Newer Drugs in the Treatment of Hypertension

I. Use of Hexamethonium Salts

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Fifty patients exhibiting relatively severe hypertensive vascular disease were treated with hexamethonium compounds for periods of 3 to 19 months, averaging 9 months per patient. Hexamethonium is a potent anticholinergic agent capable of lowering blood pressure for short periods. During prolonged administration, the initial effects upon blood pressure tend to become diminished or lost, so that in the long-term treatment of severe hypertension, hexamethonium therapy alone possesses limited value. Amelioration of symptoms, decrease in retinopathy and improvement in the electrocardiogram are noted. Five fatalities occurred during treatment, but none of these was attributed directly to drug action.

In 1949, following the synthesis of a series of methonium compounds,1 Paton and Zaimis2 demonstrated the pentamethonium and hexamethonium halides to possess potent anticholinergic actions capable of blocking both parasympathetic and sympathetic ganglia. Of these two compounds, hexamethonium was considered superior in action, and extensive clinical trial in hypertensive disease rapidly followed. Initially hexamethonium salts were administered parenterally, but after partial gastrointestinal absorption of the drug was proven by Kay and Smith,3 the oral route was also employed.

Utilizing both parenteral and oral methods of hexamethonium therapy, Smirk and Alstad,4 Mackey and Shaw,5 Fullerton and Milne,6 Campbell, Graham and Maxwell,7 Freis, Finnerty, Schnaper and Johnson,8 and Johnson, Moyer, Mills and Miller9 reported favorable results in the control of hypertension over periods up to 14 months. Tendency for the blood pressure to return toward pretreatment levels was observed with continued administration of hexamethonium so that 5 to 10-fold increases in initial parenteral doses often became necessary to maintain original effects.

Other investigators have been much less enthusiastic. Locket, Swann and Grieve,10 using principally oral hexamethonium bromide, reported failure of the drug to maintain lowered blood pressure over periods up to 13 weeks. Blainey,11 employing oral and parenteral therapy, concluded that hexamethonium was ineffective in the long-term treatment of hypertension.

Serious complications have been described by Campbell and Robertson,12 and by Bourne and Hosford.13 Four deaths definitely attributable to hexamethonium therapy have been reported by Campbell, Graham and Maxwell,7 Thomas and Williams,14 Mackey and Shaw,15 and Hirson and Kelsall.16 Proper precautions with regard to the use of these compounds have been stressed by Grimson, Orgain, Rowe and Sieber.17

Although several drugs are currently available which will lower blood pressure acutely, few possess real usefulness in the long-term treatment of hypertensive disease, particularly when administered orally, a point of personal importance to patients. Because of differences of opinion concerning the practical value of hexamethonium compounds in hypertension, an investigation was begun in 1951. The pur-
pose of this paper is to present the results of prolonged hexamethonium therapy, administered principally orally, to patients suffering from severe hypertensive vascular disease. The results of combined treatment using hexamethonium and 1-hydrizinophthalazine will be reported later.

METHODS

Fifty patients exhibiting severe, stable or progressive hypertensive vascular disease with an average systolic and diastolic blood pressure of 214/128, previously unresponsive to standard medical measures, were selected for treatment. Individuals presenting mild or labile hypertensive vascular disease or primary renal disease were excluded. According to Palmer's classification of hypertension, they may be grouped as follows: grade II, 24 patients; grade III, 24 patients; and grade IV, 2 patients. Their ages ranged between 31 and 62 years with an average of 48 years. There were 37 males and 13 females. Three patients had had previous sympathectomy (one Grimson, one Smithwick, and one Peet) with return of hypertension. Twenty-one patients presented one or more serious complications of hypertension prior to the onset of treatment. Cerebrovascular accidents had occurred in 12 patients and encephalopathy in 4 patients. Three patients experienced angina pectoris, 2 patients had previous myocardial infarction and 2 patients had suffered from congestive heart failure. Ten patients demonstrated slightly impaired renal function.

