The Effect of Hexamethonium upon Cerebral Blood Flow and Metabolism in Patients with Premalignant and Malignant Hypertension

By Charles W. Crumpton, M.D., George G. Rowe, M.D., Robert C. Capps, M.D., Ph.D., Janet J. Whitmore, M.D., and Quill R. Murphy, M.D., Ph.D.

In 13 patients with grade III or grade IV hypertensive retinopathy the effect of intramuscular hexamethonium bromide on cerebral circulation and metabolism has been studied. The results have been compared with Dewar's study of hexamethonium in less severe hypertensive patients and with Kety's results following differential spinal sympathetic block. Sixty minutes after intramuscular hexamethonium, mean arterial blood pressure fell 30 per cent, cerebral vascular resistance was reduced 29 per cent, and cerebral blood flow decreased 16 per cent. Cerebral oxygen consumption was maintained at the expense of a reduction in cerebral venous oxygen saturation.

The effect of hexamethonium upon blood flow in various organs of hypertensive patients has been reported by several investigators. Cardiac output was reduced in compensated patients. Renal blood flow decreased initially but returned to control value despite a continued reduction in arterial blood pressure. Blood flow through the abdominal viscera decreased in proportion to the fall in arterial blood pressure. The present report concerns the effect of hexamethonium upon cerebral hemodynamics and metabolism in 13 patients with severe hypertension.

Method

Thirteen hospitalized patients with premalignant or malignant hypertension were studied in the supine position. Ages ranged from 28 to 48 years. Six patients exhibited grade III and seven grade IV hypertensive retinopathy (Keith-Wagener-Barker). Mild to moderate impairment of the renal function was demonstrated by standard clinical tests, but blood nonprotein nitrogen value was within the normal range. In four of the patients a cerebral vascular hemorrhage had occurred six months to one year prior to the present study. Cardiac functional capacity was I-II. None of the group had previously received hexamethonium.

Control measurements were made, and hexamethonium was administered intramuscularly (mean average dose 1.0 mg. per kilogram). Mean arterial blood pressure fell within 5 to 30 minutes. The second blood flow determination was made 60 minutes after drug injection, at which time the blood pressure had stabilized. Cerebral blood flow (CBF) was determined by the nitrous oxide method of Kety and Schmidt. Mean arterial blood pressure (MABP) was obtained directly by a needle in the femoral artery attached to a Statham strain gage or damped mercury manometer. Blood gas analyses for oxygen, carbon dioxide, and nitrous oxide were made with the Van Slyke-Neill manometric apparatus. Venous oxygen saturation was determined by

\[
\frac{\text{Venous oxygen content}}{\text{Hemoglobin} \times 1.34}
\]

Cerebral oxygen consumption (CMRO₂) and cerebrovascular resistance (CVR) were calculated as previously described.

Results

The results are presented in tables 1 and 2. Mean arterial blood pressure fell from 181 to 111 mm. Hg, representing a decrease of 39 per cent. Cerebral vascular resistance was reduced 29 per cent. Cerebral blood flow fell from 55 to 46 cc. per 100 Gm. per minute (16 per cent). These changes were significant.
TABLE 1.—The Effects of Hexamethonium in Malignant hypertension. Blood Pressure and Blood Constituents

