ANTIHYPERTENSIVE ACTION OF DIAZOXIDE

A NEW BENZOTHIADIAZINE WITH ANTIDIURETIC PROPERTIES

BY

DUNCAN E. HUTCHEON, M.D., D.Phil.

AND

KATHERINE S. BARTHALMUS, B.S.

From the Departments of Medicine and Pharmacology, Seton Hall College of Medicine and Dentistry, Jersey City 4, New Jersey

Diazoxide is a new benzothiadiazine with antihypertensive properties. Chemically, this new congener of chlorothiazide is 3 - methyl - 7 - chloro - 1,2,4 - benzo - thiadiazine,-1,1-dioxide. Diazoxide thus lacks the free sulphamyl group of chlorothiazide and hydrochlorothiazide.

In a study of its cardiovascular actions, Rubin *et al.* (1961) reported that diazoxide produced a fall in blood-pressure in renal hypertensive dogs and metacorticoid hypertensive rats without increasing sodium excretion. On isolated aortic strip preparations, this new benzothiadiazine was shown to inhibit contractions induced by noradrenaline, 5-hydroxytryptamine, and angiotensin.

Previous studies have indicated that the blood-pressure of hypertensive patients treated with chlorothiazide may fall in the absence of a natriuretic response (Hollander *et al.*, 1959). The present study was therefore designed to examine the effects of diazoxide on the blood-pressure and renal electrolyte excretion patterns of hypertensive patients to determine whether the antihypertensive and diuretic properties of the benzothiadiazines could be separated. Changes in water and electrolyte metabolism in relation to blood-pressure responses were studied. Two of the cases were also treated with trichlormethiazide to observe the effects of combining diazoxide with a thiazide diuretic.

Cases and Methods

Observations were made on 10 patients who had diastolic blood-pressure readings consistently above 100 mm. Hg for six months or more prior to admission to the Thomas J. White Cardiopulmonary Institute. Each of the patients presented evidence of left ventricular enlargement by physical examination, chest *x*-ray examination, and electrocardiogram. Fundoscopic examination revealed arteriolar narrowing and arteriovenous nicking in each case, but no significant haemorrhages or exudates were observed.

Antihypertensive medication was discontinued during the two weeks prior to admission and for the first five to seven days of hospitalization, permitting the blood-pressure levels to become stable. Diets consisted of 1,500 calories, 43 to 47 mEq of sodium and 47 to 50 mEq of potassium daily. Fluid intake was kept constant. Urine collections of voided specimens were made every 12 hours beginning at 7 a.m. Treatment consisted of diazoxide (150 mg. twice daily), and in some cases trichlormethiazide (4 or 8 mg. twice daily) was also given.

Laboratory Methods.—Food, urine, and plasma electrolytes were measured with an internal standard flame photometer. Creatinine concentrations in the plasma and urine were determined by means of the Jaffé reaction (Smith, 1960), and Evans blue (T-1824) was used for the blood-volume determinations. Urine and plasma osmotic concentrations were measured by the freezing-point-depression method, using a Fiske osmometer. Osmolal clearance was calculated by multiplying the urine–plasma osmolal ratio by the urine volume. Solute-free water clearance was obtained by subtracting the osmolal clearance from the urine volume, $C_{H_2O} = V - C_{Osm}$ (Smith, 1960).

Results

The blood-pressure responses of six hypertensive patients treated with diazoxide for a period of four days are shown in the Table. A decrease in both systolic and diastolic pressure was observed in each case, the mean blood-pressure reductions being statistically significant ($P<0.01$). As shown in the Table, these

Effects of Four Days' Treatment with Diazoxide

Case No.	Basal Blood-pressure (mm. Hg.)		Cumulative Sodium Balance (mEq)	Cumulative Potassium Balance (mEq.)	Creatinine Clearance (ml./min.)	
	Initial	After 4 Days Diazoxide			Placebo	Drug
1	160/99	144/89	+97	−43	60	70
3	156/97	130/90	+50	+59	83	74
4	196/108	175/97	+41	+48	91	79
5	162/100	140/90	+108	−40	74	88
6	169/90	125/78	+138	+41	59	55
7	182/95	160/80	+80	−9	63	54
Mean	171/98	146/87	+86	+9	72	70

antihypertensive responses to diazoxide occurred during a period of sodium retention. Solute-free water clearance was reduced by diazoxide and the blood-volume was increased. On the other hand, no consistent changes in renal potassium excretion were noted.

