Serum Urate During Acute Gout

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ABSTRACT. ***Objective.*** To study the frequency of normal serum urate (SU) levels during acute gout in the largest studies of acute gout treatment to date.

Methods. Data collected from 2 randomized controlled clinical trials assessing the efficacy of etoricoxib or indomethacin for 7 days in acute gout were used to assess SU levels during acute gouty attacks. Efficacy was similar with both agents, so both groups were combined for analysis.

Results. A total of 339 patients were enrolled in the 2 studies; 94% were male; mean age was 50.5 years. At baseline, 14% of patients had a "true" normal SU (≤ 6 mg/dl) and 32% had SU ≤ 8 mg/dl during acute gout. Baseline mean SU was 7.1 versus 8.5 mg/dl ($p < 0.001$) in those taking allopurinol versus nonusers. Patients taking chronic allopurinol were more likely to have lower SU at baseline compared to those not taking chronic allopurinol ($p < 0.001$) during the acute attack.

Conclusion. A normal SU level at presentation does not exclude an acute gouty attack. In the largest studies of acute gout to date, attacks still occurred despite SU levels being below 6.8 mg/dl, the saturation level for urate. This may be attributed to persistence of tophi and an increased body uric acid pool. Additional studies are needed to determine the correlation between SU and the body uric acid pool as well as the relationship to timing of changes during acute gout. (J Rheumatol First Release April 15 2009; doi:10.3899/jrheum.080938)

Key Indexing Terms:
GOUT ACUTE GOUT SERUM URATE

Nonrheumatologists are often unaware that serum urate (SU) may be normal during acute episodes of gout. Even rheumatologists may consider it to be unusual[1,2]. The diagnosis of gout may be rejected when a normal SU level is found during the acute attack. Given that many assumptions are made at the time of an acute gouty attack a correct diagnosis may depend on a physician's knowledge that the SU may be within the normal range at the time of an acute gouty attack.

Three hundred thirty-nine patients with acute gout were included in the etoricoxib gout trials[3,4], which comprised the largest cohort of patients ever studied during acute gout. These data provide an opportunity to study SU and the relation between SU and other measures during the acute gout attack and following treatment. Our aim was to study the distribution of SU and frequency of normal SU levels during acute gout in the largest studies of acute gout treatment to date.

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MATERIALS AND METHODS

The 2 gout studies were identical 7-day randomized, double-blind, active-comparator-controlled, parallel-group, multicenter studies, conducted under in-house blinding procedures, to evaluate the safety, tolerability, and efficacy of etoricoxib 120 mg once daily in acute gout[3,4]. Patients were allocated to treatment assignment using a computer-generated randomized allocation schedule generated by the study statistician. Numbered containers were used to implement allocation and each patient was assigned the next number in the sequence upon being enrolled. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

Patients experiencing an acute attack of clinically diagnosed gout ≤ 48 h prior to randomization were randomly allocated to etoricoxib 120 mg once daily or indomethacin 50 mg 3 times daily. Data collected at Days 2, 5, and 8 from these 2 randomized, active-comparator-controlled trials to assess the efficacy of etoricoxib or indomethacin for 7 days in acute gout were used to assess SU levels during acute attacks. Efficacy was similar with both agents, so both groups were combined for analysis.

In the 2 gout studies[3,4], allopurinol was not to have been initiated within the 2 weeks preceding randomization. In addition, patients who were taking allopurinol prior to randomization were allowed to have undergone dose adjustments within the 2 weeks preceding randomization. Concomitant colchicine was allowed if therapy had been at a stable, low dosage (maximum 0.6 mg twice daily) for > 30 days. Patients who had taken nonsteroidal antiinflammatory drugs (NSAID), including aspirin and cyclooxygenase-2-specific inhibitors, within the last 48 h prior to randomization, were excluded. Use of any analgesic medication besides study medication was prohibited during the study. [Exceptions: (1) The use of stable, chronic, low-dose aspirin (≤ 325 mg daily) was permitted; (2) non-NSAID-containing analgesic medication (e.g., acetaminophen and acetaminophen/opioid combination reagents) was permitted until 6 h prior to baseline assessment at Visit 1.]

