The Acute Hemodynamic Effects of Diazoxide in Man

By William R. Wilson, M.D., and Ronald Okun, M.D.

In the past 10 years many new drugs that lower blood pressure have been introduced for the treatment of hypertension. Several of them have not withstood the rigors of controlled clinical trials; others have faded away because side effects precluded their successful application. The useful hypotensive drugs developed have provided the physician one means to prolong the life of the individual with malignant hypertension, hypertensive heart failure, or encephalopathy and reverse many of the signs and symptoms of the disease. The purpose of this paper is to present our observations of the acute hemodynamic effects of a new hypotensive drug, diazoxide, in man.

Diazoxide is a non-diuretic benzothiadiazine synthesized by Dr. J. G. Topliss, M. H. Sherlock, and Dr. N. Sperber of the Chemical Research Division, Schering Corporation, and subsequently evaluated for hypotensive and diuretic activities.2, 3 It lacks the free sulfamyl group that chlorothiazide possesses. It also has a methyl group in the 3 position and chloride in the 7 instead of the 6 position. When given intravenously to dogs, diazoxide decreases arterial pressure and total peripheral resistance, but increases heart rate, stroke volume, cardiac output, transmural right atrial pressure, and isometric myocardial contractile strength.4 In man arterial pressure is lowered within 30 seconds. Supine as well as standing pressures are reduced. The depressor effect lasts about 5 hours (range = 2 to 24 hours). In animals,5 and in man6-8 diazoxide may cause salt and water retention that can be eliminated by the addition of a diuretic benzothiadiazine.

Materials and Methods

All patients studied were from the Moore Clinic of the Johns Hopkins Hospital, Baltimore. Observations were made on 14 Negro subjects who were divided into three groups. The first group was composed of five hypertensive patients with an average age of 48 years, and an average mean arterial blood pressure of 132 mm. Hg. There were three women and two men. The second group was composed of five normotensive subjects with an average age of 46 years and an average mean arterial pressure of 110 mm. Hg. There were two women and three men. The third group contained four hypertensive patients whose average age was 41 years and average mean arterial pressure 131 mm. Hg. The groups did not differ in average body surface area or hypertensive classification (except the normotensive subjects).9 None of the 14 patients had received hypotensive drugs for the preceding 2 weeks.

On the day of the acute study, each patient was in a fasting state. No sedative was given. Measurements of right atrial pressure, systemic arterial pressure, cardiac output, and heart rate were made with the patient in the supine position. A small catheter was introduced through the basilic vein and advanced until its tip was lying free within the right atrium. A Courand needle was placed in a brachial artery. Pressures were recorded from the right atrium and brachial artery with Statham strain gages. Mean pressures were obtained by electrical integration. Pressure recordings were made immediately before cardiac output determinations. The catheter in the right atrium was filled with indocyanine green dye connected through a three-way stopcock to a dye reservoir and injection system. The needle in the brachial artery was connected through a short, small-bore, polyethylene tubing to the cuvette of a Gilford densitometer. Dye solutions were made up before the study and a small amount of blood was added so that the dye in the injectate would be bound to plasma. Approximately 2.8 mg. of dye were used for each injection. Dye curves were obtained by drawing blood through the densitometer with a constant speed pump after injec-
tions in the right atrium; 50 ml. of blood were used for calibration of the densitometer. Three-point calibration curves were made in each study. Cardiac output was calculated from dye curves by the Stewart-Hamilton method. Total peripheral resistance was calculated in terms of dynes sec. cm. Lead II of an electrocardiograph was recorded during each cardiac output determination in order to measure heart rate. Dye curves, heart rates, and blood pressures were recorded with a Sanborn direct-writing oscillograph. Three measurements of output and pressures were made before, and 15 and 60 minutes after drug infusion. The first two groups received diazoxide, 5 mg./Kg. The diazoxide solution was diluted 1:3 with isotonic saline solution and given through the right atrial catheter over a 5-minute period. Each subject in the third group received an equivalent volume of a sodium hydroxide solution that contained 5.529 mg. NaOH/ml. When diluted 1:3 with isotonic saline solution, the pH was identical with the vehicle of the diazoxide solution given to the other two groups.

