Diazoxide Concentration-Response Relation in Hypertension

RICHARD I. OGILVIE, M.D., JOHN H. NADEAU, M.D., and DANIEL S. SITAR, PH.D.

SUMMARY The pharmacokinetic disposition and antihypertensive response of bolus infusions of diazoxide, 1, 2, or 4 mg/kg over 5, 10, or 20 seconds, were examined in seven patients with chronic stable essential hypertension and mean arterial pressures (MAP) between 122 and 155 mm Hg off therapy. Maximal reductions in MAP were noted 2 minutes after each dose, and a linear correlation was obtained in all patients between dose or plasma diazoxide concentration and maximal change in MAP. Individual concentration-time curves were analyzed to determine the apparent volume of distribution at steady state (Vdss range, 0.178 to 0.250 liter/kg), beta t1/2 (range, 32 to 62.5 hours), and plasma clearance rate (Clp range, 2.2 to 5.3 ml/kg • hour-1) for the calculation of loading and maintenance doses designed to produce steady-state concentrations within 0.5 hours. These infusions resulted in steady-state reductions in MAP (16% to 30%) which could be predicted from the concentration-response curves of each patient after bolus infusions. With the use of kinetic principles, a diazoxide dose regimen (average load, 7.5 mg/kg at 7.5 mg/min; average maintenance, 10% of loading dose every 6 hours) produced gradual and predictable reductions in MAP in patients with accelerated hypertension, since the response was proportional to plasma diazoxide concentrations.

(Hypertension 4: 167-173, 1982)

KEY WORDS • pharmacokinetic disposition • steady state concentration response • loading and maintenance doses • accelerated hypertension • clinical dose guideline

THE non-diuretic drug, benzothiadiazine diazoxide, is a direct arteriolar vasodilator that effectively lowers arterial pressure in hypertensive patients by decreasing peripheral arteriolar resistance. After a 300 mg i.v. bolus dose, blood pressure is maximally reduced in 2 minutes, then rises rapidly over the next 10 to 40 minutes to a plateau level that is maintained for a variable length of time. This same dose of diazoxide administered over a longer period has been observed to have a plateau effect of less magnitude and shorter duration. It was postulated that, because diazoxide is highly protein-bound, the high plasma-free diazoxide concentrations initially present after rapid bolus infusions are vital to the drug's overall effect. However, successful blood pressure control has been achieved using infusion times in excess of 30 seconds or by administering small incremental doses at repeated time intervals, suggesting a correlation between plasma diazoxide concentrations and its hypotensive effect. The present study investigates this relationship in patients with chronic or accelerated hypertension.

Methods Diazoxide Pharmacokinetics and Concentration Response after Bolus Doses

Seven men with chronic stable essential hypertension and mean arterial pressures (MAP) between 122 and 155 mm Hg (X 138 mm Hg), who were off antihypertensive therapy, were studied (table 1). None had fundoscopic changes greater than Grade II (Keith Wagner) or a history of diabetes mellitus, signs or symptoms of coronary artery, cerebrovascular, or peripheral vascular disease. All patients had normal

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hematological indices, normal serum protein concentrations, and were without clinical or laboratory evidence of liver dysfunction.

Current antihypertensive medication was discontinued for 4 weeks before both parts of the study. No alterations in dietary sodium intake were made. The study was carried out in two parts, separated by a period of treatment with the usual medication to control blood pressure. Part 1 consisted of bolus doses of diazoxide administered on 2 separate days 1 week apart. On the first day, a dose of diazoxide of 1 or 2 mg/kg body weight was infused intravenously (over 5 seconds for the 1 mg/kg dose; over 10 seconds for the 2 mg/kg dose) using a Harvard servo-control pump. On the second day, the next highest dose of diazoxide was infused, either 2 or 4 mg/kg (over 10 seconds for the 2 mg/kg dose; over 20 seconds for the 4 mg/kg dose). Two subjects received 1 and 2 mg/kg doses, one subject 1 and 4 mg/kg, and four received 2 and 4 mg/kg doses.

