Studies on Tolerance to Ganglionic Blocking Agents in Man

Reversal of Depressor Action of Quaternary Ammonium Compounds

By A. S. Donta, M.D., and S. W. Hoobler, M.D.

The hypotensive effects of intravenous injections of tetraethylammonium and hexamethonium chloride diminish and finally become pressor during the course of short-term treatment with subcutaneous hexamethonium. Evidence is presented to indicate that this "tolerance" is associated with a decreased sympathetic tone in the feet and forearm and is not due to increased amounts of circulating adrenal medullary or cortical hormones. Possibilities are discussed for this apparent vascular autonomy and the locus of vasoconstriction. Cross tolerance appeared between several ganglionic blocking agents tested and extended to a minor degree to adrenergic blocking agents.

One of the main disadvantages of ganglionic blocking agents in the treatment of hypertension is the development of "tolerance." The present study seeks to identify the mechanisms and vascular areas involved in this phenomenon and also in the development of cross tolerance between several different ganglionic blocking agents.

Method

Twelve patients, with moderate to severe essential hypertension, were studied in the Cardiovascular Unit of the University of Michigan Hospital for a period of 10 to 15 days, prior to, during and after a short period of treatment with parenteral hexamethonium. Of the twelve, three (A.P., H.T., J.P.) had been submitted to bilateral supradiaphragmatic splanchnicectomy, three months to six years previously, and one (E.B.) had a dorsolumbar sympa-thectomy five years previously and an additional extension of the original operation 12 months before the study. Their renal status was variable, but at the time of the study, only two (L.G.* and M.P.) had elevated serum creatinine or nonprotein nitrogen levels, while the others were definitely within normal limits. The patients were kept on a low sodium diet and remained ambulatory in the ward during their treatment with hexamethonium. The daily dose was usually constant for each patient for the period of observation and varied between 30 and 100 mg. per day, given subcutaneously in four equal doses every six hours. In six of the patients, foot and forearm blood flows were measured by venous occlusion plethysmography in a temperature-controlled room (70 to 74 F.) with a collecting cuff pressure of 80 mm. Hg. In no case did collecting pressure exceed diastolic pressure. After the subject had rested, three series of blood flow determinations at five-minute intervals were performed, each series consisting of five observations made at 20-second intervals. After drug injections, blood flows were determined in successive series of five observations every 20 seconds until a maximum had been reached. The average of three control series was designated as the "resting" blood flow and of five consecutive determinations at the time of maximum increase as average "maximum" blood flow for the respective area.

The effects of intravenous injections of 50 to 300 mg. of tetraethylammonium chloride (TEAC) and 7 to 30 mg. hexamethonium chloride (C-6) given about 45 minutes later were studied at frequent intervals before, during and for one or two days after the treatment. The injections were given two to four hours after the therapeutic subcutaneous hexamethonium injection on the ward.

Results

A. Effects on Blood Pressure

Injection of tetraethylammonium chloride in all our patients prior to therapy by hexa-
methonium (see fig. 1) had the following effects: (1) A rapid initial rise in blood pressure, mainly systolic, developed. This lasted about 30 seconds and was associated with the well-known disagreeable tingling sensations. At the same time, the heart rate usually showed a slight increase. The peripheral vasodilatation, as measured by plethysmography, was already obvious at this stage. (2) A subsequent hypotensive response to tetraethylammonium chloride occurred. This was usually accompanied by subsidence of the initial disagreeable feelings and only a sensation of "cold" over the entire body persisted somewhat longer. The heart rate at this stage had returned to or slightly below the preinjection levels, although in occasional patients showing marked blood pressure drops there was a moderate tachycardia, as evidence of the incomplete blockade of the cardiac ganglia. Peripheral vasodilatation reached its peak during this stage, the foot and forearm resistance being reduced to one-third to one-fifth of the original values. (3) A phase during which blood pressure returned to the control levels, and the peripheral vasodilatation receded partially, lasted from 20 to 30 minutes. It was apparent that blood pressure-compensating mechanisms preceded the recovery of vasoconstrictor tone in the foot and forearm.

