Associated Factors for Allopurinol Induced Adverse Drug Reactions in Ratchaburi Hospital

ปัจจัยที่มีความสัมพันธ์กับการเกิดอาการไม่พึงประสงค์จากการใช้ยาอัลโลพูรินอล ในโรงพยาบาลราชบุรี

ชนจันทร์ เพชรรัตน์ พ.บ.,
ว.ว. อายุรกรรมโรคข้อและรูมาติสซั่ม
กลุ่มงานอายุรกรรม
โรงพยาบาลราชบุรี

Chonachan Petcharat M.D.,
Thai Board of Rheumatology Medicine
Department of Internal Medicine
Ratchaburi Hospital

ABSTRACT

Background: Allopurinol is a well-known antihyperuricemic drug, but it occasionally induces adverse drug reactions. These were reported ranging from mild to severe adverse events such as allopurinol hypersensitivity syndrome (AHS), and might result in death.

Objective: To investigate risk factors for allopurinol induced adverse drug reactions in Ratchaburi Hospital, Thailand.

Material and Method: A matched case-control study was conducted using data from medical records of patients who had prescribed allopurinol in Ratchaburi Hospital between January 2007 and September 2015. Cases were all patients who had reported allopurinol induced adverse events to Ratchaburi drug-information-center. A control who had received allopurinol at least 1 year without adverse events was selected for each case matching on age and gender. Logistic regression was used to explore risk factors for adverse events.

Results: Two hundred and sixty patients (130 cases, 130 controls) were included with mean$\pm$S.D. age of 65.0$\pm$12.7 years. AHS was reported in 23 patients. The data showed that patients who developed adverse events had more chronic kidney disease (CKD) (80.8% vs 65.4%, p=0.005), more inappropriate indication of allopurinol prescription (53.1% vs 31.5%, p=0.001) and more high starting dose of allopurinol defining $\geq$1.5 mg per unit of GFR (mg/ml/minute) (90.8% vs 82.3%, p=0.046) than those who did not. In multivariate analysis, CKD and inappropriate indication of prescription were still the independent risk factors for adverse events with OR (95%CI) 2.43 (1.17, 5.04) and 3.0 (1.36,

6.56), respectively. In contrast, co-medication and history of previous allopurinol users did not significantly associate with adverse events.

Conclusion: This finding indicated that CKD and inappropriate indication of allopurinol prescription were the risks for developing allopurinol induced adverse drug reactions.

Keywords: Allopurinol, adverse drug reaction, gout, Hyperuricemia, inappropriate use of drug, chronic kidney disease

บทคัดย่อ

ยาอัลโลพูรินอลเป็นยาลดกรดยูริกในเลือดที่นิยมใช้อย่างแพร่หลาย แต่เป็นยาที่มีรายงานอาการไม่พึงประสงค์ จากยาได้ตั้งแต่อาการน้อยจนถึงอาการรุนแรง ซึ่งอาจมีผลถึงแก่ชีวิตได้ การศึกษานี้ทำขึ้นเพื่อศึกษาหาปัจจัยเสี่ยงของการเกิดอาการไม่พึงประสงค์จากยาอัลโลพูรินอล ในผู้ที่ได้รับการสั่งจ่ายยาอัลโลพูรินอลในโรงพยาบาลราชบุรี โดยใช้วิธีการศึกษาย้อนหลังแบบ matched case-control study เปรียบเทียบลักษณะผู้ป่วยที่รายงานอาการไม่พึงประสงค์ จากยาอัลโลพูรินอล 130 คน และกลุ่มควบคุม 130 คน ที่ได้รับยาต่อเนื่องอย่างน้อย 1 ปี และไม่มีรายงานผลข้างเคียงจากยา พบว่าโรคไตเรื้อรัง และการสั่งยาอัลโลพูรินอลที่ไม่เหมาะสมตามข้อบ่งชี้ เพิ่มความเสี่ยงของการเกิดอาการไม่พึงประสงค์ ในผู้ใช้ยาอัลโลพูรินอลอย่างมีนัยสำคัญทางสถิติ ผลการศึกษานี้ เป็นข้อมูลให้แพทย์ผู้สั่งจ่ายยาตระหนัก ในการสั่งจ่ายยาตัวนี้ตามข้อบ่งชี้มากขึ้น รวมทั้งแนะนำ และติดตามผู้ป่วยอย่างใกล้ชิดในรายที่มีความเสี่ยงดังกล่าว เพื่อเป็นประโยชน์ในการลดความเสี่ยงการเกิดอาการไม่พึงประสงค์จากการใช้ยานี้