The subjects were studied in the early morning in the 12-hour postabsorptive state in a quiet controlled environment of 20°C and 40% relative humidity. They were resting recumbent with continuous monitoring of manometric blood pressures and oscilloscope recordings every 5 minutes for the first hour and at regular intervals thereafter, using a calibrated mercury column sphygmomanometer and disappearance of Korotkoff sounds as diastolic pressure. Within- and between-observer variations were less than 5 mm Hg.

After blood samples were centrifuged, the plasma was separated and frozen for later assay of diazoxide concentrations by high pressure liquid chromatography (HPLC). Plasma diazoxide concentration values for individual subjects and doses were subjected to pharmacokinetic analysis applying a two-compartment open kinetic model using an iterative least-squares curve-fitting program ASAAM-27 on an IBM 360-75 computer. Individual values were calculated for apparent volumes of distribution at steady state (Vdss) and plasma clearance (Clp) of diazoxide. Reductions in MAP (diastolic pressure plus 1/3 pulse pressure) were plotted against the plasma diazoxide concentrations over time.

Steady-State Diazoxide Concentrations and Effects

Data for diazoxide concentrations vs maximal hypotensive effect for individual subjects were used to define a diazoxide concentration (CpM) associated with a desirable hypotensive effect for that subject. The individual plasma diazoxide concentration over time curves were used to obtain the Vdss and Clp for diazoxide so as to be able to calculate loading and maintenance doses designed to produce steady-state plasma diazoxide concentrations within 0.5 hours [load in mg/kg = (CpM)(Vdss); maintenance dose in mg/kg each hour = (CpM)(Clp)].

The usual antihypertensive medication of six of the seven subjects studied in Part 1 was again discontinued for 4 weeks. Under the same conditions as in Part 1, the subjects were studied in the early morning in the 12-hour postabsorptive state in a quiet controlled environment. After 30 minutes of rest for baseline determinations, the diazoxide loading dose was infused over 30 minutes using a Harvard servo-control pump, followed by a further 3.5 hours of continuous infusion of a maintenance dose. Blood samples were drawn every 60 minutes for determination of plasma diazoxide concentrations. Sphygmomanometric blood pressures were recorded every 30 minutes. Two days later, the patients' usual antihypertensive medications were restarted.

Clinical Protocol for Hypertensive Emergencies

The average Vdss (0.214 liter/kg) and Clp (0.0036 liter/kg • hour⁻¹) for diazoxide observed in the seven subjects studied in Part 1 was used to calculate the dose-schedule guide to be applied in clinical situations. From the diazoxide concentration-response curves observed in these patients with stable essential hypertension, using regression analysis we calculated that a CpM of diazoxide of 35 mg/liter would induce an approximate reduction of 25% in MAP. We also assumed that this 25% reduction in MAP would be a safe goal in most hypertensive emergencies without compromising cerebral or coronary blood flow due to shifts in autoregulatory limits.

A protocol was established for use in the Medical Intensive Care Unit designed to result in a reduction in MAP of about 25% by infusion of a loading dose of diazoxide of 7.5 mg/kg.* The loading dose was to be administered intravenously at a rate no faster than 7.5 mg/min. As the commercial preparation of diazoxide (Hyperstat-Schering Corporation) has a concentration of 15 mg/ml, the protocol was simplified to a 0.5 ml infusion of undiluted solution each minute for a time equal to the body weight in kilograms. The loading dose could be terminated earlier if the desired blood pressure had been attained. The maintenance

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*The dose schedule guideline was calculated as follows. desired

\[ \text{CpM} = 35 \text{ mg/liter} \]

\[ \text{Vdss} = 0.214 \text{ liter/kg} \]

\[ \text{Clp} = 0.0036 \text{ liter/kg • hour}^{-1} \]

\[ \text{Loading dose} = (\text{CpM})(\text{Vdss}) = (35)(0.214) = 7.5 \text{ mg/kg} \]

\[ \text{Maintenance dose} = (\text{CpM})(\text{Clp}) = (35)(0.0036) = 0.126 \text{ mg/kg • hour}^{-1} \text{ or 0.75 mg/kg every 6 hours.} \]
dose of diazoxide was calculated to be 10% of the loading dose every 6 hours, or administered as a constant infusion. Blood samples were drawn at intervals for assay of diazoxide content.