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Sex</th>
<th>Age</th>
<th>Fundi</th>
<th>Dose (mg.)</th>
<th>Wt. (Kg.)</th>
<th>Side Effects</th>
<th>Femoral MABP mm. Hg</th>
<th>Cardiac Rate Per min.</th>
<th>CO₂ Content Vol. %</th>
<th>O₂ Content Vol. %</th>
<th>O₂ Sat. %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>D</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>A.M.</td>
<td>M</td>
<td>36</td>
<td>III</td>
<td>50</td>
<td>61</td>
<td>Nausea</td>
<td>189.149</td>
<td>75</td>
<td>100</td>
<td>53.2</td>
<td>34.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>177.128</td>
<td>73</td>
<td>96</td>
<td>60.8</td>
<td>48.0</td>
</tr>
<tr>
<td>E.J.</td>
<td>F</td>
<td>28</td>
<td>III</td>
<td>56</td>
<td>46</td>
<td>Nausea</td>
<td>195.141</td>
<td>82</td>
<td>100</td>
<td>46.4</td>
<td>33.6</td>
</tr>
<tr>
<td>O.K.</td>
<td>F</td>
<td>48</td>
<td>IV</td>
<td>100</td>
<td>85</td>
<td>Nausea</td>
<td>195.141</td>
<td>82</td>
<td>100</td>
<td>46.4</td>
<td>33.6</td>
</tr>
<tr>
<td>D.S.</td>
<td>F</td>
<td>41</td>
<td>III</td>
<td>75</td>
<td>65</td>
<td>Nausea</td>
<td>195.141</td>
<td>84</td>
<td>72</td>
<td>41.4</td>
<td>42.1</td>
</tr>
<tr>
<td>M.S.</td>
<td>F</td>
<td>35</td>
<td>III</td>
<td>50</td>
<td>65</td>
<td>Nausea, Eunana</td>
<td>179.02</td>
<td>84</td>
<td>120</td>
<td>43.3</td>
<td>47.1</td>
</tr>
<tr>
<td>W.M.</td>
<td>M</td>
<td>41</td>
<td>IV</td>
<td>40</td>
<td>59</td>
<td>Nausea</td>
<td>180.143</td>
<td>74</td>
<td>88</td>
<td>56.2</td>
<td>57.7</td>
</tr>
<tr>
<td>C.K.</td>
<td>F</td>
<td>40</td>
<td>IV</td>
<td>100</td>
<td>82</td>
<td>Pallor, Nausea</td>
<td>190.126</td>
<td>72</td>
<td>88</td>
<td>49.7</td>
<td>39.2</td>
</tr>
<tr>
<td>G.H.</td>
<td>M</td>
<td>43</td>
<td>IV</td>
<td>80</td>
<td>55</td>
<td>Nausea</td>
<td>175.107</td>
<td>110</td>
<td>85</td>
<td>40.3</td>
<td>49.5</td>
</tr>
<tr>
<td>I.C.</td>
<td>F</td>
<td>36</td>
<td>III</td>
<td>37.5</td>
<td>45</td>
<td>Nausea</td>
<td>176.100</td>
<td>80</td>
<td>100</td>
<td>51.3</td>
<td>49.4</td>
</tr>
<tr>
<td>A.K.</td>
<td>F</td>
<td>42</td>
<td>IV</td>
<td>85</td>
<td>60</td>
<td>Pallor</td>
<td>200.135</td>
<td>95</td>
<td>90</td>
<td>51.0</td>
<td>51.2</td>
</tr>
<tr>
<td>T.J.</td>
<td>M</td>
<td>28</td>
<td>IV</td>
<td>25(l,IV.)</td>
<td>60</td>
<td>Nausea</td>
<td>186.900</td>
<td>110</td>
<td>110</td>
<td>28.9</td>
<td>29.1</td>
</tr>
<tr>
<td>E.S.</td>
<td>M</td>
<td>41</td>
<td>IV</td>
<td>63</td>
<td>74</td>
<td>Weakness</td>
<td>172.70</td>
<td>88</td>
<td>85</td>
<td>56.3</td>
<td>59.2</td>
</tr>
<tr>
<td>R.M.</td>
<td>M</td>
<td>40</td>
<td>III</td>
<td>50</td>
<td>69</td>
<td>Weakness</td>
<td>186.869</td>
<td>100</td>
<td>84</td>
<td>42.0</td>
<td>43.0</td>
</tr>
</tbody>
</table>

Mean of all observations 181.111* 86 92.46 45.8 51.7 53.0 17.2 16.4 10.4 8.3 57.9 48.7

*p Represents a statistically significant change (p < 0.01).
C = control; D = after hexamethonium; Art. = arterial; IJV = internal jugular venous.

(p < 0.01). Cerebral oxygen consumption did not change significantly in spite of the reduced blood flow through the brain. This was maintained at the expense of a reduction in cerebral venous oxygen saturation. Such a reduction indicates a decrease in the ability of the cerebral circulation to meet the metabolic needs of the brain. Partial compensation did occur due to the decrease in cerebral vascular resistance. This is demonstrated in figure 1. The horizontal line indicates no change in cerebral venous oxygen saturation. The open circles represent the actual reduction in

FIG. 1. Decrease in internal jugular oxygen saturation plotted against decrease in mean arterial pressure following hexamethonium. The horizontal line at zero represents no change in cerebral venous oxygen saturation. Open circles represent the actual reduction in oxygen saturation of internal jugular venous blood for each patient following hexamethonium. Solid circles denote values calculated on the basis of no change in cerebrovascular resistance.