The main differences between the actions of tetraethylammonium chloride and those of the other ganglionic blocking agents tested (hexamethonium, pendiomide, and the trivalent ganglionic blocking agent SU-1194*) were the following: The initial blood pressure rise was missing, as were the sensations of cold and pricking with these latter drugs, and an agreeable feeling of general warmth was noted. The heart rate remained the same or decreased (especially with SU-1194), even during the initial sharp drop in blood pressure; the hypotension and peripheral vasodilatation were longer lasting and some differences in the loci of maximal response were occasionally observed. Figure 1 shows the difference in the forearm responses to tetraethylammonium chloride and hexamethonium, in a case where the foot increases were qualitatively similar.

When the injections of tetraethylammonium chloride were repeated on consecutive days

* We would like to express our thanks to Dr. F. F. Yonkman, Ciba Pharmaceutical Products, Inc., for the supply of this agent.
after therapy with hexamethonium had started, the following changes were observed: The initial rise remained the same, but the transition toward the hypotensive phase became less and less abrupt. Simultaneously, the maximum blood pressure drop became less and its duration shorter. In 11 of the 12 patients studied, a point was eventually reached where no blood pressure drop after the tetraethylammonium chloride injection occurred, while the initial rise now lasted occasionally as long as 10 minutes. The subjective feelings in response to the injection of tetraethylammonium chloride were never altered. We defined as "complete tolerance" the period when the hypotensive response in the supine position was entirely missing. Resting recumbent blood pressures, as can be seen from tables 1 and 2, usually fell somewhat during treatment with hexamethonium and then gradually rose as "tolerance" developed. The mean control blood pressure of our six patients studied by plethysmography was 171.6 ± 6.2 and had dropped to 154 ± 5.7 at the time of tetraethylammonium chloride reversals; the pressor responses to tetraethylammonium chloride and hexamethonium did not seem to bear any relation to the resting supine blood pressures, occurring at lower as well as occasionally at higher than the pretreatment levels. During this entire period, cold pressor responses were only moderately depressed, as further evidence of partial ganglionic blockade.

The other drugs were tested more rarely, usually not more than once or twice weekly. Hexamethonium given intravenously at the height of "tolerance" also exerted pressor effects in the majority of cases, while in the rest it was devoid of any depressor action. However, the rise occurred slowly and the decline also was delayed, occasionally lasting up to 30 minutes. In one instance, up to 60 mg. of hexamethonium given in infusion did not overcome the slow blood pressure rise. Pendio- midie (30 mg.) also caused a reversal to a pressor response occurring simultaneously with the reversal to tetraethylammonium chloride. The onset and offset of effect were rapid, resembling those observed after tetraethylammonium chloride. The tertiary ganglionic blocking agent SU-1194 showed a considerable difference in the two patients tested. Refractoriness to its depressor action appeared much later than that to tetraethylammonium chloride, responses to it being quantitatively equal at a time when the "TEA-floor" had risen considerably. However, after complete "tolerance" to tetraethylammonium chloride had been reached for some days, the depressor action of SU-1194 gradually lessened, and one patient became completely tolerant to it (table 3). In our limited experience with this agent, we have not seen pressor responses following its injection.

B. Effects on Blood Flow

As mentioned above, in six of our patients we studied the changes in peripheral blood flow through a muscular (forearm) and a less muscular (foot) area after injection of the same amounts of tetraethylammonium chloride and hexamethonium chloride before, during and after the period of development of tolerance. The resting blood flows of both foot and forearm did not present definite changes compared with those obtained during the pretreatment test (fig. 2). It is obvious, therefore, when the drug is given every six hours subcutaneously, that repeated vasodilatations such as are demonstrated in figure 1 do not persist, at least with the small doses used in this study. In the majority of our cases the large drop in foot resistance following the injection of tetraethylammonium chloride observed before treatment, is lessened after tolerance has developed; the mean drop in foot resistance being 56.5 per cent before and 38.3 per cent during tolerance (table 1). The mean forearm resistance, though showing more scatter, is also converted from a 36.4 per cent drop to a 2.8 per cent rise during tolerance, which difference is close to statistical significance (p = 0.06). It must be stressed that the lessened decreases in resistance are largely a result of the failure to produce a drop in blood pressure during "tolerance," while increases in blood flow still occurred, although to a somewhat lesser degree. Similar changes were observed in the response of foot and forearm circulations to intravenous hexamethonium administration (table 2). The lessened drop of foot resistance (−59.0 per
TOLERANCE TO PROLONGED GANGLIONIC BLOCKADE

Fig. 2. Hemodynamic effects of intravenous injection of tetraethylammonium chloride and hexamethonium during tolerance to hexamethonium. Patient is the same as in figure 1, after five days of treatment with hexamethonium.

