Inappropriate Prescription of Allopurinol in a Teaching Hospital

Siriporn Athisakul MD*,
Supараporn Wangkaew MD*, Worawit Louthrenoo MD*

** Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai*

Background: *Allopurinol is a drug that is widely used to treat hyperuricemia, but it is often prescribed inappropriately.*
Objective: *The authors conducted a study to look for the appropriate allopurinol prescription and diagnosis of gout in the out-patient clinics at a university hospital.*
Material and Method: *One hundred and forty-five patients who were newly prescribed allopurinol (128 males and 17 females, mean ± SD age of 58.5 ±14.1 years) were enrolled in this study.*
Result: *Only 77 (53.1%) received allopurinol with appropriate indications. Thirty-eight patients (26.2%) did not have allopurinol dose adjustment according to the patients' creatinine clearance. Among 131 patients, prescribed allopurinol for the diagnosis of gout, only 55 (42.0%) were diagnosed in accordance with the American Rheumatism Association criteria.*
Conclusion: *Inappropriate use of allopurinol (both the indication and prescribed dosage) and inappropriate diagnosis of gout are major problems even in a large teaching hospital. An educational campaign program is warranted for achieving appropriate diagnosis of gout, and eliminating the inappropriate use of allopurinol.*

Keywords: ***A****llopurinol, Drug prescription, Gout, hyperuricemia, inappropriate use of drug*

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Hyperuricemia is a common condition in clinical practice and can be seen in 3.8-40.0% of a population, depending on the population studied[1-5]. Although the degree of hyperuricemia correlates with the development of gout, up to 70.0% of patients with hyperuricemia never develop gout even after 30 years of follow-up[6]. Thus, the majority of patients with hyperuricemia do not need hypouricemic therapy, unless it is indicated clinically.

Allopurinol reduces serum uric acid by inhibiting the xanthine oxidase enzymes, which inhibit the conversion of hypoxanthine to xanthine, and xanthine to uric acid. Allopurinol can be used to treat hyperuricemia in both hypoexcretor (urine uric acid excretion < 600 mg/day) and hyperexcretor (urine uric acid > 800 mg/day). It can be used with a dose adjustment in patients with renal impairment. Clinically, it is used to treat gout, hyperuricemia in renal transplant recipients, and treat or prevent acute uric acid nephropathy in patients with hematologic malignancy receiving immunosuppressive drugs, and those with hyperuricemia associated with nephrolithiasis[7]. However, approximately 5% of patients who receive allopurinol will develop mucocutaneous adverse reaction, in which 0.1-0.4% of the reaction can be very severe and result in death[8,9].

Gout, a common acute arthritis, is a consequence of hyperuricemia. However, patients with acute arthritis and hyperuricemia do not always have gout. The diagnosis of gout requires the presence of monosodium urate (MSU) crystals in the synovial fluid from an acutely inflamed joint or a tophus. If the crystals are not identifiable, the diagnosis of gout can be made by the presence of 6 of 12 diagnostic criteria developed by the American College of Rheumatology (Table 1)[10].

Because allopurinol is often prescribed in clinical practice to treat hyperuricemia, it is often associated with adverse events. The present study was

Correspondence to : Louthrenoo W, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Phone: 053-946-449, Fax: 053-357-959, E-mail: wlouthre@mail.med.cmu.ac.th

Table 1. The American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout[10]

A. The presence of characteristic urate crystals in the joint fluid, or
B. A tophus proved to contain urate crystals by chemical means or polarized light microscopty, or
C. The presence of 6 of the following 12 clinical, laboratory, and x-ray phenomena listed below:
1. More than one attack of acute arthritis
2. Maximal inflammation developed within 1 day
3. Attack of monoarticular arthritis
4. Joint redness observed
5. First metatarsophalangeal joint painful or swollen
6. Unilateral attack involving first metatarsophalangeal joint
7. Unilateral attack involving tarsal joint
8. Suspected a tophus
9. Hyperuricemia
10. Asymmetric swelling within a joint (radiograph)
11. Subcortical cysts without erosions (radiograph)
R. Negative cultures of joint fluid for microorganisms during attack of joint inflammation

performed to determine the appropriateness of using this drug in a university hospital, and ascertain errors in the diagnosis of gout in patients who were given allopurinol.

