

Correction of Thiazide Hyperuricemia by Potassium Chloride and Ammonium Chloride

By ANDREW J. ZWEIFLER AND GEORGE R. THOMPSON

Large doses of KCl lowered serum uric acid while producing mild, apparently unrelated, uricosuria in four chlorothiazide-treated subjects. In two control subjects KCl also caused mild uricosuria, but had a negligible effect on serum uric acid concentration. Ammonium chloride decreased serum urate in all six subjects, while urinary uric acid excretion remained essentially unchanged. It is suggested that these changes in serum uric acid are secondary to redistribution of urate among body compartments.

Grande doses de KCl reduceva le concentrations seral de acido uric e produceva leve grados de apparentemente non relationate uricosuria in quatro subjects sub tractamento a chlorothiazida. In duo subjectos de controllo, KCl causava similmente leve grados de uricosuria sed exerceva non plus que un negligible effecto super le nivellos seral de acido uric. Chloruro de ammonium reduceva le urato seral in omne casos in un serie de 6 subjectos durante que le excretion urinari de acido uric remaneva essentialmente inalterate. Es postulate que iste alterationes in le nivello seral de acido uric es un effecto secundari del redistribution de urato in le diverse compartimentos corporee.

IT HAS BEEN REPORTED¹ and confirmed² that large doses of potassium chloride lower serum uric acid concentration in patients receiving thiazide diuretics, but the reason for this response has not been apparent. The results of the present investigations indicate that both KCl and NH₄Cl correct thiazide hyperuricemia and that the mechanism of this effect is primarily nonrenal.

MATERIALS AND METHODS

Six individuals were studied. Four had received chlorothiazide (1.0 to 2.0 Gm. per day) for at least one month. One of these was a female (L. A., 64 Kg.) with essential hypertension, impaired renal function (creatinine clearance 50 L./24 hr.), and past cardiac decompensation. The other three (J. M., 65 Kg.; F. B., 66 Kg.; C. W., 60 Kg.) were normotensive, nonedematous males without azotemia. The other two subjects were male medical students who were given no chlorothiazide (R. S., 88 Kg.; M. W., 78 Kg.). Investigations on all four of the thiazide-treated individuals were carried out while they lived in the Clinical Research Unit of the University of Michigan Medical Center. Although the two medical students ate and slept in the Clinical Research Unit, they continued functioning as clinical clerks on the University Hospitals wards during this time.

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Table 1.—Effect of Potassium Chloride (160 mEq./d.) on Serum and Urinary Uric Acid*

Subjects	Serum uric acid (mg.%)			Urine uric acid (mg/24 ^h)			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

*Mean of serum uric acid concentration for 3 or 4 days prior to KCl (160 mEq./day) is compared to the mean of the last 2 days of the treatment period. The mean of values of urine uric acid and the clearance ratio, for 3 or 4 days prior to KCl, is compared to the mean of all determinations during the treatment period.

†Thiazide treated.

All subjects received a diet that was relatively constant in purine and provided at least 30 calories/Kg./day. The intakes of both sodium and potassium were maintained at 90 mEq./day. Fluids were allowed as desired.

Weight and blood pressure were recorded daily, and 24 hour urine collections were completed at 800 a.m. each day. Venous blood for uric acid, creatinine, and potassium determinations was obtained frequently, and additional blood for Na⁺, Cl⁻, HCO₃⁻, and pH was collected at the beginning and the end of each treatment period. The following measurements were made on daily 24 hour urine specimens: volume; pH; uric acid; creatinine; Na⁺, K⁺, and Cl⁻ content.

All subjects underwent at least two treatment periods, one in which they received KCl 12.0 Gm./day, and another in which they took NH₄Cl 12.0 Gm./day. These salts were administered orally in the form of a syrup. The duration of the KCl period was three to four days in the patients receiving chlorothiazide and seven days in the control subjects. NH₄Cl was given for three to five days. All treatment periods were separated by at least four days. One subject (L. A.) had additional treatment periods with potassium gluconate 160 mEq./day, spironolactone-A 200 mg./day, and NaCl 256 mEq./day (administered orally).

