: cerebrovascular accidents in 6; myocardial infarction in 4, angina pectoris in 2; and paroxysmal nocturnal dyspnea in 2. In series II, the ages of the 30 patients ranged between 15 and 57 years with an average of 44 years. There were 16 males and 14 females. According to Palmer's classification the group may be divided as follows: grade II, 11 patients; grade III, 11 patients; grade IV, 8 patients. One or more serious complication of hypertension had occurred in 15 patients: cerebrovascular accidents in 5; encephalopathy in four; angina pectoris in one; and previous congestive heart failure in five. Two patients, one in each series, had undergone lumbar sympathectomy (Smithwick) with subsequent return of hypertension.

Fifty-one of the 61 patients, 25 in series I and 26 in series II, were hospitalized for periods ranging from one to six weeks for institution of therapy. Six patients in series I and 4 in series II were treated entirely on an out-patient basis. Prior to treatment each patient was thoroughly studied by conventional methods previously described.1 In all patients in both series hexamethonium therapy was instituted before hydralazine was added. Hexamethonium was administered in accordance with the principles and precautions outlined elsewhere.1 Fifty-five of the patients were given hexamethonium in oral form; parenteral therapy was reserved principally for patients demonstrating malignant hypertension, significant evidence of arterial disease, or impairment of renal function. Six patients were begun on parenteral hexamethonium chloride while in the hospital, and five were transferred to the oral form before discharge. All 31 patients in series I were receiving maximum tolerated doses of hexamethonium when hydralazine was instituted. Seven patients were rehospitalized for the addition of hydralazine; in 24 patients hydralazine was added cautiously on an out-patient basis. For the 30 patients in series II, hydralazine was added to hexamethonium when significant postural fall in the blood pressure was observed. This was usually accomplished within a week after institution of hexamethonium therapy in the hospital and within several weeks in the out-patient clinic.

The initial dose of hydralazine was 10 mg. to 25 mg. four times a day, administered with the hexamethonium on an empty stomach. Increments of 10 mg. to 25 mg. per dose were made as rapidly as tolerance permitted until the blood pressure had stabilized at a satisfactory level. During combined therapy dosage of hexamethonium ranged from 0.75 Gm. to 4.75 Gm. per day with an average dosage of 1.8 Gm. per day. Dosage of hydralazine ranged from 75 mg. to 1100 mg. per day with an average dosage of 418 mg. per day. All patients with malignant hypertension were treated initially with the rice diet in addition to drugs. As improvement occurred, gradual dietary modification was made to standard low sodium diets. Low sodium diets generally were instituted initially for most patients; liberalization of diet was allowed after control of blood pressure was achieved.

During hospitalization recumbent and standing blood pressures were recorded four times daily, and, following discharge, at approximately weekly intervals. Every six months cardiac and renal status were re-evaluated by means of urinalysis, blood nonprotein nitrogen, phenolsulphophthalein excretion test, electrocardiogram and telerontgenogram. The blood pressure response for each patient was averaged monthly and subdivided into three treatment periods (hospitalization, first four months of out-patient care, and five months plus of out-patient follow-up) in order to detect any tendency for blood pressure control to be lost or to escape during continued therapy. Although both standing and recumbent pressures were recorded and subjected to analysis, only recumbent blood pressure was used for interpretation of results.

In assessing the efficacy of therapy in controlling blood pressure, two methods of approach were used. First, for each treatment period the patients were separated into three arbitrary, previously defined groups,1 group A, “good,” group B, “fair,” group C, “poor,” according to recumbent blood pressure.
response.* Second, fall in mean recumbent blood pressure during each period was determined. Mean pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. A fall of 20 mm. Hg or greater was considered a definite response.

Retinopathy was graded according to the Keith-Wagener classification. Heart size was determined for each patient from serial teleoroentgenograms; percentage deviation from average normal heart size was calculated from the Ungerleider table.32 Patients exhibiting a deviation from normal of more than plus 10 per cent were regarded as having cardiac enlargement. During therapy an increase or decrease in percentage deviation of more than 10 per cent was considered a significant change. Renal function was evaluated by conventional excretory and concentration tests.

