Dose-Response Relation of Diazoxide in Children with Hypertension

ROBERT C. BOERTH, M.D., PH.D., AND WILLIAM R. LONG, M.D.

SUMMARY Diazoxide was administered to sixteen pediatric patients (ages 10 months to 13 years) with secondary forms of hypertension. Admission BP was 178 ± 8/130 ± 5 mm Hg (mean ± SEM). Diazoxide was administered rapidly intravenously in doses ranging from 2 to 7.5 mg/kg. A significant (P < 0.001), linear log dose-response relationship was obtained which showed that a 3 mg/kg dose of diazoxide lowered diastolic BP by an average of 30 mm Hg. In five patients reduction of diastolic BP by a single injection of diazoxide was no different than when the same total dose was given as two or three small injections repeated at fifteen to twenty minute intervals. It is concluded that 1) many hypertensive children respond significantly to doses of diazoxide smaller than the usually recommended 5 mg/kg; 2) diazoxide has a significant dose-response relationship in hypertensive pediatric patients; and 3) the desired blood pressure response in hypertensive children can be titrated using repeated small injections of diazoxide.

DIAZOXIDE IS A NONDIURETIC benzothiadiazine derivative used for the treatment of acute hypertensive crises. It is thought to act directly on vascular smooth muscle to decrease peripheral vascular resistance, thereby lowering systolic and diastolic blood pressure. Currently it is recommended that to achieve effective reduction of blood pressure in hypertensive adults, diazoxide should be administered as a rapid intravenous injection at a dose of 5 mg/kg. That one dose (5 mg/kg) and mode of administration have also been found to be effective in the acute treatment of hypertension in children. However, it is not known whether smaller doses of diazoxide are effective in reducing the blood pressure of hypertensive children, nor is it clear whether this drug can be administered in a manner other than as a single rapid intravenous injection.

The current report describes the relation between dose of diazoxide and reduction of blood pressure in hypertensive children. It also shows that blood pressure reduction in hypertensive children can be effectively titrated using multiple small injections of diazoxide repeated at 10 to 15 minute intervals.

Methods

The current study evaluates the blood pressure responses of 16 patients from 10 months to 13 years of age who were treated for hypertension at the Vanderbilt University Children's Hospital. These 16 patients received a total of 72 injections of intravenous diazoxide for the acute treatment of hypertension. Each patient received diazoxide on one to 10 different occasions. When a patient received diazoxide on more than one occasion, subsequent injections were given only after the effects of a previous injection had dissipated. All blood pressure determinations were obtained with a blood pressure cuff on the arm with each child in a supine position. Diastolic blood pressure was measured as the 4th phase of the Korotkoff sounds when both 4th and 5th phases were clearly audible; otherwise diastolic pressure was taken to be the 5th phase of the Korotkoff sounds. From the total of 72 injections, adequate blood pressure data for analysis were obtained from the hospital records following 49 of the injections. All blood pressure data for analysis were taken 15 to 20 minutes after the injection of diazoxide when the blood pressure response had stabilized.

Diazoxide was administered as a rapid i.v. injection within 10 to 20 seconds in each patient. Doses of diazoxide given to these 16 patients ranged from 2 mg/kg to 7.5 mg/kg. The linear regression of the log dose-response relation of diazoxide was determined by the method of least squares, and other statistical comparisons were made using t-tests. The criterion of significance was chosen as P < 0.05.

Results

The characteristics, admission blood pressure, phase or type of hypertension and diagnosis of each patient in this report are shown in table 1. Two of the patients had malignant hypertension with papilledema and macular star exudates. Four patients had acute elevation of blood pressure, and one of those (#11) clearly had hypertensive encephalopathy with focal blindness and convulsions which were reversed by blood pressure reduction. The other 10 patients had chronic hypertension. Fourteen of the 16 patients had a diagnosis of chronic renal parenchymal disease, one had acute poststreptococcal glomerulonephritis, and one patient had hypertension accompanying an encephalopathy of undetermined etiology. Only patient #6 had clinical evidence of heart failure. The admission blood pressure for the whole group averaged 178 ± 8/130 ± 5 mm Hg (mean ± SEM).

