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IMPACT OF SODIUM-POTASSIUM CITRATE THERAPY ON THE CIRCADIAN RHYTHM OF URINARY URIC ACID AND URATE SATURATION IN NORMAL INDIVIDUALS

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The circadian rhythm of the urinary saturation of uric acid, sodium acid urate, and ammonium acid urate was studied in 5 normal healthy male volunteers before and during 5 days of treatment with sodium-potassium citrate (1 g t.i.d., 1 g q.i.d., or 3 g t.i.d.). Urinary saturation was estimated on the relative supersaturation scale of Marshall and Robertson. Uric acid relative supersaturation varied during the day (mean±SD: -1.297 ± 1.763) and peaked above the formation product between 5:30 and 8:00 am. The peak level was reduced (but not significantly) by each treatment regimen in comparison with the control day. Overall, critical supersaturation with uric acid was noted in 46 (13%) out of 345 urine specimens, occurring mostly (83%) between 5:30 and 8:00 am. The sodium acid urate relative supersaturation also varied during the day (mean±SD: 0.329 ± 0.305) and peaked below the formation product between 8:00 and 10:30 am. It was increased by each regimen (significantly by the 3 g t.i.d. regimen), but mostly remained in or below the metastable zone. The ammonium acid urate relative supersaturation also varied (mean±SD: 0.087 ± 0.301) and peaked below the formation product between 5:30 and 8:00 am. The level was decreased by each regimen and remained in or below the metastable zone throughout the day.

In conclusion, the early morning period was the time with the highest risk of urinary uric acid supersaturation, but this supersaturation could be reduced (although not significantly) by treatment with alkali citrate. By contrast, the mean sodium acid urate and ammonium acid urate saturation levels were higher than the mean uric acid saturation, but remained mostly in or below the metastable zone with or without alkali-citrate therapy.

(Acta Urol. Jpn. **39**: 883-890, 1993)

Key words: Circadian rhythm, Uric acid, Sodium acid urate, Ammonium acid urate, Citrate therapy

INTRODUCTION

Uric acid and urate stones constitute only a small proportion (about 5%) of all urinary calculi. Uric acid has been reported to be the chief constituent of "urate" stones, which contain uric acid (2.3% of all clinical urinary stones), uric acid dihydrate (1.3%), ammonium acid urate (2.6%), and sodium acid urate (0.4%)[1]. Hyperuricosuria and increased urinary acidity are implicated in the genesis of uric acid and urate stones[2]. The highest urinary uric acid concentration has been reported to occur between 5:00 and 8:00 am in healthy individuals[3], while the urinary pH remains low throughout the night and early morning and usually shows twin peaks in the morning and evening[4]. To interpret the various critical factors when predicting the risk of urinary crystallization, Marshall and Robertson developed nomograms for estimation of the uric acid, ammonium urate, and sodium urate saturation levels (relative supersaturation and ion-activity products) to provide a more accurate assessment of the crystallization risk[5].

The aim of this study was to investigate the effects of 3 different regimens of sodium-potassium citrate in normal individuals by using fractional urine collection, and to attempt to determine the appropriate regimen for achieving acceptable diurnal variation of the urinary saturation of uric acid, ammonium urate, and sodium urate.

SUBJECTS AND METHODS

Five healthy male volunteers between 21 and 27 years old and weighing 60.8 ± 4.6 kg (mean $\pm$ SD) participated in the study. All subjects were found to be normal on the basis of physical examination and routine laboratory tests. None of them had any bowel or renal disease, and none of them were taking any medications around the time of the study. Informed consent was obtained from all subjects.

The study had 3 treatment phases, consisting of administration of sodium-potassium citrate at 1 g t.i.d., 1 g q.i.d., and 3 g t.i.d. Each phase included one control day without citrate and 5 test days with citrate. Four glasses (approximately 300 ml) of water were taken on the control day (Day 0) without citrate, while on the test days (Days 1-5) the same volume of water was taken with a dose of sodium-potassium citrate {each 1-g dose contained 448 mg (1.5 mEq) of potassium citrate, 406 mg (1.5 mEq) of sodium citrate, and 145 mg (0.75 mEq) of citric acid}. Doses were taken at 8:00 am, 1:00 pm, and 6:00 pm. An additional glass of water was taken without citrate at 8:30 pm in the t.i.d. study, while water with citrate was taken at 8:30 pm in the q.i.d. study. There was a washout pe-