TABLE 2.—The Effects of Hexamethonium in Malignant Hypertension. Cerebral Circulation and Metabolism

<table>
<thead>
<tr>
<th>Patient</th>
<th>CBF cc/100 Gm./min.</th>
<th>A-IJV O₂ Vol. %</th>
<th>CMRO₂ cc/100 Gm./min.</th>
<th>CVR mm. Hg</th>
<th>DECREASE IN MEAN ARTERIAL BLOOD PRESSURE (MM. HG)</th>
<th>DECREASE IN INTERNAL JUGULAR OXYGEN SATURATION (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.M.</td>
<td>49 53</td>
<td>6.4</td>
<td>6.7</td>
<td>3.1</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>E.J.</td>
<td>74 69</td>
<td>5.6</td>
<td>6.0</td>
<td>4.1</td>
<td>4.1</td>
<td>2.0</td>
</tr>
<tr>
<td>O.K.</td>
<td>42 34</td>
<td>6.9</td>
<td>8.5</td>
<td>2.9</td>
<td>2.9</td>
<td>4.6</td>
</tr>
<tr>
<td>D.S.</td>
<td>46 38</td>
<td>7.2</td>
<td>9.7</td>
<td>3.3</td>
<td>3.7</td>
<td>4.2</td>
</tr>
<tr>
<td>M.S.</td>
<td>46 40</td>
<td>9.5</td>
<td>8.7</td>
<td>4.3</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>W.M.</td>
<td>77 69</td>
<td>5.3</td>
<td>5.3</td>
<td>4.1</td>
<td>4.1</td>
<td>2.1</td>
</tr>
<tr>
<td>C.K.</td>
<td>52 41</td>
<td>6.5</td>
<td>7.8</td>
<td>3.4</td>
<td>3.2</td>
<td>3.6</td>
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<tr>
<td>G.H.</td>
<td>46 36</td>
<td>7.1</td>
<td>8.8</td>
<td>3.3</td>
<td>3.2</td>
<td>3.8</td>
</tr>
<tr>
<td>I.C.</td>
<td>58 42</td>
<td>5.7</td>
<td>8.7</td>
<td>3.3</td>
<td>3.7</td>
<td>3.0</td>
</tr>
<tr>
<td>A.K.</td>
<td>55 48</td>
<td>6.3</td>
<td>7.7</td>
<td>3.5</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>T.J.</td>
<td>53 31</td>
<td>7.2</td>
<td>9.1</td>
<td>3.8</td>
<td>2.8</td>
<td>3.6</td>
</tr>
<tr>
<td>E.S.</td>
<td>62 54</td>
<td>3.9</td>
<td>4.8</td>
<td>2.4</td>
<td>2.6</td>
<td>2.8</td>
</tr>
<tr>
<td>R.M.</td>
<td>51 39</td>
<td>10.3</td>
<td>13.3</td>
<td>5.3</td>
<td>5.2</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Mean 55 46* 6.8 8.1* 3.6 3.5 3.5 2.5*

C = control; D = after hexamethonium.
*Signifies a statistically significant change (p < 0.01).
†A-IJV O₂ = cerebral oxygen extraction.
cerebral venous oxygen saturation for each patient following hexamethonium. The solid
circles denote values calculated on the basis of
no change in cerebrovascular resistance. There
was not a sufficient number of values to justify
calculating a statistical curve of regression,
but the figure suggests that a majority of our
patients exhibited a progressive decrease in
cerebral venous oxygen saturation as the mean
arterial blood pressure fell. However the change
in cerebral venous oxygen saturation was not
as severe as would have occurred without a
significant cerebrovascular relaxation.

Other significant metabolic changes in-
cluded a decrease in arterial oxygen content
and a rise in cerebral venous carbon dioxide
content following hexamethonium.

**Discussion**

Cerebral blood flow and cerebral oxygen
consumption were observed to be within the
normal range in 13 patients with premalignant
or malignant hypertension. There was a
marked and consistent increase in cerebro-
vascular resistance averaging 119 per cent,
which appeared to be roughly correlated with
the grade of retinopathy.

These studies indicate that the reduction in
cerebral vascular resistance, although signifi-
cant, was not sufficient to compensate com-
pletely for the fall in blood pressure following
hexamethonium. Some information regarding
the possible mechanism of the reduction in
cerebrovascular resistance in hypertensive
patients following hexamethonium may be
obtained by comparing our results and those
of Dewar with those of Kety following
differential spinal block. Kety observed a 16
per cent reduction in cerebral vascular resis-
tance following a decrease in blood pressure
brought about by a procedure which acted on
vascular beds remote from the brain. We ob-
served a 29 per cent and Dewar a 28 per cent
reduction in cerebrovascular resistance follow-
ing parenteral hexamethonium. The blood
pressure reductions reported by Kety and by
Dewar were of comparable magnitude, while
that observed by us was of greater severity.
In each of these studies the arterial blood
pressure was lowered to approximately the
same level. It would then appear that hexa-
methonium is more effective than differential
spinal block in reducing resistance to blood
flow through the brain in hypertensive pa-
tients. This could be the result of (1) blocking
of the autonomic innervation of the cerebral
blood vessels, (2) a more profound change in
cerebral metabolites, and (3) a direct action
on the smooth muscle of the cerebral vessels.

