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The Alkalizer Citrate Reduces Serum Uric Acid Levels and Improves Renal Function in Hyperuricemic Patients Treated with the Xanthine Oxidase Inhibitor Allopurinol

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Abstract

Hyperuricemia, an integral component of metabolic syndrome, is a major health problem causing gout and renal damage. Urine alkalizers like citrate preparations facilitate renal excretion of the uric acid, but its supportive effect on xanthine oxidase inhibitors has not been tested as yet. We thus performed a randomized, prospective study, employing patients with elevated serum uric acid levels (> 7.0 mg/dL), or those treated for hyperuricemia. They were randomly enrolled into two study groups: the allopurinol monotherapy (MT) group or combination treatment (CT) group with allopurinol and a citrate preparation. Allopurinol (100 to 200 mg/day) in the absence or presence of a citrate preparation (3 g/day) was administered for 12 weeks and levels of serum uric acid, its urinary clearance (Cua), and the renal glomerular filtration rates assessed with the creatinine clearance (Ccr) were evaluated before and after the treatment. Serum levels of uric acid decreased significantly in both groups, while the change observed was much greater in CT group. Cua was significantly increased in CT group but not in MT group. Ccr was not altered in both groups in general, whereas it was significantly increased in a fraction of CT group with decreased renal function. These results indicate that an additional use of citrate preparations with xanthine oxidase inhibitors is beneficial for patients with hyperuricemia, reducing circulating uric acid and improving their glomerular filtration rates.

Keywords

allopurinol; citrate preparation; creatinine clearance (Ccr); hyperuricemia; renal function

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CONFLICTS OF INTEREST:

All authors have nothing to declare.

INSTITUTIONAL APPROVAL:

This study was performed at the Yokohama Rosai Hospital and was reviewed and approved by its local Ethical Committee.

Introduction

Hyperuricemia causes gout, which is characterized by acute as well as chronic inflammation at multiple joints through deposition of excess circulating uric acid to intra-joint space. Hyperuricemia is frequently found in the patients with metabolic disorders, such as type 2 diabetes mellitus and hyperlipidemia [1, 2], and is a risk factor for central obesity-associated metabolic syndrome [3–5]. Indeed, hyperuricemia reduces circulating adiponectin levels and thus accumulates visceral fat in these patients [6, 7]. Hyperuricemia also develops renal damage and dysfunction through deposition of uric acid to renal glomeruli and subsequent inflammation in renal parenchyma [8, 9]. This immune-mediated glomerular destruction together with deposition of uric acid to the renal tubular lumens causing blockage of urinary flow reduces the glomerular filtration rates and develops progressive deterioration of renal function in patients with hyperuricemia [10]. Thus correction of hyperuricemia particularly in middle-aged subjects with metabolic syndrome, and establishment of rational therapeutic means for reducing hyperuricemia-associated renal dysfunction are both major issues for improving public health.

The xanthine oxidase inhibitors are classic and first-line therapeutic compounds for the treatment of hyperuricemia [11–13]. They reduce production of uric acid in the liver by inhibiting the xanthine oxidase, a rate-limiting enzyme in the metabolic pathway for circulating purines [14]. In addition to these compounds, the citrate preparations, the conjugate bases of citric acid, are considered as supportive agents for the treatment of hyperuricemia and associated renal damage, as these compounds are secreted into urine where they liberate citric acid and reduce pH that prevents deposition of uric acid to renal tubules and decreases formation of urinary calculus [15–17].

Since the combinatory effects of xanthine oxidase inhibitors and citrate preparations on the correction of hyperuricemia and renal function has not been evaluated, we conducted here a prospective, randomized, comparative study for addressing the effect of a citrate preparation on the renal functions of the hyperuricemic patients treated with the xanthine oxidase inhibitor allopurinol. We found that an additional use of citrate preparations is beneficial for reducing serum levels of uric acid as well as improving glomerular filtration rates in hyperuricemic patients treated with allopurinol who have reduced renal function.

