Importance of Dissolution Rates in Producing Effective Diazoxide Blood Levels in Man

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Diazoxide blood levels, blood glucose levels, and mean blood pressure were determined following administration to hypertensive patients of single doses of diazoxide in solution, capsule, and tablet form. Blood levels were correlated with the dissolution rate of each dosage form.

DIAZOXIDE is a nondiuretic benzothiadiazine which possesses antihypertensive activity (1). During its clinical evaluation as an antihypertensive agent, a variable response was observed with the tablet dosage form of the drug. In contrast, an aqueous solution of sodium diazoxide[1] administered intravenously yielded more uniform and rapid responses. *Because hyperglycemia and other side effects occurred on prolonged administration, the oral form of diazoxide was discontinued in the chronic treatment of hypertension.* However, the intravenous form is still being used experimentally for hypertensive emergencies (2–5). Diazoxide is also now being used experimentally for the treatment of hypoglycemia (6, 7).

This paper reports the results of earlier studies devoted to determining the most suitable dosage form of diazoxide. The data obtained appear now to be of use in the design of an oral dosage form of diazoxide which would provide a rapid and uniform response in the treatment of hypoglycemia.

For each dosage form studied, the degree and time course of drug absorption after a single dose was evaluated *via* blood level measurements. In a crossover study in hypertensive subjects, the blood levels of diazoxide obtained with an alkaline solution of the drug given orally were compared with the levels obtained when the same solution was administered intravenously. Blood levels were also measured in the same subjects when the sodium salt was administered in capsule form and the free acid in tablet form.

Diazoxide blood level, blood pressure, pulse rate, and blood sugar were monitored simultaneously. The dissolution rate of each dosage form was studied to determine if there was a correlation with the blood levels obtained.

EXPERIMENTAL

Materials.—Sterile solution of sodium diazoxide containing the equivalent of 300 mg. of diazoxide in 20 ml. of water adjusted to pH 11.4 with NaOH; hard gelatin capsules containing the equivalent of 100 mg. of diazoxide as sodium diazoxide; uncoated compressed tablets containing 100 mg. of diazoxide.

Subjects.—The study was conducted with the following hypertensive subjects who were previously under continuous observation and treatment for varying degrees of moderate to severe hypertension for more than 2 years: HJ, male Negro, age 69, weight 59.6 Kg.; MP, female Negro, age 55, weight 60.9 Kg.; AB, female Negro, age 60, weight 56.0 Kg.; and OW, male Negro, age 65, weight 104 Kg.

Methods.—Observations were made while the subject was in a continuous fasting state and were started between 10:00 a.m. and 12:00 noon. No antihypertensive drugs were administered for 2 weeks prior to the study.

The sterile solution was given intravenously undiluted, at a dose of 300 mg. (20 ml.) *in about 3 min.* and orally at a dose of 600 mg. (40 ml.). The capsule and tablet were each given orally at a dose of 600 mg. In a crossover design, each subject received single doses of as many of the different preparations as was feasible at intervals of at least 10 days. Placebo capsules were given in the intervening periods. Arterial blood pressure, pulse rates, and venous blood samples to determine blood sugar and diazoxide levels were taken just prior to and up to 6 hr. after administration of the drug.

Arterial blood pressure was determined by the auscultatory method in the supine position.

Blood sugars were determined by the Somogyi-Nelson method.

Diazoxide was determined spectrophotometrically by the following method (8). Four milliters of ethyl acetate was added to 2 ml. of heparinized whole blood diluted with 1 ml. of distilled water in a glass-stoppered centrifuge tube. The tube was shaken vigorously for 1 min. and then centrifuged 1–2 min. at approximately 500 × *g*. A 2.5-ml. aliquot of the ethyl acetate layer was then transferred to another centrifuge tube containing 2.5 ml. of 4% Na_2CO_3. The tube was shaken and centrifuged as before. The absorbance of the aqueous phase was then measured at 280 mμ with a Beckman DU spectrophotometer to determine diazoxide concentration. All blood levels were corrected for zero time blanks which ranged from 1–2 mcg./ml.

Dissolution rates were determined in 20 L. of 0.1 *N* HCl contained in a 10 × 18 in. Pyrex cylinder and maintained at 37 ± 1°. The tablet or capsule to be assayed was placed in a stainless steel cylinder (25 × 64 mm.) covered at each end with a 40-mesh stainless steel screen. The stainless steel cylinder was moved in a vertical plane beneath the surface of the test fluid by means of a Stoll-Gershberg ap-

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[1] Supplied as Hyperstat by the Schering Corp.