Of the 50 patients, 40 were hospitalized for periods of two to three weeks for institution of hexamethonium therapy. Conventional examinations were employed in the evaluation of the hypertension in each patient. These always included a thorough history, complete physical examination, routine blood counts and urine analysis, blood nonprotein nitrogen determination, two-hour phenolsulfonphthalein excretion test, teleoroentgenogram of the chest, and electrocardiogram. In most instances a Mosenthal or Fishberg concentration test, intravenous pyelograms and a Regitine test for excess circulating epinephrine were obtained. During this period of observation and testing, recumbent and standing blood pressures were recorded four times daily.

Continuous hexamethonium therapy was administered by the oral route to 46 patients, and by the parenteral route to three patients. One additional patient received parenteral therapy for two months under hospital control and oral medication during outpatient care. Parenteral therapy was reserved for those patients who had significant evidence of arterial disease and moderate impairment of renal function. Treatment was continued over periods of 3 to 19 months for an average of 9 months per patient. A single exception was represented by one patient who discontinued therapy after one month because of partial ileus with distention, nausea, and vomiting.

Orally, the drug was administered on an empty stomach, at least 30 minutes before each meal and again at bedtime in order to spread the drug effect over the longest period of waking hours and to gain more uniform absorption of the drug. Recumbent and standing blood pressures were observed prior to each dose. Dosage was usually begun with 125 mg. to 250 mg. of one of the hexamethonium salts four times daily and increments of 125 mg. to 250 mg. per dose were made daily until a satisfactory blood pressure fall was obtained or until the development of distressing side effects precluded further increase.

With parenteral therapy the initial dose was 2.5 mg. to 5 mg. of the hexamethonium ion every six to eight hours. Gradual increments were made each day until the desired blood pressure response was observed. Fifty mg. was considered the maximum single dose with the exception of one patient who after prolonged treatment in the hospital required 100 mg. every 4 hours to maintain the original blood pressure effect. Seldom was it possible to induce both normal recumbent and standing blood pressures because of wide variations in pressure from recumbent hypertension to symptomatic postural hypotension.

During the course of this study 13 patients received hexamethonium bromide in doses ranging from 2 Gm. to 5 Gm. daily. Five patients received hexamethonium bitartrate 3.5 Gm. to 6.3 Gm. daily, and 45 patients, hexamethonium chloride 1.0 Gm. to 4.75 Gm. daily. It should be remembered that the percentage content of hexamethonium ion in the various salts of hexamethonium is as follows: 74 per cent in hexamethonium chloride, 55 per cent in hexamethonium bromide, and 40 per cent in hexamethonium bitartrate. Simple calculation enables a change from one preparation to another without varying the hexamethonium ion given. Four patients received parenteral hexamethonium bromide in total daily doses of 15 mg. to 600 mg. of the ion.

During the early stages of this investigation, hexamethonium bromide alone was available for trial, and retention of the bromide ion made the additional use of low sodium diets hazardous. The problem was encountered only with oral therapy and was partially solved by the addition of 1.0 Gm. of ammonium chloride for each gram of the bromide salt administered. Later, when bitartrate and chloride derivatives were substituted for the bromide salt, standard low sodium diets (300 to 500 mg. sodium) were instituted almost routinely in all grade III and grade IV hypertensive patients, and in a few of the more severe grade II patients. This may have enhanced the action of the methonium compounds.

Each patient was familiarized with the side effects of the drug and given proper precautions in self-medication. The drug was reduced or omitted if faintness was noted at the time of the prescribed
dose. Cascara sagrada was advised for control of constipation; bulk laxatives were avoided. Following the patient's discharge from the hospital, blood pressures were recorded at weekly intervals by the family physician or in our outpatient clinic. More thorough examination was made once a month in the outpatient clinic, and if necessary, adjustments were advised in the dosage of hexamethonium. Every six months the renal and cardiac systems were re-evaluated by observation of the blood nonprotein nitrogen, phenolsulfonphthalein excretion test, tele- roentgenogram of the chest, and electrocardiogram.

