Clinical Evaluation of Diazoxide

A New Treatment for Acute Hypertension

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JOHN TUCKMAN, M.D., AND JOHN MAGILL

THE effectiveness of chlorothiazide and related compounds as diuretics and antihypertensive agents has been well established. Much confusion still exists, however, regarding the exact mechanisms by which these agents reduce arterial pressure. Although it has not been fully established whether the reduction in arterial pressure following the thiazides is due solely to sodium diuresis,1 is secondary to a decrease in plasma volume,2 or is the result of removal of sodium or water from the blood vessels, the hypotensive effect seemed3 at least in some way related to sodium diuresis. It is understandable, therefore, that the synthesis of a compound that reduces arterial pressure but causes sodium retention would create much interest. Diazoxide is structurally similar to chlorothiazide (fig. 1). Rubin, Roth, and Winbury4 suggested either that this agent might represent a true separation of the antihypertensive properties associated with the benzothiazine diuretics or that it might be representative of a new class of antihypertensive agents.

Studies from this laboratory with a very alkaline solution of diazoxide have shown that it is a potent antihypertensive agent in man.5 A 300-mg. dose administered slowly in two or three divided doses intravenously caused a prompt reduction in arterial pressure, which was associated with an increase in the cardiac output and a decrease in total peripheral resistance. The reduction in arterial pressure was not associated with any signs of collapse or cerebral ischemia. The predictability of response, the ease of administration, and the lack of undesirable side effects suggested that diazoxide might be a useful agent in the therapy of acute hypertensive emergencies. The only limiting factor was its short duration of action (2 to 3 hours).

Recently a less alkaline preparation of diazoxide* has become available, which allows a 300-mg. dose to be administered rapidly in a single injection. The present communication analyzes the clinical data on 46 hypertensive patients who received diazoxide rapidly intravenously.

Methods and Materials

Forty-six hypertensive patients received diazoxide intravenously. Thirty-three were patients with moderately severe to severe hypertension and eight were patients with toxemia of pregnancy. Five patients with severe hypertension received diazoxide as the only antihypertensive agent repeatedly over a 20- to 30-day period to determine its clinical usefulness and whether drug resistance or tachyphylaxis developed. Six of the eight patients with toxemia of pregnancy received 300 mg. of diazoxide once, one received 300 mg. of diazoxide twice over a 24-hour period and the other received three 300-mg. injections at 12-hour intervals. Four patients whose arterial pressure was not reduced satisfactorily following 300 mg. of diazoxide received additional doses of 150 to 300 mg. of diazoxide 5 to 10 minutes after the initial injection.

The drug was supplied in 20-ml. ampules in a concentration of 15 mg. per ml. and pH of 11.50. The average effective dose was 300 mg. (one ampule), which was administered rapidly within 10 to 15 seconds. The speed of injection was impor-

*The diazoxide in this study was kindly supplied as Mutabase® by J. Black, M.D., Schering Corp., Bloomfield, New Jersey. The oral form of the drug has been withdrawn from use because of hyperglycemia and other reactions. The preparation for intravenous use is available.
tant in determining the duration of the hypotensive effect. When the drug was diluted (as with the original substance) the same magnitude of hypotension resulted but the duration of action was only 2 to 3 hours. The dose of diazoxide was important in determining both the magnitude and duration of hypotension. In the early stages of investigation when less than 300 mg. was administered, 100 mg. to 200 mg., the maximum fall in arterial pressure never exceeded 15 per cent while the duration of hypotension was not more than an hour.

