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Hiroshi Tsutani · Chiyo Kiriba · Shin Imamura
Nobuyuki Yoshio · Toru Nakamura · Takanori Ueda

Latent overproductive hyperuricemia increases in patients during the intermittent phase of gouty arthritis under long-term antihyperuricemic treatment

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Abstract This work was undertaken to determine baseline urate metabolism in patients during the intermittent phase of gouty arthritis in order to decide on the best treatment for hyperuricemia. Parameters affecting serum urate levels, including uric acid clearance and urinary urate excretion, were re-evaluated in 30 patients who had shown normouricemia and no gouty attacks for at least 1 year and who were receiving urate-lowering drugs. The parameters determined at 2 weeks after discontinuation of the treatment (re-evaluation) were compared with those determined at initial diagnosis (initial evaluation). The discontinuation of urate-lowering drugs at re-evaluation led to a hyperuricemic state in all patients. The serum urate levels at re-evaluation were significantly higher than those at initial evaluation. The mean quantity of urinary urate excretion in patients showing increases in serum urate levels and the number of patients classified with overproductive hyperuricemia increased at re-evaluation. There was a significant increase in γ-glutamyl transpeptidase level, but no changes in body weight or creatinine and uric acid clearance. Asymptomatic patients at intermittent phases of gout may be in a latent, but progressing, hyperuricemic state as a result of urate overproduction. Physicians should assess latent hyperuricemia periodically, and choose a treatment with xanthine oxidase inhibitor when necessary.

Key words Uricosuric agents · Allopurinol · Prevention and control · Differential diagnosis · Patient education

H. Tsutani (✉) · C. Kiriba · S. Imamura · N. Yoshio · T. Nakamura · T. Ueda
First Department of Internal Medicine, Fukui Medical University, School of Medicine, 23-3 Shimoaizuki, Matsuoka, Fukui 910-1193, Japan
Tel. +81-776-61-8345; Fax +81-776-61-8109
e-mail: htsutani@fmsrsa.fukui-med.ac.jp

T. Nakamura
Hayashi General Hospital, Fukui, Japan

Introduction

In recent years, the number of patients in Japan with hyperuricemia and gout has increased.[1] Persistent hyperuricemia can lead to urate crystal deposition, which causes attacks of gouty arthritis as well as gouty tophi, urinary tract calculi, and renal dysfunction.[2–4] Therefore, the proper management of hyperuricemia is necessary to prevent arthritis and other complications in gouty patients. Since excellent drugs for hyperuricemia are currently available, the normalization of urate levels is not a critical problem.[5] However, the proper pharmacotherapy in asymptomatic patients at intermittent phases of gout has not been well documented, although there are a few reports supporting the need for continued therapeutic compliance in patients with intermittent symptoms of gout.[6–9]

Urate-lowering drugs are chosen at the initial diagnosis based on the underlying causes for each individual patient; patients with overproductive hyperuricemia require xanthine oxidase inhibitor, and those with underexcretory hyperuricemia require uricosuric agents.[10] However, it is unclear whether drugs selected at the initial diagnosis will still be beneficial in the intermittent phase of gout, since the factors which initially induced hyperuricemia might not have had a continuing influence, and the type of hyperuricemia initially diagnosed may have altered. Thus, reports that specifically address the baseline metabolism of urate at the intermittent phase of gout can help the physician to choose a rational long-term antihyperuricemic treatment.

In the present study, we evaluated urate metabolism in gouty patients who were receiving long-term treatment for hyperuricemia. The parameters of urate metabolism in these patients were determined after treatment for hyperuricemia had been discontinued, and these were compared with baseline values at the time of initial diagnosis. The findings indicated the presence of a latent overproductive condition, and the necessity of long-term treatment for hyperuricemia as well as the modification of treatment in accordance with the latent cause of the hyperuricemia.

Patients and methods

Patients

The subjects of this study were patients with a history of typical gouty arthritis attacks who were being followed at our outpatient clinic between July 1997 and October 1998. Gout was diagnosed based on evaluation criteria established by the American Rheumatology Association (ARA).[11] The inclusion criteria for this study included a second of the assessment of urate metabolism following the resolution of arthritic symptoms and before initiating urate-lowering drug treatment at the initial diagnosis of gout (initial evaluation), no active symptoms for at least 1 year prior to enrollment, a serum urate value no greater than 6.0 mg/dl at enrollment, and the absence of any abnormality of renal function as evidenced by a serum creatinine level of 1.5 mg/dl or less.

