Adjunctive Use of a Biologic Pressor Agent, Angiotensin, in Management of Shock


The physician in practice is frequently aware of the need for an agent, other than those presently available, to maintain the blood pressure when the patient is in shock. Such an agent would afford valuable time in which to ascertain the cause of the hypotension and attempt to alleviate it.

A series of investigations over many years may have led to the discovery of such an agent. Late in the nineteenth century, Tigerstedt and Bergman demonstrated a rise in blood pressure after injection of a crude kidney extract. In the early part of the twentieth century, Volhard in Germany and Goldblatt and associates in Cleveland further established that a substance, apparently of renal origin, could produce hypertension. Finally, in 1940, this pressor substance was identified independently by Page and Helmer in the United States and by Braun-Menendez and coworkers in Argentina. In 1957, this substance, angiotensin, was synthesized for the first time by 2 groups who were working independently. Schwyzer, Iselin, Kappeler, Riniker, Rittel, and Zuber in Basle, Switzerland, and Bumpus, Schwarz, and Page in Cleveland synthesized the compound independently. The chemical substance, which the kidney apparently produces as a part of the normal mechanism for control of blood pressure, is now available for use.

In this study, an attempt was made to evaluate the effectiveness of angiotensin II in the management of shock. Special attention was given to the variation in responses of blood pressure to subcutaneous or intramuscular routes of administration. A review of the results obtained in the patients who first received angiotensin for control of shock at the John Sealy Hospital is included.

Animal Experiments

In this study of angiotensin in shock, experimental animals were used initially. Dogs were infused with high dosages for periods of from 8 to 12 hours. Some of the animals expired during infusion. Animals in the supine position received doses of angiotensin II that would raise the systolic pressure to 250 to 300 mm. Hg. Most of these dogs died of pulmonary edema. Seemingly, position was important to heart function since about 75 per cent of the animals died if the supine position was employed instead of the right lateral position. Another group of animals received the same dosages of angiotensin II after previous digitalization. Again, the supine position was used, and in this group, only about 50 per cent died from pulmonary edema. Another group of dogs was tested after a day and a half of dehydration, and this procedure offered approximately the same degree of protection as digitalization. In a period of 110 to 155 minutes, with successive increases in dose of angiotensin, there was a gradual increase in the left atrial pressure as the ventricular pressure rose (fig. 1). When the dose was increased sufficiently to elevate the arterial pressure above 300, arrhythmias occurred, and the left atrial pressure rose still more, as did the diastolic pressure in the left ventricle. Right atrial and right ventricular pressures also rose further with higher doses.

In 1 animal, during cannulation of the left ventricle, the cannula was inadvertently introduced into the ostium of a coronary artery. Since it was not realized that misplacement had occurred, the experiment was completed.

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*Supplied as Hypertensin CIBA.
The dog survived with the cannula left in place, although he developed bigeminy. Actually, it is surprising that a more serious arrhythmia did not ensue since an extremely high concentration of the drug perfused the myocardium. Two days later, the dog died of acute myocardial infarction.

Hypovolemic shock was created in 12 animals by the removal of blood over periods of 2 to 4 hours. When mean arterial pressure was below 50 to 60 mm. Hg, 0.5 mg. of angiotensin was given subcutaneously. The responses, which occurred in 3 to 9 minutes, lasted from 18 to 90 minutes with an increase of mean arterial blood pressure of 37 to 88 mm. Hg. In the same circumstances, 6 more animals were given the drug intramuscularly. Response occurred within 3 to 7 minutes, and mean arterial blood pressure increased from 38 to 86 mm. Hg. Two other experimental animals that were bled to pressure levels below 30 mm. Hg could not be sustained with angiotensin II by either the intramuscular or the subcutaneous route. Intravenous infusions of the agent maintained 2 other dogs for 30 and 20 hours, respectively.