Results

The average mean arterial pressure in the 33 patients who received 300 mg. of diazoxide undiluted rapidly was 165 ± 19 mm. Hg (table 1). One to 2 minutes following administration of the drug in these patients (initial phase) the mean arterial pressure had fallen to an average of 120 ± 15 mm. Hg (27 per cent reduction). During the next 3 to 5 minutes (second phase) there was an average rise in the mean arterial pressure to 140 ± 14 mm. Hg (or a 15 per cent reduction as compared to the control). The response of the arterial pressure and heart rate in a typical patient following 300 mg. of diazoxide administered rapidly can be seen in figure 2.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm. Hg)</th>
<th>% Change in MAP</th>
<th>Heart rate, beats/min.</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>165 ± 19</td>
<td></td>
<td>84 ± 11</td>
<td></td>
</tr>
<tr>
<td>First phase</td>
<td>120 ± 15</td>
<td>-27</td>
<td>98 ± 15</td>
<td>+17</td>
</tr>
<tr>
<td>(duration 2-4 min.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second phase</td>
<td>140 ± 14</td>
<td>-15</td>
<td>88</td>
<td>..</td>
</tr>
<tr>
<td>(average duration 4.7 ± 1.7 hr.)</td>
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</tbody>
</table>

The average duration of action of diazoxide when all patients were considered was 18 ± 12 hours. When the seven patients who had an unexplained prolonged duration of hypotension (24 to 72 hours) were excluded, however, the average duration of action was 4.7 ± 1.7 hours. The speed of injection of diazoxide exceeded 2 minutes in 10 patients. The fall in arterial pressure in these patients varied between 8 and 15 per cent while the duration of hypotension varied between 4 and 20 minutes.

Additional doses of diazoxide in the four patients whose arterial pressure did not respond to 300 mg. caused a greater than 25 per cent reduction in mean arterial pressure in two patients and no response in two patients. One of these latter patients was in terminal uremia; the other patient was in acute pulmonary edema.

The effect of repeated doses of 300 mg. of diazoxide over a 30-day period in five patients is summarized in table 2. Figure 3 demonstrates the typical effect of repeated doses of
DIAZOXIDE

Table 2

Effects of Repeated Doses of Diazoxide Intravenously in Five Hypertensive Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weight—lbs.</th>
<th>Arterial pressure—mm. Hg</th>
<th>Dose-mg.</th>
<th>Duration—hrs.</th>
<th>Total no. of injections</th>
<th>Period of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>R.S.</td>
<td>158</td>
<td>190/130 170-140/110-100</td>
<td>300</td>
<td>48 72 5</td>
<td>32 days</td>
<td></td>
</tr>
<tr>
<td>C.M.</td>
<td>139.5</td>
<td>210/110 190-160/100-85</td>
<td>300</td>
<td>24 48 7</td>
<td>30 days</td>
<td></td>
</tr>
<tr>
<td>S.S.</td>
<td>275</td>
<td>190/120 170-160/110-100</td>
<td>300</td>
<td>8 24 5</td>
<td>30 days</td>
<td></td>
</tr>
<tr>
<td>I.M.*</td>
<td>159</td>
<td>180/140 160-140/110-100</td>
<td>300</td>
<td>24 72 3</td>
<td>10 days</td>
<td></td>
</tr>
<tr>
<td>T.H.†</td>
<td>178</td>
<td>230/100 180-160/100-80</td>
<td>300-600 2-3</td>
<td>7</td>
<td>10 days</td>
<td></td>
</tr>
</tbody>
</table>

*This patient whose primary disease is suspected to be glomerulonephritis gained 6 pounds of weight in 7 days. Three days of chlorothalidone 100 mg. daily caused prompt diuresis. Since then and without any other treatment blood pressure remained 140/100 for 20 days.

†Patient was in C.H.F., was given oral diuretics and digitalis. In spite of loss of weight and clearance of C.H.F. the duration of hypotensive action of diazoxide remained essentially the same (2 to 3 hours).

diazoxide on mean arterial pressure, heart rate, and weight on a patient during this period. It can be noted that repeated doses of diazoxide are not associated with the development of drug resistance or tachyphylaxis, since the response on the last day of therapy was similar to the first. None of these patients suffered any side effects either immediately or at any time after the administration of the drug. The level of blood urea nitrogen was not altered. Only one patient, who was strongly suspected of having chronic glomerulonephritis showed a weight gain during chronic diazoxide administration. A Phthalamidimine agent (chlorothalidone) promptly caused diuresis.

Table 3 shows the effect of diazoxide on the arterial pressure and heart rate in the eight toxemic patients. None of the toxemic patients gained weight. The effect of diazoxide on the systolic and diastolic pressure on a patient with toxemia of pregnancy can be seen in figure 4.