Results

Diazoxide Pharmacokinetics and Concentration Response after Bolus Doses

Pharmacokinetics

Plasma diazoxide concentrations observed after bolus infusions declined biphasecally in a logarithmic plot over time. The results for one subject (FZ) who received diazoxide 4 mg/kg over 20 seconds are plotted in figure 1. The early distribution, or alpha phase, averaged 0.09 hours, and the late disposition, or beta phase, averaged 47.6 hours in these seven subjects (table 2). The apparent volume of distribution at steady state Vdss averaged 0.214 liter/kg, and the plasma clearance Clp averaged 3.6 ml/kg • hour⁻¹.

Concentration-Response Relationship

Maximal reductions in MAP were noted at 2 minutes after the bolus dose in all patients, followed by a return toward baseline values over a few hours (as shown in Patient FZ, fig. 1). A clear dose response was obtained in each patient (fig. 2) when the dose was plotted against the maximal change in pressure at 2 minutes. Interpatient variability in response was large and not clearly reduced by plotting the plasma diazoxide concentrations measured at 2 minutes against the observed reductions in MAP (fig. 3).

Steady-State Diazoxide Concentrations and Effect

Using pharmacokinetic data for the disposition of diazoxide derived from each individual following the bolus doses, we calculated for that individual a loading and maintenance dose schedule designed to attain and maintain a specific plasma diazoxide concentration (table 3). The plasma diazoxide concentrations achieved with these dose calculations were close to the concentrations predicted from the previously de-

TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>MAP (mm Hg)</th>
<th>LVH</th>
<th>Creatinine clearance (ml/min)</th>
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<tr>
<td>JS</td>
<td>57</td>
<td>100.4</td>
<td>155</td>
<td>+</td>
<td>104</td>
</tr>
<tr>
<td>ML</td>
<td>64</td>
<td>81.7</td>
<td>152</td>
<td>+</td>
<td>100</td>
</tr>
<tr>
<td>HN</td>
<td>64</td>
<td>97.2</td>
<td>133</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>JN</td>
<td>60</td>
<td>85.5</td>
<td>123</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>JH</td>
<td>78</td>
<td>83.5</td>
<td>154</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>FZ</td>
<td>57</td>
<td>76.0</td>
<td>124</td>
<td>0</td>
<td>101</td>
</tr>
<tr>
<td>JM</td>
<td>26</td>
<td>73.0</td>
<td>122</td>
<td>0</td>
<td>130</td>
</tr>
<tr>
<td>X</td>
<td>58</td>
<td>85.3</td>
<td>138</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>SEM</td>
<td>6.3</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure, determined as diastolic pressure + 1/3 systolic-diastolic pressure. LVH = left ventricular myocardial hypertrophy determined by radiological and electrocardiographic criteria.

TABLE 2. Pharmacokinetic Disposition of Diazoxide after a i.v Bolus Infusion of 1-4 mg/kg