Study design

All patients consented to participate in the study. Medication for hyperuricemia was discontinued for 2 weeks before an evaluation of urate metabolism, including uric acid clearance and urinary urate excretion (re-evaluation). We also evaluated other factors known to affect urate metabolism, such as renal function and body weight, as well as the presence or absence of coexisting disorders such as alcoholic liver injury. These values were compared with those measured at the time of initial diagnosis. In addition, serum urate was measured in some patients after one more week to assess the extent of any rise in the serum urate level.

Uric acid clearance

Uric acid clearance was performed as described previously.[12] Patients were instructed to fast during the early morning but drink copious amounts of water. Urine was collected over a period of 60 min, during which time blood samples were also taken. Uric acid clearance and urinary urate excretion per hour (corrected for body weight) were calculated as follows: uric acid clearance (ml/min) = [urine urate (mg/dl) × urine volume (ml/h) × 1.48 (m^2)] / [serum urate (mg/dl) × 60 (min) × body surface area (m^2)]; urinary urate excretion (mg/kg/h) = [urine urate (mg/dl) × urine volume (ml/h)] / [body weight (kg) × 100]. Uric acid clearance was used to estimate the patient's renal urate excretion ability; urinary urate excretion was used to estimate the quantity of urate producted. On the basis of uric acid clearance and the amount of urate excreted, hyperuricemia in each patient was categorized in accordance with Nakamura's classification into one of four categories[10]: overproductive type; underexcretory type; combined overproductive and underexcretory type (combined type); normal type.

Statistical analysis

The differences between medians were analyzed using the paired *t*-test.

Results

Patient characteristics

Thirty patients were enrolled in the study, and the findings from all patients were evaluated and analyzed. All patients were men, and ranged in age from 24 to 72 years (median 62 years). They had all had at least one episode of gouty attack between 2 weeks and 4 months before the initial diagnosis given in their medical records. Hyperuricemia was classified as the overproductive type in 10% (3 patients), the underexcretory type in 60% (18 patients), the combined type in 20% (6 patients), and normal type in 10% (3 patients) of the patients. The treatment period for gout ranged from 1 to 12 years (median 4 years). All patients had been free from symptoms for at least 1 year prior to entering the study. None of the patients experienced attacks of gout during the study period, and there was no evidence of renal complications such as decreased renal function or urinary tract calculi during the study period.

Urate dynamics

All patients had normalized serum urate concentrations on entering this study and were receiving treatment for hyperuricemia. However, they all showed elevated levels of serum urate 2 weeks after the cessation of the therapy (Fig. 1). The mean serum urate level after discontinuation of treatment was 3.3 mg/dl higher (range 1.0–5.6 mg/dl) than when the study started.

To examine how serum urate level increased following discontinuation of the urate-lowering drugs, the serum

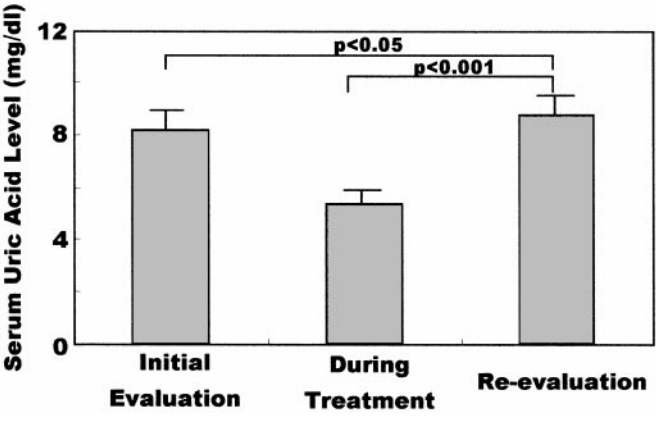

Fig. 1. Serum urate levels at initial diagnosis (initial evaluation), after enrolling in the study (during treatment), and following discontinuation of treatment (re-evaluation). Antihyperuricemic drugs were discontinued in patients with gout for 2 weeks before re-evaluation. The *bars* represent the means and standard deviations of 30 patients

urate level was determined 1 week after discontinuing the drugs in five patients. The mean serum urate values then were already significantly elevated, and were approximately 80% of the values measured at 2 weeks after discontinuing therapy (Fig. 2).