RESULTS

Constipation, dry mouth, and blurred vision were common reactions experienced by most patients. Usually these effects diminished but seldom disappeared after prolonged drug administration. Constipation was generally well controlled by mild laxatives prescribed daily. Urecholine was employed in a few instances without evident benefit. Symptoms of paralytic ileus occurred in two patients while receiving daily doses of 1.5 Gm. of hexamethonium chloride and 2 Gm. of hexamethonium bromide respectively; each patient made an uneventful recovery after temporary discontinuance of the drug. Impotence and difficulty with urination were moderately troublesome among the male patients. By omission of one or two doses before contemplated intercourse, impotence occasionally could be avoided. One patient, while receiving large parenteral doses of hexamethonium under hospital control, developed acute urinary retention. No serious bladder difficulties were encountered in those patients receiving oral therapy.

Of the 50 patients, six stopped treatment because of disturbing side effects and of these, three presented definite problems of emotional instability.

Five deaths occurred during hexamethonium therapy, four from cerebrovascular accidents, and one from renal insufficiency with uremia. One of the patients who succumbed from a cerebrovascular accident also demonstrated progressive renal failure. Three of these patients had suffered cerebral accidents and the other two had known impairment of renal function prior to institution of treatment. No death could be attributed definitely to drug therapy. During treatment two patients ex-

pered their first cerebral hemorrhage but recovered. Three patients developed mild congestive failure which responded to conventional therapeutic measures. One of these had exhibited heart failure previously. Four patients, three with known coronary artery disease before treatment, suffered myocardial infarction with survival in all. The average age of patients with serious complications was 49 years and the average in the fatality group was 44 years. In but a single instance, that of myocardial infarction occurring during a period of induced hypotension, was the drug thought to be directly responsible for the complication.

Effect upon Symptoms

Headaches, dizziness, dyspnea, and palpitation were diminished in most patients. Symptomatic improvement usually correlated closely with reduction in blood pressure. Several patients with only minor blood pressure response obtained relief from headaches. A few patients complained of more fatigue and weakness during treatment. Some patients complained of increased nervousness, but in others this symptom was improved. Of three patients who had associated coronary heart disease and the anginal syndrome, one noted more frequent angina pectoris in association with postural hypotension.

Effect upon Blood Pressure

Excessive hypotensive responses frequently were noted upon initiation of hexamethonium therapy and considerable caution was demanded to prevent overdosage. The drug effects were always greater upon systolic than diastolic pressure and greater on standing than recumbent pressure. With three exceptions a recumbent diastolic pressure of 100 mm. Hg or less was not maintained beyond one or two months of treatment. In this series, age apparently was not a determining factor in the blood pressure response.

Table 1 presents the effect upon blood pressure of continuous administration of the hexamethonium compounds over prolonged periods. The pretreatment blood pressure figures represent an average of numerous readings recorded from each patient during the months prior to
and during hospitalization. With treatment, the blood pressure response is divided into three periods: (1) while ambulatory in the hospital; (2) during the first four months of outpatient care, and (3) during the period of late outpatient care ranging from 5 to 19 months (average 10.6 months). For purposes of classifying the response of blood pressure to treatment, the patients are divided arbitrarily into three groups for each treatment period.

Table 1.—Effect upon Blood Pressure

<table>
<thead>
<tr>
<th>Grade</th>
<th>Average Age</th>
<th>Average BF Before Treatment</th>
<th>Hospital 40 patients</th>
<th>During First 4 Months 30 patients</th>
<th>5-19 Months 37 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group C</td>
</tr>
<tr>
<td>II</td>
<td>48</td>
<td>Recumbent 202/124</td>
<td>9*</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standing 182/122</td>
<td>13</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>49</td>
<td>Recumbent 220/132</td>
<td>6</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standing 195/126</td>
<td>17</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>34</td>
<td>Recumbent 216/138</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standing 181/130</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>Recumbent</td>
<td>16</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standing</td>
<td>32</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

* Numerals refer to number of patients.