Serum and urinary uric acid were determined by a modified colorimetric method.³ Creatinine was determined utilizing the Jaffe reaction on a "Technicon" Auto-Analyzer. Serum and urinary sodium, potassium, and chloride were determined by emission spectrophotometry, using an E.E.L. flame photometer. Serum carbon dioxide combining power was measured with a Natelson microgasometer. Blood pH was determined from heparinized venous blood, using a Radiometer microglass electrode pH meter. Urine pH was determined with a Beckman pH meter.*

RESULTS

Effect of KCl

As can be seen in table 1, serum uric acid concentration fell substantially in three of four thiazide-treated patients, and slightly in the fourth, during

*We wish to thank Dr. William Mikkelsen of the Rackham Arthritis Research Unit in whose laboratory the uric acid determinations were performed, and Dr. J. Chandler who supervised the performance of all of the other tests in the laboratories of the Clinical Research Unit.

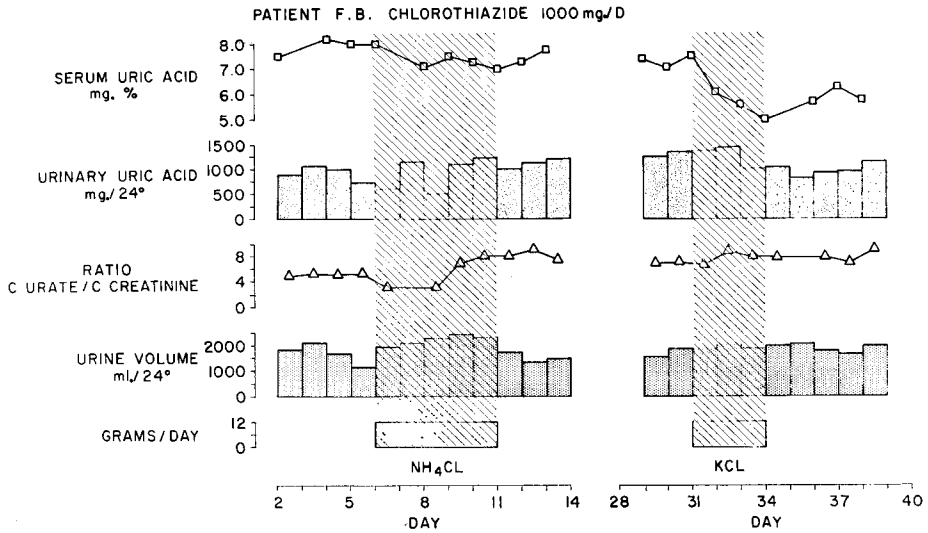


Fig. 1.—Daily variations in the serum uric acid, urine urate, urate clearance: creatinine clearance ratio, and urine volume, during control and treatment periods with NH_4Cl and KCl . This patient (F. B.) had been taking chlorothiazide, 1.0 Gm. per day, for over one month prior to, and during the study. Note the absence of significant uricosuria and the large drop of serum uric acid during the KCl period.