Comparisons with the initial diagnosis

When serum urate levels at re-evaluation were compared with those at the initial evaluation they were significantly elevated (Fig. 1). In 19 patient (63%), the serum urate levels were higher than those documented at the time of the initial diagnosis. When we analyzed the findings for changes in the quantity of urinary urate excretion, uric acid clearance, creatinine clearance, body weight, and γ-glutamyl transpeptidase (γGTP), there were no significant differences among all patients for these factors. However, in the 19 patients with elevated serum urate levels at re-evaluation, the mean quantity of urinary urate excreted and the serum γGTP were significantly elevated (Table 1).

When each patient with gout was categorized again on the basis of uric acid clearance and urinary urate excretion, five patients showed overproductive hyperuricemia. Three patients were changed to overproductive type from normal type, and two patients were changed to combined type from underexcretory type because of increasing quantities of urinary urate excretion (Fig. 3). Five patients exhibited a decrease in uric acid clearance at re-evaluation. However, these patients were originally classified as having underexcretory hyperuricemia, so there was no new transition to the underexcretory type.

When we evaluated the balance among serum urate levels at initial diagnosis and at re-evaluation in relation to duration of urate-lowering treatment, there was no significant relationship among them.

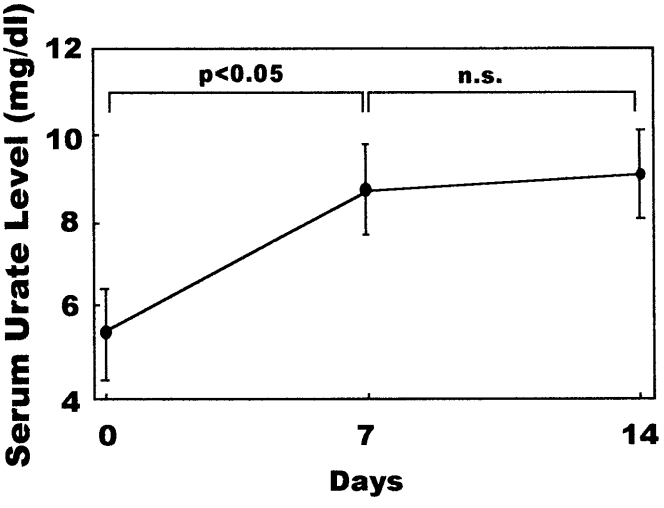

Fig. 2. Serum urate levels following discontinuation of treatment in patients with gout. Values represents the mean and standard deviation for five patients

Discussion

All patients in the present study showed abnormal elevations of serum urate following discontinuation of hyperuricemia therapy for 2 weeks. These findings suggest that the potential for intermittent hyperuricemia persists, and that discontinuation of drug therapy may accelerate its recurrence. Thus, patients who are not fully compliant with the therapy are prone to the rapid redevelopment of hyperuricemia, which may then lead to recurrent attacks of gouty

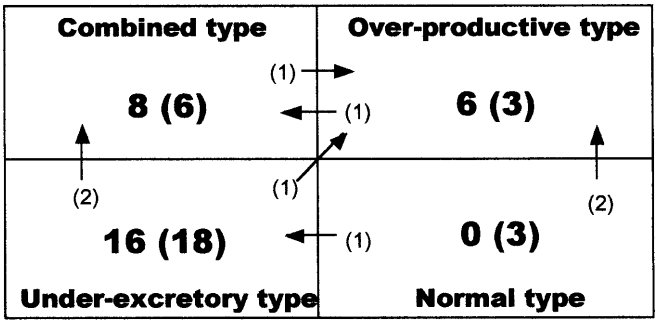

Fig. 3. The numbers of hyperuricemic patients of different types. The numbers of patients at re-evaluation are shown in large figures, and the numbers at the initial evaluation are shown in large figures in parentheses. *Arrows* and *small figures in parentheses* represent the numbers of patients that changed type at re-evaluation

Table 1. Parameter changes in patients with and without elevated serum urate levels at re-evaluation