Table 1.—Responses of Blood Pressure and Extremital Circulation to Intravenous Tetraethylammonium Chloride before, during and after Tolerance to Ganglionic Blockade by Hexamethonium

<table>
<thead>
<tr>
<th>Test Dose</th>
<th>Mean Blood Pressure</th>
<th>% Change in Mean Blood Pressure</th>
<th>% Change in Foot Resistance</th>
<th>% Change in Forearm Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>M. P.</td>
<td>300</td>
<td>168.5</td>
<td>150.0</td>
<td>155.7</td>
</tr>
<tr>
<td>C. C.</td>
<td>300</td>
<td>165.5</td>
<td>154.0</td>
<td>188.5</td>
</tr>
<tr>
<td>M. V.</td>
<td>300</td>
<td>178.0</td>
<td>178.0</td>
<td>160.5</td>
</tr>
<tr>
<td>H. T.</td>
<td>300</td>
<td>169.5</td>
<td>141.5</td>
<td>149.0</td>
</tr>
<tr>
<td>E. B.</td>
<td>300</td>
<td>197.0</td>
<td>141.5</td>
<td>201.0</td>
</tr>
<tr>
<td>J. P.</td>
<td>250</td>
<td>151.0</td>
<td>162.0</td>
<td>167.0</td>
</tr>
</tbody>
</table>

Mean

<table>
<thead>
<tr>
<th>Test Dose</th>
<th>Mean Blood Pressure</th>
<th>% Change in Mean Blood Pressure</th>
<th>% Change in Foot Resistance</th>
<th>% Change in Forearm Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>M. P.</td>
<td>168.5</td>
<td>150.0</td>
<td>155.7</td>
<td>−15.4</td>
</tr>
<tr>
<td>C. C.</td>
<td>165.5</td>
<td>154.0</td>
<td>188.5</td>
<td>−9.4</td>
</tr>
<tr>
<td>M. V.</td>
<td>178.0</td>
<td>178.0</td>
<td>160.5</td>
<td>−10.4</td>
</tr>
<tr>
<td>H. T.</td>
<td>169.5</td>
<td>141.5</td>
<td>149.0</td>
<td>−26.8</td>
</tr>
<tr>
<td>E. B.</td>
<td>197.0</td>
<td>141.5</td>
<td>201.0</td>
<td>−13.2</td>
</tr>
<tr>
<td>J. P.</td>
<td>151.0</td>
<td>162.0</td>
<td>167.0</td>
<td>−6.0</td>
</tr>
</tbody>
</table>

Mean

S.E., standard error of the mean.

Mean blood pressure is calculated as systolic + diastolic.

Resistance calculated as mean blood pressure / blood flow in ml./100 ml. of limb vol./min.

54.8 cent to −21.8 per cent respectively) and especially the clear conversion to vasoconstriction in the forearm (from a mean of −53.4 per cent to +23.8 per cent, which is statistically significant) are also obvious. An interesting comparison is that between the blood pressure changes induced by these drugs and the resistance changes of the regional circulations studied. Although the mean hypotensive responses to both tetraethylammonium chloride and hexamethonium were approximately equal, the drop in forearm resistance induced by tetraethylammonium chloride in the pre-"tolerant" stage was much less than that in-
Table 2.—Responses of Blood Pressure and Extremital Circulation to Intravenous Hexamethonium before, during and after Tolerance to Ganglionic Blockade by Hexamethonium