KCl administration. A mild decrement was also observed in one of the control subjects, but no real change occurred in the other. In general, these decreases in serum urate were accompanied by rises in urinary uric acid excretion. Utilizing the "student's t-test," the changes in serum uric acid were statistically significant ($p < 0.02$) while those of the urinary uric acid were not ($p > 0.1$)—with the exception of C. W., and in his case the increment in uric acid excretion was significant ($p < 0.01$), whereas the serum change was not ($p > 0.1$). The rise in uric acid excretion in subject F. B. was very small, particularly when viewed in light of the high basal excretion rate and the major decline in serum uric acid produced by KCl (fig. 1). As illustrated in fig. 2, subject L. A. experienced a drop in serum uric acid of over 1 mg. per cent during the first 24 hours of KCl administration, although there was no uricosuria during this period, and it was only during the second and third days of KCl therapy that uric acid excretion increased. In patient J. M. the marked decrease of serum uric acid during KCl administration was paralleled by mild uricosuria, but the subsequent rise to pretreatment blood levels occurred in the absence of any accompanying urate retention (fig. 3). C. W. clearly developed uricosuria during the first day of KCl administration which persisted throughout the treatment period, but the change in serum uric acid in his case was small (fig. 4). The two nonthiazide-treated subjects responded in a manner very similar to C. W.—i.e., the changes in serum uric acid were minimal, while uricosuria was apparent (fig. 5).

Thus, although KCl produced a reduction in serum uric acid, and an in-

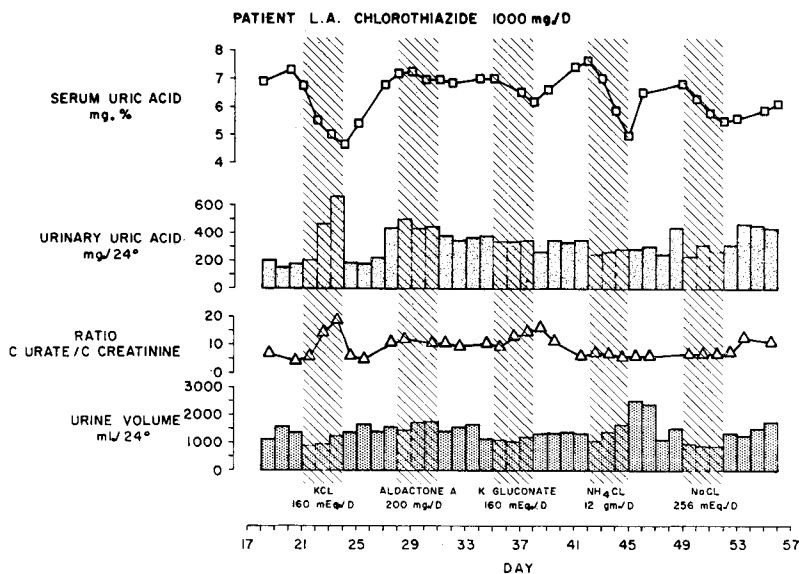


Fig. 2.—Daily variations in serum uric acid and urate excretion were observed in subject L. A. during control and various treatment periods. Prior to, and during this study, she was taking chlorothiazide 1.0 Gm. per day. Note that with KCl administration the serum uric acid fell over 1.0 mg. per cent during the first day of therapy, associated with little change in urate excretion.