riod of at least 2 weeks between each phase of the study. The subjects ate ordinary meals at 7:00 am, noon, and 5:00 pm and a snack at 9:30 pm. Urine was collected every 2.5 hours from 5:30 am (when the subjects awoke) to 11:00 pm (when they went to sleep). The first morning urine obtained at 5:30 am was not included in the evaluation because of difficulty in determining pH during the sleeping period. The pH was measured with a glass electrode, and urine volume was also measured immediately after voiding. The urinary concentrations of uric acid [UA] (mmol/l) and sodium [Na] (mmol/l) were analyzed using a Hitachi 705 autoanalyzer[6], while the urinary ammonium concentration [NH3] (mmol/l) was measured using the Indophenol reaction method[7].

The urinary saturation values were calculated using nomograms for estimating the urinary relative supersaturation (RS) of uric acid, sodium acid urate, and ammonium acid urate according to the method of Marshall and Robertson[5] as follows.

Uric acid relative supersaturation (UA RS):

$$UA\ RS = 1.0999 \times \ln[UA] - 12.7025 \times \ln(pH) + 21.1057$$

Sodium acid urate relative supersatura-

Table 1. The means of urinary pH, urinary uric acid relative supersaturation (UA RS), sodium acid urate relative supersaturation (Na Acid Urate RS) and ammonium acid urate relative supersaturation (NH3 Acid Urate RS) for each day on each regimen

	Urinary pH	UA RS	Na Acid Urate RS	NH3 Acid Urate RS
Cit 1g t.i.d.				
Day 0	6.097 ± 0.666	-1.229 ± 1.743	0.211 ± 0.324 ⌉	0.069 ± 0.255
Day 1	6.010 ± 0.700	-0.770 ± 1.859	0.284 ± 0.282 ⌐*	0.168 ± 0.233
Day 5	6.353 ± 0.752	-1.534 ± 1.895	0.385 ± 0.259 ⌋	0.038 ± 0.226
Cit 1g q.i.d.				
Day 0	5.988 ± 0.592	-0.834 ± 1.650	0.227 ± 0.339	-0.025 ± 0.339
Day 1	6.242 ± 0.596	-1.345 ± 1.648	0.362 ± 0.279	0.116 ± 0.255
Day 5	6.215 ± 0.624	-1.225 ± 1.564	0.358 ± 0.288	0.066 ± 0.286
Cit 3g t.i.d.				
Day 0	6.009 ± 0.456	-1.096 ± 1.422	0.181 ± 0.304 ⌐** ⌐**	0.115 ± 0.333
Day 1	6.509 ± 0.770	-1.771 ± 1.928	0.471 ± 0.307 ⌋** ⌊**	0.261 ± 0.314 ⌐**
Day 5	6.444 ± 0.701	-1.778 ± 1.911	0.433 ± 0.258	-0.039 ± 0.351 ⌋
Overall				
Day 0	6.032 ± 0.574 ⌐* ⌐**	-1.053 ± 1.604	0.206 ± 0.320 ⌐** ⌐**	0.053 ± 0.314 ⌐**
Day 1	6.253 ± 0.717 ⌋* ⌊**	-1.295 ± 1.847	0.373 ± 0.297 ⌋** ⌊**	0.181 ± 0.274 ⌐**
Day 5	6.337 ± 0.695 ⌋	-1.512 ± 1.796	0.392 ± 0.268 ⌋	0.021 ± 0.293 ⌋**
Total	6.215 ± 0.679	-1.297 ± 1.763	0.329 ± 0.305	0.087 ± 0.301