<table>
<thead>
<tr>
<th>Patient</th>
<th>α t 1/2 (hr)</th>
<th>β t 1/2 (hr)</th>
<th>Vdss (liter/kg)</th>
<th>Clp (ml/kg•hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JS</td>
<td>0.102</td>
<td>40.3</td>
<td>0.202</td>
<td>3.2</td>
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<tr>
<td>ML</td>
<td>0.091</td>
<td>45.0</td>
<td>0.235</td>
<td>4.5</td>
</tr>
<tr>
<td>HN</td>
<td>0.083</td>
<td>60.0</td>
<td>0.178</td>
<td>2.2</td>
</tr>
<tr>
<td>JN</td>
<td>0.047</td>
<td>54.7</td>
<td>0.209</td>
<td>2.6</td>
</tr>
<tr>
<td>JH</td>
<td>0.079</td>
<td>62.5</td>
<td>0.250</td>
<td>3.9</td>
</tr>
<tr>
<td>FZ</td>
<td>0.087</td>
<td>38.4</td>
<td>0.192</td>
<td>3.5</td>
</tr>
<tr>
<td>JM</td>
<td>0.109</td>
<td>32.0</td>
<td>0.234</td>
<td>5.3</td>
</tr>
<tr>
<td>Mean</td>
<td>0.085</td>
<td>47.6</td>
<td>0.214</td>
<td>3.6</td>
</tr>
</tbody>
</table>

| ± (SEM) | ± 0.004 | ± 0.4 | ± 0.009 | ± 0.4 |

α t 1/2 = half-time of the early or distribution phase. β t 1/2 = half-time of the late or elimination phase. Vdss = apparent volume of distribution in the steady state. Clp = plasma clearance of diazoxide. SEM = standard error of the mean.

FIGURE 1. Mean arterial pressure (solid line) and plasma diazoxide concentrations (dashed line) observed in Patient FZ with chronic stable hypertension given diazoxide (4 mg/kg i.v.) over 20 seconds.
Figure 2. Semilogarithmic plot of the effects of a bolus dose of diazoxide on the blood pressure response in seven patients with chronic stable essential hypertension. The bolus doses of diazoxide, 1 to 2 mg/kg (+) or 4 mg/kg (Δ), were given over 5, 10, or 20 seconds (r = -0.76, F_{1,11} = 14.7, p < 0.01).

Figure 3. Relationship of plasma diazoxide concentration to blood pressure response in seven patients with stable essential hypertension given bolus doses of diazoxide, 1 to 2 mg/kg (+) or 4 mg/kg (Δ), over 5, 10, or 20 seconds (r = -0.62, F_{1,11} = 6.87, p < 0.05).

determined kinetic parameters. These concentrations were readily maintained for 3.5 hours in all subjects; a plot of blood pressure and concentration for one patient (FZ) is given in figure 4. The smooth reduction in blood pressure is readily apparent and contrasts with the marked variations in blood pressure observed in the same patient after a 4 mg/kg bolus dose (figure 1). The reductions in MAP observed over the 3.5-hour maintenance-dose period were quite close to the reductions predicted from the individual plots of plasma diazoxide concentrations against Δ MAP at 2 minutes after the bolus infusions (fig. 3 and table 3).

To investigate further the relationship between plasma diazoxide concentrations at steady state C_{p,m} and reductions in MAP, a plot was made of the C_p at 1 hour after the bolus infusions against the Δ MAP (fig. 5). In every instance, the plot of C_{p,m} against Δ MAP observed during the 3.5-hour maintenance-infusion study was in close relation to the C_p vs effect line drawn from results of the bolus infusions. After linear regression analysis, the 95% confidence limits for reductions in MAP at a plasma diazoxide concentration of 35 mg/liter were -16.3% to -22.3%, with an average reduction of -19.3%. A steady-state plasma diazoxide concentration higher than the 35 mg/liter predicted from bolus dosing would be required in this group of patients to reduce the MAP by 25%.
Clinical Protocol for Hypertensive Emergencies

Three patients considered to have a hypertensive emergency received diazoxide infusions and had repeated determinations of plasma diazoxide.