Nine of the patients received two different doses of diazoxide, and one child received three different doses. The various doses of diazoxide in each child were separated in time so that the blood pressure effects of a preceding dose had dissipated prior to administration of another dose. The reductions in diastolic blood pressure produced by different doses of diazoxide were shown in figure 1. These 10 individual log dose-response relations revealed several important points. First, there was marked variability of responsiveness among the individual patients. For example, at a dose of 2 mg/kg one child's diastolic blood pressure decreased 4 mm Hg, while another patient's diastolic pressure was reduced by 30 mm Hg. Second, in every patient an increased dose of diazoxide produced a greater reduction in diastolic blood pressure. Third, the slopes of the 10 individual log dose-response relations were remarkably similar.

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Table 1. Characteristics and Diagnoses of Hypertensive Children Receiving Diazoxide

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Blood Pressure</th>
<th>Adm. BP</th>
<th>Phase</th>
<th>Injections</th>
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<tr>
<td>1</td>
<td>10/12</td>
<td>M</td>
<td>170/120</td>
<td>A</td>
<td>2</td>
<td></td>
<td>HUS</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>M</td>
<td>160/120</td>
<td>B</td>
<td>1</td>
<td></td>
<td>CN</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>F</td>
<td>170/150</td>
<td>B</td>
<td>4</td>
<td></td>
<td>CRF</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>F</td>
<td>150/112</td>
<td>W</td>
<td>3</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>F</td>
<td>194/130</td>
<td>W</td>
<td>10</td>
<td></td>
<td>CP</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>F</td>
<td>124/110</td>
<td>W</td>
<td>3</td>
<td></td>
<td>CRF</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>M</td>
<td>185/130</td>
<td>W</td>
<td>9</td>
<td></td>
<td>HSN</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>W</td>
<td>190/150</td>
<td>W</td>
<td>3</td>
<td></td>
<td>CP</td>
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<td>10</td>
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<td>CP</td>
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<tr>
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<td>F</td>
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<td></td>
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<tr>
<td>15</td>
<td>11</td>
<td>W</td>
<td>170/130</td>
<td>W</td>
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<td></td>
<td>CG</td>
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<tr>
<td>16</td>
<td>13</td>
<td>W</td>
<td>170/110</td>
<td>W</td>
<td>7</td>
<td></td>
<td>LN</td>
</tr>
</tbody>
</table>

Abbreviations: Adm. BP = Blood pressure upon admission to hospital (mm Hg); Phase = phase of hypertension; A = acute hypertension; C = chronic hypertension; M = malignant hypertension; Injections = number of individual injections of diazoxide in each patient; HUS = Henoch-Schonlein purpura; CN = congenital nephrosis; CG = chronic glomerulonephritis; E = encephalopathy of undetermined etiology; CP = chronic pyelonephritis; CRF = chronic renal failure of undetermined etiology; HSN = Henoch-Schonlein nephritis; AG = acute poststreptococcal glomerulonephritis; OU = obstructive uropathy; LN = lupus nephritis.

Table 2 shows the age, phase or type of hypertension, total serum protein, serum albumin and creatinine clearance of each of the 10 patients whose dose-response curves are shown in figure 1. In order to determine if the differences in individual drug responsiveness were due to these various factors, the reductions in diastolic blood pressure produced by a dose of 3 mg/kg were determined from the 10 individual curves and compared to the other parameters. As can be seen in table 2, there was no correlation between increased responsiveness to diazoxide (i.e., increased reduction of diastolic blood pressure at a dose of 3 mg/kg) and the patient's age, phase or type of hypertension (chronic vs acute or malignant), serum protein or albumin concentration, or creatinine clearance.