		Patients without increased Sua (n = 30)		Patients with increased Sua (n = 18)	
		Initial	Second	Initial	Second
Uua	(mg/kg/h)	0.41 ± 0.11	0.48 ± 0.16	0.39 ± 0.12	0.52 ± 0.16*
Cua	(ml/min)	4.8 ± 1.4	5.3 ± 2.2	5.1 ± 1.5	5.4 ± 2.0
Ccr	(ml/min)	91.6 ± 22.5	90.6 ± 24.1	92.2 ± 26.2	89.7 ± 21.6
BW	(kg)	67.8 ± 10.1	68.5 ± 9.7	67.8 ± 9.9	68.4 ± 9.3
γGTP	(IU/l)	43 ± 34	58 ± 42	42 ± 32	68 ± 45*

Sua, serum urate level; Uua, urinary urate excretion; Cua, uric acid clearance; Ccr, creatinine clearance; BW, body weight; γGTP, γ-glutamyl transpeptidase. Means and standard deviations were obtained at the initial diagnosis of gout (initial) and at re-evaluation (second)
* $P < 0.05$ in paired t-test

arthritis.[6–8,13] In addition, hyperuricemia has recently been identified as a separate risk factor for renal and ischemic cardiac disorders.[14] This also underscores the importance of proper management of hyperuricemia in patients with intermittent symptoms of gout.

An interesting finding in this study was that patients had higher serum urate levels at re-evaluation than the levels documented at the time of the initial diagnosis. The development of hyperuricemia is thought to result from overproduction of urate in the body and/or underexcretion via the kidneys. As assessed in this study, the patients showing elevated urate levels at re-evaluation showed a higher urinary excretion of urate at re-evaluation than at initial evaluation, while they did not show any change in uric acid clearance. The numbers of underexcretory-type and normal-type patients decreased, while the numbers of overproductive-type as well as combined-type patients increased at re-evaluation as a result of the increase in urinary urate excretion. These findings reflect increased urate production in patients with intermittent phases of gouty arthritis.

To clarify why an increase in latent overproductive hyperuricemia is observed during the intermittent phase, we checked several parameters that affect the induction of hyperuricemia. Patients with hyperuricemia due to a known casual factor, such as obesity, alcoholism, or diuretic use, become normouricemic following an acute gouty attack, because they are careful to remove these factors.[15] On the other hand, they tend not to care about it during the intermittent phase. In the present study, a statistical correlation was found between elevated urate levels and γGTP levels, indicating that an increase in latent serum urate levels depends on having a life style which induces hyperuricemia, such as taking alcohol. Otherwise, no definitive factors were found which affected urate overproduction, not even the duration of the gout or a change in body weight. No patients took thiazides or any other medication.

An acute gouty attack is often directly associated with a reduction in serum urate levels.[15,16] It is suggested that this is based on the pain-induced cortisol or interleukin-6 produced at inflammatory sites,[16,17] which limit the serum urate produced during the acute phase of a gouty attack. Thus, the acute gouty attack itself does not appear to affect the urate level and excretion at the initial diagnosis, when the gouty attack has already settled and urate levels and excretion are relatively lower than those at re-evaluation.

The type of hyperuricemia often varies with the duration of gout, and patients with a long history of gout often demonstrate an underexcretory pattern of hyperuricemia.[18] During the present study, we were unable to detect such trends in uric acid clearance (a parameter of renal excretion of urate) and serum creatinine (a parameter of renal function) between the initial diagnosis and the re-evaluation. However, some patients with an underexcretory pattern of hyperuricemia also showed decreases in uric acid clearance. This finding is in agreement with those of previous studies.[18]

Rational therapy for gout involves the selection of drugs that target the cause of hyperuricemia. Some patients in the present study demonstrated increased urate production with a transition to an overproductive type of hyperuricemia. This emphasizes the need for a periodic assessment of urate metabolism, and modifications of the antihyperuricemic therapy to include xanthine oxidase inhibitor when necessary, in patients being treated for gout. In addition, patients should be encouraged to moderate their eating and drinking habits.[6,19]

In conclusion, we evaluated urate metabolism in patients receiving long-term therapy for hyperuricemia. The discontinuation of drugs brought about hyperuricemia, and the production of urate increased during remission of the gout. These findings indicate the need for continued compliance with oral therapy for hyperuricemia. Physicians should recognize latent overproductive conditions by periodic assessment, and modify the treatment to improve overproductive hyperuricemia.

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