Material and Method

A computer search at the pharmacy section, Chiang Mai University Hospital for out-patients aged > 16 years, who were prescribed allopurinol from 1 April 2005 to 30 June 2005 was carried out. From lists of the search, the medical records of the patients were reviewed. The present study period was chosen prior to planning the study in October 2005 in order to avoid bias in the prescription of the study drug. In addition to demographic data, clinical diagnosis or conditions where allopurinol was given, indication and contraindication, dosage, renal function (creatinine clearance), as well as complication of allopurinol therapy were collected from patients' medical records. The creatinine clearance was calculated by using the Cockcroft-Gault equation, a formula that requires the body weight and serum creatinine[11]. Dose adjustment of allopurinol in those with renal impairment followed guideline developed by Hande et al[8]. The diagnosis of gout was made according to the criteria developed by the American College of Rheumatology. The specialists who prescribed allopurinol were also recorded. The present study was approved by the Ethic Committee of the Faculty of Medicine, Chiang Mai University.

Statistical analysis

Continuous variables were reported as mean $\pm$ standard deviation (SD) and range. Categorical variables were reported as percent.

Results

During the study period, 145 patients (128 males and 17 females) were given allopurinol and their medical records were reviewed. The demographic data of the patients studied and their associated medical conditions are shown in Table 2. Allopurinol was administered at a dosage of 50 mg/day, 100 mg/day, 200 mg/day and 300 mg/day to 6 (4.1%), 76 (52.4%), 28 (19.3%) and 35 (24.1%) patients, respectively, with a mean daily dose of 161.0 $\pm$ 84.5 mg/day.

Table 3 shows details of the physicians who prescribed allopurinol, indication and dose adjustment according to the creatinine clearance of the patients. Allopurinol was most commonly prescribed by internists. It was prescribed with appropriate indications in 77 patients (53.1%) and without appropriate indications in 68 (46.9%). Among the 77 patients who received it with appropriate indications, four were hematological patients receiving chemotherapy, ten were renal transplant recipients, and eight were asymptomatic hyperuricemia (> 13.0 mg/dl in males and 10.0 mg/dl in females). The remaining 55 patients had gouty arthritis. Indications for using allopurinol in these gouty patients were recurrent acute arthritis of more than 3 times/year, tophaceous gout, and the presence of renal calculi in 26, 24 and 14 patients, respectively, in which each individual patient might have more than one indication.

Thirty-eight patients (26.2%) received allopurinol without dose adjustment for their creatinine clearance. Ten of these patients received allopurinol with an appropriate indication. Three of them were renal transplant recipients and one was a tophaceous gout patient; they received allopurinol at a higher dose than the recommended dosage for bringing serum uric acid down to below normal.

According to the medical records, one hundred and thirty one patients were prescribed allopurinol for the diagnosis of gout. Fifty-five patients (42.0%) were correctly diagnosed as having gout. MSU crystals were identified from the tophus in 24 patients. Of 49 patients who had acute arthritis, MSU crystals were identified in 16, in whom arthrocentesis was performed. Fifteen

Table 2. Demographic data of the patients studied

Demographic data	(N = 145)
Sex, male:female	128:17
Mean ± SD age in years (median range)	58.5 ± 14.1 (61.0-70.0)
Mean ± SD serum uric acid in mg/dL (range)	7.1 ± 4.4 (3.1-18.2)
Mean ± SD creatinine clearance in ml/min (range)	27.9 ± 21.7 (6.0-85.0)
Associated medical conditions	N%
Hypertension	84 (57.9)
Chronic renal disease	54 (37.2)
Dyslipidemia	49 (33.8)
Diabetes mellitus	27 (1836)
Ischemic heart disease	23 (15.9)
Ischemic cerebrovascular disease	10 (6.9)
Chronic alcoholism	5 (3.4)
History of gastrointestinal hemorrhage	3 (2.1)