The average log dose-response relation of the 49 single injections of diazoxide for which adequate blood pressure data were available for analysis is shown in figure 2. The different doses of the injections were divided into a low, middle, or high dose group. When the 49 individual points were subjected to linear regression analysis by the method of least squares, a statistically significant log dose-response relationship was demonstrated (P < 0.001). The blood pressure prior to the injection of diazoxide was no different between the low, middle, and high dose groups: 173 ± 9/123 ± 5 mm Hg, 170 ± 7/124 ± 3 mm Hg, and 170 ± 6/125 ± 3 mm Hg, respectively. Thus, the greater reduction of diastolic blood pressure seen with higher doses of diazoxide was due to an increased effect of the drug and

Figure 1. Effect of dose of diazoxide on reduction of diastolic blood pressure in 10 individual hypertensive pediatric patients. Nine patients received two different doses of diazoxide, and one patient received three different doses. Responses in each child are connected by a line.

Figure 2. Log dose-response relation to diazoxide in hypertensive children. Symbols show mean dose and mean response for low, middle and high dose groups. N = number of responses in each group. Vertical brackets show standard error of the mean for responses in each dose group. Horizontal brackets show standard error of the mean for the doses in each dose group.
not to differences in the levels of pretreatment blood pressure.

In several children it was found that diastolic blood pressure could be effectively reduced by the administration of repeated intravenous injections of small doses of diazoxide. Five patients (patients #3, 4, 5, 11 and 13 in table 1) received two or three small i.v. bolus injections of diazoxide at 10 to 15 minute intervals in an attempt to control their blood pressure. These same patients also received the same cumulative amount of diazoxide (average of 6 mg/kg) given as a single rapid injection on another occasion. To determine whether the effects of diazoxide were any different when the drug was given as several small injections at 10 to 15 minute intervals instead of a single injection, the stable reductions of diastolic blood pressure in these five children were compared between the two modes of drug administration (fig. 3). Two of these five children had acute hypertension, two had malignant hypertension and one had chronic hypertension. Three patients showed a slightly smaller reduction in blood pressure when diazoxide was given as a single dose, and two children demonstrated an increased effect with the amount given as a single bolus. There was no significant difference between the two modes of drug administration in the average reduction of diastolic blood pressure for the group. Thus, the cumulative blood pressure response to repeated small doses of diazoxide was comparable to the effect produced by a single injection.

The side effects observed in the 16 children receiving diazoxide are shown in table 3. No side effects were noted in half the patients. The most frequent side effect observed was hyperglycemia occurring in five children. Blood glucose levels ranged from 144 to 824 mg/100 ml and were obtained from one to six hours following injection of diazoxide. None of the children demonstrated any morbidity as a result of the hyperglycemia. Nausea, vomiting, localized burning of the arm upon injection of diazoxide and trembling each occurred in three patients. None of the side effects was noted to be serious, and all remitted spontaneously without sequelae.

Discussion

The current study represents the first clear demonstration in man of a dose-related reduction of blood pressure produced by diazoxide. This dose-response relationship was shown by two different ways. First, 10 individual hypertensive children received two or three different doses of diazoxide. In each patient a larger dose of diazoxide produced a greater reduction in diastolic blood pressure. Furthermore, the slopes of the 10 individual log dose-response curves were very similar (fig. 1). Second, when the blood pressure data from the entire group of 16 patients were analyzed, there was a highly significant, linear log dose-response relationship to diazoxide as shown in figure 2.