**Preliminary Trials in Normal Human Subjects**

At a prison farm in Texas, prisoners are granted a slight reduction of sentence if they submit to some forms of controlled experimentation. For this study, angiotensin was given intravenously for 1 to 2 hours to 32 prisoners. Six of them received the drug subcutaneously. Most of the subjects were young, healthy, and normotensive. In figure 2, the response to a single subcutaneous dose of angiotensin II (0.15 mg.) is shown. Response occurred within 3 minutes and lasted for approximately 10 minutes. Data on 5 of the control subjects are shown in table 1. These data adequately illustrate that there is a definite individual difference in response to a single subcutaneous injection of angiotensin II.

**Clinical Findings**

Angiotensin II was then utilized in patients initially only after the proper individual dosages were predetermined. For example, when angiotensin II was to be used during mitral commissurotomy, the dosage level that would not precipitate an arrhythmia was determined the day before. The response of a 42-year-old white female patient with mitral stenosis is shown in figure 3. Even with stenosis of the mitral valve, an appreciable increase in blood pressure was achieved.
USE OF ANGIOTENSIN IN MANAGEMENT OF SHOCK

Table 1
Controls—Single Subcutaneous Injection of Angiotensin II

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Pulse increase or decrease</th>
<th>Dose (in gamma)</th>
<th>Time for response (min.)</th>
<th>Systolic B.P. increase</th>
<th>Diastolic B.P. increase</th>
<th>Duration of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>M</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>M</td>
<td>2</td>
<td>100</td>
<td>5</td>
<td>22</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>M</td>
<td>6</td>
<td>150</td>
<td>3</td>
<td>30</td>
<td>25</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>M</td>
<td>8</td>
<td>200</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>M</td>
<td>20</td>
<td>500</td>
<td>1</td>
<td>37</td>
<td>15</td>
<td>43</td>
</tr>
</tbody>
</table>

Table 2
Response of Patients in Shock to Angiotensin II

<table>
<thead>
<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Sex</th>
<th>Pulse increase or decrease</th>
<th>Dose/min. (gamma)</th>
<th>Time for response (min.)</th>
<th>Systolic B.P. increase</th>
<th>Diastolic B.P. increase</th>
<th>Time on drug (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shock 2°—bilateral neck dissection</td>
<td>51</td>
<td>M</td>
<td>24</td>
<td>2½</td>
<td>10</td>
<td>25</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Shock 2°—bilateral sympathectomy</td>
<td>64</td>
<td>M</td>
<td>15</td>
<td>2</td>
<td>20</td>
<td>30</td>
<td>15</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>Hemorrhagic shock—extensive scalp resection</td>
<td>53</td>
<td>F</td>
<td>10</td>
<td>1½</td>
<td>5</td>
<td>25</td>
<td>10</td>
<td>290</td>
</tr>
<tr>
<td>4</td>
<td>Endotoxic shock (bowel obstruction)</td>
<td>42</td>
<td>F</td>
<td>20</td>
<td>1</td>
<td>15</td>
<td>15</td>
<td>10</td>
<td>960</td>
</tr>
<tr>
<td>5</td>
<td>Shock 2°—CVA</td>
<td>71</td>
<td>M</td>
<td>25</td>
<td>1.2</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Neurogenie shock (epidural block)</td>
<td>36</td>
<td>F</td>
<td>10</td>
<td>1½</td>
<td>10</td>
<td>50</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Postoperative shock; previous myocardial infarct</td>
<td>60</td>
<td>M</td>
<td>40</td>
<td>1</td>
<td>3</td>
<td>45</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>Hemorrhagic shock</td>
<td>78</td>
<td>M</td>
<td>25</td>
<td>1½</td>
<td>15</td>
<td>20</td>
<td>15</td>
<td>105</td>
</tr>
<tr>
<td>9</td>
<td>Hemorrhagic shock</td>
<td>48</td>
<td>M</td>
<td>30</td>
<td>2½</td>
<td>30</td>
<td>35</td>
<td>20</td>
<td>285</td>
</tr>
<tr>
<td>10</td>
<td>(After hemorrhage controlled, blood replaced. Patient taken off angiotensin and arfonad required to keep blood pressure down.)</td>
<td>48</td>
<td>M</td>
<td>8</td>
<td>5</td>
<td>30</td>
<td>55</td>
<td>30</td>
<td>260</td>
</tr>
</tbody>
</table>