คำสำคัญ : ยาอัลโลพูรินอล อาการไม่พึงประสงค์จากยา กรดยูริกในเลือดสูง การสั่งยาอัลโลพูรินอลที่ไม่เหมาะสมตามข้อบ่งชี้ โรคไตเรื้อรัง

Introduction

Allopurinol, a xanthine oxidase inhibitor, is a well-known antihyperuricemic drug for management of gout, nephrolithiasis with high urinary uric acid excretion and tumor lysis syndrome prevention.[1] Furthermore, some previous studies showed that allopurinol might be beneficial role to slow renal progression in hyperuricemic patients with chronic kidney disease (CKD).[2-4] Despite these clinical utilities, allopurinol can cause adverse reactions in 2%-8% of users,[5] ranging from cutaneous hypersensitivity reactions to Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and allopurinol hypersensitivity syndrome (AHS), which causes death in up to 37.5%.[6]

Although the adverse events of allopurinol probably result from individual idiosyncrasies,[7] the strong associations of between the genetic marker, HLA-B*5801 and allopurinol-induced SJS/TEN was reported with odds ratio (OR) 348.3 in Thai population.[8, 9] Although the HLA-B*5801

testing will identify the risk of allopurinol induced SJS/TEN, it has a low positive predictive value.[8] Furthermore, the test is not available and costly in some area. Therefore, the clinical risk factors associated with allopurinol induced adverse reactions might be useful for allopurinol initiators. Previous studies reported the association between old age, female, impaired renal function, high starting dose, diuretic therapy and allopurinol induced adverse events.[10-12] Among interesting issues about the benefit of allopurinol in hyperuricemic patients with CKD, the data in negative side effect issues are limited. Also, the clinical risk factors for allopurinol induced adverse events in Thailand has rarely been studied. The aim of this study was to investigate the risk factors for allopurinol induced adverse events in Ratchaburi Hospital, Ratchaburi Province, Thailand.

Material and Method

The study was conducted at Ratchaburi Hospital, a 855-bed hospital located in Ratchaburi Province, Thailand. All prescriptions in Ratchaburi Hospital were recorded in the computer database since 2007. A matched case-control study was designed. All case and control patients were retrospectively identified through the computer database of prescription using HOSxP programme. All 18 years and older patients who had been prescribed allopurinol in Ratchaburi Hospital between 1 January 2007 and 30 September 2015 were eligible for inclusion in the study. A case was defined as any patient who had been reported allopurinol induced adverse events to Ratchaburi drug information center by himself or his physician. For cases, the allopurinol induced adverse events were confirmed by pharmacists and identified to possible, probable and certain categories of WHO-UMC causality drug allergy system.[13] The patients who had reports of previous allopurinol allergy from prescription of other hospitals were excluded.

Controls were identified among the patients who had been prescribed allopurinol and continued to receive allopurinol at least 1 year without any adverse effect report. Controls were matched in a 1:1 ratio to case patients according to the variables sex and age (as close as possible). Cases or controls who were prescribed allopurinol and continued taking this medication from other hospital or lacked of sufficient clinical information were excluded.

Potential clinical risk factors for allopurinol induced adverse event were ascertained by abstracting medical records. Data obtained included age at allopurinol prescribed date, sex, underlying illness, concomitant medications (diuretics, antihypertensive drugs, colchicines, nonsteroidal anti-inflammatory drugs, aspirin, and statins), history of other drug allergy and the pattern of allopurinol usage. For the pattern of allopurinol usage, we explored many information. First, reasons for the use of allopurinol including gout, renal stone, prevention of tumor lysis syndrome and asymptomatic hyperuricemia were explored. Second, inappropriate indication of allopurinol prescription was determined and

defined as any reason of prescription other than what the 2012 ACR guidelines for management of gout recommended (gout patients with tophi, two acute gouty attacks per year or more, urolithiasis with gout, or CKD stage 2 or more with gout),[14] prevention of tumor lysis syndrome, and urolithiasis without gout. Third, starting dose of allopurinol was recorded. Furthermore, starting dose of allopurinol ≥1.5 mg per unit of estimated glomerular filtration rate (GFR) [milligram per milliliter per minute (mg/ml/min)] was calculated to determine risk for adverse events because previous study reported this association.[11] The last, the history of previous allopurinol use with interrupting the continuity of treatment more than 1 month was explored.

