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Investigations of the efficacy of ascorbic acid therapy in cystinuria

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Summary. We investigated ascorbic acid therapy for cystinuria in a study of seven healthy control persons and seven cystinuric patients. The study lasted 9 days. During the first period, we collected 24-h urine specimens from all subjects on 3 consecutive days. Starting on day 4, all were given 5 g ascorbic acid/day for a period of 6 days. On the last 3 days, 24-h urine specimens were again collected. Quantitative amino acid determination was performed using an HPLC method described elsewhere. During ingestion of ascorbic acid, the mean excretion of cysteine by the control group increased from 134.1 to 159 μmol/day, whereas the excretion of cystine decreased from 107.1 to 82 μmol/day. The corresponding values for the cystinuric patients increased from 352.4 to 452.1 μmol/day for cysteine and decreased from 4,131.6 to 3,663.2 μmol/day for cystine. Thus, ascorbic acid seems to have only mild reducing properties in respect to cystine.

Key words: Cystinuria – Cysteine- Cystine – Ascorbic acid therapy

Cystinuria is a congenital metabolic disease characterized by excessive urinary excretion of cystine and recurrent stone formation. Cystine excretion rates of up to 12 mmol/day have been reported [1, 5]. The solubility of cystine at normal urinary pH is about 1.3 mmol/l [5]. Thus, lifelong therapy is extremely important for cystinuric patients.

High oral intake of ascorbic acid is well known for the clinical treatment of cystinuria. Ingested at up to 5 g/day, this reducing agent should change the redox equilibrium of cystine and its monomer, cysteine, which is much more soluble, the result being that concentration of cysteine is increased and that of cystine, decreased [1, 2].

In the present study we investigated the efficacy of ascorbic acid therapy in healthy control persons and cystinuric patients. Quantitative amino acid determination was performed using an HPLC method whose main advantage is its precise determination of both cysteine and cystine values [3].

Subjects and methods

The study lasted 9 days. During the first period, we collected 24-h urine specimens from seven healthy control persons and seven cystinuric patients on 3 consecutive days. Starting with day 4, all subjects were given 5 g ascorbic acid/day for a period of 6 days. On the last 3 days, 24-h specimens were again collected (Table 1). There were no dietary restrictions except the recommendation of a fluid intake of 2 (control group) or 4 l/day (cystinuric group).

Urine was collected directly into a sampling flask containing sulfosalicylic acid (SSA) as a preservative fluid (100 ml 30% SSA/2.5 l container). Samples were stored at 4°C until analysis. As indicated in a previous study [3], this procedure is essential for the stability of cysteine. Collecting urine in SSA immediately decreases the pH to a level of 1–2, which prevents the oxidation of cysteine for 5 days.

Reversed-phase HPLC with precolumn derivatization of amino acids was used for determinations of cysteine and cystine [3]. One of the degradation products of ascorbic acid is oxalic acid. This, ingestion of megadoses of ascorbic acid could increase the excretion of oxalic acid and, hence, the risk of calcium oxalate stone formation. We used ion-exchange chromatography [4] to determine the excretion of oxalic acid by our subjects.

Results

In the absence of therapy, the healthy control group showed a mean cysteine excretion value of 134.1 μmol/day and a mean cystine excretion level of 107.1 μmol/day.

Table 1. Design of the study

Day	Treatment	Urine collection
1		24-h urine
2		
3		
4	Ascorbic acid 5 g/day	
5		
6		
7		24-h urine
8		
9		