*$p < 0.5$, **$p < 0.01$
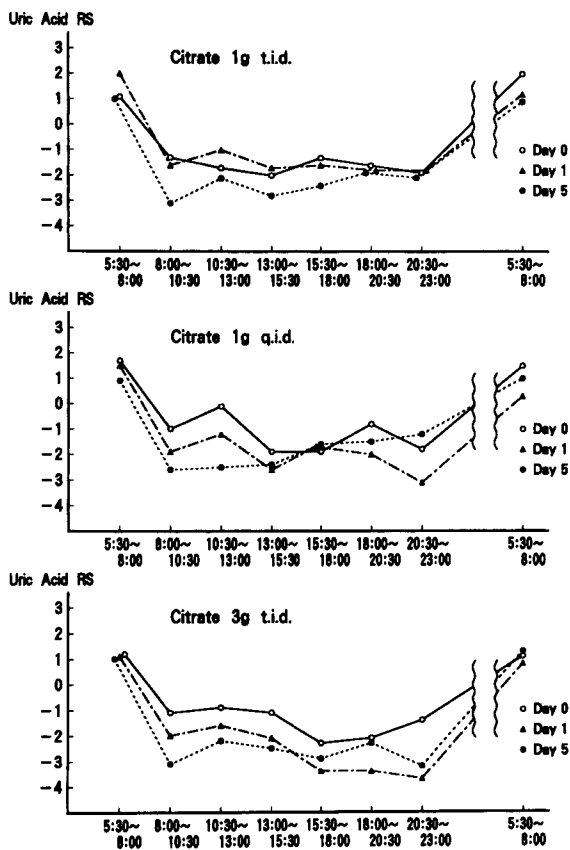
	5:30~8:00	8:00~10:30	10:30~13:00	13:00~15:30	15:30~18:00	18:00~20:30	20:30~23:00	5:30~8:00
Citrate 1 gm t.i.d.								
Day 0	1.1± .3	-1.3± .8	-1.7± .9	-2.0±1.0	-1.3± .6	-1.6± .4	-1.9± .5	2.0± .4
Day 1	2.0± .4	-1.6± .7	-1.0± .7	-1.7± .8	-1.6± .4	-1.8± .7	-1.8± .4	1.2± .2
Day 5	1.0± .2	-3.1± .3	-2.1± .9	-2.8± .5	-2.4± .5	-1.9± .8	-2.1± .6	.9± .2
Citrate 1 gm q.i.d.								
Day 0	1.7± .2	-1.0± .5	- .1± .7	-1.9± .9	-1.9± .3	- .8± .5	-1.8± .3	1.5± .3
Day 1	1.5± .3	-1.9± .3	-1.2± .5	-2.6± .3	-1.7± .5	-2.0± .4	-3.1± .4	.3± .3
Day 5	.9± .2	-2.6± 1	-2.5± .3	-2.4± .7	-1.6± .2	-1.5± .4	-1.2± .6	1.0± .2
Citrate 3 gm t.i.d.								
Day 0	1.2± .3	-1.1± .4	- .9± .5	-1.1± .7	-2.3± .5	-2.1± .3	-1.4± .5	1.1± .3
Day 1	1.1± .3	-2.0± .4	-1.6± .6	-2.1± .4	-3.3± .3	-3.3± .6	-3.7± .2	.8± .2
Day 5	1.0± .4	-3.1± .3	-2.2± .8	-2.5± .3	-2.9± 1	-2.3± .5	-3.3± .2	1.2± .5

$+p<0.10.$ $*p<0.05.$ $**p<0.01$

Fig. 1. Diurnal variation of the urinary uric acid saturation (mean±SE) in normal individuals on three sodium-potassium citrate regimens. The values "0" and "1" indicate the solubility and formation products, respectively. The right column (5:30~8:00) represents the following day shown for reference

tion (NaHU RS):

$$NaHU\ RS = 0.3005 \times \ln([Na] \times [UA]) + 1.8852 \times \ln(pH) - 4.7201$$

Ammonium acid urate relative supersaturation (NH_4U RS):

$$NH_4U\ RS = 0.2408 \times \ln([NH_3] \times [UA]) + 0.7754 \times \ln(pH) - 2.1751$$

These values were presented on a relative scale in which zero indicated the solubility product and a value of 1 represented the formation product.

The Bonferroni method was used for statistical comparisons between the control day (Day 0) and the test days (Days 1–5)[8].

