Allopurinol prescription patterns among patients in a Saudi tertiary care centre

Naji A. Dwid, SBIM*, Mohamed M. Cheikh, SBIM, Ahmed S. Mandurah, MBBS, Khaldoun A. Shikh-souk, MBBS, Khaled R. Al-Khatib, SBIM and Ans R. Ahmed, SBIM

Doctor Soliman Fakeeh Hospital, Jeddah, KSA

Original Article

Objective: Physicians frequently prescribe allopurinol for uric acid deposition disorders. However, reports have emerged of the inappropriate use and overprescription of allopurinol. We conducted this study to determine the rate of inappropriate prescription of allopurinol in a Saudi institution.

Methods: This cross-sectional descriptive study was conducted on all adult patients who had been prescribed allopurinol in Doctor Soliman Fakeeh Hospital Jeddah KSA. Demographic data and laboratory results were retrieved from patients' electronic health records (EHR). We considered valid indications of allopurinol as significant hyperuricemia (>13 mg/dL in men and >10 mg/dL in women), confirmed gout, hyperuricosuria of more than 1100 mg/day, uric acid stones or recurrent calcium oxalate kidney stones, malignancy, and haemolysis. The possible valid indications were unconfirmed gout and unconfirmed type of kidney stones, whereas no documented indication or insignificant hyperuricemia was considered as an invalid indication.

Results: We included 1978 patients in this study. The cohort was composed of 76.4% men and 23.6% women. The mean ± standard deviation of age of this patient cohort was 53 and 4 months, whereas no documented indication or insignificant hyperuricemia was considered as an invalid indication.
Introduction

Allopurinol is widely used by more than 1.2 million patients in the United States and the United Kingdom. It is prescribed for patients with uric acid deposition disorders such as gouty arthritis, uric acid and recurrent calcium oxalate kidney stones, and tumour lysis syndrome.

One of the most common reasons for the prescription of allopurinol is asymptomatic hyperuricemia, defined as a serum uric acid level greater than 7.0 mg/dL, measured using the automated enzymatic (uricase) method. This is a very common condition, with prevalence in the general population reaching up to 25% in males and 15% in females. The majority of patients will continue being asymptomatic and will not develop any uric acid deposition disorder.

As hyperuricemia itself is not a disease but merely a risk factor, starting treatment in this group of patients is still controversial and is restricted to specific cases. Patients who will benefit from allopurinol are those who have sustained marked hyperuricemia despite lifestyle modifications, with uric acid levels above 13 mg/dL in men or 10 mg/dL in women (normal ranges are 3.5–7.2 mg/dL for males and 2.6–6.0 mg/dL for females). Treatment is also indicated in cases in which hyperuricemia is related to a genetic defect, in clinical disorders associated with accelerated cell turnover (malignancy, haemolysis, chemotherapy, etc.), and in the presence of uric acid excretion exceeding 1100 mg daily.

There are many reports of the overprescription of allopurinol, which seems to be an international problem. Unfortunately, none of these studies provide specific reasons for this common malpractice that may affect the lives of hundreds, if not thousands, of patients. As unnecessary drug treatments carry unnecessary side effects and risks, unnecessary prescriptions go against one of the fundamental ethical principles of medical practice – 'do no harm'.

The primary objective of this study was to determine the rate of prescription of allopurinol without clear or correct indications. We aim to raise awareness about the unnecessary usage of allopurinol that might cause serious but preventable side effects.

Materials and Methods

This was a cross-sectional retrospective descriptive study of all adult patients who had been prescribed allopurinol in Doctor Soliman Fakeeh Hospital (DSFH) Jeddah, KSA, during the period from 1/1/2016 until 1/1/2017.

Eligible patients were identified by examining all prescriptions of allopurinol (both in generic and brand names such as Loric, Zyloric, and No-Uric) in the hospital’s pharmacy system. Patient demographic data and laboratory results were taken from their hospital electronic files. We extracted relevant indications as recorded by the prescribing physicians from the pharmacy notes and the electronic health records.

Our pharmacy system allows medications prescription with 'no documented indication', as it does not mandate that physicians specify a diagnosis for each new prescribed medication or during the refill of medications. For some medications, further instructions must be sent to insurance companies (such as medications that are expensive, controlled, or narcotics). Other medications, however, tend to be re-prescribed specially if the patient has been taking them over a long period and comes for medication refill clinics. Non-physicians are not permitted to order or reorder medications.