Subjects and methods

Patient enrollment

This study was reviewed and approved by the Ethics Committee of the Yokohama Rosai Hospital. Written consent for participating in this study was obtained from all subjects enrolled. 70 subjects who had hyperuricemia with serum uric acid levels of 7.0 mg/dL or higher, or those diagnosed as having hyperuricemia in the past were enrolled into this study. The patients treated with any stimulants for uric acid excretion were excluded. Dosages of all medicines except allopurinol and a citrate preparation, which were used for the treatment of other health problems observed at the time of enrollment, were kept unchanged throughout the study. The subjects were randomly enrolled into two groups: the allopurinol monotherapy (MT) group and the combination treatment (CT) group with allopurinol and a citrate preparation. The specific citrate preparation consisting of potassium-sodium-hydrogen-citrate at a ratio of 6:6:3:5 was used in this study. These patients were treated with allopurinol ranged from 100 mg (once/daily, p.o.) or 200 mg (twice/daily, p.o.) (mean $\pm$ standard deviation dosage of allopurinol: MT group 113.3 ± 34.6 mg, CT group 100 ± 0.0 mg, statistically not significant between the two groups; median dosage of allopurinol: MT group 100 mg, CT group 100 mg) or in combination with a citrate preparation (3 g/day, p.o.) for 12 weeks.

Laboratory Test

The laboratory test was performed before and after the treatment indicated above. The study methods are shown in Fig. 1. Briefly, subjects were informed to consume low purine diet for 3 days prior to the test, are were fasted overnight. On the day of the test, they drank 500 mL of water at 9:00 am and urinated 30 minutes after the water intake [18]. Thereafter, blood pressure was monitored in subjects, and blood sampling and urine collection for 60 minutes were performed. We measured urine volume, pH, osmolality and specific gravity, serum uric acid, potassium, creatinine and blood urea nitrogen (BUN) and calculated creatinine clearance (Ccr), uric acid clearance (Cua), urinary uric acid excretion and Cua/Ccr ratios by using obtained parameters.

Statistical analysis

Two-tailed Student t-test, Fisher's test and Wilcoxon test were used for intergroup comparisons of the patients' background characteristics, such as sex, age and body weight, as listed in Table 1. One-way analysis of variance was employed for statistical estimation of the results obtained in the laboratory test. Two-tailed p values less than 0.05 was considered as significant. Inter-group comparisons of the parameters were adjusted with the amounts of allopurinol used at the time of enrollment by using ANCOVA, because there was a difference in such allopurinol amounts between the two groups. The SAS 9.1 software program (SAS Institute Japan Ltd., Tokyo, Japan) was used for all statistical analyses.

Results

Of 70 subjects enrolled, 3 subjects were withdrawn from this study: 2 were due to adverse events of the compounds used, while 1 was by decline of the informed consent. Seven subjects who did not completed the 12-week treatment with the compounds, and 4 subjects who showed Ccr over 200 mL/min were excluded from the analyses. Thus, 56 subjects (MT group: 30; CT group: 26) were forwarded into actual data analyses.

Patient background characteristics are listed in Table 1. There was no statistical difference between the two groups in all parameters listed. Mean BMI levels of all subjects was 26.7 kg/m² (MT group: 26.2 kg/m²; CT group: 27.2 kg/m²), and 31 patients (55%) of all subjects had BMI levels as 25 kg/m² or higher. Thirty-six patients (64%) of all subjects had hyperlipidemia, 32 patients (57%) for hypertension, and 14 patients (25%) for type 2 diabetes mellitus. Thus, 16 patients (29%) of all subjects enrolled had 25 kg/m² or higher BMI levels (thus had obesity) and at least two complications. Thirty-one patients (55%) of all subjects had Ccr values with 90 mL/min or less (MT group: 16 patients (53%); CT group: 15 patients (58%)). Some patients had been already treated with allopurinol before starting this study, thus serum uric acid levels before and after the treatment was influenced by the amounts of the allopurinol already used. Therefore, inter-group comparisons of the parameters were adjusted with prior use of allopurinol and with baseline values of each parameter.

Results obtained in the laboratory test are shown in Table 2. The treatment did not change urine pH levels in MT group, while it significantly elevated (from 5.8 to 6.3) in CT group (Fig. 2A), consistent with the known effect of a citrate preparation [19, 20]. There was also a significant difference in the urine pH values between MT and CT groups after the treatment.

The treatment also reduced Cua in CT group significantly, while it did not change in MT group (Fig. 2B). Cua values showed no differences between MT and CT groups before the treatment, while it was significantly higher in CT groups than in MT group after the treatment. Urinary uric acid excretion did not show any significant difference before and after the treatment in each group and among the two groups after the treatment. The

treatment did not cause statistically significant difference in Cua/Ccr values in MT and CT groups.