<table>
<thead>
<tr>
<th>Test Dose mg.</th>
<th>Mean Resting Blood Pressure</th>
<th>% Change in Mean Blood Pressure</th>
<th>% Change in Foot Resistance</th>
<th>% Change in Forearm Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>M. P. 15</td>
<td>168.5</td>
<td>160.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C. C. 15</td>
<td>165.5</td>
<td>154.0</td>
<td>183.0</td>
<td>—</td>
</tr>
<tr>
<td>M. V. 36</td>
<td>160.0</td>
<td>178.0</td>
<td>165.0</td>
<td>10.6</td>
</tr>
<tr>
<td>H. T. 15</td>
<td>166.0</td>
<td>141.5</td>
<td>143.5</td>
<td>15.7</td>
</tr>
<tr>
<td>E. B. 15</td>
<td>183.0</td>
<td>141.5</td>
<td>182.0</td>
<td>18.9</td>
</tr>
<tr>
<td>J. P. 7.5</td>
<td>—</td>
<td>168.0</td>
<td>172.0</td>
<td>—</td>
</tr>
<tr>
<td>Mean S.E.</td>
<td>168.5</td>
<td>155.5</td>
<td>169.1</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>±3.8</td>
<td>±6.0</td>
<td>±6.4</td>
<td>±1.4</td>
</tr>
</tbody>
</table>

*p = 0.19

*p = 0.01

duced by hexamethonium. On the other hand, the conversion of the initial forearm vasodilatation to a constriction occurred more uniformly with hexamethonium than with tetraethylammonium chloride.

The marked initial reduction of foot resistance with both substances still occurred with tetraethylammonium chloride during "tolerance," while the hexamethonium effect was much weaker.

C. Studies Concerning the Mechanism of Tolerance

I. Adrenergic Factors. It has been shown that strong doses of tetraethylammonium chloride may release epinephrine from the adrenals by direct stimulation, and this property has been used as a diagnostic test in pheochromocytoma. We therefore investigated the possibility that, in our patients, rising amounts of circulating adrenergic substances might not only be responsible for maintaining the basal resting blood pressure during tolerance, but their acute release might explain the blood pressure rises occurring after tetraethylammonium chloride and hexamethonium, given intravenously in the "tolerant" state.

The areas of vasoconstriction, however, are different. In figure 3, obtained from patient E.B. during tolerance to hexamethonium, the blood pressure rise following 5 micrograms of norepinephrine equals that of 300 mg. of tetraethylammonium chloride. Norepinephrine, however, acts almost entirely on the foot circu-

fig. 3. Comparison of hemodynamic changes of equipressor doses of tetraethylammonium chloride and norepinephrine; tolerant patient.
### Table 3. Hypotensive Action of Drugs before and after Development of "Tolerance" to Hexamethonium

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug</th>
<th>Blood Pressure (mm. Hg) Before &quot;Tolerance&quot;</th>
<th>Max. Response to Drug (mm. Hg) Before</th>
<th>Max. Change after TEA Before</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. P.</td>
<td>Dibenzyline 1 mg./Kg. i.v.</td>
<td>198/114</td>
<td>-18/-8</td>
<td>-30/-18</td>
</tr>
<tr>
<td>J. P.</td>
<td>Dibenzyline 1 mg./Kg. i.v.</td>
<td>193/120</td>
<td>-13/-22</td>
<td>-58/-38</td>
</tr>
<tr>
<td>G. F.</td>
<td>Regitine 10 mg. i.v.</td>
<td>185/120</td>
<td>-12/-14</td>
<td>-42/-17</td>
</tr>
<tr>
<td>E. B.</td>
<td>Regitine 5 mg. i.v.</td>
<td>198/140</td>
<td>-8/-16</td>
<td>-44/-21</td>
</tr>
<tr>
<td>G. F.</td>
<td>SU 1194 250 mg. i.v.</td>
<td>196/134</td>
<td>-39/-24</td>
<td>-46/-16</td>
</tr>
<tr>
<td>S. C.</td>
<td>SU 1194 150 mg. i.v.</td>
<td>240/120</td>
<td>-70/-8</td>
<td>-82/-10</td>
</tr>
<tr>
<td>S. C.</td>
<td>Histamine 0.025 mg. i.v.</td>
<td>202/122</td>
<td>-54/-22</td>
<td>-24/-16</td>
</tr>
<tr>
<td>G. F.</td>
<td>Protovatertrine 0.1 mg. i.v.</td>
<td>200/126</td>
<td>-55/-35</td>
<td>-48/-17</td>
</tr>
</tbody>
</table>

Before "Tolerance" blood pressures represent the usual readings. Responses to tetraethylammonium chloride before and after "tolerance" refer to the test performed nearest to the time of administration of the drug in question and usually within 12 hours. Dose of tetraethylammonium chloride given intravenously was variable but the same for any one patient.