Analyses were descriptive in design. All analyses were conducted in the overall cohort and in the subgroups as follows: concurrent allopurinol

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(yes/no); sex; race (White, Black, other); attack type (monoarticular/polyarticular); number of previous attacks (categories 1–2, 3–4, or 5 or more); and frequency of prior attacks per year. Between-group comparisons of means was done using test statistics, while comparisons of proportions were done using chi-squared statistics.

Study patients had 2 blood draws (Day 1 and Day 8 or at discontinuation if earlier than Day 8). Blood was drawn at baseline/entry (presentation with acute gout and meeting entry criteria) and again on Day 8 once, at the study visit, which could be any time of day. SU was measured by the uricase enzyme method. A normal SU was defined as ≤ 8 mg/dl as usually reported by laboratories and ≤ 6 mg/dl ("true normal": below uric acid saturation). A change of 1 mg/dl in SU was considered a meaningful increase or decrease.

RESULTS

A total of 339 patients were included in the analyses. The study population was 94% male, 45% White, 22% Asian, 18% Hispanic American, 7% Black, and 7% other ethnicity. The mean (standard deviation) age was 50.5 (13.0) years, and the median age was 50 years (range 22–93 yrs).

At baseline, mean SU was 7.1 versus 8.5 mg/dl ($p < 0.001$) in those taking allopurinol versus nonusers, respectively (Table 1). This difference persisted on Day 8 (following treatment), where mean SU was 7.3 versus 8.8 mg/dl ($p < 0.001$), in those taking allopurinol versus nonusers, respectively.

A SU ≤ 8 mg/dl was observed in 32% (n = 102) of patients overall, including 49% (n = 27) of patients taking allopurinol versus 29% (n = 82) of those not taking allopurinol ($p < 0.0001$) (Table 2). A SU ≤ 6 mg/dl was observed in 11% (n = 32) of patients overall, including 29% (n = 16) of patients taking allopurinol versus 11% (n = 32) of those not taking allopurinol.

At baseline, 13.8% (n = 26) of patients had previously taken colchicine (but were not necessarily taking it at baseline). During the study, 17.5% (n = 33) of patients were receiving concomitant colchicine.

No significant differences were observed between those taking allopurinol and nonusers in baseline white blood cell counts. Higher baseline mean SU was noted in patients with more frequent prior gouty attacks per year (1–3 vs > 4 gouty attacks per yr; mean SU 8.3 vs 9.4 mg/dl, respectively; $p < 0.05$). This difference persisted following treatment: at Day 8, 8.6 vs 9.6 mg/dl, respectively ($p > 0.05$). There also were differences in SU following treatment according to attack type (monoarticular vs polyarticular; mean SU 8.4 vs 9.0 mg/dl, respectively; $p < 0.05$).

Table 1. Comparison of mean serum urate (SU) (combined treatments) by allopurinol use.

	Baseline		Day 8	
	Mean (SD)	p	Mean (SD)	p
Serum urate (SU), mg/dl				
Allopurinol yes	7.2 (2.2)	< 0.001	7.3 (2.1)	< 0.001
Allopurinol no	8.5 (2.1)		8.8 (1.9)	

Table 2. Proportion (n) of patients with serum urate (SU) ≤ 6 mg/dl and SU ≤ 8 mg/dl during acute gout at baseline (combined treatments) by allopurinol use.