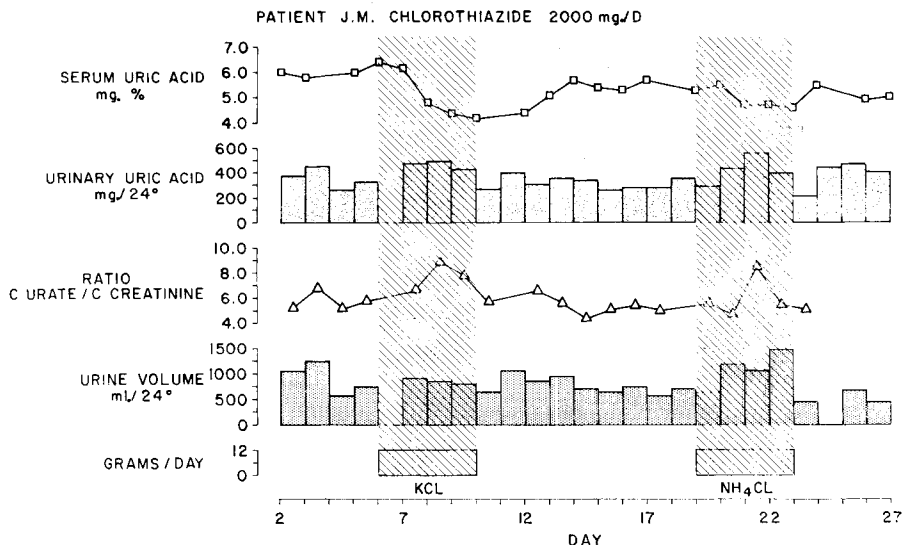


Fig. 3.—Daily variations in serum uric acid and urate excretion in subject J. M., who received 2.0 Gm. per day of chlorothiazide prior to and during this study. Note that following KCl administration the serum urate concentration rose to its pretreatment level, unassociated with a decrease in urate excretion below baseline values.

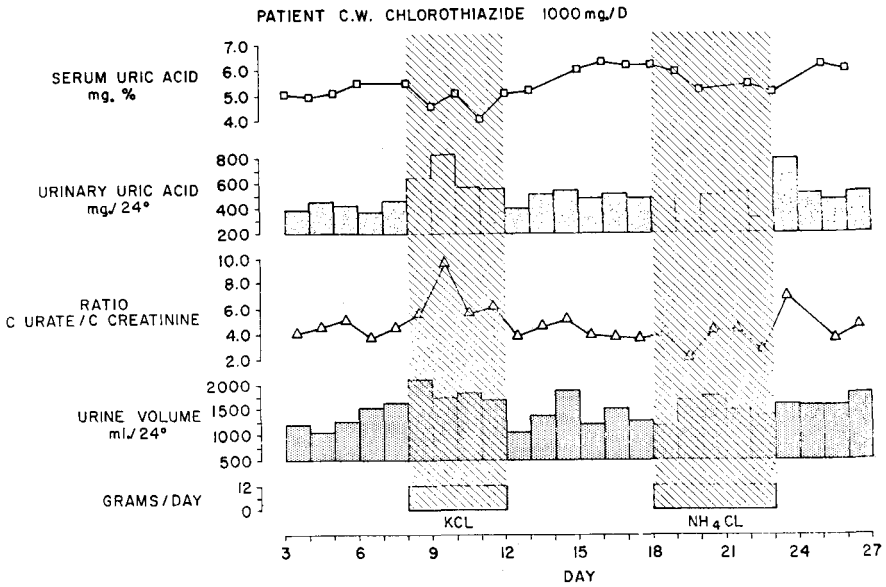


Fig. 4.—Daily variation in serum uric acid and urate excretion in patient C. W. Note that KCl administration produced a definite uricosuria, but only variable changes in serum uric acid.