Table 3. Details of allopurinol prescribed by physicians, indication for its use and dose adjustment according to creatinine clearance

	Number of allopurinol prescriptions	Appropriate indication		Inappropriate indication	
		Correct dose adjustment, n (%)	Incorrect dose adjustment, n (%)	Correct dose adjustment, n (%)	Incorrect dose adjustment, n (%)
Internists	96	61 (63.5)	7 (7.3)	22 (22.9)	6 (6.3)
- Rheumatologists	25	24 (96.0)	1 (4.0)	-	-
- Other internists	47	26 (55.3)	4 (8.5)	14 (29.8)	3 (6.4)
- Medical residents	24	11 (45.8)	2 (8.3)	8 (33.3)	3 (12.5)
Familymedicine physicians	14	2 (14.3)	1 (7.1)	5 (35.7)	6 (42.9)
Orthopedists	9	2 (22.2)	1 (11.1)	3 (33.3)	3 (33.3)
Other specialists	26	2 (7.7)	1 (3.8)	10 (38.5)	13 (50.0)
Total	145	67 (46.2)	10 (6.9)	40 (27.6)	28 (19.3)

patients met 6 of the 12 criteria for the diagnosis of gout according to the American College of Rheumatology. The remaining 76 patients (58.0%) diagnosed with gout did not meet the diagnostic criteria.

During the study period, no adverse event of allopurinol was observed.

Discussion

The present study found that the patients received allopurinol, or the physician prescribed it with appropriate indications in only 53.1% of cases, and the diagnosis of gout was made correctly according to the American College of Rheumatology criteria in only 42.0% of cases.

Allopurinol was once ranked one of the 10 most common prescription drugs in the United States[12]. Unfortunately, this drug has been associated with significant adverse drug reactions that can sometimes result in death[8,9]. In a review of 80 cases with allopurinol hypersensitivity syndrome, only nine of 67 patients (13.4%), in whom data were available, were given allopurinol with appropriate indications. Twenty of these 80 patients (25.0%) died[13]. In a discharge audit from a large teaching hospital, 80.0% of the discharge prescriptions for allopurinol deviated from the published dosing guidelines, and one-half of the patients who developed allopurinol-related hypersensitivity had been prescribed the agent for the treatment of asymp-

tomatic hyperuricemia[8]. Use of thiazide diuretics or ampicillin along with allopurinol can potentiate mucocutaneous adverse reactions[14]. Another study found that 11 of 50 (22.0%) hospitalized patients who received a new prescription for allopurinol received either an excessive dose or had no appropriate indications[15]. An error in the prescription of allopurinol was found in 23.0-39.0% of patients in a recent retrospective review from the internet-accessible error reporting system in the United States[16].

It should be noted that only 42.0% of the presented patients, who were prescribed allopurinol for the diagnosis of gout actually had gout, according to the American College of Rheumatology diagnostic criteria, or 58.0% of the patients received allopurinol without the definite diagnosis of gout. When examining the pathophysiology of hyperuricemia and gout, relative impairment of uric acid excretion was found in 80.0-90.0% of patients with gout[17,18]. Therefore, uricosuric agents (probenecid, benzbromarone, and sulfinpyrazone) should be the drugs of choice. However, in clinical practice, as seen in the present study, xanthine oxidase inhibitor or allopurinol is more often prescribed. The reason why allopurinol is most often prescribed is because it can be used in hyperuricemic patients whose uricosuric agents are ineffective in lowering serum uric acid level. It can be used in those patients who are hyperexcretor or with renal calculi, those who have tophaceous deposits, and those with renal insufficiency. It should also be noted that all of the presented patients studied had a creatinine clearance of less than 85.0 ml/min. The reason for the decrease in creatinine clearance in these patients was not clear. It might be that the majority of the presented patients had co-morbid diseases, such as, chronic renal insufficiency, hypertension, diabetes mellitus, and atherosclerosis. Moreover, those who had gout or tophaceous gout might have taken non-steroidal anti-inflammatory drugs that also could affect their renal function.