In five of the six pregnant patients who were in labor the fall in arterial pressure following diazoxide was associated with temporary cessation of labor. Pitocin induction was necessary for reinition of labor in these patients.

In six patients small amounts of diazoxide inadvertently leaked into the subcutaneous tissues. Although associated with a severe burning sensation which lasted 1 to 2 hours, no sloughing of tissues occurred. One patient received 300 mg. of diazoxide in the brachial artery; this resulted in the immediate flushing

Figure 3

Effect on mean arterial pressure, heart rate, and weight on one patient who received diazoxide (intravenously) repeatedly.

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of the hand and an increase in temperature and a burning pain in the forearm, which lasted for 1 hour.

Discussion

Diazoxide administered intravenously is a potent antihypertensive agent that reduces arterial pressure without producing signs of collapse or cerebral ischemia. Previous studies have shown that the fall in arterial pressure was consistently associated with an increase in cardiac output (+40 per cent) and decrease in total peripheral resistance (−41 per cent). These changes in cardiac output and total peripheral resistance persisted long after the peak action of the drug had been reached. The mechanism of the reduction in total peripheral resistance is not clear from these studies, but animal data suggest that diazoxide causes reduction in peripheral resistance by direct action on the arteriolar muscle. From the cardiac and cerebral hemodynamic standpoint, diazoxide resembles hydralazine, since both agents cause an increase in the cardiac output, heart rate, and cerebral blood flow. Actual cerebral blood flow determinations have not been performed in this laboratory but the lack of signs of cerebral ischemia accompanying the reduction in arterial pressure and the increase in cardiac output strongly indicate that there is at least maintenance of the cerebral blood flow even at the point of the greatest magnitude of hypotensive action of diazoxide. It is significant also that the level of blood urea nitrogen did not increase following the intravenous administration of diazoxide in the 10 patients studied. Detailed effects of diazoxide on the renal circulation will be the subject of a separate communication.

Although diazoxide chemically resembles chlorothiazide, it is pharmacologically different. When chlorothiazide is administered intravenously, (1) it is not as potent as when administered orally, (2) there is a delay in hypotensive action of at least 1 to 2 hours, and (3) there is an increase in urinary output and decrease in cardiac output. When diazoxide is administered intravenously, (1) it is more effective than by mouth, (2) there is an immediate onset of hypotensive action within 1 to 2 minutes, and (3) there is a decrease in urinary output and an increase in cardiac output. Like chlorothiazide, diazoxide causes hyperglycemia. While only a transitory hyperglycemia was noted in the patients studied here following intravenous diazoxide (blood sugar had returned to control values by 24 hours) studies from other laboratories indicate that a more prolonged hyperglycemia follows the oral administration of diazoxide. The transitory nature of hyperglycemia following intravenous diazoxide would seem harmless, particularly since repeated doses of diazoxide over a prolonged period are seldom indicated.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Initial phase</th>
<th>Second phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic mm. Hg</td>
<td>175 ± 28.8</td>
<td>129 ± 24.8 (-26%)</td>
<td>141 ± 15.5 (-20%)</td>
</tr>
<tr>
<td>Diastolic mm. Hg</td>
<td>112.5 ± 7.5</td>
<td>72.5 ± 14.1 (-35%)</td>
<td>82 ± 6.5 (-26%)</td>
</tr>
<tr>
<td>MAP mm. Hg</td>
<td>144 ± 16.1</td>
<td>100 ± 11.9 (-31%)</td>
<td>112.5 ± 6.5 (-22%)</td>
</tr>
</tbody>
</table>

Figure 4

Effect of diazoxide on arterial blood pressure in patient with toxemia.
DIAZOXIDE

No reason can be given for the apparent importance of the speed of injection in determining both the magnitude of the blood pressure fall and the duration of the hypotensive effect. It should be emphasized, however, that when less than 300 mg. of diazoxide is administered or when 300 mg. is not administered in a 10- to 15-second period only a short hypotensive response is noted. Similarly, no explanation can be given for the complete lack of hypotensive effect that is noted in some patients.