Students’ t test for paired data was used for statistical analysis of the data before and after infusion within each group at each measured time interval. Statistical comparisons (t tests) were also made between the hypertensive patients given diazoxide and those receiving the NaOH buffer solution.

Results

The pertinent data are recorded in table 1. Group averages for the control, 15- and 60-minute observations are presented together with standard errors of the means. In addition, the individual changes in systemic arterial pressure and cardiac output are shown in figures 1 and 2, respectively.

Systemic arterial pressure. At the 15- and 60-minute periods following diazoxide the hypertensive patients had a significant decrease in supine mean arterial pressure of greater than 20 mm. Hg. The normotensive patients had a similar reduction in arterial pressure at both periods. The control subjects

Table 1

<table>
<thead>
<tr>
<th>Hemodynamic Effects of Diazoxide 5 mg./Kg. Intravenously in Five Hypertensive Patients and Five Normotensive Subjects and Effects of an NaOH Buffer Solution in Four Hypertensive Patients</th>
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<tr>
<td><strong>A. Hypertensive patients given diazoxide, average values, 5 patients</strong></td>
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<tr>
<td>Supine mean arterial pressure, mm. Hg</td>
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<td>Pulse rate, beats/min.</td>
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<td>Peripheral resistance, dynes sec. cm.³</td>
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| **B. Normotensive subjects given diazoxide, average values, 5 patients** | | |
| Supine mean arterial pressure, mm. Hg | 110 ± 4 | 87 ± 3 | < 0.02 | 89 ± 3 | < 0.01 |
| Pulse rate, beats/min. | 78 ± 6 | 105 ± 4 | < 0.01 | 95 ± 4 | N.S. |
| Cardiac index, L./min./M.² | 3.0 ± 0.2 | 4.6 ± 0.4 | < 0.02 | 4.2 ± 0.5 | < 0.05 |
| Stroke index, ml./min./M.² | 39 ± 2 | 44 ± 5 | N.S. | 45 ± 5 | N.S. |
| Supine mean rt. atrial pressure, mm. Hg | 3.0 ± 5 | 3.0 ± 0.5 | N.S. | 3.0 ± 0.7 | N.S. |
| Peripheral resistance, dynes sec. cm.³ | 1555 ± 125 | 860 ± 80 | < 0.01 | 955 ± 140 | < 0.01 |

| **C. Hypertensive patients given NaOH buffer solution, average values, 4 patients** | | |
| Supine mean arterial pressure, mm. Hg | 131 ± 6 | 132 ± 7 | N.S. † | 127 ± 8 | N.S. † |
| Pulse rate, beats/min. | 77 ± 8 | 77 ± 7 | N.S. | 80 ± 6 | N.S. |
| Cardiac index, L./min./M.² | 2.9 ± 0.1 | 2.7 ± 0.1 | N.S. | 3.0 ± 0.5 | N.S. |
| Stroke index, ml./min./M.² | 38 ± 3 | 36 ± 2 | N.S. | 40 ± 9 | N.S. |
| Supine mean rt. atrial pressure, mm. Hg | 4.0 ± 0.75 | 3.75 ± 0.75 | N.S. | 3.5 ± 0.5 | N.S. |
| Peripheral resistance, dynes sec. cm.³ | 1975 ± 95 | 2093 ± 135 | N.S. | 2020 ± 350 | N.S. |

*Standard error of the mean.
†Not significant at the 5-per cent level.
‡See text.
given the NaOH buffer solution showed no significant changes in arterial pressure.