**Results**

All 61 patients experienced symptoms from hexamethonium which tended to diminish but did not disappear entirely during treatment. The most common of these recurrent troublesome reactions were dryness of the mouth, episodes of faintness, constipation, blurred vision, feelings of weakness and fatigue, and impotence. At the time when hydralazine was added to hexamethonium, approximately one-fourth of all the patients experienced a transient increase in the number of episodes of weakness and faintness. Later there was amelioration of the postural symptoms from hexamethonium in some patients in series I, due to decrease in dosage of hexamethonium (from an average dose of 2.4 mg. per day before hydralazine to 1.8 mg. per day after hydralazine).

Forty-five of the 61 patients, 22 in series I and 23 in series II, initially experienced one or more hydralazine effects. The most frequently encountered reactions were headache, palpitation, nausea, nasal congestion, and mild edema. These symptoms generally were much less severe and troublesome than those resulting from hexamethonium and, with few exceptions, tended to disappear or diminish greatly during continued administration of the drug. Gradual titration of hydralazine dosage unquestionably decreased unpleasant side reactions to the drug. Four of the 61 patients, one in series I and three in series II, discontinued both drugs after less than five months, primarily because of distressing symptoms from hexamethonium. One patient discontinued hydralazine upon the advice of his personal physician. Three additional patients in series I took both drugs irregularly, and in them follow-up was inadequate.

**Complications**

Table 1 presents the complications encountered during therapy.

Seven deaths occurred among the 61 patients, four in series I after the addition of hydralazine and three in series II. These include fatalities

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**Table 1.—Complications Observed During Therapy**

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<tr>
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<tbody>
<tr>
<td>Deaths</td>
<td>4*</td>
<td>3</td>
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<tr>
<td>Combined cardiac and renal failure</td>
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<td>Cerebral vascular accident and uremia</td>
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<td>Congestive heart failure</td>
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<td>Probable myocardial infarction</td>
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<td>Subarachnoid hemorrhage</td>
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<td>Cerebral hemorrhage</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Uremia and hexamethonium poisoning</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Nonfatal complications</td>
<td>4</td>
<td>4</td>
<td></td>
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<tr>
<td>Coronary insufficiency</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Congestive heart failure</td>
<td>1</td>
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<tr>
<td>Cerebral thrombosis</td>
<td>1</td>
<td>1</td>
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<td>Late systemic reactions to hydralazine</td>
<td>1</td>
<td>6</td>
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</table>

* Numerals refer to number of patients.

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* Group A includes those patients whose average blood pressure fell to 160/110 or less; group B comprises those patients whose average blood pressure fell to 180/115 or less; and group C contains those patients whose average blood pressure response failed to reach the latter level.
from cardiac causes, cerebral vascular accidents, and renal insufficiency. In one patient exhibiting malignant hypertension and death in uremia, acute hexamethonium poisoning was suspected. Four nonfatal complications had occurred among the 31 patients in series I before hydralazine was added. Among all 61 patients in both series, six nonfatal complications occurred during combined hexamethonium-hydralazine therapy, four in series I and two in series II. Initial episodes of coronary insufficiency in two patients were attributed to hydralazine; the other complications were ascribed to the severity of the hypertensive disease itself.