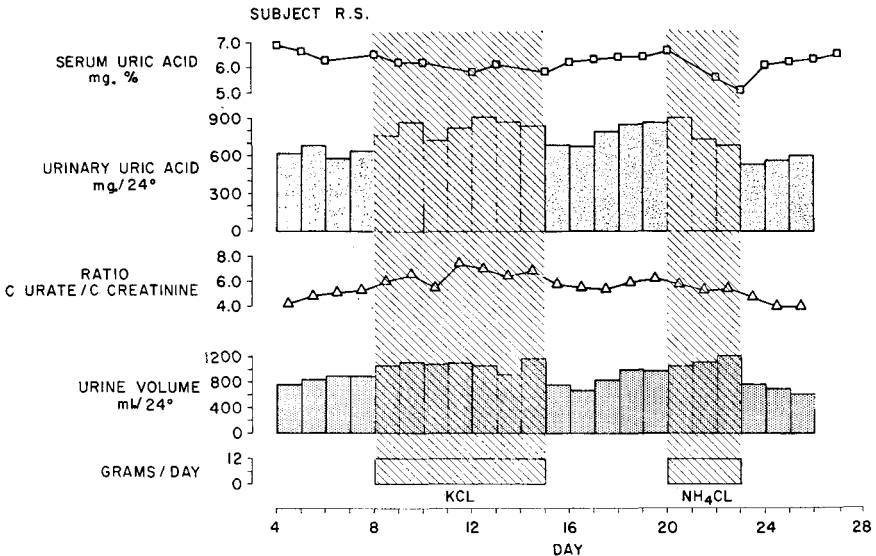


Fig. 5.—Daily variations in serum uric acid, urine urate, urate clearance: creatinine clearance ratio, and urine volume, during control and treatment periods with NH_4Cl and KCl. This subject (R. S.) was not taking chlorothiazide.

creased urinary urate excretion, these two phenomena did not parallel each other, and in some cases definitely discordant changes were observed.

Mild diuresis occurred during KCl administration in all subjects except L. A. This was most prominent in C. W. and the two nonthiazide-treated subjects. These latter two individuals excreted approximately 70 per cent of the potassium load administered, while thiazide-treated patients L. A. and

Table 2.—Effect of Potassium Chloride (160 mEq./d.) on Serum Potassium, Bicarbonate, Uric Acid, Blood pH, and Urinary Potassium (Excretion)*

Subject	Uric Acid (mg.%)			Serum Potassium (mEq./l.)			Serum Bicarbonate (mEq./l.)			Venous Blood pH			Urine Potassium (mEq./24 ^h)		
	Pre-KCl	KCl	Change	Pre-KCl	KCl	Change	Pre-KCl	KCl	Change	Pre-KCl	KCl	Change	Pre-KCl	KCl	Change
L.A.†	6.96	4.85	-2.11	3.50	4.79	+1.29	26.3	28.2	+1.9	7.35	7.35	0.0	52	131	+79
F.B.†	7.33	5.30	-2.03	2.37	2.85	+0.48	32.6	33.6	+1.0	7.42	7.44	+0.02	52	125	+73
J.M.†	6.05	4.30	-1.75	3.50	3.75	+0.25	32.9	32.6	-0.3	7.41	7.38	-0.03	72	-	-
C.W.†	5.28	4.60	-0.68	4.01	3.91	-0.10	29.4	26.2	-3.2	7.37	7.42	+0.05	74	180	+106
M.W.	5.55	5.50	-0.05	5.03	4.79	-0.24	30.7	29.8	-0.9	7.38	7.37	-0.01	69	184	+115
R.S.	6.60	5.95	-0.65	4.68	4.38	-0.30	30.3	28.6	-1.7	7.38	7.40	+0.02	58	183	+125

*Serum electrolyte and uric acid concentrations before KCl administration (160 mEq./day) are compared to those at the end of the treatment period. The average urinary potassium for 3 days prior to KCl is compared to the mean of all daily excretions throughout the treatment period.

†Thiazide treated.

F. B. excreted less than 45 per cent. Subject C. W., who had the least change in serum uric acid in the thiazide group, excreted nearly 60 per cent of the administered potassium.

Serum potassium concentration dropped slightly in subjects M. W. and R. S. (nonthiazide-treated) and was essentially unchanged in subject C. W. In subjects J. M. and F. B. the serum potassium rose slightly but remained at subnormal limits; in subject L. A. it promptly rose to normal range. Serum pH and bicarbonate were unchanged by KCl therapy (table 2).

Subject L. A. was also given treatment periods of spironolactone, potassium gluconate, and sodium chloride. Spironolactone elevated the serum potassium concentration to that produced by KCl, but caused little change in serum or urine uric acid (fig. 6). Potassium gluconate produced a prompt rise in serum potassium concentration and a modest decline in serum uric acid, while having no effect on urinary uric acid. Sodium chloride also produced a fall in serum uric acid without altering urinary urate excretion.