In these patients on a limited sodium and water intake there were no signs of oedema formation while receiving diazoxide. However, when fluid and sodium were not restricted the patients gained weight and were prone to develop pitting oedema of the ankles. Water and sodium retention during diazoxide therapy could be antagonized by the administration of a chlorothiazide diuretic in patients with compensated heart disease. The drug was felt to be contraindicated in most cases with congestive heart failure.

The mean rates of endogenous creatinine clearance during diazoxide therapy did not differ significantly from the control values. These results agreed with those of Taylor *et al.* (1961), who studied the renal effects of diazoxide in water- and saline-loaded rats. These authors also reported that diazoxide caused sodium retention with no observable change in glomerular filtration rate.

Side-effects.—While on diazoxide, two cases developed several paroxysms of supraventricular tachycardia and one patient complained of a feeling of weakness. No postural hypotension was noted. In one patient with a history of diabetes mellitus there was an increase in fasting blood-glucose concentrations from 164 to 272 mg./100 ml. during the period of therapy with a combination of diazoxide (100 mg. twice daily) and trichlormethiazide (4 mg. daily).

Case Reports

Case 1.—The data in Fig. 1 were obtained during the admission of a 44-year-old woman with hypertensive cardiovascular disease, atrial fibrillation, and minimal signs of chronic congestive heart failure. The patient received 0.1 mg. of digitoxin daily. After a five-day control period, diazoxide was given in a dose of 150 mg. twice daily. Both systolic and diastolic blood-pressure levels fell and the patient went into a state of positive sodium balance as the result of the diminished urinary sodium excretion. Urine volume decreased from 2,310 to 1,530 ml./24 hours while renal potassium excretion rose from 48 to 72 mEq/24 hours On the sixth day of therapy trichlormethiazide (4 mg. twice daily) was added and sodium excretion increased from 14 to 141 mEq/24 hours. Potassium excretion also increased following the addition of trichlormethiazide. In spite of the natriuretic effect of the combined therapy, no additional lowering of the blood-pressure was observed during this period.

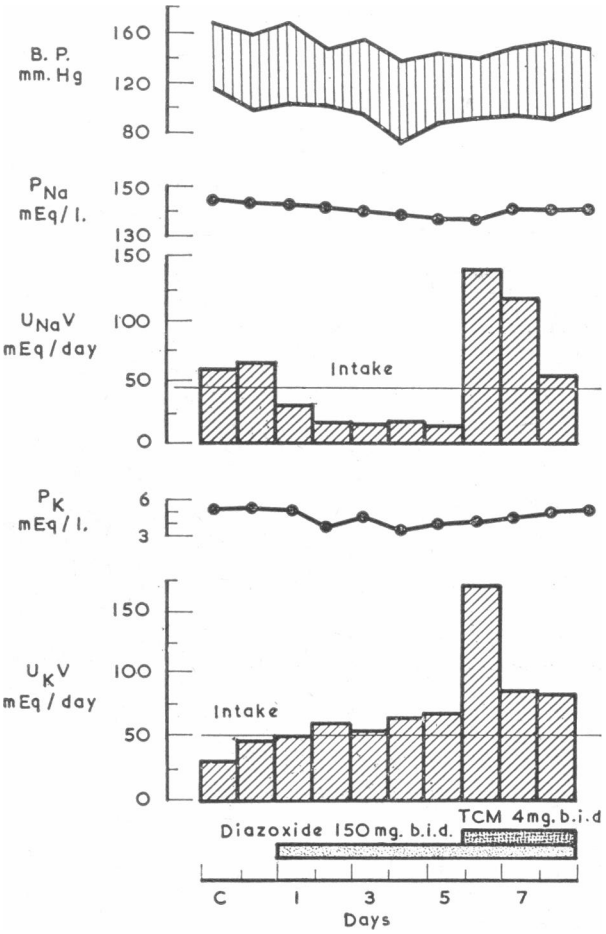

FIG. 1.—Case 1. Changes in blood-pressure and sodium and potassium excretion during diazoxide and trichlormethiazide (TCM) therapy.

