

# The Effect of Diazoxide, Potassium Chloride, and Ammonium Chloride on Serum and Urinary Uric Acid

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I would like to tell you about two studies in which we have recently been involved, at the University of Michigan. The first concerns the effects of diazoxide on uric acid excretion. Diazoxide is chemically similar to chlorothiazide (Fig. 101), differing by the absence of a free sulfamyl group. However, its pharmacologic effects are quite different. Studies following the oral administration of diazoxide have shown that it lowers blood pressure, as does chlorothiazide, but has antidiuretic properties, decreasing sodium, potassium and chloride excretion.<sup>1-4</sup> It has also been found to produce hyperglycemia, to an extent prohibiting its usefulness for chronic administration.<sup>5,6</sup> However, intravenously it produces a prompt fall in blood pressure and has thus been recommended for the treatment of hypertensive crisis.<sup>7</sup>

The effect of intravenous diazoxide upon blood pressure, electrolyte, and uric acid excretion was studied, but only the last will be recorded here in any detail. The effects of 300 mg. of diazoxide (the usual recommended dose) was studied in nine subjects; one subject received 600 mg. and another 300 mg. of intravenous diazoxide plus 1.5 Gm. of oral probenecid. The effect of 300 mg. of chlorothiazide given intravenously was also studied in four of these subjects.

Figure 102 depicts the changes in urinary uric acid. Both 30 mg. and 600 mg. doses of diazoxide produced a decrease in urate excretion. This effect was completely blocked by probenecid. Chlorothiazide, given intravenously, produced a urate diuresis, as has been previously demonstrated by Dr. Demartini.<sup>8</sup> The urate clearance:creatinine clearance ratio was similarly affected (Fig. 103), demonstrating that these changes in uric acid excretion were not solely due to changes in the glomerular filtration rate.

The effects of these two drugs are compared and summarized in Fig. 104. We postulate that diazoxide in 300 mg. and 600 mg. doses decreases urate excretion by blocking renal tubular secretion of uric acid. Intravenous chloro-

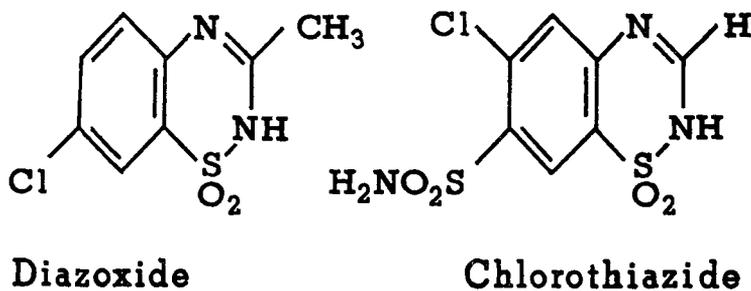
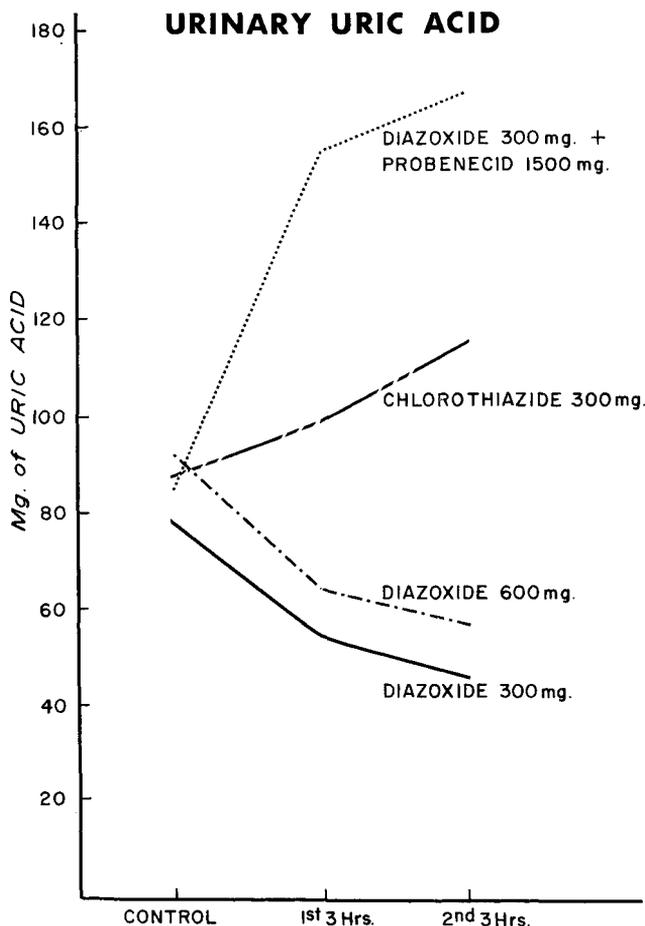


Fig. 101.—Chemical structure of diazoxide and chlorothiazide.

