# Ascorbic Acid-Induced Uricosuria

## A Consequence of Megavitamin Therapy

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**The effect of ascorbic acid on the serum and urinary uric acid was studied in 14 subjects. Two to 6 h after the ingestion of 4.0 g of ascorbic acid, the fractional clearance of uric acid increased to 202% ± 41% of the control value. This uricosuria was inhibited by pyrazinamide and by low-dose acetylsalicylic acid, but was not accompanied by an increase of the creatinine clearance. Ascorbic acid did not diminish protein-bound uric acid. In 3 subjects who ingested 8.0 g of ascorbic acid for 3 to 7 days the serum uric acid decreased by 1.2 to 3.1 mg/dl as a result of a sustained uricosuria. These results suggest that ascorbic acid could invalidate studies involving the measurement of uric acid and obscure the diagnosis of gout in some cases. Theoretically it could precipitate attacks of gouty arthritis or renal calculi in predisposed persons. These observations show a pharmacologic effect of megadoses of a simple vitamin.**

THE WIDESPREAD USE of vitamins in megadoses has recently become a subject of controversy. Diseases associated with the excessive ingestion of certain vitamins are well known (1, 2) and new adverse effects have now been described (3-6).

Ascorbic acid is currently consumed in large doses for a variety of conditions including the common cold and schizophrenia (7, 8). However, only the antiscorbutic activity and the reducing properties of ascorbic acid have recognized therapeutic value (9). Although this vitamin has a well-documented role in many pathways of intermediary metabolism (9-14), adverse reactions appear to be uncommon. The precipitation of renal calculi is a hazard (15-17). Uric acid calculus formation could result from an increased excretion of uric acid or from urine acidification. As a weak organic acid, ascorbic acid is potentially capable of acting through both mechanisms. Many weak organic acids including another vitamin, nicotinic acid, have been found to modify the renal clearance of uric acid (4, 18).

In the present study we have evaluated the effect of ascorbic acid on the renal handling of uric acid. The results show that this vitamin causes a significant uricosuria by means of a renal tubular mechanism.

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### Materials and Methods

Ten men and 4 women (5 with gout, 3 with asymptomatic hyperuricemia, 6 with normouricemia) were admitted to the Clinical Investigation Unit of The Wellesley Hospital. Erythrocyte hypoxanthine-guanine phosphoribosyltransferase was normal. Patients were maintained on a 2600-cal, 70-g protein, purine-free diet. No subject was taking a drug known to interfere with uric acid metabolism or excretion. Laboratory studies showed the following ranges of values: serum uric acid, 3.5 to 10.1 mg/dl; urine uric acid, 219 to 826 mg/24 h; creatinine clearance, 60 to 130 ml/min; and the ratio of the uric acid clearance to the creatinine clearance, 2.2% to 14.0%. Informed consent was obtained from all subjects participating in this study.

Experiments were conducted to ascertain the effect of a single dose of ascorbic acid on the urinary excretion of uric acid. The patients were fasted except for water and colchicine for 12 h before and during each study. Urine was collected during four 2-h collection periods from 0700 to 1500. One hour before the first collection period, 500 ml of water was administered orally. At the end of each collection period, a volume of water 1 dl in excess of the previous collection volume was ingested. The urine samples were each analyzed for creatinine, uric acid, glucose, pH, sodium, chloride, potassium, and phosphate. Blood was drawn at 0800 and at 1200 for creatinine, uric acid, sodium, chloride, potassium, and phosphate measurements.

After a control period from 0700 to 0900, the test drugs were ingested. This experimental format was used for individual drug studies as follows: (a) no medication; (b) ascorbic acid, 0.5, 2.0, or 4.0 g; (c) ascorbic acid, 4.0 g, with acetylsalicylic acid, 0.6 g; (d) acetylsalicylic acid, 0.6 g; (e) ascorbic acid, 4.0 g, with pyrazinamide 3.0 g; and (f) pyrazinamide, 3.0 g. Effervescent ascorbic acid (Redoxon®*) was used in these experiments. There were at least 48 h between each drug study. Pyrazinamide was always the last drug tested because of its prolonged effect.

The effect of the chronic administration of ascorbic acid on uric acid excretion was evaluated in three subjects using a dose of 2.0 g of noneffervescent ascorbic acid four times per day for 3 to 7 days. Blood and a 24-h urine sample for uric acid and creatinine were collected each day before, during, and after the period of ascorbic acid ingestion.

The effect of ascorbic acid on the binding of uric acid to plasma protein was studied in vitro by a modification of the method of equilibrium dialysis described by Klinenberg and Kippen (19), using plasma samples obtained from four subjects. Ascorbic acid concentrations were 0, 1.0, 3.0, 10.0, and 20.0 mg/dl. In-vivo plasma levels of ascorbic acid are normally less than 3.0 mg/dl (20).