**Pulse rate.** The mean pulse rates of the three groups were approximately equal in the control periods. Fifteen minutes after diazoxide infusion, a significant increase in pulse rate occurred in both the hypertensive and normotensive subjects. The average increases were 28 beats per minute (p < 0.01), and 27 beats per minute (p < 0.01), respectively. One hour after diazoxide, the tachycardia was still present in the hypertensive group, but had decreased toward control values in the normotensive subjects. Infusion of the NaOH buffer solution did not alter heart rate appreciably at either time interval.

**Cardiac index and stroke index.** Fifteen minutes after diazoxide the average cardiac index of the hypertensive group increased from 3.0 to 4.0 L/min./M² (p < 0.01). A significant increase of 1.6 L/min./M² (p < 0.02) was also seen in the normotensive group. One hour after the infusion, the mean cardiac indices for both of these groups decreased slightly but were still significantly different from their control values. The control subjects who were given the NaOH buffer solution showed no significant alterations in cardiac index at either period. Calculated stroke indices did not differ appreciably from control values in each group at either time.

**Right atrial pressure.** Right atrial mean pressures were normal in the three groups in the control period. Following infusion of diazoxide to the first two groups, or the NaOH buffer solution to the control subjects, right atrial pressure showed no significant change.

**Peripheral resistance.** Fifteen minutes after diazoxide the peripheral resistance of the hypertensive patients decreased from 1,875 to 1,105 dynes sec. cm⁻⁵ (p < 0.01); a similar reduction was still present at 60 minutes. In the normotensive group, peripheral resistance decreased from 1,555 to 860 dynes sec. cm⁻⁵ (p < 0.01) at 15 minutes, and to 955 dynes sec. cm⁻⁵ (p < 0.01) at 1 hour after diazoxide. Infusion of the NaOH solution produced no significant changes in peripheral resistance.

**Group comparisons.** Group comparisons were made only between the hypertensive patients given diazoxide and those given the control NaOH solution. Significant differences (at the 5-per cent level or better) were observed in supine mean arterial pressure, pulse rate, cardiac index (15-minute period only), and peripheral resistance at both 15 and 60 minutes after infusion.

**Discussion**

The mechanism responsible for the immediate depressor effect of intravenous diazoxide
adequate amounts had patients hypertensive emergencies. One given. us hypertensive in the treatment of six patients with various hypertensive emergencies. Three of the patients had a sharp depressor response when adequate amounts (3 to 5 mg./Kg.) were given. One of these three patients had hypertensive encephalopathy, the second patient had severe hypertension associated with a ruptured cerebral aneurysm, and the third patient had severe epistaxis and advanced hypertension. The hypotensive effect occurred within a few minutes and lasted 2½ to 12 hours (average 7 hours). The average decrease in supine mean arterial pressure following nine infusions in this group was 25 mm. Hg. Many of the symptoms related to hypertension were relieved. Somnolence and other side effects sometimes seen after other parenteral hypertensive drugs were not observed following intravenous diazoxide. These three patients recovered and are now receiving other hypotensive drugs orally.

The other three patients had malignant hypertension with terminal chronic renal disease and are now dead. Evaluation of their response to diazoxide was complicated by the introduction of other drugs in one instance and by the rapid progression of the malignant phase of the disease in the other two patients. When doses of 3 to 5 mg./Kg. of diazoxide were employed, a significant decrease in systemic arterial pressure was observed even in this group. A recent study of the acute changes following the administration of intravenous diazoxide (5 mg./Kg.) to six other hypertensive patients (three with diabetic glucose tolerance tests) showed no clinically important increases in blood sugar at intervals of 5, 15, 30, 60, and 180 minutes after infusion of the drug.12

On the other hand, chronic oral administration of diazoxide may produce a number of untoward reactions. Diazoxide can precipitate hyperglycemia in latent diabetic subjects when given alone. One patient developed severe polyuria, thirst, weight loss, hyperglycemia, and ketonuria after doses of 100 to 300 mg. given daily for 10 weeks. When the drug was stopped, the symptoms and signs of diabetes mellitus disappeared within 10 days as the blood sugar decreased to normal. A recent controlled, double-blind trial of oral diazoxide combined with trichlormethiazide revealed significant elevations of postprandial blood sugars of 15 of 30 hypertensive patients.