RESULTS

The urinary pH was 6.215 ± 0.679 (mean $\pm$SD) (Table 1), ranging from 4.62 to 7.56, with peaks at 8:00~10:30 am and 1:00~3:30 pm. In particular, it was 5.355 ± 0.316 between 5:30 and 8:00 am. The urinary uric acid concentration was 2.284 ± 1.275 mmol/l, the urinary sodium concentration was 122.049 ± 49.836 mmol/l, and the urinary ammonium concentration was 27.965 ± 32.353 mmol/l[6].

The uric acid relative supersaturation (RS) was -1.297 ± 1.763 (Table 1), ranging from -4.3364 to 3.1145, and the uric acid saturation (as estimated by the relative supersaturation) exceeded the solubility product in 97.5% (73/75) of the urine samples obtained between 5:30 and 8:00 am and in 8.9% (24/270) of urine obtained at other times. The mean saturation peaked between 5:30 and 8:00 am and exceeded the formation product on Days 0-1, but it decreased following the administration of citrate. Citrate therapy reduced the supersaturation significantly a few times varying within undersaturation but not significantly in the early morning (Fig. 1). In addition, the uric acid relative supersaturation exceeded the formation product in 46 out of 345 (13.3%) urine specimens. Critical supersaturation (UA RS>1) occurred between 5:30 and 8:00 am in 17 of the 22 (77.3%) critically supersaturated urine specimens from the group given citrate at 1 g t.i.d., as well as in 11 of 14 (78.6%) critically supersaturated urine specimens from the group given citrate at 1 g q.i.d., and in all 10 (100%) critically supersaturated urine specimens from the group given 3 g t.i.d. No critically supersaturated urine specimens were obtained between 3:30 pm and 11:00 pm. However, none of the citrate regimens tested was effective in significantly reducing the supersaturation of uric acid.

The sodium acid urate relative supersat-

Table 2. Diurnal variation of urinary sodium acid urate saturation (mean± SE)in response to the three citrate regimens

	5:30~8:00	8:00~10:30	10:30~13:00	13:00~15:30	15:30~18:00	18:00~20:30	20:30~23:00	5:30~8:00
Citrate 1 gm t.i.d.								
Day 0	.38±.07	.59±.08	.31±.12	.29±.13	.15±.12	-.07±.09	-.18±.08	.14±.06
Day 1	.14±.06	.56±.13	.44±.11	.23±.12	.26±.14	.32±.15	.13±.15	.19±.07
Day 5	.40±.03	.81±.08	.39±.08	.42±.15	.25±.9	.41±.06	.08±.07	.32±.05
Citrate 1 gm q.i.d.								
Day 0	.36±.08	.58±.11	.27±.13	.39±.11	.23±.13	-.12±.10	-.12±.14	.31±.05
Day 1	.31±.05	.74±.08	.46±.11	.11±.14	.46±.09	.37±.14	.16±.10	.29±.07
Day 5	.38±.05	.82±.07	.46±.08	.54±.05	.22±.09	.14±.10	-.02±.08	.32±.04
Citrate 3 gm t.i.d.								
Day 0	.42±.05	.45±.16	.13±.12	.14±.13	.35±.08	-.03±.08	-.18±.02	.25±.08
Day 1	.25±.08	.76±.09	.62±.08	.65±.11	.61±.14	.59±.03	.04±.13	.25±.02
Day 5	.32±.07	.70±.09	.54±.04	.66±.07	.32±.04	.56±.10	.13±.09	.24±.12

+p<0.10. *p<0.05. **p<0.01

Table 3. Diurnal variation of urinary ammonium acid urate saturation (mean± SE) in response to the three citrate regimens

	5:30~8:00	8:00~10:30	10:30~13:00	13:00~15:30	15:30~18:00	18:00~20:30	20:30~23:00	5:30~8:00
Citrate 1 gm t.i.d.								
Day 0	.45±.06	.29±.05	.05±.07	.02±.11	.01±.05	-.14±.04	-.20±.06	.42±.07
Day 1	.42±.07	.29±.07	.25±.06	.05±.09	.05±.09	.03±.10	-.07±.09	.33±.07
Day 5	.27±.05	.14±.06	-.07±.06	-.03±.08	-.10±.06	-.04±.08	-.21±.07	.33±.08
Citrate 1 gm q.i.d.								
Day 0	.50±.10	.24±.08	-.01±.06	-.12±.14	-.18±.09	-.27±.10	-.33±.09	.41±.07
Day 1	.41±.07	.22±.11	.11±.07	-.16±.09	.09±.08	.02±.10	-.12±.06	.36±.06
Day 5	.42±.06	.13±.09	-.03±.03	-.01±.12	-.05±.10	-.14±.10	-.24±.04	.45±.06
Citrate 3 gm t.i.d.								
Day 0	.67±.11	.32±.10	.04±.10	.01±.12	.11±.07	-.17±.07	-.17±.04	.64±.07
Day 1	.64±.07	.48±.05	.29±.04	.23±.09	.11±.12	.08±.06	-.27±.09	.52±.04
Day 5	.39±.06	-.02±.12	-.09±.11	-.17±.09	-.31±.06	-.09±.12	-.45±.11	.43±.09