Uric acid was measured by the uricase method (21). Because ascorbic acid is known to absorb in the ultraviolet range,

* Roche Labs, Nutley, New Jersey.

its effect on the uricase assay was assessed. When ascorbic acid up to 4 mg/ml was freshly dissolved in water or urine, the optical density at 292 nm spontaneously decreased slowly and stabilized after 60 to 90 min. Addition of uricase then gave the same uric acid value found without ascorbic acid. This effect decreases with storage. No such drift was evident in the urine from patients given ascorbic acid at the time the uricase assay was done. Thus the uricase method was a valid measure of uric acid in these studies.

The serum sodium potassium, chloride, and creatinine were measured by the Technicon SMA 6/60 (4 + 2) multichannel biochemical analyzer*. The urine creatinine was measured by the method of Brod and Sirota (22). Phosphate measurements were done by a Technicon A.A.I. autoanalyzer*. The pH of freshly collected urine was measured by a Radiometer pH Meter, Model 22 with a scale expander†. The erythrocyte hypoxanthine-guanine phosphoribosyltransferase was assayed by a radiochemical method (23).

To ensure that effervescent and noneffervescent ascorbic acid had comparable acidity, the pH of 1.0 g of each in 1 litre of water was compared. The values were found to be pH, 3.9, and pH, 3.6, respectively.

All statistics were done using the paired or unpaired two-tailed Student's *t* test. All values are described as the mean plus or minus the standard deviation unless otherwise indicated.

## Results

### SINGLE-DOSE STUDIES

In 9 subjects 4.0 g of ascorbic acid caused a maximum increase to 202% ± 41% of control values for the ratio of the uric acid clearance to the creatinine clearance ($C_{ur}/C_{cr}$) 2 to 6 h after its administration (Figure 1*A*). The peak effect varied between Period 3 and Period 4 in different patients. In contrast, 0.5 and 2.0 g of ascorbic acid increased the $C_{ur}/C_{cr}$ to 128% ± 6% and 152% ± 24% of control values respectively (Figure 1*A*). When no ascorbic acid was given, the $C_{ur}/C_{cr}$ increased to 131% ± 11% of the control value. A statistically significant increase ($P < 0.01$) above the trial without medication only occurred with 4.0 g of ascorbic acid. The serum uric acid concentrations remained constant during these studies.

Ascorbic acid potentially could increase the clearance of uric acid by a decrease in the binding of uric acid to protein, by an increase in the glomerular filtration rate or by an alteration in the renal tubular handling of uric acid. Urate binding to plasma proteins in vitro was not decreased by ascorbic acid in concentrations from 0 to 20 mg/dl, which includes the range of physiologic and higher non-physiologic plasma concentrations. In addition no increase in the mean creatinine clearance from the control period was found after the ingestion of 4.0 g of ascorbic acid.

The mechanism by which ascorbic acid affected the renal tubule was studied by showing its interaction with acetylsalicylic acid and pyrazinamide. In three of the four patients studied there was a complete inhibition of ascorbic acid induced uricosuria while in one patient this was not observed. The maximum increase of 202% ± 41% of $C_{ur}/C_{cr}$ with ascorbic acid alone was diminished to 132% ± 72% when acetylsalicylic acid was ingested with ascorbic acid in these four subjects (Figure 1*B*). Pyrazinamide reversed the uricosuric effect of ascorbic acid such that the $C_{ur}/C_{cr}$ decreased to 42% ± 19% of control

* Technicon Corporation, Tarrytown, New York.
† The London Company, Cleveland, Ohio.