For baseline laboratory tests, serum uric acid and serum creatinine level were investigated from medical records. The creatinine clearance (CrCl) was calculated with the Cockcroft and Gault formula.[15] The patients who had CrCl less than 60 mg/ml/min were defined as CKD stage 3 or more.[16]

Adverse events including cutaneous, hepatic, renal, hematologic side effects were recorded. Cutaneous adverse events were extracted from medical record including maculopapular rash, erythyma multiforme, exfoliative dermatitis, SJS/ TEN. Hepatic adverse events were defined as liver transaminase levels that were elevated more than 3 times above upper normal limits and not explainable by other causes. Renal adverse events were defined as elevated serum creatinine levels of more than 1.5 milligrams per deciliter (mg/dL). Eosinophilia was eosinophil count >500 per cubic millimeter. Diagnosis of AHS followed the diagnostic criteria for AHS.[12] This study was approved by institutional review board of Ratchaburi Hospital.

Statistical Analysis

Patient characteristics and adverse drug events were described by using descriptive statistics. Characteristics that were not part of the matching process for case-patients and controls were compared using Chi-square tests, Fisher's exact tests, or *t* tests. Univariate logistic regressions were used to determine the association of variables and adverse events. The variables which were different between two group with $p<0.1$ from univariate analysis, and those were considered as factors of interest would further be analysed in multiple logistic regression model (enter method). For all tests performed, a two-tailed p-value <0.05 was considered as denoting statistical significance. The statistical software SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA) was employed for all the analyses performed.

Results

During 1 January 2007 to 30 September 2015, there were 4,999 patients who were prescribed allopurinol in Ratchaburi Hospital. Among this period, 150 allopurinol users had reported the allopurinol induced adverse events to Ratchaburi drug information center. After excluded 20 patients who reported previous

allopurinol allergy from prescription of other hospitals (13 patients) and lacked of sufficient clinical information (7 patients), the remaining 130 case-patients were enrolled in the study. The author identified and included 130 controls matching on sex and age according inclusion and exclusion criteria. Mean±S.D. age of case-patients and controls was 64.8 ±13.0 years; 61.5% were male. Mean±S.D. body weight of case-patients (61.3±12.5 kilograms) was lower than mean±S.D. body weight of controls (63.5±12.9 kilograms). Mean±S.D. serum uric acid level of all participants was 8.7±1.6 milligrams per deciliter (mg/dL). The reasons of allopurinol prescription were gout (60.0%), asymptomatic hyperuricemia (35.4%), tumor lysis syndrome prevention (3.8%) and renal stone (0.8%).

Risk factors for allopurinol induced adverse events

The details of clinical characteristics other than matching variables comparing the cases who reported adverse events and the controls who received allopurinol without adverse events were shown in Table 1. In univariate analysis, CKD stage 3 or more and the starting dose of allopurinol ≥1.5 mg per unit of estimated GFR were significantly associated with allopurinol induced adverse events, p=0.005 and p=0.046, respectively. Whereas, there were fewer cases than controls who had been prescribed allopurinol according to gout, p=0.043. Surprisingly, about half of patients (53.1%) with allopurinol adverse events were prescribed without established appropriate indication of allopurinol prescription that were more than controls, p=0.001. In contrast, body weight, other comorbid disease such as hypertension, co-medication and history of previous allopurinol users were not significantly associated with developed allopurinol induced adverse events in this study.

In multivariate analysis, the prescription of allopurinol in chronic kidney disease stage 3 or more and inappropriate indication of prescription were found as the significant independent risk factors for allopurinol induced adverse events after adjusted with variables; proportion of allopurinol prescription according to gout, body weight less than 50 kilograms, co-medication with beta-blocker and starting dose of allopurinol ≥1.5 mg per unit of estimated GFR, as shown in Table 2.