	SU ≤ 6 mg/dl		SU > 6 mg/dl	
	%	n	%	n
Allopurinol yes (n = 55)	29.1	16	45.5	25
Allopurinol no (n = 284)	11.3	32	78.2	222
Total (n = 339)	14.2	48	72.9	247
	SU ≤ 8 mg/dl		SU > 8 mg/dl	
Allopurinol yes (n = 55)	49.1	27	25.5	14
Allopurinol no (n = 284)	28.9	82	60.2	171
Total (n = 339)	32.2	109	54.6	185

DISCUSSION

In the largest studies of acute gouty arthritis to date[3,4], 14% of patients had a "true" normal SU (≤ 6 mg/dl) and 32% had a normal SU when normal SU was defined as ≤ 8 mg/dl by many laboratories during their acute gouty attack. Twenty-nine percent of patients taking allopurinol had a baseline "true" normal SU (≤ 6 mg/dl) and 49% of patients taking allopurinol had a baseline SU ≤ 8 mg/dl during their acute gouty attack. Thus, patients receiving chronic allopurinol treatment were more likely to have lower SU at the onset of the acute gouty attacks compared to patients not receiving chronic allopurinol. Nevertheless, attacks still occurred in patients on allopurinol treatment. This may be attributed to persistence of tophi, need for larger doses, or longer duration of treatment with allopurinol or need for maintaining lower SU levels.

It has been suggested that SU is often within the normal range during acute gout[5-7]. Logan, *et al* studied 38 patients and reported that SU is often within the normal range during acute gout, and suggested that SU frequently falls during acute gout[5]. The upper limit of the normal range of SU in their laboratory was 0.45 mmol/l or 8.1 mg/dl for men. Schlesinger, *et al*[6] studied the frequency of normal SU levels in 59 patients with acute gout. The upper limit of the normal range of SU in their laboratory was 8 mg/dl for men. The proportion of patients with SU levels within the normal range during acute gout were 39% and 43% in the Schlesinger and Logan studies, respectively.

Urano, *et al*[7] found SU to be significantly lower in acute gout than in the intercritical phase ($p < 0.0001$); a normal SU level was found in 49% of their 41 patients. The upper limit of the normal range of SU in their laboratory was 7.5 mg/dl for men. They also reported that the change in SU was closely associated with C-reactive protein (CRP) and plasma interleukin 6 (IL-6) levels. Increased urinary excretion of uric acid, estimated by percentage change in fractional excretion of uric acid, during acute gout significantly correlated with CRP levels during an attack. Urano, *et al* concluded that the decrease in SU during acute gout is associated with increased urinary excretion of uric acid. They

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proposed that an inflammatory process may play a role in the mechanism of acute gouty attacks, possibly mediated by IL-6 production.

The occurrence of acute gout in the presence of allopurinol use may occur early in treatment or with SU movements associated with starting/stopping treatment. We do not have information regarding the length of time patients were taking allopurinol, or on patient compliance with allopurinol treatment. Of note, allopurinol may not have been initiated within the 2 weeks preceding randomization. In addition, patients who were taking allopurinol prior to randomization were allowed to have undergone dose adjustments within the 2 weeks preceding randomization.

Although SU levels < 8 mg/dl are generally considered to be normal, levels > 6.8 mg/dl are above saturation level and may allow deposition of gouty crystals. A SU level of approximately 6.8 mg/dl is the concentration at which monosodium urate crystals begin to precipitate[8,9]. A normal SU should be considered below 6.8 mg/dl, not as accepted and reported by many laboratories as 8 mg/dl. In our patients, attacks still occurred despite SU levels being below 6.8 mg/dl, the saturation level for urate.

McCarty described 4 situations where normouricemia accompanies gouty arthritis[10]. These include: patients who never had urate levels high enough to saturate their serum at 37°C; patients who have hyperuricemia due to a known factor, such as treatment with diuretics or alcoholism who become normouricemic when this factor is removed; normouricemia during an acute gouty attack attributed to the frequent fall in SU due to increased uric acid diuresis; and normouricemia due to treatment with allopurinol or a uricosuric drug.

A normal SU should be considered below 6.8 mg/dl, not — as accepted and reported by many laboratories — as 8 mg/dl. A normal SU level at presentation does not exclude an acute gouty attack. This may occur due to persistence of tophi and an increased body uric acid pool. In addition, it may be that in some patients SU may not sufficiently represent their uric acid pool. Additional studies are needed to further understand the correlation between SU and the body uric acid pool as well as the relationship to timing of changes during acute gout.

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