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. Although both recumbent and standing blood pressure averages are recorded in this classification, the effect upon recumbent blood pressure alone is used for interpretation of results. A survey of master blood pressure charts maintained for each patient reveals that those patients whose recumbent blood pressure response was classified in group A exhibited "good" control of pressure by drug therapy. Similarly, those patients included in group B manifested only "fair" control of pressure. Patients in group C demonstrated variable reduction in blood pressure but must be considered to be "poorly or inadequately" controlled by hexamethonium as judged from effects upon recumbent pressure.

Hexamethonium therapy was initiated in 40 patients while under observation in the hospital. Ten additional patients were started on treatment in the outpatient clinic so that a total of 50 patients were observed during the first four months of outpatient care. Thirty-seven patients continued therapy from 5 to 19 months (average 10.6 months). Thirteen patients, seven grade II and six grade III, of the original group treated are not included in the late follow-up period. In eight of these blood pressure was poorly controlled and drug therapy was either discontinued or altered by the addition of other drugs. The remaining five patients exhibited variable control of blood pressure, but treatment was discontinued because of undesirable side effects in two, an essentially normal level of pressure following myocardial infarction in one, and excessive postural hypotension in one; the fifth patient was lost from follow-up.

Among those patients with hypertension of grade II severity good blood pressure control was maintained during the three treatment
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periods as follows: 9 of 15 during hospitalization, 6 of 24 during the first four months of outpatient care, and 1 of 17 during the late period of follow-up. For these same three treatment periods, good control was observed in the patients exhibiting grade III hypertension as follows: 6 of 23, 1 of 24, and 1 of 18. Of the two patients with grade IV hypertension, one did well during hospitalization but not subsequently. The second patient exhibited only fair control during hospitalization, for comparable periods), but the value of such an effect upon the hypertensive process is not yet known.

Among those patients with good control of pressure (group A), low sodium diets were employed concurrently in the three treatment periods as follows: six patients during hospitalization, one during the first four months, and two during the late follow-up period.*

Effect upon Retinopathy

Table 2 presents the number of patients with each degree of hypertensive retinopathy initially, and shows the subsequent changes after completion of follow-up periods of 3 to 19 months. Of 45 patients followed personally, three exhibited progressive retinal changes, two from grade II to grade III, and one from grade III to grade IV retinopathy. Blood pressure was inadequately controlled in these three, and each was classified in group C.

Eleven patients showed regression of retinopathy: nine from grade III to grade II, one from grade IV to grade III, and one from grade IV to grade II. Of this group blood pressure control was inadequate in five, fair in two, and good in four. It is of interest that changes in the optic fundi may regress even though blood pressure is but partially controlled. In the remaining 31 patients, retinopathy remained unchanged.

One of 3 who showed progression, 8 of 11 who showed regression, and 12 of 31 who had unchanged retinopathy followed low-sodium diets.

Effect upon Electrocardiogram

Table 3 presents the electrocardiographic changes before and after 6 to 12 months of treatment. Thirty-one patients initially showed the well-recognized S-T segment and T-wave changes associated with hypertension, and 26 of these had follow-up electrocardiograms.

* Group B patients who received low sodium diets were as follows: 4 of 9 patients in the hospital, 4 of 10 patients during the first four months, and 3 of 12 patients during the late follow-up period. Group C patients using low sodium diets during the same three treatment periods were as follows: 10 of 15, 16 of 32 and 10 of 22.
Seven patients demonstrated reversion of their S-T segment and T-wave abnormalities to normal. Of these seven, six had good blood pressure control and the seventh was classified as inadequate blood pressure control in spite of some reduction in pressure. None of the patients with "left ventricular strain" pattern exhibited a significant increase in these changes, and no patient with an initially normal electrocardiogram developed the "strain" pattern. In no instance was left axis deviation converted to a normal electrical axis. Two of the 7 patients whose electrocardiograms reverted to normal and 11 of the remaining 19 patients followed who retained the "strain" pattern were given salt-restricted diets.