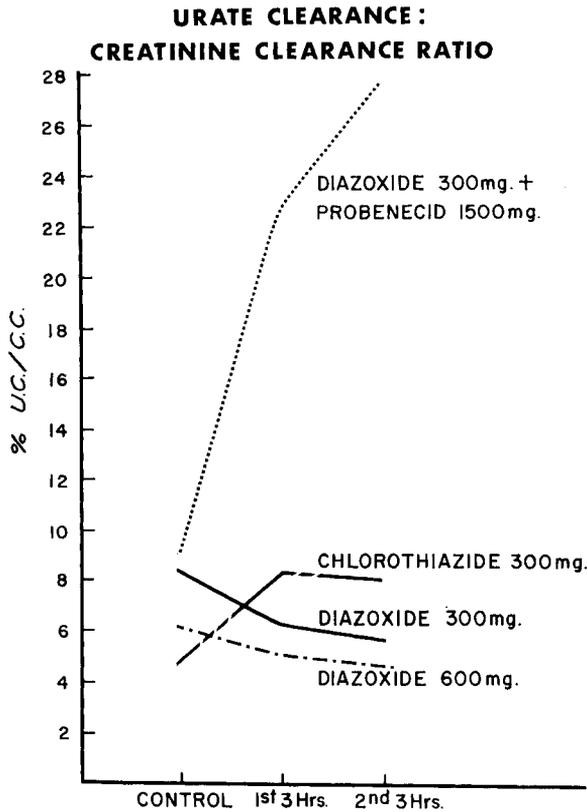


**Fig. 102.**—Urinary excretion of uric acid, expressed as milligrams of uric acid per three hour collection of urine. A control specimen was obtained, following which the drug was given, and two subsequent three hour specimens obtained.

thiazide, however, produces a urate diuresis by also blocking tubular reabsorption of uric acid (oral chlorothiazide, presumably due to lower blood concentration, causes urate retention by only blocking tubular secretion).

The second study concerns the effect of potassium chloride and ammonium chloride on thiazide hyperuricemia. This study was carried out in the Clinical Research Unit at the University of Michigan Medical Center in conjunction with Dr. Andrew J. Zweifler.

It has been reported that large doses of potassium chloride lower serum uric acid concentration in patients receiving the thiazide diuretics.<sup>9,10</sup> We attempted to confirm this, and hopefully to find an explanation. Four subjects receiving chlorothiazide for at least one month were studied, as were two control subjects not receiving the drug. Following base line studies, the subjects were given potassium chloride and ammonium chloride, 12 Gm. daily



**Fig. 103.**—Urate clearance:creatinine clearance ratio, expressed as per cent. This is calculated for each three hour urine collection.

as the syrup. Each salt was given separately for 3 to 5 days, with a control period between the experiments.

As seen in Table 22, following potassium chloride administration, serum uric acid fell substantially in 3 of the 4 thiazide-treated patients, but only slightly in the fourth. A mild decrement was also observed in one of the control subjects. These changes were accompanied by rises in the urinary uric acid and urate clearance:creatinine clearance ratio.

However, subject F. B. experienced a marked fall in serum uric acid (2.0 mg. per cent), while the mean urinary uric acid rose only 13 mg. per 24 hours. The serum uric acid decreased 1.75 mg. per cent in subject J. M., accompanied by a mild uricosuria, but the subsequent rise to pre-treatment levels following discontinuation of potassium chloride was accompanied by only minimal changes in urate excretion. Subject L. A.'s serum uric acid dropped 1 mg. per cent during the first 24 hours of potassium chloride administration, yet the urinary excretion of uric acid was unaltered during this same period. Subsequently, she did develop a urate diuresis.

Serum uric acid decreased in all subjects during ammonium chloride administration (Table 23). In those receiving chlorothiazide this response was

**DIAZOXIDE****CHLOROTHIAZIDE**Blood Pressure**Immediate Hypotension****Delayed Hypotension****Short Duration****Longer Duration**Sodium Excretion**Decreased****Increased**Potassium Excretion**Decreased****Increased**Chloride Excretion**Decreased****Increased**Urine Acidity**Increased****Decreased**Uric Acid Excretion**Decreased****i. v. - Increased  
oral - Decreased**

**Fig. 104.**—Summary and comparison of the effects of intravenous diazoxide and chlorothiazide.

generally less than that produced by potassium chloride, while the reverse was true in those subjects not taking the diuretic. Urinary excretion of uric acid either decreased or remained unchanged in all subjects except J. M. Serum sodium and potassium levels were altered very little by ammonium chloride, though there was a tendency to increased urinary excretion of these electrolytes. Serum carbon dioxide combining power was decreased. Urine volume was substantially increased.