The finding in the current study of a significant relationship between dose of diazoxide and reduction of blood pressure in man is not unexpected from a pharmacological viewpoint. In animal studies increased doses of diazoxide have been shown to produce greater reduction of peripheral vascular resistance and greater decreases in blood pressure in both dogs6-10 and normotensive and mineralocorticoid hypertensive rats.11 However, in previous reports in man, no clear relationship between hypotensive effect and dose of diazoxide has been demonstrated. In many of the previous clinical studies a single dose of either 5 mg/kg or 300 mg was utilized.12-18 There are other reports which utilized different doses of diazoxide. The results from those studies suggest a marked variability of individual responsiveness to diazoxide, but they also suggest a relationship between dose of diazoxide and reduction of blood pressure. In the first clinical report on diazoxide, Kakavias and Finnerty showed that a dose of 2 mg/kg produced a stable reduction of mean arterial pressure of greater than 40 mm Hg in one patient (their fig. 2).19 Lockwood and coworkers20 and Johnson and Kapur21 have shown significant reduction of blood pressure in hypertensive adults receiving diazoxide in a dose of 3 mg/kg. In another study Johnson found no effect on blood pressure with a dose of 2 mg/kg administered over 20 minutes, whereas significant reduction of blood pressure occurred at a dose of 4 mg/kg administered intravenously within 30 seconds.22 Miller and coworkers23 showed that a total dose of 150 mg reduced diastolic blood pressure of hypertensive patients by an average of greater than 30 mm Hg. They also showed similar reduction of diastolic blood pressure with doses of 150, 300 and 600 mg.

![Figure 3. Comparison of stable diastolic blood pressure reduction produced by cumulative dose versus same dose as a single injection in five hypertensive children (patients #3, 4, 5, 11 and 13 in table 1). Cumulative dose was given as two or three injections at 10 to 15 minute intervals. Total cumulative dose and single dose were the same in each patient (average = 6 mg/kg). Responses in each patient are connected by a line. Symbols at the edges of the panel show mean responses for the group (no significant difference of mean responses).](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td>3</td>
<td>nausea and vomiting</td>
</tr>
<tr>
<td>3</td>
<td>burning sensation (localized)</td>
</tr>
<tr>
<td>3</td>
<td>trembling</td>
</tr>
<tr>
<td>1</td>
<td>rigidity of injected arm</td>
</tr>
</tbody>
</table>
However, the different doses were apparently given to different patients, and thus wide individual variation in responsiveness to diazoxide may have obscured a dose-response relationship in that study. Several investigators have reported that some hypertensive adult patients did not respond to a single intravenous injection of 300 mg of diazoxide, but a second or third injection within 10 to 15 minutes produced significant reduction of blood pressure in those patients.\textsuperscript{24-26} Thus, the data available to date suggest wide individual variability of responsiveness to diazoxide, a finding which is clearly demonstrated by the results of the current study.

The demonstration of a significant dose-response relationship in man together with the observed variability of individual responsiveness to diazoxide suggest that reduction of diastolic blood pressure in hypertensive patients can and should be titrated with diazoxide. The recommended dose of 5 mg/kg is an average dose and is not necessarily correct for an individual patient as shown in figure 1. Some of the pediatric patients in this report had significant reduction in diastolic blood pressure with doses of diazoxide as low as 2 mg/kg whereas others required doses greater than 5 mg/kg to obtain any significant reduction of blood pressure. The reason for the individual variability in responsiveness to diazoxide is not apparent in the current study. Pearson and Breckenridge\textsuperscript{27} have suggested that hypertensive adult patients with reduced renal function have an increased responsiveness to diazoxide because less of the drug is bound to serum proteins. However, it appears unlikely that this could explain the variation of individual responsiveness to diazoxide in the current study since there was no relationship between blood pressure reduction and creatinine clearance or serum protein concentrations, as shown in table 2.

Another factor which may be important in determining responsiveness to antihypertensive drugs is the status of the plasma volume and extracellular fluid volume. Finnerty and coworkers\textsuperscript{28} have shown that expansion of the plasma and extracellular fluid volumes decreases the responsiveness to diazoxide in hypertensive adult patients. Plasma volume and extracellular fluid volume were not measured in the patients in the current report. Therefore it is possible that the individual variability in responsiveness to diazoxide as shown by the separation of individual dose-response lines along the dose axis (fig. 1) was due to differences between patients in the relative state of the plasma and extracellular fluid volumes. However, this possibility seems less likely with the observation that the one child with heart failure (\#6, table 1) and obvious clinical evidence of expanded blood and extracellular fluid volumes did not show decreased responsiveness to diazoxide but rather had a 40 mm Hg reduction of diastolic blood pressure at a dose of diazoxide of only 2 mg/kg. Furthermore, it is very unlikely that changes or differences of these fluid compartments influenced the separate dose-response relations in these same patients for the following reason. Half of the patients whose data are shown in figure 1 initially received the higher dose of diazoxide, while the other patients received the lower dose of diazoxide first. However, the slopes of the 10 individual dose-response curves were very similar, strongly suggesting that any change of plasma or extracellular fluid volume between the different doses of diazoxide in each patient did not alter the relationship between dose and blood pressure reduction.