We considered appropriate indications for allopurinol to be malignancy, haemolysis, confirmed gouty arthritis based on the American College of Rheumatology classification criteria, high uric acid levels with uric acid or calcium oxalate kidney stones, marked asymptomatic hyperuricemia (uric acid levels above 13 mg/dL in males and 10 mg/dL in females), and hyperuricosuria (urinary excretion of uric acid exceeding 1100 mg/day).

Inappropriate or not-valid prescription was considered if there was no documented indication or insignificant hyperuricemia (levels below those stated as indication). Unconfirmed gout with undocumented criteria or arthrocentesis, or unconfirmed kidney stones were considered as possible valid prescriptions.

Descriptive statistics (mean, percentage, and standard deviation) for continuous variables and frequencies for categorical variables were calculated using the Statistical Package for Social science (SPSS) version 25 software program.

Results

During the period of 1/1/2016 to 1/1/2017, a total of 1978 adult patients (>18 years old) were prescribed allopurinol in our hospital. Out of these patients, 76.4% (n = 1511) were males and 23.6% (n = 467) were females. The sample is thus disproportionately male. The mean ± standard deviation (SD) for age was 53.4 ± 15 years. Among the study population, 20.3% of patients were less than 40 years old, 68.6% of patients were aged between 40 and 70 years old, and 11.1% were above 70 years old.

Conclusion: This study revealed a markedly high number of allopurinol prescriptions without a clear indication in our centre. This approach may potentially expose patients to serious side effects of allopurinol without added benefits.
The mean ± SD of years since the first prescription was 1.53 ± 2.188 years. More than half of the patients had elevated uric acid levels and only 4% had significant hyperuricemia (Table 1).

Allopurinol was prescribed without a valid indication in 1539 patients (77.8% of the total sample) (Table 2). There was no documented indication by the prescribing physician for 771 patients (representing 39% of all prescriptions) and 768 patients were prescribed allopurinol for insignificant hyperuricemia.

Thirty patients (1.6%) were prescribed allopurinol for confirmed gout as per the American College of Rheumatology (ACR) classification criteria, 14 while 111 patients (5.6%) were labelled to have gout but without documented criteria or arthrocentesis. Malignancy and haemolysis accounted for 117 patients (5.6%) and 1 patient (0.1%), respectively (Table 2).

One hundred and fourteen patients (5.5%) were given allopurinol for kidney stones. Only 5 of those patients (0.2%) were found to have a uric acid stone, and 4 patients (0.1%) had recurrent calcium oxalate stones, while the rest of the patients (105 patients) did not undergo any analysis to determine the type of stones.

Discussion

Our results indicate that a significant number of patients in our institution, nearly four-fifths (77.8%) of the examined patients, were prescribed allopurinol inappropriately. More than a third of the patients (39%) did not have an indication documented by the prescribing physician, while 38.8% were prescribed allopurinol for insignificant hyperuricemia. There is no solid evidence to suggest any benefit in treating asymptomatic hyperuricemia, unless in specific situations.

These results are comparable to what has generally been reported in the literature. The largest study to our knowledge that has investigated the inappropriate use of xanthine oxidase inhibitors included 461 patients, and in only 43 of them (9%) the indications were appropriate.15 In a study of 165 patients, allopurinol was prescribed without appropriate indication in 70.5% of patients.10 Several other smaller studies have reported high rates of inappropriate prescription, although lower than our findings. A study from Singapore11 and another from Thailand12 showed inappropriate prescription in 18 patients (64%) and 68 patients (46.9%), respectively. In a study that examined patients who developed allopurinol hypersensitivity reactions, therapy with allopurinol was unnecessary in 7 out of the 10 patients, based on current guidelines.1 A similar but much older study found that only one patient out of the 8 included had an appropriate indication.13 In the same article, 4 studies with a total number of 72 patients were discussed, reporting that 40.2% of them had no appropriate indication to be on allopurinol. It is worth noting that this study used similar criteria to ours in defining the valid indications for allopurinol prescription.13

Although allopurinol is a well-tolerated and effective medication, it has many side effects that range from mild gastric upset or minimal rash to severe life-threatening conditions, such as Steven Jonson syndrome (SJS), toxic epidermal necrolysis (TEN), allopurinol hypersensitivity syndrome, and drug rash with eosinophilia and systemic symptoms (DRESS syndrome).16-18 Approximately 0.4% of patients on allopurinol may suffer from allopurinol hypersensitivity syndrome.18,19 Furthermore, in some studies, allopurinol accounted for 17.4% of cases of SJS and TEN.20 These side effects can be fatal; the mortality rates for SJS and TEN are around 30%,21 and allopurinol hypersensitivity syndrome is associated with a mortality rate of 18–32%.16