Seven of the 61 patients, one in series I and six in series II, developed late systemic reactions to hydralazine which necessitated discontinuance of the drug in each instance. Six of these reactions were characterized by symptoms and signs suggestive of rheumatoid arthritis; and one patient exhibited, in addition, pleuritis with effusion, pericarditis with effusion, fever, and “L.E.” cells in the peripheral blood. The features of these reactions are presented in detail elsewhere.33

**Effect Upon Blood Pressure**

Table 2 presents the blood pressure responses of all 61 patients treated with hexamethonium and hydralazine in combination, according to the arbitrarily defined groups A, B, C. Fifty of the 61 patients continued combined therapy for five months or longer and were satisfactorily followed. Thirty of the 31 patients in series I had been treated with hexamethonium alone for five months or longer before hydralazine was added. The failure of hexamethonium alone to maintain good control of blood pressure, except for one of 30 patients, throughout prolonged therapy is apparent in table 2. This loss of blood pressure control occurred despite increases in dosage of hexamethonium to maximum tolerated levels in each patient. The addition of hydralazine to these same patients in series I, however, resulted in far better control of blood pressure during prolonged observation. Ten of 26 patients were well controlled. In series II, an approximately equal proportion of patients demonstrated “good” control of blood pressure during each treatment period. There was no tendency for control of pressure to be lost during prolonged therapy. Ten of 24 patients remained well controlled. The better results in series II during initial periods of treatment are attributed to earlier titration of more effective combined drug dosage. After five months of combined therapy no significant differences are noted between results in series I and series II.

Table 3 presents an analysis of the fall in the mean recumbent blood pressure during
each treatment period as compared with pre-treatment averages. In series I the tendency for the blood pressure to rise during prolonged therapy with hexamethonium alone is again evident so that in the late follow-up period only 10 of 30 (33 per cent) patients demonstrated a fall in mean pressure of 20 mm. Hg or greater. After the addition of hydralazine to these same patients, however, a fall in mean pressure of this magnitude was observed in 17 of 26 during the first four months of outpatient care and in 20 of 26 (77 per cent) patients during the late follow-up period. In series II approximately three-fourths of the patients exhibited a fall in mean pressure of 20 mm. Hg or greater throughout each treatment period.

The majority of patients in both series I and series II who had a “good” (group A) or “fair” (group B) blood pressure response to combined therapy in the late treatment period exhibited a fall in mean recumbent blood pressure of 20 mm. Hg or greater. Nine of 14 group C patients in both series exhibited a fall in mean recumbent pressure of this magnitude, yet demonstrated relatively “poor” blood pressure control.

Effect Upon Retinopathy

In series I during treatment with hexamethonium alone no progression of retinopathy was observed and the fundi of six patients improved as follows: five from grade III to grade II and one from grade IV to grade III. After the addition of hydralazine to these patients, two patients with grade III fundi improved to grade II, and the retinopathy of two patients, with “poorly” controlled blood pressure, worsened from grade II to grade III. In series II retinopathy did not progress in any patient during combined therapy, and the fundi of 11 patients improved as follows: three from grade IV to grade II, five from grade IV to grade III, and three from grade III to grade II.

Effect Upon Heart Size

Prior to therapy 23 patients (8 in series I and 15 in series II) had enlarged hearts; the remaining 38 patients had normal-sized hearts.

In series I during treatment with hexamethonium alone one patient with “good” control of blood pressure demonstrated a significant decrease in heart size, and two patients with “poorly” controlled blood pressure exhibited a definite increase in heart size. In series I after the addition of hydralazine and during combined therapy no patient demonstrated a significant increase or decrease in heart size. In series II during combined hexamethonium-hydralazine therapy two patients, both of whom initially were in congestive heart failure and subsequently had “poor” control of blood pressure, showed a significant decrease in heart size, while one patient with “poor” blood pressure control exhibited a significant increase in heart size.

Effect Upon Electrocardiogram

Thirty-six patients, 18 in each series, demonstrated ST-T changes of “left ventricular strain pattern” prior to therapy. In series I during treatment with hexamethonium alone, four patients showed improvement in the “strain pattern”, and in three of these the ST-T changes reverted entirely to normal. After addition of hydralazine to this group and during combined therapy, four patients demonstrated improvement in the ST-T pattern, with reversion to normal in two instances, while one patient demonstrated an increase in the “strain pattern”. In series II during combined therapy 8 of 18 abnormal electrocardiograms improved, and in six of these there was a complete reversal of the ST-T “strain pattern” to normal.