It should also be noted that arthrocentesis and synovial fluid analysis was performed in only 16 of 49 (32.6%) patients who had acute arthritis, signifying that arthrocentesis is seldom performed at the out patient clinic of the authors' institution in patients with acute arthritis. The diagnosis of gout can be made immediately by examining synovial fluid. In a survey on the frequency of synovial fluid analysis from 54 hospitals in the United States, a synovial fluid analysis rate of 3.9 times/month (median 1.5 times) was found. The majority of analyses were carried out in hospitals with an active rheumatology training program[19]. In one study, the diagnosis of gout was changed after arthrocentesis and synovial fluid analysis was performed in 26.0% of cases[20]. Therefore, synovial fluid analysis is a mandate in all patients with acute arthritis, particularly in those where crystal-associated arthritis is suspected. Normally, there is no need to perform synovial fluid MSU crystal identification under polarized light microscopy, as an examination under ordinary light microscopy has a sensitivity and specificity of 69.0 and 97.0% respectively[21].

There were several limitations in the present study. Firstly, was the diagnosis of gout. As the data were collected from the out-patient medical records, some important information, particularly the diagnostic criteria for gout, might not have been recorded. This would make the diagnosis of 'definite gout' lower than it should be. Secondly, only 32.6% of patients who presented with acute arthritis had arthrocentesis; therefore, the possibility of diagnosing gout with the presence of MSU crystals in the synovial fluid from these patients was diminished. Thirdly, in the present study the authors did not follow whether a dose adjustment of allopurinol according to the guideline in patients with renal insufficiency could bring down serum uric acid to less than 6.0 mg/dl. However, previous studies had shown that allopurinol at a dosage of 300 mg/day in those with normal renal function, or at a recommended dose in patients renal insufficiency, could not bring serum uric acid to less than 6.0 mg/dL[22,23]. Lastly, the authors did not search for any possible drug interaction with allopurinol in the present study.

In conclusion, inappropriate use of allopurinol (both the indication and prescribed dosage) is still a major problem, even in a large university hospital. An educational campaign program for general physicians is warranted to eliminate the inappropriate use of allopurinol, which in turn can avoid unnecessary life threatening, adverse reactions of this agent. A gout educational program for general physicians is also needed for appropriate diagnosis, and appropriate use of hypouricemic agents.

References

1. Prior IA, Rose BS, Harvey HP, Davidson F. Hyperuricaemia, gout, and diabetic abnormality in Polynesian people. Lancet 1966; 1: 333-8.
2. Hall AP, Barry PE, Dawber TR, McNamara PM. Epidemiology of gout and hyperuricemia. A long-term population study. Am J Med 1967; 42: 27-37.