It is alarming to find significant evidence for the prescription of allopurinol with no clear indication in several studies from different parts of the world. We suspect that there are different factors at play that may explain this phenomenon. Some prescriptions may originate from physicians’ need to act on every abnormal value in laboratory reports. Patients may be pushing doctors to prescribe allopurinol if they have the misconception that a high uric acid level is somehow harmful. Patients’ expectations are known to influence prescription habits. This is a recognised barrier to efforts to reduce drug usage, as seen in the over-prescription of antibiotics.22 In addition, there are indications that allopurinol is being used for unlicensed indications, such as cardiovascular disease.15 It is not clear if the patients and the prescribing doctors are fully aware of the risk-benefit balance regarding the use of allopurinol.

The ultimate responsibility rests with the physician, whose duty is to provide optimal medical care. This care should include weighing the risk-benefit ratios of any intervention.

### Table 1: Uric acid level at first prescription.

| Hyperuricemia Type          | Frequency | Percentage |
|-----------------------------|-----------|------------|
| Marked hyperuricemia        | 79        | 4          |
| Insignificant hyperuricemia | 1037      | 52.4       |
| Normal levels               | 456       | 23.1       |
| Not documented              | 406       | 20.5       |
| Total                       | 1978      | 100        |

Marked hyperuricemia: males more than 13 mg/dL and females more than 10 mg/dL; insignificant hyperuricemia: more than 7.3 mg/dL in males and more than 6.1 in females.

### Table 2: Distribution of the study population according to the indications of allopurinol prescription.

| Indication                                | Frequency | Percentage |
|-------------------------------------------|-----------|------------|
| Not documented                            | 771       | 39.0       |
| Insignificant hyperuricemia               | 768       | 38.8       |
| Significant hyperuricemia                 | 66        | 3.5        |
| Gouty arthritis (confirmed)               | 30        | 1.6        |
| Gouty arthritis (not confirmed)           | 111       | 5.6        |
| Uric acid stone                           | 5         | 0.2        |
| Recurrent calcium oxalate stone           | 4         | 0.1        |
| Kidney stone (not analysed)               | 105       | 5.2        |
| Malignancy                                | 117       | 5.9        |
| Haemolysis                                | 1         | 0.1        |
| Total                                     | 1978      | 100.0      |

Marked hyperuricemia: males more than 13 mg/dL and females more than 10 mg/dL; insignificant hyperuricemia: more than 7.3 mg/dL in males and more than 6.1 in females.
Every physician has a role to play in raising their patients and colleagues’ awareness of this problem. The Alliance for Academic Internal Medicine and the American College of Physicians (ACP) framework was established with the aim to train physicians for whom high-value care is a normal practice. The framework states that physicians should understand the benefits, harms, and relative costs of the interventions that they are considering. They should choose interventions and care settings that maximise benefits and minimise harms, and they should decrease or eliminate interventions that provide no benefits or may be harmful. Part of this process involves the duty to re-evaluate any prescribed medication on a regular basis. It is common in medical practice to face patients with an empty box of medication, in our case allopurinol, who ask for a reorder, as this is their ‘routine medication’.

Treating laboratory results without clinical purpose and benefit-risk weighting, or re-prescribing without confirming clear indications, are the easy and fast options. This is the result of what is called intuitive or ‘fast’ thinking. The alternative process is analytical or ‘slow’ thinking. The first is comparable to a knee- jerk reaction, acting on intuition, and requires minimal cognitive effort from the person. The second is more difficult because it requires higher cognitive functions and analytical clinical reasoning. The clinician will have to answer a series of questions such as why was this patient prescribed allopurinol in the first place? and ‘Are the indications valid as per current guidance and evidence’? In clinical practice, both thinking processes are important, and there are at least six models of clinical reasoning described in the literature that integrate both intuitive and analytical elements.

Our study has several limitations. Although the data retrieved were digital and thus easy to search, this was a retrospective study. As expected, information may be missing due to poor documentation in electronic files. Some cases labelled as inappropriate prescriptions might have a valid indication. Difficulties in retrieving some of the information has also restrained our comments on the prevalence of side effects on our patients’ population. We did not include any data on the use of other uric acid lowering agents. However, as seen in other studies, allopurinol is by far the most widely used drug in these situations.

Conclusion

Allopurinol was prescribed in our large cohort of patients without clear and valid indications in 77.8% of the cases. This exposes patients to the risk of developing serious side effects without the addition of evidence-based benefits. Physicians should apply basic principles of clinical reasoning before prescribing any drug, including allopurinol.