Although the exact mechanism of the hypotensive action is not understood, our experience indicates that diazoxide administered intravenously is an ideal agent for the treatment of all types of acute hypertension. Its advantages are many. The standard dosage of 300 mg. (one ampule) eliminates the need for individual titration. The immediate onset of action (1 to 2 minutes) accomplishes the goal of therapy rapidly. The maintenance of cardiac output eliminates the danger of collapse or cerebral ischemia. Finally, it can be administered repeatedly without the development of drug resistance, which makes it a practical effective agent.

These advantages in the treatment of the patient with acute hypertensive disease become more evident when the drug is compared with the other antihypertensive agents commonly employed. Reserpine in a dosage of 2.5 to 5 mg. administered intramuscularly every 8 to 12 hours has been the most popular agent used. Admittedly the standard dosage eliminates the need for individual titration. Reserpine has a slow onset of action, however, since its antihypertensive action is not manifest for 2 to 3 hours. If immediate reduction in arterial pressure is necessary, some other agent must be used. Furthermore, reserpine can seldom be administered for more than 48 to 72 hours without producing excessive drowsiness, flushing of the face, nasal congestion, and occasionally signs of Parkinsonism. Because of the possibility of shock during anesthesia obstetricians are reluctant to use reserpine in toxemic patients who frequently require cesarean section. Admittedly the cessation of labor following diazoxide administration may be a disadvantage. It probably represents part of a generalized relaxation of the smooth muscle and is not a toxic reaction of the drug. Awareness of this development and institution of oxytocics will promptly restart labor.

When immediate reduction in arterial pressure is mandatory, hexamethonium by intravenous injection has been the treatment of choice. Although the onset of action of intravenous hexamethonium is almost immediate, great care must be taken in its administration to prevent collapse. It is necessary to titrate each patient individually. The drug is contraindicated in the presence of coronary ischemia because of the marked reduction in cardiac output. Hexamethonium is not effective in combating the hypertension of toxemia.

Although it is not necessary to titrate hydralazine when administered intravenously, its administration is frequently associated with objectionable tachycardia and throbbing headache. It is seldom as effective in reducing the arterial pressure as reserpine and hexamethonium.

Veratrum has been quite effective in the management of the hypertension of acute toxemia but it has not been as useful in the management of acute hypertension in the non-pregnant patient. The need for individual titration, the frequent incidence of nausea and vomiting, and the frequent tachyphylaxis with repeated administration greatly limits its usefulness.

Although sodium retention has not been observed following diazoxide administered intravenously, one of the patients who received diazoxide repeatedly over a 7-day period did gain weight. It would seem desirable, therefore, particularly in the hypertension of toxemia where sodium retention plays an important role, to administer a diuretic concomitantly.

Summary

Forty-six hypertensive patients have received diazoxide intravenously. Three hun-
dried milligrams (one ampule) administered rapidly undiluted resulted in a 27 per cent average reduction in mean arterial pressure in 1 to 2 minutes. During the next 3 to 5 minutes the arterial pressure increased gradually to a 15 per cent average reduction as compared to the control. The average duration of diazoxide in these patients was $4.7 \pm 1.7$ hours. No signs of postural hypotension, cerebral ischemia, or collapse were noted. At the peak of hypotensive action there was a 41 per cent average reduction in total peripheral resistance.

Repeated doses of diazoxide in both non-pregnant patients with acute hypertension and pregnant patients with toxemia adequately controlled the arterial pressure and were not associated with the development of drug resistance. The standard dosage of 300 mg. (one ampule), the immediate onset of action and the moderately long duration of action, the maintenance of cardiac output, the lack of significant side effects, and the fact that it can be administered repeatedly without the development of drug resistance make diazoxide administered intravenously the ideal therapy for acute hypertension.

References


Addendum

Additional experience with diazoxide administered intravenously has shown that a dose of 300 mg. in hypertensive patients weighing over 150 pounds may produce only a slight reduction in arterial pressure for a short duration, e.g., a duration of action of 30 to 60 minutes instead of 4 to 5 hours. If a satisfactory fall in arterial pressure does not follow 300 mg. of diazoxide, the dosage of diazoxide should be increased to 5 mg. per Kg.
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