Currently it is recommended that in order to be effective, diazoxide must be administered as a single intravenous injection given rapidly within 10 to 30 seconds.\textsuperscript{14} The explanation for this mode of administration has been the finding that 90% of an administered dose of diazoxide is bound to human plasma proteins.\textsuperscript{29-31} Mroczek and coworkers\textsuperscript{32} studied 15 adult patients with essential hypertension of whom seven had chronic hypertension and eight had accelerated hypertension. They found that the rate of i.v. administration of diazoxide (6–8 sec vs 10 min) to the group with chronic hypertension did not influence the reduction of blood pressure, but no change in blood pressure was seen in the group with accelerated hypertension when the diazoxide was administered slowly. However, there are data which conflict with the concept that diazoxide must be administered rapidly in order to be effective. Johnson and Kapur\textsuperscript{33} performed a crossover study in 10 hypertensive patients given diazoxide as a 30 second injection or a 30 minute infusion, and Crout and coworkers\textsuperscript{34} performed a similar crossover study in seven hypertensive patients, administering diazoxide as a 10 second injection compared to a 10 minute infusion. In both studies the magnitude and duration of blood pressure reduction were not related to the rapidity of diazoxide administration. Significant reduction of blood pressure in hypertensive patients has also been achieved when diazoxide was administered orally.\textsuperscript{19} The results in the current study show that reduction of diastolic blood pressure in hypertensive children is of the same magnitude whether the dose of diazoxide is given as a single injection or as multiple smaller injections repeated at 10 to 15 minute intervals (fig. 3). Thus, our findings together with others in the literature suggest that rapidity of diazoxide administration does not influence the magnitude of response.

It should be pointed out that of the five children in the current report treated with both a single injection and repeated smaller injections, two had malignant hypertension, two had acute hypertension and one had chronic hypertension. There was no relationship between the phase or type of hypertension and the response to slowly administered diazoxide. The discrepancy between our results and those of Mroczek et al.\textsuperscript{14} may be due to important differences in the etiology of the hypertension since all the patients in the study of Mroczek and coworkers had essential hypertension whereas all the children in this report had secondary hypertension. Another difference in these two studies is the age of the hypertensive patients (children vs adults). Thus it is very difficult to compare the results between the two studies.

The results in the current study indicate that diazoxide is a safe and effective drug for the acute treatment of hypertension in children. Over the dosage range studied, diazoxide has a significant log dose-response relationship in hypertensive children such that larger doses produce greater reduction in diastolic blood pressure. Although marked individual variation occurs in responsiveness to diazoxide, blood pressure of many hypertensive children is significantly reduced by doses of diazoxide smaller than the 5 mg/kg usually recommended. Because of the variability of responsiveness between patients, because of the significant dosee-
response relationship and because the effectiveness of diazoxide is not related to rapidity of injection, we feel that acute therapeutic reduction of diastolic blood pressure in hypertensive children can be obtained more safely and effectively by titrating the desired blood pressure response using 2 mg/kg intravenous injections of diazoxide repeated at 10 to 15 minute intervals.

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References


Corrections

Stanger et al: Circulation 56: 159, 1977. On p 168, table 4, the description of vascularity in chest roentgenograms in Asplenia should read “usually decreased” and in Polysplenia should read “usually increased.”

Brown et al: Circulation 55: 329, 1977. On p 333, expression 14, the quantity in parentheses should be:

\[
\left( \frac{\rho \min - \rho w}{A \min - A w} \right)^2
\]
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