Effect of NH₄Cl

The mean serum uric acid concentration decreased significantly ($p < 0.05$) in every subject during NH₄Cl administration (table 3). In those receiving chlorothiazide this response was generally less than that produced by KCl, while the reverse was true in those subjects not taking the diuretic. Urinary uric acid excretion either decreased or remained unchanged in every case except one (J. M.). Serum bicarbonate concentration and pH were lower at the end of this treatment period in each instance (table 4). Serum sodium and potassium levels were altered very little by NH₄Cl administration, although there was a tendency to increased urinary excretion of these electrolytes. Urine volume was also substantially increased during this therapy period in all subjects, but most prominently in F. B. and J. M.

DISCUSSION

These data reveal that KCl lowers serum uric acid in thiazide-treated individuals, while having little influence on subjects not receiving thiazides.

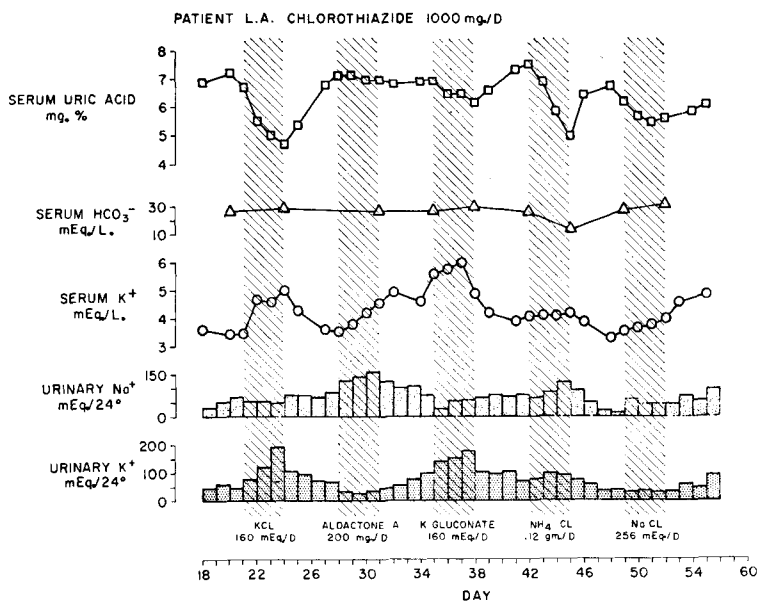


Fig. 6.—Daily variations in serum uric acid, bicarbonate, and potassium, and urinary excretion of sodium and potassium ions, in patient L. A., induced by various treatment regimens. Note the lack of correlation between serum potassium and uric acid concentrations.

This effect is apparently not due to increased urinary excretion of uric acid alone, since it can appear in the absence of uricosuria and can subside without subsequent urate retention. KCl also has a mild uricosuric effect, which is of similar magnitude in normal subjects and in those receiving chlorothiazide. NH_4Cl , on the other hand, decreases serum uric acid in subjects with or without thiazide therapy while at the same time tending to decrease urate excretion.

The ability of KCl to correct thiazide hyperuricemia cannot be attributed to its effect on serum potassium concentration, because equivalent elevation of serum potassium produced by spironolactone did not influence the serum uric acid level. Also, impressive decrements of serum uric acid occurred during KCl administration even when this treatment produced relatively minor rises of serum potassium, and rises not necessarily to the normal range.

We had suspected that the serum uric acid lowering effect of KCl in thiazide-treated subjects might be related to its reported⁴ ability to correct extracellular alkalosis in such individuals. It was for this reason that NH_4Cl was administered and measurements of blood pH and bicarbonate were obtained throughout the study. It was found that NH_4Cl , in a dose which increased blood acidity, *did* exert a definite hypouricemic effect; however, KCl produced no significant alterations in blood pH or bicarbonate content during treatment periods that resulted in substantial decreases in serum uric acid. In fact, the response to KCl did not correlate with changes in the con-