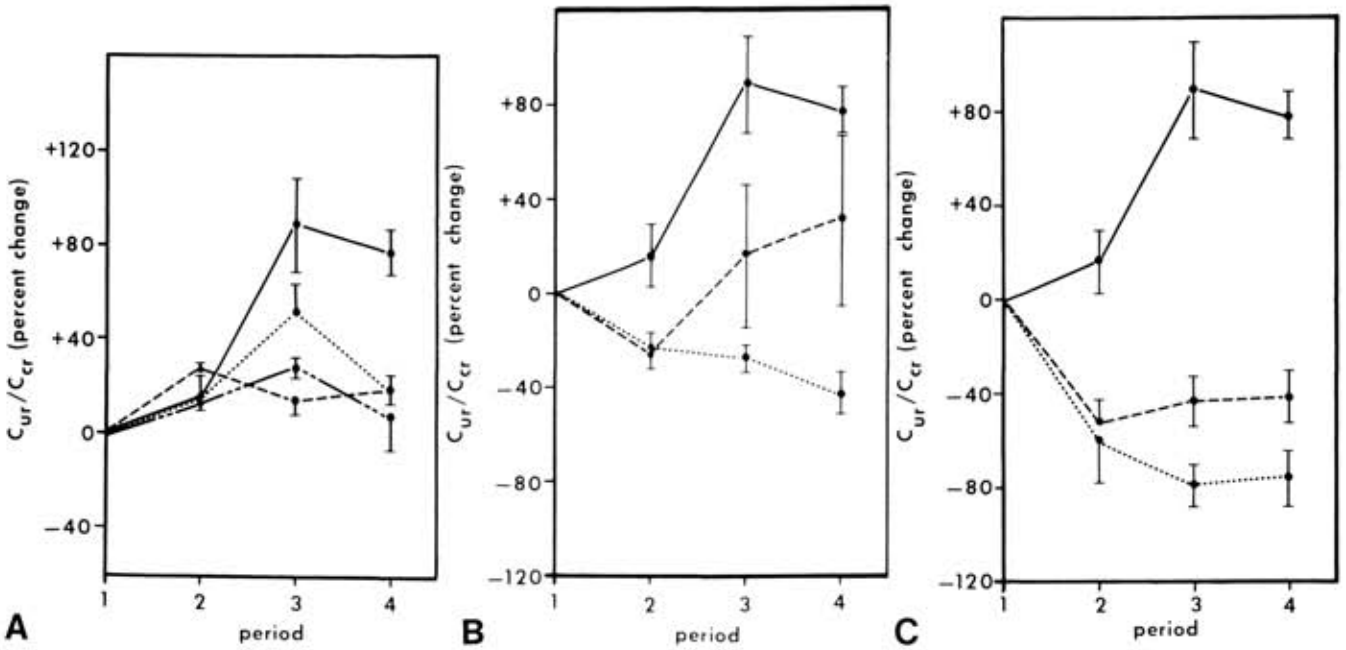


**Figure 1.** The effect of ascorbic acid on the renal handling of uric acid. The mean ratio of uric acid clearance to creatine clearance ($C_{ur}/C_{cr}$) (±SEM) is expressed as a percentage change from the control value (Period 1). Each period represents a 2-h collection. **A.** Ascorbic acid was administered as follows: 0 g ($n = 4$, —·—·—); 0.5 g ($n = 3$, – – – –); 2.0 g ($n = 4$, · · · · · ·); and 4.0 g ($n = 9$, ———). The control values for $C_{ur}/C_{cr}$ were 5.5% ± 1.4%, 6.7% ± 2.3%, 6.6% ± 1.6%, and 5.4% ± 1.1% respectively. **B.** The effect of acetylsalicylic acid (0.6 g) on the uricosuria induced by ascorbic acid (4.0 g) is illustrated as follows: ascorbic acid alone ($n = 9$, ———); ascorbic acid plus acetylsalicylic acid ($n = 4$, – – – – –); and acetylsalicylic acid alone ($n = 4$, · · · · · ·). The control values for $C_{ur}/C_{cr}$ were 5.4% ± 1.1%, 6.0% ± 1.0%, and 7.2% ± 1.5% respectively. **C.** The effect of pyrazinamide (3.0 g) on the uricosuria induced by ascorbic acid (4.0 g) is illustrated as follows: ascorbic acid alone ($n = 9$, ———); ascorbic acid plus pyrazinamide ($n = 5$, – – – – – –); and pyrazinamide alone ($n = 3$, · · · · · ·). The control values for $C_{ur}/C_{cr}$ were 5.4% ± 1.1%, 4.9% ± 1.0%, and 3.6% ± 1.0% respectively.

values during Period 3 (Figure 1C).

The urine hydrogen ion concentration increased by 2.6 ± 1.4, 1.8 ± 1.8, and 0.5 ± 0.8 μeq/litre during Periods 2, 3, and 4 respectively in eight subjects. These changes were not statistically significant.

LONG-TERM STUDIES

The chronic administration of 8.0 g of ascorbic acid daily to three subjects was evaluated (Table 1). In the three patients the mean daily $C_{ur}/C_{cr}$ was increased to 174% ± 24% ($P < 0.01$) of the control values. This increase was maintained throughout the period of ascorbic acid administration and for 1 to 2 days thereafter. The serum uric acid declined in the three patients by 1.5, 3.1, and 1.2 mg/dl during the 7, 6, and 3 days of ascorbic acid intake respectively.

No side effects of ascorbic acid were recorded except for mild diarrhea in one subject following the ingestion of 4.0 g of ascorbic acid.