Figure 3
Effect of trichlormethiazide combined with diazoxide at two-dosage levels on postprandial blood sugars. Note the marked hyperglycemia in six of the 15 patients receiving TCZ and diazoxide, 400 mg./day. Most, but not all, of the reactors had diabetic glucose tolerance tests.

has been investigated by Rubin and co-workers3,4 using Haddy’s technic to determine segmental forelimb resistance in dogs. The fall in resistance across the total vascular bed is caused mainly by the fall in small vessel resistance. This resistance is offered chiefly by the arterioles. Since intravenous diazoxide produced similar decreases in arterial pressures and increases in blood flow in man, it is possible that its acute depressor effect is related to a decrease in systemic arteriolar tone. Both animal and human studies suggest that diazoxide does not produce venous pooling, since cardiac output increases and right atrial pressures either rise during infusion in dogs,4 or do not change significantly in man, as measured 15 minutes after infusion.

Initial clinical experience with parenteral diazoxide suggests that it may be useful in the treatment of malignant hypertension and other hypertensive emergencies.10,11 One of us (W.R.W.) has used intravenous diazoxide in the treatment of six patients with various hypertensive emergencies. Three of the patients had a sharp depressor response when adequate amounts (3 to 5 mg./Kg.) were given. One of these three patients had hypertensive encephalopathy, the second patient had severe hypertension associated with a ruptured cerebral aneurysm, and the third patient had severe epistaxis and advanced hypertension. The hypotensive effect occurred within a few minutes and lasted 2½ to 12 hours (average 7 hours). The average decrease in supine mean arterial pressure following nine infusions in this group was 25 mm. Hg. Many of the symptoms related to hypertension were relieved. Somnolence and other side effects sometimes seen after other parenteral hypertensive drugs were not observed following intravenous diazoxide. These three patients recovered and are now receiving other hypotensive drugs orally.

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on varying doses of diazoxide combined with a fixed dose of trichlormethiazide (fig. 3).\textsuperscript{13} None of the patients was taking insulin. The combination of diazoxide and trichlormethiazide evoked a hyperglycemic response especially, but not exclusively, in patients with a diabetic glucose tolerance test. Hirsutism was another untoward effect of the combination of trichlormethiazide and diazoxide in this study. Eight women noted increased hair on the face, extremities, and chest. Trials of oral diazoxide in man have ceased in England,\textsuperscript{14} and in this country. Future investigations in animals of the mechanism of the hyperglycemic effect of diazoxide singly, and combined with a thiazide diuretic, however, seem warranted. The completed studies of diazoxide in animals and in man have contributed additional support to the hypothesis that the depressor effect of the benzothiadiazines may be independent of their actions on the renal excretion of sodium.

Summary and Conclusions

The acute hemodynamic effects of the non-diuretic benzothiadiazine, diazoxide, were measured in five hypertensive patients and five normotensive subjects.

In both groups diazoxide produced a significant and prompt reduction in supine arterial blood pressure, an increase in heart rate and cardiac output, a marked decrease in peripheral resistance, but no change in right atrial mean pressure or stroke volume. The depressor effect of this drug in man is caused by a reduction in systemic arteriolar tone.

Chronic oral administration of diazoxide, when combined with a diuretic benzothiadiazine, is associated with a significant incidence of hyperglycemia especially, but not exclusively, in patients with diabetic glucose tolerance tests. Hirsutism is another untoward reaction. The mechanisms of these toxic effects are not known.

The rapid onset of its depressor action and the lack of reduction in cardiac output suggest that parenteral diazoxide may be a useful drug in selected patients with hypertensive emergencies. Additional cautious trial of intravenous diazoxide in patients with severe hypertension seems indicated, although further evaluation may reveal other side effects that will preclude its usefulness even in such circumstances.

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References

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