+p<0.10. *p<0.05. **p<0.01

uration was 0.329±0.305 (Table 1), ranging from −0.4273 to 1.0352 {two values which exceeded the formation product ($>$ 1.0) were obtained between 8:00 and 10:30 am on Day 5 with the 1 g q.i.d. regimen and at the same time on Day 1 with the 3 g regimen}. The mean saturation remained largely (86.4%, 298/345 urine samples) within the metastable zone between the solubility product of 0 and the formation product of 1, and it peaked between 8:00 and 10:30 am. Saturation was increased by all 3 citrate regimens in comparison with Day 0, and the increase was significant in a few times with the 1 g regimen and from 10:30 am to 3:30 pm as well as from 6:00 to 8:30 pm with the 3 g t.i.d. regimen (Table 2).

The mean ammonium acid urate relative supersaturation was 0.087±0.301 (Table 1), ranging from −0.6799 to 0.8643. The saturation remained in the metastable zone (59.1%, 204/345 urine specimens) or below the solubility product and never exceeded the formation product. It was decreased by all 3 citrate regimens in comparison with the control day, and there was a significant decrease in saturation from 8:00 am to 6:00 pm with the 3 g t.i.d. regimen (Table 3).

A significant correlation between the pH and the uric acid relative supersaturation was shown by regression analysis (UA RS = −2.429 × (pH) + 13.798, r = −0.9348, p< 0.01, N=345). The relationship between pH and the sodium acid urate relative supersaturation was also significant (NaHU RS = 0.195 × (pH) − 0.886, r=0.4346, p<0.01, N=345). Furthermore, the relationship between pH and the ammonium acid urate relative supersaturation was significant (NH₄U RS = −0.160 × (pH) + 1.079, r= −0.3605, p<0.01, N=345).

DISCUSSION

A protein-rich diet increases the serum and urinary concentrations of uric acid; approximately 650 mg of uric acid is excreted in the urine following a protein intake of 100 g, and 200 mg more uric acid will be excreted for each additional 30 g of protein[9]. The serum uric acid level peaks at noon and reaches a minimum early in the morning (8:00 am)[10]. Excretion of uric acid peaks after meals and is also at its minimum very early in the morning (midnight to 6:00 am)[10].

However, the urinary uric acid concentration reaches its highest level at this time because of the relatively low urine volume[11]. The urine pH is low (5.0~5.5) in the early morning, but this is followed by

the morning alkaline tide and two other postprandial tides[4]. Thus, early morning urine is often (97.5% in this study) supersaturated with uric acid because the urinary uric acid concentration is maximal and the urinary pH is at its lowest. Tiselius et al. have confirmed these facts and also reported that the urinary saturation with sodium urate remains low throughout the day[12].

The diurnal variation of urinary uric acid saturation has been found to be unexpectedly large in normal individuals, while the sodium urate and ammonium urate saturation levels varied in a narrow range but were higher on the average than the uric acid saturation level. Therefore, prevention and treatment for uric acid stones should be directed towards elimination of the urinary uric acid saturation peaks with a minimal increase in the sodium urate and ammonium urate levels. The present study demonstrated that an additional evening dose of citrate on top of the conventional t.i.d. regimen does not sufficiently reduce the early morning uric acid saturation.