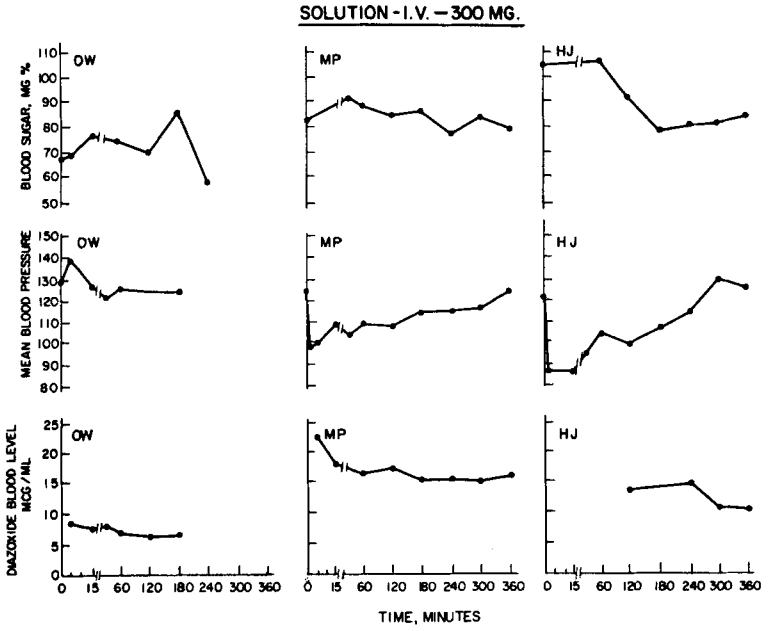

Fig. 1.—Relationship between diazoxide blood level, mean blood pressure, and blood glucose following intravenous administration of single doses of 300 mg. of diazoxide (dissolved in 20 ml. of water at pH 11.4) to each of three subjects.

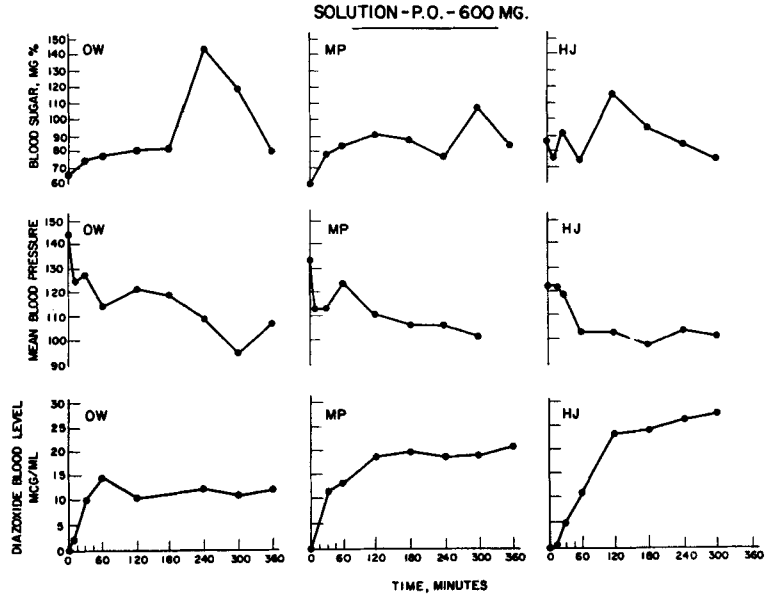

Fig. 2.—Relationship between diazoxide blood level, mean blood pressure, and blood glucose following oral administration of single doses of 600 mg. of diazoxide (dissolved in 40 ml. of water at pH 11.4) to each of three subjects.

paratus. Of necessity, solutions or dispersions were added directly to the test fluid by allowing them to flow from a volumetric pipet held midway between the stirrer and the wall of the Pyrex cylinder. The test fluid was stirred continuously with a four-blade turbine type propeller at 240–260 r.p.m. for both liquid and solid dosage forms. A small sample of fluid was removed at suitable intervals for spectrophotometric determination of diazoxide content.

RESULTS AND DISCUSSION

Pharmacological Effects of Diazoxide

Antihypertensive Effect.—Blood pressure responses, blood sugar concentrations, and diazoxide blood level were monitored for each subject. One single administration, a minimal blood level of 10 mcg./ml. was generally necessary for a drop of at least 15–20 mm. in mean arterial blood pressure, regardless of the dosage form or route of administration. This is clearly shown in Figs. 1–4 where blood sugar concentration, mean arterial blood pressure—diastolic +1/3 (systolic-diastolic)—and diazoxide blood level are plotted as a function of time for each dosage form.