Case 2.—The action of diazoxide in a 52-year-old woman with essential hypertension treated with a chlorothiazide derivative is shown in Fig. 2. Trichlormethiazide (8 mg. twice daily) produced a natriuretic response which lasted for four days. The diastolic blood-pressure did not fall, however, until the fifth and sixth days, when the patient was in a state of positive sodium balance. During the period of diuretic therapy the blood-volume decreased from 4,113 to 3,850 ml. The addition of diazoxide to the regimen resulted in a further decrease in sodium output, while arterial blood-pressure dropped to a lower level and blood-volume increased to 4,240 ml.

Case 3.—The effects of diazoxide on the osmolal and free water clearance in a 54-year old man with hypertensive cardiovascular disease are shown in Fig. 3. This patient had atrial fibrillation and received 0.1 mg. of digitoxin daily throughout the study. During the control period there was a wide diurnal variation in free water clearance with a tubular reabsorption of solute-free water during the period from 7 a.m. to 7 p.m. and a positive free-water clearance at night. The average clearance for the last two control days was 220 ml./24 hours. After the administration of diazoxide, the tubular reabsorption of solute-free water increased so that beginning on the first day of therapy free water clearance assumed a negative value for the entire

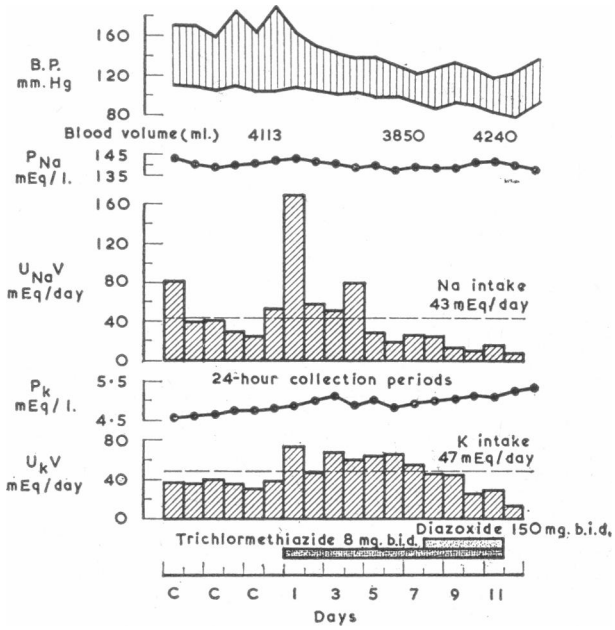

FIG. 2.—Case 2. Changes in blood-pressure, blood volume, and sodium and potassium excretion after trichlormethiazide and diazoxide.

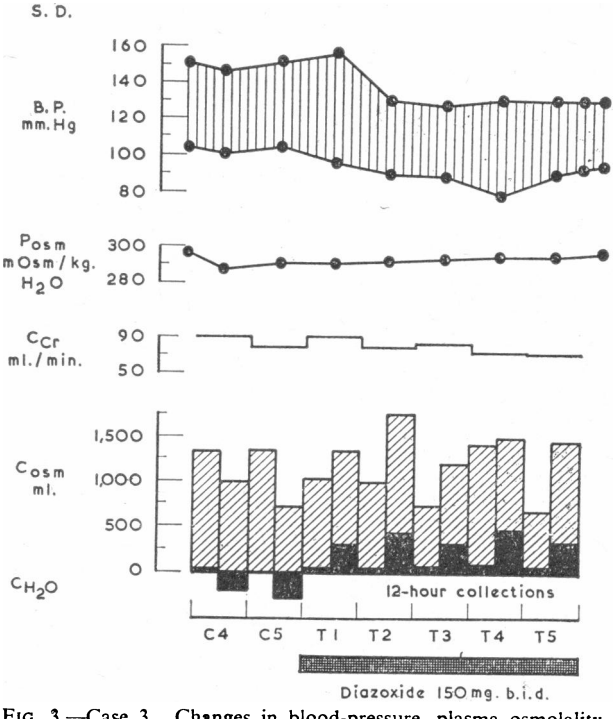

FIG. 3.—Case 3. Changes in blood-pressure, plasma osmolality, and creatinine, osmolal, and free water clearance during diazoxide therapy.