**Effect upon Heart Size**

Detailed measurements of the cardiac shadow on films and adjustment according to weight and height by use of the Ungerleider Chart permitted calculation of percentage of deviation from average normal heart size. Patients grouped in table 4 as having moderately enlarged hearts had a percentage deviation from normal of plus 11 to 20 per cent. Those grouped as having markedly enlarged hearts had a deviation of plus 20 per cent or more. All follow-up teleoroentgenograms were made after at least six months of treatment.

The hearts of five patients, initially normal in size, showed progressive enlargement. Only in one of these was good blood pressure control observed, and there was no evidence of heart failure or myocardial infarction to explain the increased heart size. Low sodium diets were utilized in three patients of this group.

In two patients with moderately enlarged hearts initially, a decrease in heart size to within normal limits accompanied a reduction in blood pressure to near normal levels. Salt restriction was employed in the diets of both patients.

**Effect upon Electrocardiogram**

<table>
<thead>
<tr>
<th>ECG</th>
<th>Before Treatment</th>
<th>During Treatment</th>
<th>No follow-up ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal............</td>
<td>14*</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Left Axis Deviation only...</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>&quot;Left Ventricular strain&quot; pattern......</td>
<td>31</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Totals............</td>
<td>50</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

* Numerals refer to number of patients.

Of five patients with marked cardiac enlargement before hexamethonium therapy, three showed no significant change in heart size; two showed a slight increase in heart size, one occurring with left ventricular failure, and the other following myocardial infarction. Two of these patients had fair blood pressure control, but the remaining three exhibited no significant lowering of blood pressure. Three of these patients, including the two with increasing heart size, followed low sodium diets.

**Effect upon Renal Function**

Before initiating therapy and at regular intervals thereafter, renal pathology and function were determined by conventional examinations. Intravenous pyelograms revealed only a few minor abnormalities.

Thirteen patients had mild to moderate albuminuria which disappeared during treatment in five. Three patients developed mild...
proteinuria. Of 40 patients with normal renal function initially, 3 developed slight impairment of function as evidenced by well-controlled phenolsulfonphthalein tests. Two of 10 patients with impaired renal function showed progressive renal damage and death. One died of uremia in the thirteenth month of treatment; the other succumbed during acute hypertensive encephalopathy after four months of treatment. In the former patient, a check of renal function made three months prior to death revealed no progression in previously impaired renal function.

**Discussion**

Hexamethonium is a powerful anticholinergic compound capable of lowering blood pressure in most patients during initial periods of therapy. No significant differences in potency were noted among the three halide salts employed when dosages were compared according to content of hexamethonium ion. The oral bromide salt, however, provided the constant hazard of bromism, and in two patients, elevation of blood bromide concentration above 200 mg. per 100 cc. demanded discontinuance of the drug. Reduction in pressure may be maintained for periods varying from four to eight months after which the initial blood pressure control is occasionally maintained but usually becomes diminished or lost. Partial relief from the side reactions of the drug also occurs, but these side effects often remain sufficiently troublesome to prevent further increase in drug dosage when additional blood pressure effect is desired. This was observed in the four patients receiving parenteral hexamethonium as well as those treated with the oral preparation. The three postsympathectomy patients proved unusually sensitive to the postural hypotensive effects of the drug and were able to maintain a more satisfactory blood pressure response with continued therapy. Postural hypotension represents the most frequent and troublesome action of the drug and commonly prevents dosage adequate for good recumbent effect. In only three patients was it possible to maintain a recumbent diastolic pressure of 100 mm. Hg or less beyond two months.

Relief from hypertensive symptoms occurred in many, and surprisingly enough, in a few patients as hypertension returned, headaches remained absent or diminished. Decrease in retinopathy and improvement in the electrocardiogram occurred in a few patients. Heart size and renal function were not significantly affected by drug therapy. In some patients, progression of hypertension seemed temporarily retarded and in a few, life expectancy appeared definitely increased.