Most of the experimental evidence indicates
that the cerebral sympathetics play a minor
role in the regulation of cerebral vascular
resistance in hypertensive patients which
would tend to discredit the first possibility.?
Since the changes in cerebral venous oxygen
and carbon dioxide were comparable in both
the differential spinal block and our hexa-
methonium studies, this would hardly account
for the difference observed in the cerebral
vascular resistance. It seems, therefore, that
the most likely explanation is a direct action
of hexamethonium on cerebral blood vessels.

Dewar observed essentially no change in
cerebral blood flow following hexamethonium
in six hypertensive patients. Five of his
patients had grade II and one had grade IV
hypertensive retinopathy. Administration of
hexamethonium resulted in a reduction in
mean arterial blood pressure from 153 to 107
mm. Hg (30 per cent). All of the patients in
our series had either grade III or grade IV
hypertensive retinopathy. Following hexa-
methonium there was a 39 per cent reduction
in mean arterial blood pressure and a 16 per
cent decrease in cerebral blood flow. In both
studies the cerebral vascular resistance was
reduced by approximately 30 per cent. There-
fore, in our patients the cerebral blood vessels
were incapable of relaxing to a degree sufficient
to maintain normal cerebral blood flow in
contrast to Dewar’s observations. It seems
likely that the severity of the hypertensive
vascular disease could account for the reduc-
tion in cerebral blood flow. These studies seem
to indicate that the mean arterial blood pres-
sure should not be acutely reduced with
hexamethonium by more than 30 per cent of
the control value in patients with premalign-
ant or malignant hypertensive vascular
disease.

Morris reported a 39 per cent reduction in
mean arterial blood pressure in normotensive
patients following hexamethonium infusion. He observed a 30 per cent decrease in cerebral blood flow compared with our 16 per cent change from the control value. However in his patients the cerebral arterial perfusion pressure following hexamethonium was 62 mm. Hg. This degree of hypotension probably accounts for the differences in our results. The slight increase in blood volume, due predominantly to an increase in plasma volume observed by Morris following hexamethonium, might play a role in lowering the arterial oxygen content.

**Summary**

1. The effect of hexamethonium bromide upon cerebral hemodynamics and metabolism was studied in 13 patients with severe hypertension.

2. Sixty minutes after intramuscular hexamethonium mean arterial blood pressure fell 39 per cent, cerebral vascular resistance was reduced 29 per cent, and cerebral blood flow decreased 16 per cent.

3. Cerebral oxygen consumption was maintained at the expense of a reduction in cerebral venous oxygen saturation.

4. The possible mechanisms of action of hexamethonium upon the cerebral vascular bed are discussed.

5. These studies, in conjunction with the observations of Dewar, seem to indicate that the mean arterial blood pressure should not be acutely reduced with hexamethonium by more than 30 per cent of the control value in patients with either premalignant or malignant hypertensive vascular disease.

**Summario in Interlingua**

1. Le effecto de bromido de hexamethonium super le hemodynamiche e metabolismo cerebral eseva studiate in 13 patientes con sever hypertension.

2. Sexanta minutas post le administration intramuscular de hexamethonium le valores median del pressio arterial cadea per 39 pro cento; le resistentia vascular in le cerebro eseva reduite per 29 pro cento; e le fluxo sanguine in le cerebro suffreva un reduction de 16 pro cento.

3. Le consumption cerebral de oxygeno eseva mantenite al costo de un reduction del saturation cerebro-venal de oxygeno.

4. Le possibile mechainismo del action de hexamethonium super le base vascular del cerebro es discutite.

5. Iste studios—conjunctemente con le observationes de Dewar—pare indicar que in patientes con morbo vascular hypertensive in phases premaligne o maligne le valores median del pression arterial non deberea esser reduite acutemente per plus que 30 pro cento del valores de controlo.

**Acknowledgments**

We wish to acknowledge the technical assistance of Miss Beryl Welch and Mrs. Audrey Peterson.

We are indebted to Dr. A. Dale Console for the supply of hexamethonium.

**References**


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