Table 1 Frequencies and univariate logistic regression of clinical characteristics and allopurinol usage patterns of case-patients who reported allopurinol adverse events (N = 130) and controls who did not (N = 130)

Factor	Cases n (%)	Controls n (%)	P*
Body weight <50 kg	24 (18.5)	16 (12.3)	0.169
Comorbid disease			
Hypertension	86 (66.2)	82 (63.1)	0.604
Diabetes mellitus	31 (23.8)	26 (20)	0.454
Dyslipidemia	57 (43.8)	55 (42.3)	0.802
Stroke	8 (6.2)	3 (2.3)	0.123
IHD	2 (1.5)	3 (2.3)	1.000**
CKD stage 3 or more	105 (80.8)	85 (65.4)	0.005
Liver disease	1 (0.8)	2 (1.5)	1.000**
Co-medications			
Colchicine	59 (45.4)	70 (53.8)	0.172
Statin	54 (41.5)	50 (38.5)	0.613
Diuretic	30 (23.1)	25 (19.2)	0.448
Aspirin	20 (15.4)	26 (20.0)	0.330
NSAID	25 (19.2)	26 (20.0)	0.876
ACEI	21 (16.2)	20 (15.4)	0.865
ARB	14 (10.8)	14 (10.8)	1.000
CCB	51 (39.2)	50 (38.5)	0.899
Beta blocker	27 (20.8)	40 (30.8)	0.065
Alpha blocker	9 (6.9)	8 (6.2)	0.802
Hydralazine	7 (5.4)	3 (2.3)	0.197
Indications of prescription			
Gout	70 (53.8)	86 (66.2)	0.043
Tumor lysis	6 (4.6)	4 (3.1)	0.519
Nephrolithiasis	2 (1.5)	0 (0)	0.156
AHU	52 (40.0)	40 (30.8)	0.120
Inappropriate indication	69 (53.1)	41 (31.5)	0.001
Starting dose ≥300 mg/d	49 (37.7)	37 (28.5)	0.114
Starting dose/Crcl ≥1.5***	118 (90.8)	107 (82.3)	0.046
Previous allopurinol usage	9 (6.9)	5 (3.8)	0.272

**p*-value calculated by Chi-square test except otherwise indicated.

**Fisher exact test.

***starting dose/Crcl ≥1.5, starting dose of allopurinol ≥1.5 mg per unit of GFR (mg/ml/min). Abbreviations: kg, kilogram; mg/d, milligram per day; IHD, ischemic heart disease; CKD, chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drug; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; AHU, asymptomatic hyperuricemia.

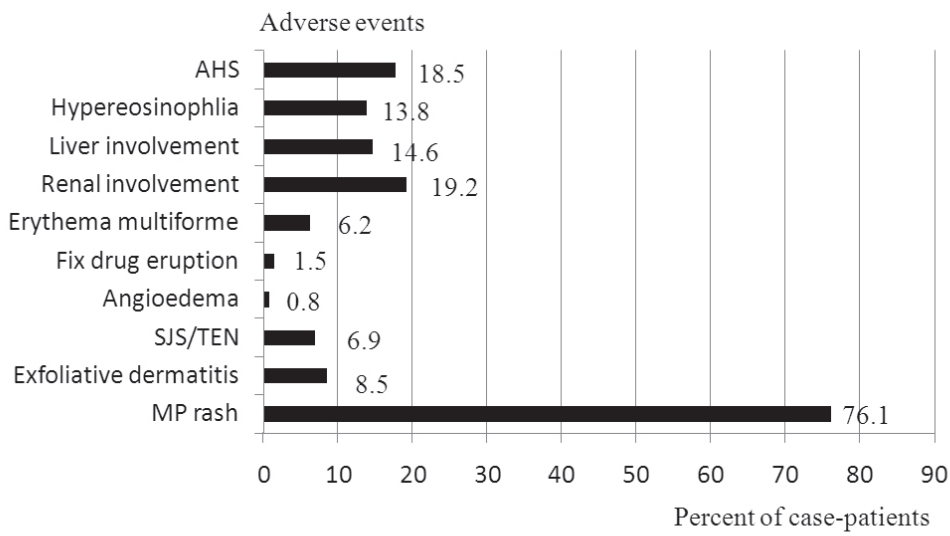
Table 2 Multiple logistic regression of risk factors for allopurinol induced adverse events

	Odd ratio	95% CI	P
Body weight <50 kg	1.20	0.57-2.50	0.632
Co-medication with beta blocker	0.56	0.31-1.01	0.055
CKD stage 3 or more	2.43	1.17-5.04	0.018
Indication prescription regarding gout	1.41	0.64-3.12	0.393
Inappropriate indication	3.00	1.36-6.56	0.006
Starting dose/CrCl ≥1.5*	1.05	0.41-2.68	0.916

*starting dose/CrCl ≥1.5, starting dose of allopurinol ≥1.5 mg per unit of GFR (mg/ml/min). Abbreviations: CI, confidence interval; OR, odds ratio; kg, kilogram; CKD, chronic kidney disease.