![Figure 4](http://circ.ahajournals.org/)

**Fig. 4.** Nontolerant patient. Hemodynamic effects of tetraethylammonium chloride before and after Dibenzyline infusion.
usually associated with this drug when hypertension is due to adrenergic substances (table 3). Moreover, the acute rise in pressure after tetraethylammonium chloride is also not due to epinephrine release, since it cannot be prevented by prior infusion with Dibenzyline (fig. 4). Similar results were obtained with the less specific adrenergic blocking agent, Regitine, an imidazoline derivative, tried repeatedly in two other patients (table 3). With this agent, the blood pressure decreases following tolerance were considerably reduced more or less in parallel with reductions in the response to tetraethylammonium chloride. These experiments suggest that epinephrine is not present in increased amounts in the blood in the tolerant state.

II. Vascular Reactivity. Direct vasodilators, such as histamine, were still active during the refractory state, indicating that reactivity of the vascular wall is not diminished during tolerance (table 3).

III. Adrenocortical Mechanisms. Although direct measurements of the output of 17-keto-steroids were not done, three of our patients, who became completely or partially tolerant to hexamethonium treatment, showed either no decrease or a mild rise in total circulating eosinophils during their treatment; body weight of our patients also showed a downward trend, as they were on a low sodium diet.

Discussion

I. Explanation of the Conversion of the Acute Depressor Effect of Tetraethylammonium Chloride to a Pressor One

The pressor action of tetraethylammonium chloride has been ascribed to adrenaline release, but its persistence in our experiments after Dibenzyline makes this explanation unlikely.

Another possibility would be the activation of pressor pathways not blocked by tetraethylammonium chloride, such as the ones described by Freyburger and co-workers in the dog. The afferent limb of this reflex arc might rise from aortic and carotid chemoreceptors which can be stimulated by tetraethylammonium chloride and hexamethonium under partial blockade. Such chemoreceptor stimulation would then increase blood pressure through channels which might not be vulnerable to ganglionic blocking agents.

A final possibility, which we favor, is that tetraethylammonium chloride is directly vasoconstrictor, in the concentration momentarily reached following an initial injection. A number of authors have reported acute vasoconstrictor effects of tetraethylammonium chloride on local vascular beds. We believe that when sympathetic vasomotor tone is inhibited, the vasodilator and depressor component of the action of tetraethylammonium chloride is absent, while the vasoconstrictor effect remains and hence the blood pressure rises. If sympathetic tone is suppressed, the drug becomes pressor as after multiple injections in the dog, after corticotropin (ACTH) administration, and after total sympathectomy in man. Such an action would explain the initial blood pressure rises that frequently precede the depressor phase when tetraethylammonium chloride is rapidly injected intravenously. The pressor effect of hexamethonium in our experiments may possibly have the same explanation, although it is said not to have a local vasoconstrictor action in animals. The irregularity and delay in appearance of pressor effects in the tolerant state makes this clinical observation less certain than those involving tetraethylammonium chloride. We believe that the vasoconstrictor effects are not the indirect result of ganglionic blockade (e.g. differential blockade of vasodilators) in a tolerant patient, but are more likely a side effect peculiar to tetraethylammonium chloride itself, like paresthesias and other signs of excitation of peripheral structures which do not occur with other acutely acting ganglioplegic drugs.

II. Explanation of the Mechanism of "Tolerance" to Hexamethonium

It seems certain that establishment of "tolerance" to ganglionic blocking agents is not, as in the case of many other drugs, due to increased efficiency of inactivation, since they are not destroyed or inactivated in the body. Renal excretion is probably not intensified.
Furthermore, during hexamethonium treatment, "tolerance" to parasympathetic blocking effects on the pupil, gut or salivary secretion does not appear, according to the observations of Morrison. The development of "tolerance" to adrenergic blocking drugs has also been reported with Dibenzyline.