During the past year, this procedure, predetermination of dosage level and administration of angiotensin, has been used routinely in every case of mitral valvulotomy. Ordinarily, during the finger manipulation of the mitral valve, the patient's blood pressure will drop to shock levels. Sometimes, as much as 3 to 10 minutes are required to restore the blood pressure to normal levels, with the result that the surgeon may have to wait with the finger in the atrium for periods of 3 to 5 minutes between manipulations. Thus, the finger might have to remain inside the atrium for as long as an hour. With angiotensin, the pressure returned to the original level in a period of 30 to 40 seconds, and the mitral valve could be manipulated within 1 minute. Obviously, this increased the efficiency and safety of the procedure and could be utilized without development of arrhythmias. In all the patients, systolic pressures did not exceed 140 to 150 mm. Hg with the use of angiotensin II.

Patients with severe mitral stenosis seemed to respond less to the same doses of angiotensin II than did those with milder stenosis. One patient with constrictive pericarditis did not respond at all to intravenous infusion of the drug. Two weeks after pericardiectomy, the same amount of angiotensin II administered over the same period of time elicited a moderate response.

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The effects of angiotensin II administration to patients in shock can be seen in Table 2. Patient 10, in whom the aorta was replaced from the left to the diaphragm, developed a clotting defect and began to hemorrhage through the graft. Because blood was accumulating in the chest, this hemorrhage was unrecognized for a period of hours. The patient failed to respond to norepinephrine, and an infusion of angiotensin was utilized with good response. The patient was maintained on this preparation for 72 hours, and the hemorrhage was discovered and corrected. Forty-five minutes after replacement of the blood, angiotensin was discontinued. The patient then developed hypertension (systolic pressure of 200 mm Hg), so that within 1 hour, the patient, who was hypertensive preoperatively, had been taken off angiotensin and then, of necessity, was given a vasodilator to prevent excessive elevation of arterial pressure.

Another patient, on entering the recovery room after hysterectomy, went into shock for no known reason (Fig. 4). Since she did not respond to norepinephrine, an infusion of angiotensin II was given which caused the blood pressure to rise to 85 to 90 mm Hg. Administration of angiotensin II was continued for 2 hours and then terminated without further difficulty.

At this time, no patient who has been treated with angiotensin II has had renal shutdown. Two of the patients who were given the drug have died. One died apparently of cerebral vascular accident during shock. This patient received norepinephrine first, then angiotensin II. The other patient had toxic hepatitis with acute liver necrosis at autopsy, presumably due to inadvertent administration of massive doses of chlorpromazine. She was on norepinephrine for 3 days and then on angiotensin for 3 more days. The remaining patients have done as well as might have been expected with other therapy and, in some instances, better. No cardiac irregularities or other untoward effects have been observed that might be attributable to the angiotensin II.

Comment

On the basis of these studies, angiotensin II seems to be effective in elevating blood pressure during shock, whether it is administered subcutaneously or intramuscularly. The delay in response and the prolongation of effectiveness of this agent, when given by subcutaneous injection, are probably caused by the slower rate of absorption when this route is utilized.

In clinical use, angiotensin has consistently produced a rise in blood pressure and a decrease in pulse rate without untoward side-effects. It has been found as effective as norepinephrine and, in fact, appears to be useful in some instances in which norepinephrine fails. There was no evidence of tachyphylaxis in its use. The means by which this agent acts is not thoroughly understood, and much experimental work is in progress to determine the exact mechanism of its action. Only when this is known will the indications and limitations of its use be well defined.

References


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