3. Darmawan J, Valkenburg HA, Muirden KD, Wigley RD. The epidemiology of gout and hyperuricemia in a rural population of Java. J Rheumatol 1992; 19: 1595-9.
4 Mikkelsen WM, Dodge HJ, Valkenburg H. The distribution of serum uric acid values a population unselected as to gout or hyperuricemia: Tecumseh, Michigan 1959-1960. Am J Med 1965; 39: 242-51.
5 Bunnag SC, Sitthi-Amorn C, Chandraprasert S. The prevalence of obesity, risk factors and associated diseases in Klong Toey slum and Klong Toey government apartment houses. Diabetes Res Clin Pract 1990; 10 Suppl 1: S81-S87.
6 Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987; 82: 421-6.
7 Wortmann RL, Kelley WN. Gout and hyperuricemia. In: Harris ED Jr, Budd RC, Firestein GS, Genovese MC, Sergent JS, Ruddy S, et al, editors. Kelley's textbook of rheumatology. 7th ed. Philadelphia: Elsevier Saunders; 2005: 1402-29.
8 Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med 1984; 76: 47-56.
9 McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalised patients. Ann Rheum Dis 1981; 40: 245-9.
10 Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977; 20: 895-900.
11 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.
12 Rucker TD. The top-selling drug products: how good are they? Am J Hosp Pharm 1980; 37: 833-7.
13 Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum 1986; 29: 82-7.
14 Hande KR. Evaluation of a thiazide-allopurinol drug interaction. Am J Med Sci 1986; 292: 213-6.
15 Devlin JW, Bellamy N, Bayliff CD. Observations and effects of educational consults on allopurinol prescribing. Can J Hosp Pharm 1992; 45: 21-7.
16 Mikuls TR, Curtis JR, Allison JJ, Hicks RW, Saag KG. Medication errors with the use of allopurinol and colchicine: a retrospective study of a national, anonymous Internet-accessible error reporting system. J Rheumatol 2006; 33: 562-6.
17 Louthrenoo W, Kasitanon N, Sukitawut W, Wichainun R. A clinical study of crystal-proven gouty arthritis in a university hospital. J Med Assoc Thai 2003; 86: 868-75.
18 Becker MA. Clinical gout and the pathogenesis of hyperuricemia. In: Koopman WJ, editor. Arthritis and allied conditions. 14th ed. Philadelphia: Lippincott, Williams & Wilkins; 2001: 2281-313.
19 Hasselbacher P. Variation in synovial fluid analysis by hospital laboratories. Arthritis Rheum 1987; 30: 637-42.
20 Eisenberg JM, Schumacher HR, Davidson PK, Kaufmann L. Usefulness of synovial fluid analysis in the evaluation of joint effusions. Use of threshold analysis and likelihood ratios to assess a diagnostic test. Arch Intern Med 1984; 144: 715-9.
21 Gordon C, Swan A, Dieppe P. Detection of crystals in synovial fluids by light microscopy: sensitivity and reliability. Ann Rheum Dis 1989; 48: 737-42.
22 Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, Herrero-Beites A, Garcia-Erauskin G, Ruiz-Lucea E. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. Ann Rheum Dis 1998; 57: 545-9.
23 Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. J Rheumatol 2006; 33: 1646-50.

การศึกษาการสั่งยา allopurinol ที่ไม่เหมาะสม ในโรงเรียนแพทย์

ศิริพร อธิกสกุล, ศุภราภรณ์ วังแก้ว, วรวิทย์ เลาห์เรณู

ยา allopurinol เป็นยาที่นิยมใช้ในการรักษาภาวะกรดยูริกในเลือดสูงแต่มักได้รับการสั่งจ่ายที่ไม่เหมาะสม การศึกษานี้ทำขึ้นเพื่อศึกษาพฤติกรรมการสั่งจ่ายยา allopurinol และการวินิจฉัยโรคเกาต์ที่แผนกผู้ป่วยนอกของโรงเรียนแพทย์ ในจำนวนผู้ป่วยใหม่ 145 รายที่ได้รับการสั่งจ่ายยานี้ (เพศชาย 128 ราย เพศหญิง 17 ราย อายุเฉลี่ย 58.5 $\pm$ 14.1 ปี) พบว่าเพียง 77 ราย (53.1%) เท่านั้นที่ได้รับการสั่งจ่ายยาด้วยข้อชี้บ่งที่เหมาะสม ผู้ป่วยจำนวน 38 ราย (26.2%) ไม่ได้รับการปรับขนาดยาตามหน้าที่การทำงานของไต ผู้ป่วย 131 รายที่ได้รับการวินิจฉัยโรคเกาต์ในเวชระเบียน พบว่ามีเพียง 55 ราย (42.0%) เท่านั้นที่ได้รับการวินิจฉัยตรงตามเกณฑ์ของ American College of Rheumatology โดยสรุป การสั่งจ่ายยา allopurinol ที่ไม่เหมาะสม (ทั้งตามข้อชี้บ่งและขนาดยา) รวมทั้งการให้การวินิจฉัยโรคเกาต์ ยังเป็นปัญหาที่พบได้บ่อยในโรงเรียนแพทย์ การรณรงค์ให้การศึกษาเกี่ยวกับเรื่องนี้จึงมีความจำเป็นเพื่อให้มีการวินิจฉัยโรคเกาต์ที่ถูกต้อง และมีการสั่งจ่ายยา allopurinol อย่างเหมาะสม