Table 3.—Effect of Ammonium Chloride (12 Gm./d.) on Serum and Urinary Uric Acid*

Subjects	Serum uric acid (mg.%)			Urine uric acid (mg./24 ^o)			Urate Clearance:Creatinine Clearance (Expressed as per cent)		
	Pre-NH ₄ Cl	NH ₄ Cl	Change	Pre-NH ₄ Cl	NH ₄ Cl	Change	Pre-NH ₄ Cl	NH ₄ 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

*Mean of serum uric acid concentrations for 2 or 3 days prior to NH₄Cl (12.0 Gm./day) is compared to the mean of the last 2 days of the treatment period. The mean of values of urine uric acid and the clearance ratio for 3 days prior to NH₄Cl is compared to the mean of all determinations during the treatment period.

†Thiazide treated.

Table 4.—Effect of Ammonium Chloride on Serum Uric Acid, Bicarbonate, and Blood pH*

Subject	Serum Uric Acid (mg.%)			Serum Bicarbonate (meq/l.)			Venous Blood pH		
	Pre-NH ₄ Cl	NH ₄ Cl	Change	Pre-NH ₄ Cl	NH ₄ Cl	Change	Pre-NH ₄ Cl	NH ₄ Cl	Change
L.A.	7.50	5.45	-2.05	25.9	14.4	-11.5	7.31	7.15	-0.16
F.B.	8.06	7.15	-0.91	32.3	25.0	-7.3	7.42	7.35	-0.07
J.M.	5.43	4.65	-0.78	35.4	28.1	-7.3	7.39	7.33	-0.06
C.W.	6.23	5.25	-0.98	27.1	20.3	-6.8	7.41	7.39	-0.02
M.W.	6.40	5.95	-0.45	30.7	25.4	-5.3	7.39	7.31	-0.08
R.S.	6.47	5.35	-1.12	32.3	24.8	-7.5	7.36	7.30	-0.06

*Serum bicarbonate and uric acid concentrations and venous blood pH before NH₄Cl administration are compared to values at the end of the treatment period.

centration of any of the measured serum or urinary factors except the per cent excretion of the administered potassium load. Those subjects who showed the greatest hypouricemic response to KCl excreted a smaller proportion of the potassium load than those who had a lesser response. This suggests that the hypouricemic effect of KCl is related to its ability to correct a potassium deficiency, and as it does not coincide with changes in serum potassium concentration, it must be assumed that the deficit is intracellular.

The mechanism of the renal effect of KCl is not completely apparent from our data. Increased urine flow will tend to decrease uric acid reabsorption^{5,6} and perhaps some of the urine urate changes produced by KCl are related to this phenomenon, since diuresis was observed in almost all subjects during KCl administration. However, in at least one thiazide-treated subject, uricosuria was observed in the absence of any increase in urine volume. Renal excretion of weak acids may also be favored by increased urine pH,^{7,8} and the urine may become more alkaline during potassium loading.⁹ However,

in dogs⁵ and in man¹⁰ it has been demonstrated that uric acid excretion is relatively uninfluenced by urine pH. Furthermore, in some of our studies uricosuria was observed during KCl administration without any change in urine pH. If tubular secretion of uric acid were modified by the concentration of potassium and/or hydrogen ions within renal tubular cells, KCl therapy might alter the intracellular concentration of these ions and thus produce the observed effect on uric acid excretion.