## Discussion

Uric acid is normally handled in the kidney by glomerular filtration and bidirectional tubular transport involving reabsorption and secretion (24). Our observations have shown that ascorbic acid increases the fractional clearance of uric acid by its action at a renal tubular site. Ascorbic acid is excreted by glomerular filtration and tubular reabsorption (25, 26). The active transport of ascorbic acid has also been shown in other tissues (27-30). Alteration of these processes by probenecid (30, 31), sulfinpyrazone (31), and acetylsalicylic acid (30, 32, 33) has resembled the effects of these drugs on the renal handling of uric acid. The modification of the uricosuric effect of ascorbic acid by acetylsalicylic acid and pyrazinamide implies that related renal sites of activity may exist for these compounds.

The uricosuric action of a single dose of ascorbic acid was dose-dependent in that 4.0 g, but not 2.0 g or 0.5 g, were effective. Plasma concentrations of ascorbic acid are themselves dose-dependent only up to 1.5 g (33). At this dosage the plasma level reaches a plateau (33), and the renal threshold level of 1.4 mg/dl (34) may be achieved.

The chronic administration of 8.0 g of ascorbic acid per day in three of our subjects resulted in a sustained uricosuria and a substantial diminution of the serum uric acid. Because doses as high as 30 grams per day are being used therapeutically (35), the effects of ascorbic acid may have important theoretical clinical implications. First, the ingestion of large doses of ascorbic acid may invalidate studies of the serum and urinary uric acid by the effect on its renal clearance and could obscure the diagnosis of gout. If a colorimetric assay for uric acid is used, then spurious elevations may occur from ascorbic acid acting as a nonurate chromogen (36). Second, ascorbic acid has been implicated in the precipitation of oxalate, uric acid, and cystine stones by acidification of the urine (15-17). No significant change in urinary acidification was observed with a single dose of ascorbic acid in this study. However, the increased quantity of uric acid in the urine could be an important factor in the formation of uric acid stones especially in subjects who normally overexcrete uric acid. The normal modest conversion of ascorbic acid to oxalate is accelerated in certain persons and may result in the precipitation of oxalate stones in the urine (37, 38). Third,

**Table 1. Effects of Long-Term Ascorbic Acid Therapy***

| Subject | Day | Vitamin C | Serum Uric Acid | Urine Uric Acid | $UUA/UC_r$ | $C_{ur}/C_{cr}$ (increase) |
|---|---|---|---|---|---|---|
| | | *g/day* | *mg/dl* | *mg/24 h* | | % |
| 1 | 1 (control) | 0 | 6.1 | 324 | 0.28 | 0 |
| | 2 | 8 | 6.6 | 475 | 0.37 | 22 |
| | 3 | 8 | 4.7 | 655 | 0.48 | 122 |
| | 4 | 8 | 5.3 | 543 | 0.39 | 61 |
| | 5 | 8 | 4.9 | 471 | 0.35 | 55 |
| | 6 | 8 | 5.0 | 567 | 0.37 | 63 |
| | 7 | 8 | 4.7 | 489 | 0.35 | 63 |
| | 8 | 8 | 4.6 | 531 | 0.43 | 105 |
| | 9 | 0 | 4.5 | 456 | 0.41 | 97 |
| | 10 | 0 | 4.8 | 456 | 0.31 | 30 |
| 2 | 1 (control) | 0 | 9.8 | 313 | 0.28 | 0 |
| | 2 | 8 | 9.4 | 415 | 0.32 | 11 |
| | 3 | 8 | 9.1 | 470 | 0.38 | 36 |
| | 4 | 8 | 8.8 | 502 | 0.41 | 72 |
| | 5 | 8 | 7.5 | 521 | 0.45 | 75 |
| | 6 | 8 | 8.0 | 561 | 0.49 | 103 |
| | 7 | 8 | 7.6 | 511 | 0.40 | 87 |
| | 8 | 0 | 6.7 | 449 | 0.38 | 51 |
| | 9 | 0 | 7.8 | 474 | 0.40 | 61 |
| | 10 | 0 | 7.7 | 292 | 0.28 | 12 |
| 3 | 1 (control) | 0 | 4.1 | 557 | 0.46 | 0 |
| | 2 | 8 | 4.0 | 805 | 0.71 | 59 |
| | 3 | 8 | 3.2 | 524 | 0.52 | 59 |
| | 4 | 8 | 2.9 | 846 | 0.54 | 65 |

* Ascorbic acid was administered chronically in a dose of 8.0 g per day. The fractional clearance of uric acid is expressed as a percentage of the control clearance on Day 1. $UUA/UC_r$ = ratio of uric acid to creatinine; $C_{ur}/C_{cr}$ = ratio of uric acid clearance to creatinine clearance.

the diminution in the serum uric acid may precipitate acute gouty arthritis in predisposed individuals (39). Fourth, ascorbic acid-induced uricosuria can be reversed by low-dose acetylsalicylic acid. Finally, this effect of ascorbic acid serves to illustrate a pharmacological action of mega-doses of a simple vitamin in man.

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