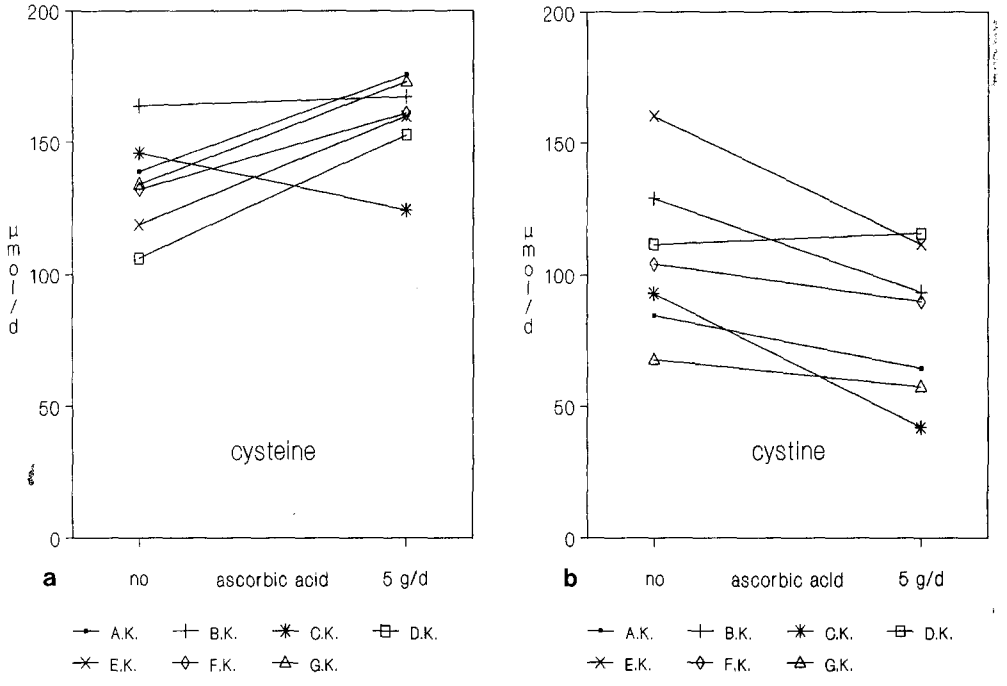

Fig. 1a, b. Excretion of **a** cysteine and **b** cystine by the health control group in the absence and presence of ascorbic acid ingestion ($n=7$)

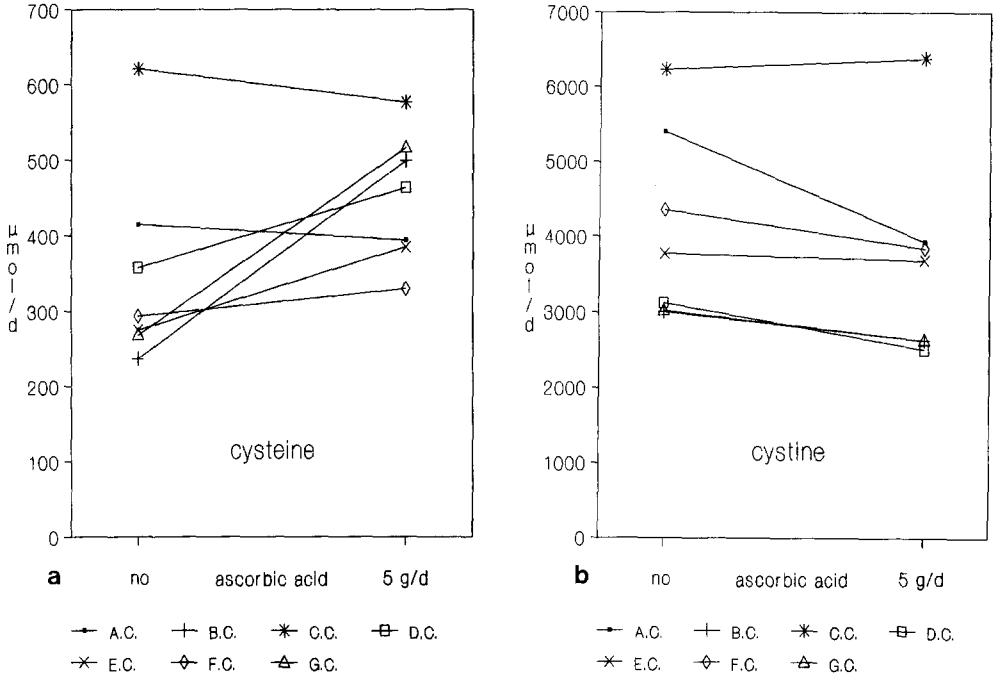

Fig. 2a, b. Excretion of **a** cysteine and **b** cystine by cystinuric patients in the absence and presence of ascorbic acid ingestion ($n=7$)

During ingestion of ascorbic acid, the excretion of cysteine increased to 159 µmol/day, whereas that of cystine decreased to 82 µmol/day. Mean values were calculated for all subjects over the 3 days of each test period. Both of the observed changes were significant ($P<0.05$).