Intravenously, at 5 mg./Kg., the solution produced a rapid and profound fall in pressure which was well sustained for 3 to 4 hr. However, in subject OW, a male weighing 104 Kg., 3 mg./Kg. of diazoxide yielded apparently inadequate blood levels and, therefore, failed to lower blood pressure.

Orally, at 6–10 mg./Kg., the solution produced

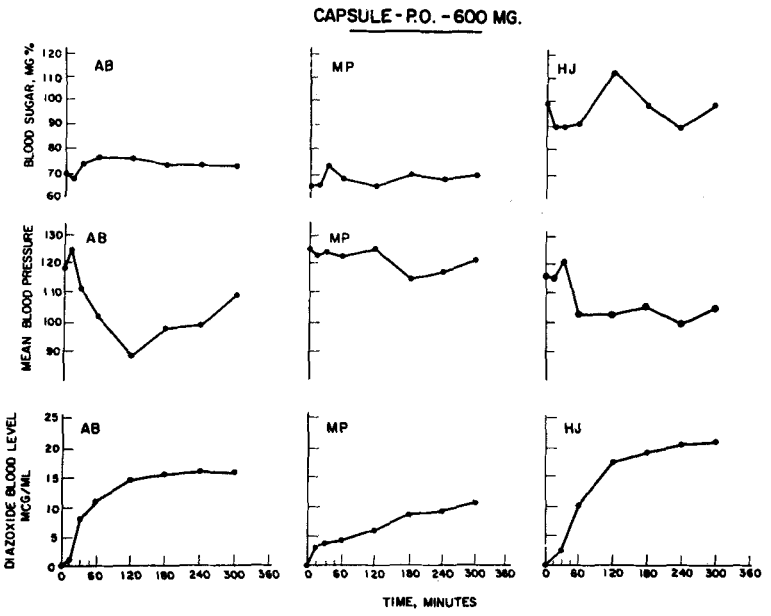

Fig. 3.—Relationship between diazoxide blood level, mean blood pressure, and blood glucose following oral administration of single doses of 600 mg. of diazoxide (as sodium diazoxide) in gelatin capsules to each of three subjects.

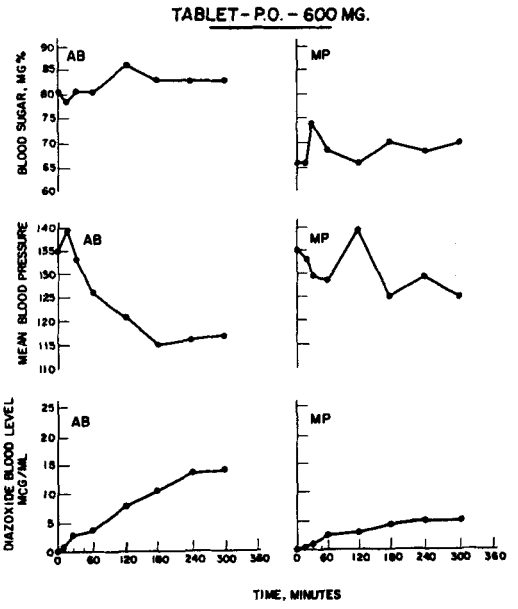

Fig. 4.—Relationship between diazoxide blood level, mean blood pressure, and blood glucose following oral administration of single doses of 600 mg. of diazoxide in tablets to each of two subjects.

blood levels over 10 mcg./ml. and a significant decrease in mean blood pressure which was well sustained for up to 6 hr.

Subject MP, who failed to respond to the capsules or tablets at 10 mg./Kg., had a maximum blood level of about 11 and 5 mcg./ml. with capsule and tablet, respectively.

Hyperglycemic Effects.—In view of the recent experimental use of diazoxide in the treatment of hypoglycemia (6, 7), the blood sugar data obtained with the various preparations are of interest. As seen in Fig. 1, hyperglycemic responses were absent when the solution was given intravenously at a dose of 300 mg. (3–5 mg./Kg.). When the solution was given orally (Fig. 2) at a dose of 600 mg. (6–10 mg./Kg.), higher blood levels and a hyperglycemic response were observed in each subject. Subject MP required a level of about 19 mcg./ml., HJ over 14 mcg./ml. (solution and capsule), and OW about 10 mcg./ml. for an adequate blood sugar response.