Blood uric acid concentration is determined primarily by the balance between the rates of its production and renal excretion. Other factors which may, at least theoretically, influence it are the rate of gastrointestinal excretion and changes in distribution of urate among body compartments. Our data indicate that the decrease in serum uric acid produced by NH_4Cl and by KCl in thiazide-treated individuals is not due primarily to increased urinary excretion. Rather, the finding of a tendency toward a decrease in renal urate excretion with NH_4Cl suggests that administration of this substance may inhibit uric acid production. KCl, on the other hand, usually increases urinary uric acid content, and so it is difficult to accept that its effect is due to impairment of urate production. The apparent correlation between the hypouricemic effect of KCl and repletion of an intracellular potassium deficit suggests another possible mechanism, which also could explain the response to NH_4Cl , redistribution of uric acid. This hypothesis, however, must be based on two assumptions: (a) that uric acid movement across cell membranes is determined somewhat by the H_3O^+ gradient across these membranes and (b) that cells are potassium depleted and relatively acidotic in certain thiazide-treated subjects. Neither assumption is unreasonable. Uric acid is a weak acid with a pK_a of 5.75 and therefore theoretically¹¹ its distribution among body compartments may be influenced by the phenomenon of "non-ionic diffusion." This phenomenon follows from the fact that biological membranes may be more permeable to the un-ionized than the ionized form of weak acids and bases and may allow concentration gradients of these substances to develop if there is an initial difference in hydrogen-ion concentrations between the two sides. In fact, Lassen¹² has demonstrated that uric acid is transported into human erythrocytes more rapidly as extracellular pH is decreased and has presented evidence to support his suggestion that this is due to non-ionic diffusion.

It is undisputed that thiazide therapy produces extracellular alkalosis and at least a transient period of potassium loss. Potassium depletion induced by other means results in acidosis of intracellular fluid.¹³ It is therefore possible that intracellular pH *may* be depressed in thiazide-treated individuals, although this has yet to be measured.

If uric acid *is* subject to non-ionic diffusion, and if some thiazide-treated subjects are potassium depleted and have an acidotic intracellular space, the following interpretation of our data may be rendered: (1) KCl administration lowers blood uric acid in those thiazide-treated subjects who are potassium depleted, because it tends to correct this deficiency, thereby causing an elevation of intracellular pH resulting in uric acid movement into cells from extracellular fluid; (2) NH_4Cl administration lowers serum uric acid in all

subjects because it produces extracellular acidosis while having little effect on intracellular pH, thereby inducing a movement of uric acid into the cells, then relatively more alkaline than the extracellular fluid.

The failure of blood uric acid to fall as much during administration of an equimolar amount of potassium gluconate as it did with KCl does not necessarily confound the hypothesis that cellular potassium repletion is central to the effect of KCl, since, as has been recently emphasized by Kassirer et al.,¹⁴ the ability of potassium salts to correct potassium deficiency depends heavily on the concomitant administration of chloride ion. Similarly, the response to sodium chloride, may be related to the provision of large amounts of chloride ion which might facilitate the retention of the ample dietary source of potassium in our patients.

If these assumptions are correct, they also provide a clue to one of the mechanisms of production of hyperuricemia by thiazides, which is still the subject of debate.^{15,16} One effect of thiazide therapy on urate in the body may be a redistribution from the intracellular to the extracellular space, secondary to the development of extracellular alkalosis, with or without an associated intracellular acidosis. The existence of such a mechanism could explain the fact that serum uric acid concentration may rise during thiazide therapy while there is no decrease in urinary uric acid excretion.^{16,17}

Direct measurements of changes in erythrocyte urate content, fecal uric acid excretion, or rate of synthesis of uric acid were not carried out in this study. Therefore, the possibilities that large doses of KCl and NH₄Cl may either decrease the production or increase the nonrenal excretion of uric acid have not been excluded by our findings. A purely renal effect, however, has been excluded. Further studies of the mechanism of the influence of electrolytes on uric acid metabolism are in order.

SUMMARY

The effects on serum and urine uric acid of KCl and NH₄Cl administration in four chlorothiazide-treated and two control subjects were studied. Serum uric acid decreased in three of the four thiazide-treated patients following KCl therapy but not in the control subjects. Potassium chloride also produced a moderate uricosuria, but this effect could not be directly linked with the changes in serum uric acid. Ammonium chloride administration resulted in a fall in serum urate in all subjects, with minimal effects on urate excretion. It is suggested that these changes could be due to shifts in uric acid between the intracellular and extracellular spaces.*

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