Fewer complications and better therapeutic results were recorded for patients in the grade II hypertensive group than for those classified as grade III. Neither age nor the duration of hypertension prior to initiation of therapy appeared to be determining factors in the treatment response. Dramatic reduction in blood pressure and regression of retinopathy were observed in two patients with malignant hypertension, one of whom received the bromide derivative and a normal sodium chloride intake.

The concurrent employment of low sodium diets may have enhanced individual blood pressure responses but apparently has not altered significantly the results of long-term drug therapy in this series.

No deaths attributable to hexamethonium therapy were encountered. Of many major complications observed during the course of this study, only one can be directly related to drug effect. This patient, previously diagnosed as having coronary heart disease and myocardial infarction, suffered a second myocardial infarction during a period of excessive drug-induced hypotension. The incidence of complications in this series appears to reflect the severity of the disease treated rather than a deleterious effect of the drug utilized. However, because of the many immeasurable factors involved, it is impossible to exonerate the drug completely as a contributing force to the complications.

Hexamethonium compounds are a valuable addition to the armamentarium of drugs in the treatment of hypertension when blood pressure control is urgent or desirable for limited periods. For this purpose it is very probably the best single drug available today. Oral administration, even though drug absorption from the gut is variable, appears feasible.
for the usual patient, but in the acute hypertensive state with cerebral, cardiac or renal complications, the parenteral route affords a more evenly controlled blood pressure and is preferred. Our results with prolonged oral and parenteral therapy have not been satisfactory. The hexamethonium compounds when used alone appear to possess limited value in the long-term treatment of severe hypertensive vascular disease. The effect on mild or labile hypertension was not tested owing to difficulty in evaluation of treatment results.

Coronary artery disease, encephalopathy, fresh or old cerebral thrombosis, or renal insufficiency present potential hazards to the use of methonium compounds. When blocking agents of this type are considered for blood pressure control, extreme caution must be observed.

SUMMARY

1. Fifty patients exhibiting relatively severe, stable or progressive hypertension were treated with hexamethonium compounds over periods of 3 to 19 months for an average of 9 months per patient.

2. Good control of blood pressure by hexamethonium as evidenced by average recumbent blood pressure levels of 160/110 or less was recorded for three treatment periods as follows: (1) during hospitalization, 16 patients (40 per cent); (2) during first four months of outpatient care, 8 patients (16 per cent); (3) during the subsequent 5 to 19 months, 3 patients (6 per cent). Postural changes in blood pressure were uniformly greater.

3. Hexamethonium is a potent anticholinergic agent capable of lowering blood pressure for short periods. During prolonged administration the initial effects upon blood pressure tend to become diminished or lost, so that in the long-term treatment of severe hypertension, hexamethonium therapy alone possesses limited value.

4. Frequent amelioration of hypertensive symptoms and occasional decrease in retinopathy and improvement in the electrocardiogram are noted. Heart size and renal function have not been altered significantly.

5. Five deaths occurred during the treatment period, but in no instance was the fatality attributed directly to drug action. In addition many serious complications were observed, but these, with one exception, appear to reflect the severity of the hypertensive disease rather than a deleterious effect of the drug itself.

SUMARIO ESPAÑOL

Cincuenta pacientes exhibiendo enfermedad hipertensiva vascular relativamente severa fueron tratados con compuestos de hexamethonium por periodos de 3 a 19 meses, con un promedio de 9 meses por paciente. El hexamethonium es un agente anticolinérgico potente capaz de disminuir la presión arterial por periodos cortos. Durante la administración prolongada, los efectos en la presión arterial disminuyen o desaparecen, de manera que en el tratamiento a largo la hipertensión el hexamethonium solamente tiene un valor limitado. Mejoramiento de síntomas, disminución en retinopatía y mejoramiento en el electrocardiograma se observaron. Cinco mortalidades ocurrieron durante el tratamiento, pero ninguna fue atribuible a la acción directa de la droga.

REFERENCES

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