The data in Figs. 1–4 are consistent with the results reported by Tabachnick (9) who postulates ". . . diazoxide hyperglycemia is in part, a result of epinephrine or adrenergic mediator release. This conclusion is extremely attractive, since one can postulate that the blood pressure fall, which results from the administration of diazoxide, would certainly elicit a reflex discharge of adrenergic mediators in an attempt to maintain a homeostatic environment . . . ." This is further supported by Kvam and Stanton (10), who reduced the hyperglycemic response to diazoxide by prior treatment with a β-adrenergic blocking agent. These workers also imply that endogenous corticosteroids play a role in the hyperglycemic response.

Blood Level Studies.—The blood levels recorded in Fig. 2 clearly show that diazoxide was well absorbed when given orally as an aqueous solution of the sodium salt. The lower blood levels obtained with sodium diazoxide capsules in subjects HJ and MP (Fig. 3) and with diazoxide tablets in subjects MP and AB (Fig. 4) indicate that less drug was absorbed from these dosage forms during the test period than from the solution given orally.

The apparent plateau levels (Fig. 1) of diazoxide concentrations in the blood after the initial decline, which is representative of a distributive phase, is in agreement with previous unpublished studies indicating a biological half life of 2–3 days in man (11). In the present studies, 24-hr. urinary recoveries of diazoxide averaged about 6% for the four subjects.

Since a drug must be in solution before it can be absorbed, the rate at which a drug goes into solution

TABLE I.—DISSOLUTION RATES OF DIAZOXIDE DOSAGE FORMS

Dosage Forms	% Dissolved[a] Time, min. 5	10	15	30	45	60
Soln.	100	100	..	..	..	..
Capsule	3	20	32	50	68	83
Tablet	3	8	13	31	52	65

[a] Mean, ±5%, of duplicate determinations.

TABLE II.—DISSOLUTION RATE OF SODIUM DIAZOXIDE DOSAGE FORMS AFTER DISPERSING IN 50 ml. OF 0.1 *N* HCl

Dosage Forms	% Dissolved Time, min. 5	10	15	30
Soln.[a]	100	100	..	..
Soln.[b]	100	100	..	..
Capsule[a]	94	95	95	98
Capsule[b]	90	95	95	97

[a] Dissolution rate in 20 L. of 0.1 *N* HCl. [b] Dissolution rate in 20 L. of 1% pH 7.2 phosphate buffer.

from its dosage form (dissolution rate) can affect the peak blood level, the time at which the peak occurs, and the total amount of drug absorbed. The correlation between dissolution rate and biological availability has been demonstrated for several drugs (12–17). Dissolution rate measurements, therefore, were carried out with each preparation (Tables I and II) in order to explain the differences in absorption between dosage forms observed in these studies.

The diazoxide dissolution rates ranked in the same order as the blood levels obtained with the various oral dosage forms. The superior results obtained with the solution orally were puzzling at first, since sodium diazoxide is quantitatively converted to diazoxide (pKa, 8.5) in 0.1 *N* HCl, a solvent in which it is poorly soluble (about 80 mcg./ml. at 37°). Visual examination of the dosage forms during the dissolution process indicated why the solution yielded higher blood levels. When the solution was added to the stirred dissolution medium (0.1 *N* HCl), the appearance of solid phase (diazoxide) was transient, the resulting diazoxide redissolving rapidly. In contrast, the contents of the hard gelatin capsule remained as a pasty mass within the cartridge for some time after the gelatin capsule had dissolved.

When the dissolution rate of the solution was measured under simulated *in vivo* conditions, it remained unchanged (Table II). In this study, 20 ml. of solution was first gently dispersed in 50 ml. of 0.1 *N* HCl [approximate volume of gastric fluid in man (18)]. The dispersion was then added to 20 L. of 0.1 *N* HCl or 20 L. of 1% pH 7.2 phosphate buffer (to simulate duodenal pH) and the dissolution rate measured.

Pretreatment of the solution with 0.1 *N* HCl precipitated about 98% of the drug as diazoxide (5 mg. remained in solution). In spite of this, the dispersed particles of diazoxide formed from sodium diazoxide solution retained their high dissolution rate, which would account for the excellent *in vivo* performance. The dissolution rates imply that acid precipitation of sodium diazoxide from solution yields diazoxide particles that are small enough to redissolve rapidly.

When the contents of three sodium diazoxide capsules were subjected to the same pretreatment as the solution, the dissolution rate increased considerably. The increase was probably due to elimination of the gelatin capsule and predispersal of the drug in the dissolution medium. However, it is improbable that this pretreatment mimics the behavior of the capsules in the stomach.

SUMMARY

The effect of dosage form on absorption of diazoxide was studied in human hypertensive subjects.

Antihypertensive and hyperglycemic responses were correlated with diazoxide blood level.

Dissolution rate and extent of diazoxide absorption were found to be related.

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