<table>
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<tr>
<th>Table 4.—Effect of Hexamethonium alone and in Combination with Hydralazine upon Fundi, Heart Size, Electrocardiogram and Renal Function</th>
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<tbody>
<tr>
<td>Series</td>
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<td>Fundi</td>
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<td>Heart size</td>
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<td>ECG</td>
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<tr>
<td>Renal func.</td>
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</table>

* Numerals refer to number of patients.
Effect Upon Renal Function

Before treatment 36 patients (15 in series I and 21 in series II) showed proteinuria, and eight patients (three in series I and five in series II) exhibited impaired renal function as measured by the standard laboratory tests. In series I, during therapy with hexamethonium alone, one patient developed impairment of renal function which subsequently progressed and two patients developed slight proteinuria. In both series, during combined hexamethonium-hydralazine therapy, three patients with impaired renal function (two in series I and one in series II) exhibited progressive impairment of function terminating in renal insufficiency and death in uremia. During combined therapy one patient in series I developed slight proteinuria.

Discussion

Hexamethonium and hydralazine administered simultaneously constitute a potent combination of hypotensive drugs, capable of achieving and maintaining for prolonged periods significant reduction of blood pressure in the majority of patients exhibiting severe hypertensive vascular disease. Previous extended experiences with hexamethonium administered alone indicated this compound to have limited utility in severe hypertensive disease because of the gradual loss of blood pressure control after months of continued therapy. The addition of hydralazine to a group of patients responding poorly to long-term hexamethonium treatment resulted in further reduction of mean blood pressure and more satisfactory control of blood pressure for most individuals. In these patients it permitted reduction in average daily dosage of hexamethonium; slight amelioration of the side-effects from hexamethonium followed. No appreciable difference was noted in the final results between the late and early addition of hydralazine to hexamethonium therapy, although in the latter instance initial effects upon blood pressure were better due to earlier titration of hydralazine dosage. During combined therapy no tendency for blood pressure control to "escape" was evident after months of uninterrupted therapy.

Especially gratifying were the responses of nine patients suffering from malignant hypertension, four of whom had impaired renal function and three of whom had nitrogen retention. The rice diet, later modified to standard low sodium diet, was used initially in all nine patients. Eight patients exhibited reversal of the malignant phase, one while receiving hexamethonium alone, and seven during combined treatment, initially instituted. Two of the nine patients subsequently died; one patient responded poorly to therapy and died of uremia and possible hexamethonium poisoning; the other succumbed to subarachnoid hemorrhage from cerebral aneurysm several months after discontinuing both drugs. It has been our experience that the young malignant hypertensive patient who possesses good renal function is particularly sensitive and responsive to combined drug and dietary therapy. Our observations generally are in accord with those reported by Schroeder.27, 34

Dietary restriction of sodium has been demonstrated to potentiate the hypotensive effect of hexamethonium,26 and hydralazine2, 35 used separately. Sodium restriction may have played some part in decreasing blood pressure in many of our patients. Its exact contribution is difficult to assess in a clinical study of this type.

During combined hexamethonium-hydralazine therapy, approximately one-fifth (20 per cent) of all patients exhibited improvement in retinopathy and in the electrocardiogram. It is to be noted that improvement in retinopathy and in the electrocardiogram had already occurred in a significant number of patients in series I during treatment with hexamethonium alone; hence the addition of hydralazine produced relatively little further change in these areas. Little effect was noted either upon heart size or renal function during combined therapy.

Although in most patients partial relief was obtained from the unpleasant reactions to hexamethonium during prolonged treatment, in many patients these effects continued to constitute a major problem, actually causing four patients to discontinue the drugs altogether and three others to take medication sporadically. Severe postural hypotension was
a potential hazard throughout treatment. Symptoms from hydralazine were less severe and troublesome and tended to disappear in nearly all patients. Two patients without previous evidence of coronary disease experienced attacks of chest pain associated with minor electrocardiographic changes and were considered to have mild acute coronary insufficiency. No patient with preexisting angina experienced an increase in frequency or severity of pain during treatment with hydralazine. No instance of gastrointestinal bleeding was observed.