These data confirm that potassium chloride does lower serum uric acid in thiazide-treated individuals, while, in our experience, having little influence on subjects not receiving this drug. Further, this effect is not solely due to increased urinary excretion of uric acid, as it can appear in the absence of uricosuria and subside without subsequent urate retention. Potassium chloride also produces a mild uricosuria, of similar magnitude in both normal subjects and those taking chlorothiazide.

These effects were not correlated with changes in serum potassium concentration, as equivalent elevation of serum potassium was produced by spironolactone without effect on serum uric acid. Also, impressive decrements of serum uric acid occurred which were accompanied by only minor rises in serum potassium.

**Table 22.—Effect of Potassium Chloride (160 mEq./d.) on Serum and Urinary Uric Acid**

Subjects	Serum uric acid (mg. %)			Urine uric acid (mg./24 <sup>h</sup> )			Urate Clearance: Creatinine Clearance (Expressed as per cent)		
	Pre-KCl	KCl	Change	Pre-KCl	KCl	Change	Pre-KCl	KCl	Change
L. A.*	6.96	4.85	-2.11	180	430	+250	6.50	12.90	+6.40
F. B.*	7.33	5.30	-2.03	1260	1273	+13	7.40	8.66	+1.26
J. M.*	6.05	4.30	-1.75	350	463	+113	5.70	7.80	+2.10
C. W.*	5.28	4.60	-0.68	425	653	+228	4.50	6.85	+2.35
M. W.	5.55	5.50	-0.05	785	857	+72	6.20	6.84	+0.64
R. S.	6.60	5.95	-0.65	633	826	+193	4.85	6.49	+1.64

\*Thiazide treated.

**Table 23.—Effect of Ammonium Chloride (12.0 Gm./d.) on Serum and Urinary Uric Acid**

Subjects	Serum uric acid (mg. %)			Urine uric acid (mg./24 <sup>h</sup> )			Urate Clearance: Creatinine Clearance (Expressed as per cent)		
	Pre-NH <sub>4</sub> Cl	NH <sub>4</sub> Cl	Change	Pre-NH <sub>4</sub> Cl	NH <sub>4</sub> Cl	Change	Pre-NH <sub>4</sub> Cl	NH <sub>4</sub> Cl	Change
L. A.*	7.50	5.45	-2.05	340	260	-80	5.80	6.46	+0.66
F. B.*	8.06	7.15	-0.91	923	922	-1	5.60	5.90	+0.30
J. M.*	5.43	4.65	-0.78	307	420	+113	5.20	6.05	+0.85
C. W.*	6.23	5.25	-1.08	490	420	-70	3.87	3.54	-0.33
M. W.	6.40	5.95	-0.45	773	683	-90	5.60	4.90	-0.70
R. S.	6.47	5.35	-1.12	833	770	-63	5.80	5.43	-0.37

\*Thiazide treated.

No significant alterations in blood pH or bicarbonate content occurred. However, the subjects experiencing the greatest hypouricemic response to potassium chloride excreted a smaller proportion of the potassium load than did those who had a lesser response. This suggested that the hypouricemic effect of potassium chloride might be related to its ability to correct intracellular potassium deficiency, and thus intracellular alkalosis. Ammonium chloride produced an increase in blood acidity.

With the aid of two basic assumptions, the effects of potassium chloride and ammonium chloride may be explained. These are: (a) that uric acid movement across cell membranes is determined by the H<sup>+</sup> ion gradient across the cell membrane and (b) that cells are potassium-depleted, and relatively acidotic, in certain thiazide-treated subjects.

Uric acid is a weak acid. It has been demonstrated<sup>11</sup> that biologic membranes are more permeable to un-ionized than ionized weak acids and bases, therefore allowing concentration gradients to develop if there is a difference in hydrogen ion concentration between the two sides of the membrane. Weak acids will tend to accumulate on the alkaline side. Dr. Lassen in Denmark has shown that uric acid transport into human erythrocytes is accelerated by lowering extracellular pH.<sup>12</sup>

Accepting these assumptions, the following interpretation of our data may be rendered:

- 1) Potassium chloride administration lowers serum uric acid in those

thiazide-treated individuals who are potassium depleted, because it tends to correct this deficiency, thereby elevating intracellular pH, resulting in uric acid movement into cells from the extracellular fluid.

2) Ammonium chloride lowers serum uric acid in all subjects because it produces extracellular acidosis, while having little effect on intracellular pH, thereby inducing movement of uric acid into the cells, now relatively more alkaline than the extracellular fluid.

If these assumptions are correct, they explain our data, and the observations of Dr. Ayvazian<sup>13</sup> and others<sup>14</sup> that serum uric acid concentration rises during thiazide treatment while there is yet no decrease in urinary uric acid excretion. We have not, of course, excluded the possibilities that large doses of potassium chloride may either decrease production of uric acid or increase its nonrenal excretion.

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