Characteristics of allopurinol induced adverse events

Of 130 case-patients who developed allopurinol induced adverse events, 23 patients (17.7%) were reported allopurinol hypersensitivity syndrome. Skin rash was the most common adverse reaction (100%) in case–patients (maculopapular rash 76.1%, exfoliative dermatitis 8.5%, SJS/TEN 6.9%, angioedema 0.8%, fixed drug eruption 1.5%, erythema multiforme 6.2%) followed by renal involvement (19.2%). The profiles of adverse events were shown in Figure 1. The median time (IQR) from allopurinol initiation to adverse event was 7.9 (7.4 - 13.5) weeks. Among case-patients, 24 patients were admitted to the hospital and 1 patient with AHS died.



Abbreviations: AHS, allopurinol hypersensitivity syndrome; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; MP rash, maculopapular rash

Fig.1 Characteristics of adverse events (N=130 case-patients).

Discussion

In this study, the author retrieved data from the computer database of Ratchaburi Hospital, the largest hospital in western of Thailand. Because a mortality of AHS was found in Ratchaburi Hospital in April 2015, this study was conducted to identify the risk factors for allopurinol induced adverse events using case control study. The present study showed that the independent risk factors for allopurinol induced adverse events were CKD stage 3 or more, and inappropriate indication of allopurinol prescription after adjusted with the variables; proportion of allopurinol prescription according to gout, body weight 50 kg or more, allopurinol prescription with beta-blocker and starting dose of allopurinol of ≥1.5 mg per unit of estimated GFR. The association between CKD and allopurinol induced adverse events was similar to those found in previous studies, upto 86% of AHS having CKD.[17-19] Furthermore, a recent study conducted in Taiwan, Yang CY's study also showed that renal disease increased the risk for allopurinol hypersensitivity with OR (95% CI) 1.49 (1.38-1.61).[20] In addition, the subgroup findings with the allopurinol users regarding tumor lysis syndrome prevention (10 patients), the proportion of CKD in the patients with allopurinol adverse events was also more than the patients without adverse events, 83.3% (5/6 patients) and 50.0% (2/4 patients), respectively.

Association between renal function and adverse events of allopurinol is explained by the pharmacokinetic of allopurinol. After allopurinol is absorbed in GI tract and it is rapidly metabolized into an active metabolite, oxypurinol, which is subsequently excreted by the kidneys. In patients with normal kidney fuction, the mean half life of oxypurinol is 23 hours.[21] As kidney function declines, the half life of oxypurinol increases, causing it to accumulate over a long time period and reach higher steady state concentrations.[12] On the other hand, Ryu HJ, et al conducted a study in Korea and found that renal disease associated with allopurinol adverse events but not reach statistical significance.[10] The difference of patient characteristics might result in the different finding. The characters of patients (mean age, renal function and proportion of asymptomatic hyperuricemia) in Yang's study were similar to the present study while patients in Ryu's study were younger and less chronic kidney disease.[10, 20]

Although indication for antihyperuricemic drug in 2012 ACR guidelines for management of gout was documented,[22] the previous study in Thailand showed only 53.1% received allopurinol with appropriate indications.[23] The present study showed the patients with inappropriate prescription of allopurinol were 42.3% of all participants and these increased the risk for allopurinol induced adverse events with OR (95% CI) 2.99 (1.36-6.56). Kumar A et al. reported a mortality from AHS in a patient with inappropriate allopurinol prescription.[24] Furthermore, Yang CY's study also showed that using allopurinol in asymptomatic hyperuricemia increased the risk for allopurinol hypersensitivity with OR (95% CI)

2.08 (1.94-2.24).[20] Therefore, indication of allopurinol prescription is a important issue and a preventable factor of allopurinol induced adverse events.

The author found no association of starting allopurinol dosage, co-medication factors as diuretics, statins and antihypertensive drugs with allopurinol induced adverse events in this study. These replicated the result of Yang's study.[20]

To the author's knowledge, this is the largest case-control study in Thailand to investigate clinical risk factors for allopurinol induced adverse events and there have been few studies focusing on this topic in Asia. Also, the data regarding the allopurinol users including the patients with tumor lysis syndrome prevention have rarely been reported.