Recently, Rodman challenged clinically the conventional t.i.d. regimen of alkalizing salts because of poor drug compliance; instead, he proposed that alternate-day doses of alkaline potassium salts could be given every other day for the prophylaxis of the uric acid stones which produce the recurrent gravel/colic syndrome; this would enhance the postprandial alkaline tide which provides the normal defense against such calculi[13]. The postprandial alkaline tide is absent in patients with such calculi, so an intermittent increase in urinary pH (simulating the normal postprandial alkaline tide) is suggested to protect against uric acid stone formation. Rodman's regimen is based on pH monitoring and aims to maintain the urinary pH close to 7.0 for as much of the day as possible. For this purpose, however, doses of alkaline salts between meals and before sleeping appear to be more effective and rational.

Sodium-potassium citrate or slightly acidic complex salts {1 g (=3.75 mEq) t.i.d.}

also increase the 24-hour urinary Na excretion by approximately 170 mg[6]. However, the risk of forming sodium urate crystals seems to be rather low and is certainly less than the risk of forming uric acid crystals[12]. In this study, however, the sodium urate saturation was mostly (86.4 %) in the metastable zone suggesting the potential risk of heterogenous nucleation and increased by citrate therapy. Although the increase was not significantly different from the control level, the maximum saturation reached 1.035 in an individual urine, exceeding the formation product. This occurs not so often but may be clinically significant, because a large dose of sodium-potassium citrate may result in urinary supersaturation with monosodium urate. A phase transformation from uric acid to monosodium urate has also been implicated in urinary monosodium urate crystal formation[12,14]. Pak et al.[15] reported that the urine was supersaturated with monosodium urate and monoammonium urate in 16 randomly selected patients with hyperuricosuric calcium oxalate nephrolithiasis.

There seems to be an etiological link between the urinary uric acid level and a propensity to develop calcium oxalate stones, although this is largely based on empirical observations. Heterogenous nucleation of calcium oxalate on sodium urate crystals and inhibition of the growth and aggregation of calcium oxalate crystals by the binding of colloidal urate to urinary glycosaminoglycans have been implicated in the link between uric acid levels and calcium oxalate stones[16]. However, it has also been suggested that this link occurs because the peak of urinary uric acid supersaturation coincides with the peak of calcium oxalate supersaturation[12].

In conclusion, the conventional alkali citrate regimens do not appear very promising for reducing the risk of uric acid crystallization. However, this study conducted in normal individuals suggests that the early morning is the critical period for uric acid crystallization and should be targeted in any attempt to reduce the urinary uric acid saturation with a special

consideration paid to the sodium urate saturation. Further clinical trials are necessary to answer the question of whether or not larger doses of citrate after dinner and before sleep can safely reduce the risk of early morning uric acid crystallization in patients with urate stones.

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和文抄録

尿酸と尿酸塩の尿中飽和度の日内変動におよぼすクエン酸塩の影響

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　健常男性5名を対象に，クエン酸塩（3g分3，4g分4，あるいは，9g分3）を投与し，尿酸と尿酸塩の尿中飽和度の日内変動を検討した．Marshall and Robertson の相対過飽和度により測定した．尿酸の相対過飽和度は日内で変動し（平均±SD：−1.297±1.763），5時30分〜8時で最高値となり，結晶生成度積を越えた．対照日に比較して，それぞれのクエン酸投与により最高値は有意ではなかったが低下傾向を示した．全体として，尿345サンプルの分析結果で，尿酸の不安定過飽和状態は13％（46サンプル）に見られ，その83％は午前5時30分〜8時に見られた．酸性尿酸ナトリウムの相対過飽和度は日内で変動し（平均±SD：0.329±0.305），午前8時〜10時30分で最高値となり，クエン酸投与により，その飽和度は上昇したが，準安定過飽和状態以下であった．酸性尿酸アンモニウムの相対過飽和度も日内で変動し（平均±SD：0.087±0.301），午前5時30分〜8時に最高値となり，クエン酸投与により飽和度は低下し，一日中準安定過飽和状態以下であった．

　以上より，早朝が尿酸に関しては，結晶化の危険性が明らかに高いが，クエン酸投与により有意ではないが低下させることができた．酸性尿酸ナトリウムと酸性尿酸アンモニウムの飽和度は平均では尿酸の飽和度より高かったが，一日中ほとんど準安定飽和度以下での変動であった．

（泌尿紀要 **39**：883-890, 1993）