Case 1

A 25-year-old man (RM) weighing 61 kg was admitted with malignant hypertension and acute pulmonary edema secondary to proliferative glomerulonephritis and moderate uremia (serum creatinine, 5.5 mg/dl; serum albumin, 3.0 g/dl; total serum protein, 4.9 g/dl). He was infused with 7.5 mg/kg of diazoxide over 2 hours, and his MAP was reduced by 24%. This reduction was maintained over the next 60 hours by an infusion of 7.5 mg/hr, which maintained a plasma diazoxide concentration of 44 mg/liter (fig. 6 top). Due to the patient's noncompliance in taking oral medications, the study was repeated 4 weeks later. The 7.5 mg/kg dose (given over 75 minutes) resulted in a 27% reduction in MAP and a plasma diazoxide concentration of 37 mg/liter. This was maintained by the usual maintenance dose of 7.5 mg/hr until oral medications were initiated.

*Plasma diazoxide concentrations were predicted from kinetic data of single bolus doses (table 2). Observed concentrations are means of values from the end of the load to the end of the 3-hour maintenance infusion.

†The percent change in MAP was predicted from concentration-response curves constructed after single bolus doses (fig. 3). The observed changes in MAP are the average of values from the end of the load to the end of the 3-hour maintenance infusion.
Case 2

A 56-year-old man (DK) weighing 62 kg was admitted with accelerated hypertension secondary to chronic glomerulonephritis (serum creatinine, 2.8 mg/dl; serum albumin, 4.8 g/dl; total serum protein, 8 g/dl). He was infused with 7.5 mg/kg of diazoxide over 62 minutes, at the end of which he experienced some chest discomfort and nausea. The MAP was decreased by 26% (fig. 6 center). In spite of a maintenance dose of 7.5 mg/hr, the MAP was variable, and 12 hours later a second load of 7.5 mg/kg was infused along with propranolol 8 mg i.v. The plasma diazoxide concentration of 50 mg/liter after the second load resulted in adequate blood pressure control and was maintained by a dose of 10 mg/hr.

Case 3

A 17-year-old female (SM) (gravida 1 para 0) was admitted in spontaneous labor at 35 weeks' gestation, otherwise normal physical examination, and only a trace of protein on urinalysis. One hour after delivery with a blood pressure of 180/120 mm Hg, no previous family or personal history of hypertension, and was maintained by a dose of 10 mg/hr.

Discussion

This study demonstrates a close relationship between steady-state plasma diazoxide concentrations and hypotensive effect with either bolus infusions of diazoxide (fig. 3) or maintenance infusions in the post-distribution state and in accelerated hypertension (fig. 6). The failure of earlier studies to demonstrate a relationship between plasma diazoxide concentrations in the post-distribution state and hypotensive effect is probably due to pharmacokinetic and reflex homeostatic mechanisms operative under the transient conditions induced by bolus dosing with diazoxide.

There is good evidence that relates the free or unbound fraction of plasma diazoxide against its hypotensive effect in man. The effect of rapid injections of diazoxide in hypertensive patients with renal dysfunction correlated well with the degree of renal impairment. The reduction in blood pressure correlated well with the patients' plasma urea concentration, which in turn was correlated with the percent of unbound diazoxide. It is also evident that rapid injections of diazoxide have a rapid but transient effect on blood pressure (fig. 1). The proportion of unbound diazoxide may be increased with increasingly rapid injections that limit the amount of albumin available as binding sites. However, rapid redistribution of free drug results in a marked decrease in plasma diazoxide concentrations with increases in blood pressure toward baseline values. In addition, diazoxide infusions result in an immediate increase in heart rate and cardiac output as well as increased peripheral renin activity over 1 to 2 hours. These homeostatic mechanisms would also decrease the hypotensive effect of diazoxide, and in the face of decreasing plasma diazoxide concentrations, the blood pressure would return toward baseline values (fig. 1). By creating steady-state plasma diazoxide concentrations and presumably steady-state free drug fractions, a steady-state hypotensive effect has been demonstrated (fig. 4 and table 3).