In our experiments "tolerance" has been demonstrated not to be associated with total cessation of sympathetic activity, since foot vasodilatation still followed acute injections of ganglionic blocking agents. In the muscular areas and possibly elsewhere, sympathetic vasomotor tone is apparently considerably reduced; if we can judge by forearm blood flow measurements before and during "tolerance," such reduction is not associated with an increase in resting blood flow in the "tolerant" patient. Hence some compensating mechanism has restored the vasoconstriction. Humoral substances such as epinephrine and norepinephrine have been excluded by the failure to note a fall in blood pressure following infusion of Dibenzyline in the tolerant patient (table 3). Adrenocortical activity might compensate although eosinophil counts do not give evidence of increased glucocorticoid excretion during "tolerance." The "cerebral pressor substance" of Taylor and Page might play a role or the natural tendency of the vasculature to resume its "normal" contracted state might explain the restoration of normal muscle flow in the absence of sympathetic tone.

The situation would then resemble that in the totally sympathectomized hypertensive whose blood pressure is restored to high levels by unknown, probably intrinsic, compensations and who then fails to respond with a drop in blood pressure to ganglionic blocking agents. The chemically sympathectomized patient is still responsive to other vasodilators such as histamine and protoveratrine according to our observations, and it may be that with these other drugs, the refractory state may be overcome. In any event the failure of ganglionic blocking drugs to lower supine blood pressure, failures of sympathectomy and local denervations probably have their root in the nature of the compensatory mechanisms involved. It is to be hoped that further study of these reactions will lead to a better understanding of the role of sympathetic tone in hypertensive disease.

Conclusions
1. In man under chronic partial ganglionic blockade with hexamethonium, the usually depressor effects of intravenous tetraethylammonium and hexamethonium chloride in the supine position decrease and later become pressor.
2. During such a blockade, the resting foot and forearm blood flows, as studied in six cases, are not appreciably higher than the control values; the test injections elicit definite but less prominent increases in foot blood flow, indicating persistence of sympathetic tone to this area; the forearm blood flow response is considerably reduced, and increases in forearm flow are frequently observed, especially with hexamethonium.
3. Reasons are given for suggesting that the pressor action of tetraethylammonium chloride is a result of its direct vasoconstrictor action in the absence of a concomitant depressor effect.
4. Evidence is presented for exclusion of increases of sympathoadrenal and cortical hormones as the mechanism of tolerance, and other possibilities are discussed.
5. Cross tolerance developed between the various quaternary and tertiary-N ganglionic blocking agents studied (tetraethylammonium chloride, hexamethonium, pendimide, SU-1194) and extended to a minor degree also to the adrenergic blocking agents Regitine and Dibenzyline.

Sumario Español
1. En el hombre sujeto a un bloqueo ganglionic parcial con hexametinon, los efectos usualmente depresores del cloruro de tetraetilamonomo intravenoso y hexametion en la posición recostada disminuyen y luego se tornan en presores.
2. Durante tal bloqueo, la circulación del pié descansado y el antebrazo, según estudios en seis casos, no son apreciablemente más altos que los valores controles; las inyecciones de prueba produjeron aumentos definitivos pero menos prominentes en la circulación del pié,
indicando persistencia de tono simpático a esta área; la repuesta de la circulación del antebrazo estuvo considerablemente reducida y aumentos en el antebrazo fueron frecuentemente observados, especialmente con hexamethonium.

3. Se dan razones sugiriendo que la acción presora del cloruro de tetraetilamonio es un resultado directo de su acción vasoconstrictora en la ausencia de un efecto depresor concomitante.

4. Se presenta evidencia para excluir aumentos de hormonas simpatoadrenales y corticales como un mecanismo de tolerancia y otras posibilidades se discuten.

5. Tolerancia cruzada se desarrolló entre los varios agentes cuaternarios y terciarios-N blockeadores gangliónicos estudiados (cloruro de tetraetilamonio, hexamethonium, pendimide, Su-1194) y se extendió en grado menor también a los agentes bloqueadores adrenérgicos Regitine y Dibenzyline.

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