This study had some limitations. First, ours was a retrospective study from a single center, and we acknowledge that unmeasured factors might have influenced the outcomes. Because cases were defined as the patients who had reported allopurinol induced adverse event to Ratchaburi drug information center, any patient with adverse event who did not reported to the center was missed. Furthermore, the effect of established genetic factor of allopurinol adverse events, HLA-B*5801, cannot be determined from our analysis. Therefore, further studies are still needed to confirm the results of the present study. Despite the limitations, this study supports the contention that CKD and inappropriate indication of prescription are the risks of allopurinol adverse events. In the present study, the median time from allopurinol starting until adverse events presented was 7.9 weeks. Thus, the advice for the new allopurinol user with CKD should be advised to close follow-up and beware side effects of allopurinol especially within 2 months after drug initiation.

Conclusion

The findings represent an important step in understanding the risk factors for allopurinol induced adverse events in Thailand. This study showed that CKD and inappropriate indication of allopurinol prescription are the risks for allopurinol induced adverse events. Physicians should be cautious when prescribing allopurinol to patients with impaired renal function and avoid using unnecessarily allopurinol in hyperuricemic patients.

Acknowledgments

The author thanks to all participants including Mr. Arkane Prapanpote for providing the allopurinol induced adverse events data from Ratchaburi drug information center and Mr Wirote Thudsaringkansakul for assistance in HOSxP program management..

Conflict of interest

The author declared no conflict of interest.

References

1. Mikuls T. Antihyperuricemic agents. In: Firestein GS, Budd RC, Gabriel SE, et al, editors. Kelley's textbook of rheumatology. 9th ed. Philadephia: Elsevier Saunders; 2013. p.1001-13.
2. Siu YP, Leung KT, Tong MK, et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51-9.
3. Sezer S, Karakan S, Atesagaoglu B, et al. Allopurinol reduces cardiovascular risks and improves renal function in pre-dialysis chronic kidney disease patients with hyperuricemia. Saudi J Kidney Dis Transpl 2014;25:316-20.
4. Kim Y, Shin S, Kim K, et al. Effect of Urate Lowering Therapy on Renal Disease Progression in Hyperuricemic Patients with Chronic Kidney Disease. J Rheumatol 2015;42:2143-8.
5. McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalised patients. Ann Rheum Dis 1981;40:245-9.
6. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum 1986;29:82-7.
7. Emmerson BT, Hazelton RA, Frazer IH. Some adverse reactions to allopurinol may be mediated by lymphocyte reactivity to oxypurinol. Arthritis Rheum 1988;31:436-40.
8. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009;19:704-9.
9. Somkrua R, Eickman EE, Saokaew S, et al. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Med Genet 2011;12:118.
10. Ryu HJ, Song R, Kim HW, et al. Clinical risk factors for adverse events in allopurinol users. J Clin Pharmacol 2013;53:211-6.
11. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum 2012;64(8):2529-36.
12. Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. Nat Rev Rheumatol 2016;12:235-42.
13. World Health Organization (WHO), Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment. WHO [online]. [Cited 2016 March 23] Available from URL: http://www.who-umc.org/Graphics/24734.pdf.
14. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012;64:1447-61.

15. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
16. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137-47.
17. 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.
18. Lee HY, Ariyasinghe JT, Thirumoorthy T. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? Singapore Med J 2008;49:384-7.
19. Dalbeth N, Stamp L. Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. Semin Dial 2007;20:391-5.
20. Yang CY, Chen CH, Deng ST, et al. Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan. JAMA Intern Med 2015;175:1550-7.
21. Day RO, Graham GG, Hicks M, et al. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. Clin Pharmacokinet 2007;46:623-44.
22. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431-46.
23. Athisakul S, Wangkaew S, Louthrenoo W. Inappropriate prescription of allopurinol in a teaching hospital. J Med Assoc Thai 2007;90:889-94.
24. Kumar A, Kansal D, Chaudhary UK, et al. Allopurinol inappropriate use in case of asymptomatic hyperuricemic patient causes fatal Allopurinol hypersensitive syndrome: lesson to all. Int J Basic Clin Pharmacol 2015;4:1302-4.

ว่างขาว

หน้า 100