24-hour period. The tubular reabsorption of solute-free water for the six days of therapy was calculated to be 315 ml./24 hours. Sodium excretion decreased from an average control value of 78 mEq/24 hours to 11 mEq on the sixth day of diazoxide therapy. The administration of diazoxide had no apparent effect on endogenous creatinine clearance, indicating that the fluid retention was not due to a reduced glomerular filtration rate. Blood-pressure fell from an average of 156/105 mm. Hg during the control period to 128/88 mm. Hg by the third day of therapy.

Discussion

Previous observations have indicated that the antihypertensive property of chlorothiazide and its congeners was not directly due to a natriuretic effect. Hollander *et al.* (1959), for example, reported that chlorothiazide maintained a lowered blood-pressure in hypertensive patients treated with fludrocortisone (9α-fluorohydrocortisone) during a period of positive sodium balance. In the present study the fall in blood-pressure produced by diazoxide was also accompanied by sodium retention. These results therefore support the view that a depletion of total body sodium is not the primary mechanism responsible for the decrease in blood-pressure caused by the benzothiadiazine drugs. The decrease in vascular reactivity which has been observed during the administration of chlorothiazide (Mendlowitz *et al.*, 1960) may therefore be due to a direct inhibitory effect on the peripheral arteriole.

In addition to causing sodium retention, diazoxide was observed to decrease solute-free water clearance. Taylor *et al.* (1961) also noted a reduction in free water clearance after diazoxide in dogs during water diuresis. This decrease in free water clearance is of interest in relation to the mechanism of the sodium and water retention during diazoxide therapy. The benzothiadiazine diuretics have been shown to decrease free water clearance in dogs (Earley *et al.*, 1961), control subjects (Heinemann *et al.*, 1959; Takasu and Hutcheon, 1960), and cases of nephrogenic diabetes insipidus (Wenzl *et al.*, 1961). Calesnick and Brenner (1961) reported that chlorothiazide reduced free water clearance in diabetes insipidus by an action similar to that of the antidiuretic hormone. It is therefore possible that diazoxide shares this effect on the tubular reabsorption of solute-free water with the chlorothiazide diuretics, while it lacks their natriuretic action. Increased tubular reabsorption of sodium would then be expected during this state of water retention to maintain the osmolal concentration of the plasma within normal limits.

The fluid-retaining property of diazoxide was antagonized by thiazide diuretics. This observation indicated that the occurrence of salt and water retention should not prevent the clinical development of diazoxide as a useful antihypertensive agent.

Summary

Metabolic balance studies were undertaken in seven hypertensive patients to evaluate the action of diazoxide, a new chlorothiazide congener. Three additional cases were treated under general ward conditions.

In contrast to chlorothiazide, diazoxide reduced urine volume and renal sodium excretion. An increase in total blood-volume was observed during diazoxide therapy and the patients gained weight. Some patients developed ankle oedema when dietary sodium was not restricted.

In spite of its antidiuretic effects, diazoxide caused a significant drop in systolic and diastolic blood-pressure. Chlorothiazide diuretics such as trichlormethiazide antagonized the sodium-retaining properties of diazoxide without interfering with its antihypertensive action.

The results of this study support the view that the antihypertensive action of chlorothiazide and its congeners is independent of their effects on renal sodium excretion.

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"COLOMYCIN"—LABORATORY AND CLINICAL INVESTIGATIONS

BY

GEOFFREY TAYLOR, M.D., D.Path.
Lecturer in Clinical Pathology

AND

HOWARD ALLISON, M.B., Ch.B., D.Path.
Senior Registrar

Department of Clinical Pathology, the Royal Infirmary, Manchester

"Colomycin" ("colistin") is an antibiotic originally isolated by Koyama *et al.* (1950) from the micro-organism *Bacillus colistinus*. Although only recently introduced into this country, colomycin has been available elsewhere for some time, and reports from Japan, Italy, France, and the United States have claimed it to be an effective antibiotic against a wide range of Gram-negative organisms. The antimicrobial spectrum of colomycin closely resembles that of polymyxin B, but the methane sulphonate of colomycin is reported to have fewer toxic effects than unsubstituted polymyxin B.

We report the results of laboratory and clinical studies with colomycin methane sulphonate.

Materials and Methods

The organisms examined in the laboratory study consisted of 227 recently isolated pathogens. In each case the minimum inhibitory concentration (M.I.C.) of colomycin was determined, using a serial dilution tube technique. In addition a disk sensitivity was carried out using 8-mm. blotting-paper disks impregnated with