It had been predicted from the boluses that a plasma diazoxide concentration of 35 mg/liter would be associated with a 25% reduction in MAP. However, the steady-state experiment demonstrated that a higher plasma diazoxide concentration would be required for a constant 25% reduction in MAP. Differences in the free-drug fraction with the bolus doses or the increased heart rate, cardiac output, and stimulated renin-angiotensin system may be responsible for the increased drug concentration requirement during steady-state infusions. The required concentration is considerably higher than what remains 3 hours after a single bolus dose of diazoxide of 4 mg/kg (fig. 1), pointing to the need for larger dose requirements for a continuous hypotensive effect.

In contrast to the early findings in human experimentation, changes in skeletal muscle or hindlimb vascular resistance of dogs were directly related to the concentration of diazoxide in the perfusate. More recently, it has been demonstrated in this laboratory that post-distribution plasma diazoxide concentrations were correlated to arterial pressure in anesthetized open-chest dogs with a right heart bypass. A plasma diazoxide concentration of 3.5 mg/liter was associated with a 20% reduction in MAP in contrast with the 35 mg/liter required in the present study. The calculated free concentrations would be similar in both species as 57% is protein-bound in the dog and 95% is bound in man. In this animal study, low diazoxide concentrations reduced arterial resistance in slow transit-time circulatory beds such as the splanchnic bed, but higher concentrations were required to reduce arterial resistance in fast transit-time beds such as the skeletal muscle. This is consistent with the lack of effect on forearm vascular resistance in humans observed with a 300 mg bolus dose and again points to the need of higher diazoxide concentrations for a sustained hypotensive effect.

Early kinetic studies of diazoxide in humans indicated a long plasma t1/2 (17 to 35 hours), with considerable variability. Stable isotope dilution mass fragmentography extended the t1/2 from 20 to 53 hours in four subjects with extensive biotransformation, as less than one-third of a dose appeared unchanged in the urine. The HPLC assay used in the
present study is specific and sensitive without interference from the major metabolite, and the prolonged time of observation allowed definition of a long plasma t1/2 of 47.6 hours, with a range of 32.0 to 62.5 hours (table 2). The variation in apparent volumes of distribution between subjects was somewhat less than the variation in half-lives.

Although there was variation in the kinetic disposition of diazoxide, the interindividual variation in response was also striking (fig. 5). At a plasma diazoxide concentration of 35 mg/liter, the 95% confidence limits for the reduction in MAP ranged from −19.3% to −22.3%. At 30 mg/liter, the range was from −14.9% to −20.9%, and at 20 mg/liter, from −11.3% to −17.3%. The individual concentration-response curves indicated differences in sensitivity to diazoxide. This is not surprising, in view of the complexity of hypertension, age differences, and many other variables in this population. For this reason, small loading doses are recommended, so that the hypotensive response is carefully titrated over time. The loading dose should not be given over less than 1 hour, as the disposition phase may be incomplete before this time (figure 4).

We recommend a slow loading dose of diazoxide of 7.5 mg/min until the desired hypotensive effect has been achieved, usually not greater than a 25% reduction in MAP to maintain blood supply to the brain, eyes, and heart. An average total dose is 7.5 mg/kg body weight, but because of variations in kinetic disposition and responsiveness, the dose may be higher or lower in individual patients. If the desired blood pressure reduction has not been achieved after 7.5 mg/kg has been administered, the loading dose may be continued but the infusion rate should be halved to 3.75 mg/min to avoid precipitous hypotension. Once the desired blood pressure reduction has been achieved, a maintenance dose of 10% of the total loading dose may be given every 6 hours or as a continuous infusion. Occasionally, a small dose of propranolol (10 mg i.v.) given as adjunctive therapy may reduce renin release but is usually not effective in limiting increases in heart rate. Oral antihypertensive therapy with agents such as hydralazine or prazosin with a beta blocker can usually be instituted within 24 to 48 hours when the i.v. diazoxide is discontinued. As with other dose schedules, these recommendations are only guidelines that must be modified for individual patients.

Acknowledgments

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