The mean urinary volume of the control group was 1,864 ml in the absence of therapy and 1,845 ml during ingestion of ascorbic acid, and the corresponding value for the cystinuric patients during the two test periods was 3,800 and 3,731 ml, respectively. The cystinuric patients showed an increase in mean cysteine excretion (from 352.4 to 452.1 µmol/day; not significant) and a significantly ($P<0.05$) decreased excretion of cystine form 4,131.6 to 3,663.2 µmol/day during intake of ascorbic acid. Individual excretion curves calculated for cysteine and cystine in the two test groups are shown in Figs. 1 and 2.

Calculation of the urinary cystine: cysteine ratio enables one to estimate the influence of ascorbic acid therapy on both cystine and cysteine excretion. High intake of ascorbic acid was successful in three of our patients (group A: B.C., D.C., G.C.; Fig. 2): their mean ratio changed from 10.29 to 5.6. The ratio of the other four patients (group B) was 12.43 in the absence of treatment and 10.6 during therapy (Table 2). These two groups

Table 2. Urinary cystine: cysteine ratio of the test groups during the study

	Ascorbic acid ingestion	
	No	5 g/day
Healthy control group ($n=7$)	0.799	0.519
Cystinuric patients:		
Group A ($n=3$)	10.29	5.26
Group B ($n=4$)	12.43	10.6

Table 3. Concentration (C) and excretion (E) of oxalic acid during the study

	Ascorbic acid ingestion	
	No	5 g/day
Healthy control group ($n=7$):		
C (mmol/l)	0.206	0.318*
E (mmol/day)	0.363	0.559*
Cystinuric patients ($n=7$):		
C (mmol/l)	0.162	0.234 (NS)
E (mmol/day)	0.536	0.77 (NS)

* $P<0.05$; NS, not significant

Table 4. Effect of ascorbic acid ingestion on the urinary concentration of cystine in cystinuric patients

	Ascorbic acid ingestion	
	No	5 g/day
Asper et al. [2] ($n=3$, μmol/l)	2,247.2	1,165.2
Present study ($n=7$, μmol/l)	1,185.5	1,000.2

differed in that the patients in group A showed a mean cystine excretion value of 3,050 μmol/day, whereas those in group B exhibited a mean level of 4,943 mmol/day.

The effect of high-dose oral ascorbic acid on the concentration and excretion of urinary oxalate in both test groups is shown in Table 3. Daily excretion of oxalic acid in the control group increased from 0.363 to 0.559 mmol/day. The cystinuric patients excreted means of 0.536 mmol oxalate/day in the absence of therapy and 0.770 mmol/day during the intake of ascorbic acid. The 54% rise in oxalic acid excretion (healthy control group) was signficant ($P<0.05$).

Discussion

The cystine excretion by both test groups decreased during ingestion of ascorbic acid. However, as these reductions (control group, 23%; cystinuric patients, 11%) were slight, ascorbic acid seems to have only mild reducing properties in respect to cystine.

Because of the instability of cysteine, only few data on the concentration or excretion of both amino acids are available in the literature. Asper and Schmucki [1] and Asper et al. [2] investigated concentrations of cysteine and cystine and the influence of ascorbic acid ingestion on these amino acids using an electrochemical method. As these authors did not use 24-h urine specimens in their study, data on excretion are not available. Checking 91 urine samples from 3 cystinuric patients, Asper et al. found a mean cystine concentration of 2,247.2 μmol/l, nearly twice that found in our patients (Table 4). During ingestion of ascorbic acid in the study by Asper et al., this value decreased by about 48% to 1,165.2 μmol/l. We could not confirm this marked reduction in cystine excretion in the present study. Our data indicate that ascorbic acid therapy seems to be of therapeutic use only in patients excreting less than about 3,000 μmol cystine/day.

As depicted in Table 3, the high intake of ascorbic acid increased oxalic acid excretion by both test groups in the present study. This enhancement was probably attributable to the ingestion of ascorbic acid, since the method used to measure urinary oxalate (ion-exchange chromatography) does not interfere with ascorbate [6]. Our cystinuric patients showed a basic oxalate excretion of 0.536 mmol/day (range, 0.222–0.682 mmol/day), a value that would normally be indicative of hyperoxaluria. Considering the fluid intake of our patients (4 l/day), the high excretion of oxalate seems to have resulted from an increase in urinary volume. Thus, high excretion rates of urinary oxalate during ingestion of ascorbic acid do not indicate an enhanced risk of calcium oxalate stone formation in cystinuric patients as long as the latter follow the recommendation that their fluid intake be about 4 l/day.

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