The treatment did not change Ccr values both in MT group and in CT group (Fig. 2C), while there was a statistical difference between MT and CT groups after the treatment. We focused on the changes of Ccr values in the subjects who had decreased renal function. We considered the subjects with Ccr values less than 90 mL/min as those with reduced renal function determined as “chronic kidney diseases (CKD)” [21]. In this specific subgroup, the treatment significantly increased Ccr values from 71.0 to 85.8 mL/min in CT group (15 subjects) ($p=0.0067$), while no significant changes were observed in MT group (16 subjects) (Fig. 2D).

The treatment significantly reduced serum uric acid levels from 7.3 mg/dL to 6.8 mg/dL in MT group, and from 7.5 mg/dL to 6.3 mg/dL in CT group (Fig. 2E). Reduction induced by the treatment was statistically significant in both groups, while the decrease was much greater in CT group (by 16%) than in MT group (by 6.8%). These results suggest that an additional use of a citrate preparation reduces serum uric acid levels in the presence of allopurinol.

There were no statistically significant changes in serum creatinine, BUN, urine volume, urine osmolality or urine specific gravity before and after the treatment in both groups. Neither group showed significant changes in blood pressure and serum potassium concentrations before and after the treatment. During the study, we encountered adverse events in 1 subject in MT group (mildly decreased platelet count) and 1 subject in CT group (mild rhinorrhea). The relationship between these adverse events with the treatment was not clear for both cases. There were no adverse events attracting major clinical concerns throughout the study.

Discussion

In this study, we employed 70 hyperuricemic subjects and performed a randomized, perspective study for evaluating importance of the urine alkalizer citrate preparation on the treatment of hyperuricemia in the presence of the xanthine oxidase inhibitor allopurinol. We found that a citrate preparation was beneficial for reducing serum uric acid levels by increasing urinary uric acid excretion in the patients with hyperuricemia treated with allopurinol. We also found that a citrate preparation increased the glomerular filtration rates in a fraction of subjects who had reduced Ccr. It is known that citrate preparations increase urine pH by accumulating HCO_3^- in urine, and eliminate uric acid calculi by decomposing the uric acid crystal [15–17]. An additional use of uric acid excretion stimulators with citrate preparations further reduces uric acid calculi in the kidney [22, 23]. Thus, citrate preparations appear to be beneficial for preventing deterioration of renal function in the patients with CKD who also have elevated levels of serum uric acid and are treated with allopurinol.

Decomposition of uric acid crystallized on the renal tubular lumens is one of the mechanisms underlining citrate preparation-mediated improvement of the renal glomerular filtration rate. Citrate preparations also prevent renal epithelial cell damage caused by crystallization of oxalate and calcium oxalate at the tubular lumens in patients with renal calculus [24, 25]. Further, urinary excretion of citrate in itself is proposed to be one of the mechanisms that improve renal function by these compounds, as citrate administration delays progression of chronic renal disorders in animals [26], and improves renal function in patients with polycystic kidney disease [27]; In both conditions, any calculi or crystals, which would be therapeutic targets of citrate preparations, are not formed in the tubular

lumens. In addition to these proposed activities, there may be as yet undiscovered mechanisms that underlie the effect of citrate on the improvement of renal function in various renal disorders, thus further studies are necessary for elucidating exact mechanisms of citrate preparation-mediated improvement of renal function.

The long-term beneficial effect of allopurinol is questionable on the preservation of renal function in hyperuricemic patients [28], although this compound is known to reduce progression of various renal disorders [29, 30]. In addition, the allopurinol metabolite oxypurinol, which is normally excreted into urine [31], accumulates in circulation in patients with reduced renal function, and can cause serious immune-mediated hypersensitivity reactions [32, 33]. In our study, we did not find any beneficial effects of allopurinol on patients' glomerular filtration rates. Thus, an additional use of citrate preparations with allopurinol is particularly important for treating hyperuricemic patients with compromised renal function, because citrate can improve their renal glomerular filtration rates and help reducing dosages of allopurinol.

Middle-aged patients with hyperuricemia frequently develop components of metabolic syndrome, such as hypertension, obesity, type 2 diabetes mellitus and hypertension [1,2], as we encountered during conduction of this study. Since all of these pathologic conditions potentially cause renal damage, co-existing hyperuricemia may further accelerate deterioration of renal function in these patients [34]. Indeed, recent studies have revealed inverse association of urine pH with the degrees of insulin resistance and presence of risk factors for CKD [35–38]. Thus, citrate preparations, which have a beneficial effect on renal function, should be considered as first-line medicines for the management of hyperuricemic patients with metabolic syndrome, as they may improve patients' renal functions.