That combined hexamethonium-hydralazine therapy may not prevent serious or fatal vascular complications of hypertension is evidenced by the incidence of deaths (seven patients or 11 per cent), and nonfatal complications (six patients or 9.8 per cent) observed during the study. The late systemic reactions to hydralazine observed in seven (11 per cent) patients were a serious and unexpected development, necessitating withdrawal of the drug in each of these patients, and corticotropin and cortisone therapy in one before recovery ensued. The troublesome reactions from hexamethonium, including postural hypotension, and the potential complications from hydralazine do not seem to warrant the use of combined hexamethonium-hydralazine in the long-term treatment of patients with mild essential hypertension.

**Summary**

(1) Sixty-one patients with severe hypertensive vascular disease, including nine patients with malignant hypertension, were treated with combined hexamethonium-hydralazine over periods of from 5 to 22 months for an average of 10 months per patient.

(2) In the majority (76 per cent) of these patients definite reduction in recumbent blood pressure (fall in mean recumbent blood pressure of 20 mm. Hg or greater) was achieved and maintained throughout therapy, and approximately 40 per cent of the patients treated in the late follow-up period demonstrated “good” control of recumbent blood pressure (average recumbent pressure 160/110 or lower). No tendency for initial blood pressure reduction or control to be lost was observed.

(3) When hydralazine was added to 31 patients who had been under treatment with hexamethonium alone for periods of 5 to 26 months (average 10 months), further reduction in mean blood pressure and more satisfactory control of recumbent blood pressure were achieved in the majority of instances.

(4) The late addition of hydralazine to hexamethonium produced equally good eventual blood pressure reduction and control as did the initial combination of the two drugs; in the latter instance, however, better results during combined therapy were achieved earlier.

(5) Improvement in retinopathy and in the electrocardiogram occurred in one-fifth of all patients during combined therapy, while little appreciable effect upon renal function or heart size was noted.

(6) Vascular complications incident to the hypertensive process were not prevented by therapy. Seven deaths (11 per cent) occurred, only one of which was attributed to the drugs. Six nonfatal complications also appeared during treatment.

(7) Late systemic reactions to hydralazine were observed in seven (11 per cent) patients; in one patient the illness simulated disseminated lupus erythematosus and necessitated corticotropin and cortisone therapy.

(8) Combined hexamethonium-hydralazine therapy together with rigid dietary restriction of sodium constitutes at present an effective form of treatment for malignant hypertension and severe essential hypertension when renal function is good. The hazard of late systemic reactions to hydralazine limits the usefulness of this drug in the long-term therapy of hypertension.

**Summario in Interlingua**

Sexanta-un patientes con sever morbo vascular hypertensive esseva tractate con hexamethonium in combinationes con hydralazina pro periodos usque a 22 menses. Le resultatos obtenite in le controlo del pression sanguine esseva considerabilemente melior con le terapia combine que con hexamethonium sol, sin reguardo a si le hydralazina esseva addite
al hexamethonium initialmente o plus tarde. Esseva notate un melioration del retinopathia e del configurationes electrocardiographic. In 8 ex 9 casos le maligne phase del morbo hypertensive esseva revertite. Tardive reactiones systemic a hydralazina esseva notate in 7 patients. Un morte esseva possibilemente attribuibile a toxicosis hexamethonial. Therapia combinate de hexamethonium e hydralazina insimul con rigide restrictiones dietari de natrium representa hodie un efficace forma de tractamento pro maligne hypertension e sever hypertension essential si le functionamento renal es bon. Le riso de retardate reactiones systemic a hydralazina limita le utilitate de iste droga in le therapia hypertensive a longe durantia.

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