Conclusions

A citrate preparation significantly increased urine pH levels and urinary uric acid excretion, and reduced serum uric acid levels in the subjects treated with allopurinol. This combination therapy also improved renal glomerular filtration effectively in a fraction of patients with reduced renal function. Thus, an additional use of citrate preparations with allopurinol is beneficial for the treatment of patients with hyperuricemia.

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Fig. 1. A study method used in this study

56 subjects with hyperuricemia who completed the study among 70 subjects employed were randomly enrolled into two groups: monotherapy (MT) and combination therapy (CT) groups. They were subsequently treated with the indicated compounds for 12 weeks. The laboratory test explained in the main text was performed before and after the treatment.

Fig. 2. Changes of renal parameters before and after the treatment in MT and CT groups

Changes of urinary pH (A), uric acid clearance (B), urinary creatinine clearance (All subjects) (C) urinary creatinine clearance (subject with reduced Ccr values) (D) and uric acid (E) before (Before) and after (After) the treatment are shown in A, B, C, D and E, respectively.

Circles and bars indicate mean $\pm$ standard deviation values obtained from indicated subject groups. ★: $p < 0.05$, n.s.: not significant, compared to the conditions indicated. CT: combination therapy, MT: monotherapy

Table 1

Patients' background characteristics

Patients' background characteristics		All (56)	MT group (30)	CT group (26)	P-values
Sex (Male: Female)		47:9	25:5	22:4	1.0000
Age (y)		56±15	56±16	55±14	0.7475
Body weight (kg)		74±15	70±12	78±18	0.0565
Degree of obesity	BMI <25 kg/m ²	45% (25)	50% (15)	38% (10)	0.4296
	BMI ≥25 kg/m ²	55% (31)	50% (15)	62% (16)	
Complications	Hyperlipidemia	64% (36)	57% (17)	73% (19)	0.2669
	Hypertension	57% (32)	60% (18)	54% (14)	0.7875
	Diabetes mellitus	25% (14)	27% (8)	23% (6)	1.0000
Baseline Creatinine Clearance (Ccr)	91 mL/min	45% (25)	47% (14)	42% (11)	0.8888
	71 to 90 mL/min	29% (16)	20% (6)	38% (10)	
	51 to 70 mL/min	13% (7)	20% (6)	4% (1)	
	50 mL/min	14% (8)	13% (4)	15% (4)	
Previous allopurinol treatment (Yes: No)		21:35	15:15	6:20	0.0538

Values indicate means ± standard deviation of the parameters indicated. (MT group: n = 30; CT group: n = 26)

Numeric in parentheses indicates numbers of subjects

CT: combination therapy, MT: monotherapy

Table 2

Changes in renal parameters before and after the treatment

Parameters	Group	Before Treatment	After Treatment	P values [*]	P values of group comparison ^{**}
Urinary pH	MT group	6.1±0.8	6.1±0.7	P=0.6981	P=0.0425
	CT group	5.8±0.5	6.3±0.6	P=0.0011	
Cua (mL/min)	MT group	4.7±1.9	4.4±1.8	P=0.4741	P=0.0179
	CT group	4.4±1.7	5.1±2.0	P=0.0352	
Urinary uric acid excretion (mg/Kg/hour)	MT group	0.35±0.15	0.30±0.12	P=0.0977	P=0.0634
	CT group	0.32±0.12	0.32±0.13	P=0.9666	
Cua/Ccr (%)	MT group	5.4±2.1	5.1±1.5	P=0.3594	P=0.1409
	CT group	5.2±2.0	5.5±1.8	P=0.4092	
Serum uric acid (mg/dL)	MT group	7.3±1.1	6.8±1.0	P=0.0184	P=0.0966
	CT group	7.5±1.3	6.3±0.9	P<0.0001	
Ccr (mL/min)	MT group	91.8±35.1	88.2±30.0	P=0.3838	P=0.0350
	CT group	89.8±28.9	97.2±31.2	P=0.1649	

Each value indicates means ± standard deviation. (MT Group: n = 30; CT Group: n = 26)

^{*} P values are obtained by comparing values of before and after the treatment.^{**} P values are obtained by comparing values of MT and CT groups.

CT: combination therapy, MT: monotherapy