Recommendations

Our institution should conduct educational programs for staff (residents, specialists, and consultants) to emphasise the importance of prescribing medications for valid indications. This should include medication reconciliation upon admission, discharge, or—most importantly—in outpatient settings and refill clinics. Our pharmacy must also establish a mandatory step for entering a valid diagnosis for any prescribed drug.

Source of funding

We would like to express our gratitude to Al Zaidi Chair of Research in Rheumatic Diseases (ZCRD) for supervising and funding this project.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This study was conducted in Doctor Soliman Fakeeh Hospital (DSFH), Jeddah, Kingdom of Saudi Arabia (KSA) after obtaining the ethical approval from the institutional review board (IRB) in the hospital.

Authors contributions

All of the authors participated in data collection and organisation. NAD wrote the initial and final draft of the introduction. ASM and KAS helped in writing and defining the results and tables. KRA and ARA contributed to the literature review and references. SAM and MMC wrote the discussion section. HAN supervised the group work and managed logistics and the critical revision. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgment

We would like to express our gratitude to Prof. Hani Almoallim for his major contribution in designing and conducting this research. We would also like to thank Dr. Sami Alobaidi for his contributions and supervision. We would like to express our appreciation for Al Zaidi Chair of Research in Rheumatic Diseases (ZCRD) for supervising and funding this project.

References

1. Carnovale C, Venegoni M, Clementi E. Allopurinol overuse in asymptomatic hyperuricemia: a teachable moment. JAMA Intern Med 2014 Jul 1; 174(7): 1031–1032.
2. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012; 64(10): 1431–1446. 2012 Oct.
3. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denucci CA, Matlaga BR, et al. Medical management of kidney stones: AUA guideline. J Urol 2014 Aug; 192(2): 316–324.
4. Fink HA, Wilt TJ, Eismen KE, Garamella PS, MacDonald R, Rutks IR, et al. Recurrent nephrolithiasis in adults. Recurrent nephrolithiasis in adults: comparative effectiveness of preventive
medical strategies. Agency for Healthcare Research and Quality (US); 2012.
5. Coiffier B, Altman A, Pui C-H, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008 Jun 1; 26(16): 2767–2778.
6. Lin KC, Lin HY, Chou P. Community based epidemiological study on hyperuricemia and gout in Kin-Hu, Kinmen. J Rheumatol 2000 Apr; 27(4): 1045–1050.
7. Dincer HE, Dincer AP, Levinson DJ. Asymptomatic hyperuricemia: to treat or not to treat. Cleve Clin J Med 2002 Aug; 69(8): 594, 597, 600–602 passim.
8. Yü T, Gutman AB. Uric acid nephrolithiasis in gout. Predisposing factors. Ann Intern Med 1967 Dec; 67(6): 1133–1148.
9. Yu TF. Urolithiasis in hyperuricemia and gout. J Urol 1981 Oct; 126(4): 424–430.
10. Jamal A-B, Salma A-H, Wafa A-S, Ghadah A, Roaa A. The prescription of allopurinol in a tertiary care centre: appropriate indications and dose adjustment. Clin Med Insights Arthritis Musculoskelet Disord 2012 Jan 31; 5: 53–57.
11. Lee HY, Ariyasinghe JT, Thirumoorthy J. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction? Singap Med J 2008 May; 49(5): 384–387.
12. Athisakul S, Wangkaew S, Louthrenoo W. Inappropriate prescription of allopurinol in a teaching hospital. J Med Assoc Thai 2007 May; 90(5): 889–894.
13. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum 1986 Jan; 29(1): 82–87.
14. Neogi T, Jansen TLTA, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. Gout classification criteria: an American College of Rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis 2015; 74(10): 1789–1798. 2015 Oct 1.
15. Pasina L, Brucato AL, Djade CD, Di Corato P, Ghidoni S, Tettamanti M, et al. Inappropriate prescription of allopurinol and febuxostat and risk of adverse events in the elderly: results from the REPOSI registry. Eur J Clin Pharmacol 2014 Dec 1; 70(12): 1495–1503.
16. Yang C-Y, Chen C-H, Deng S-T, Huang C-S, Lin Y-J, Chen Y-J, et al. Allopurinol use and risk of fatal hypersensitivity reactions. JAMA Intern Med 2015 Sep 1; 175(9): 1550.
17. Yaylacı S, Demir MV, Temiz T, Tamer A, Uslan MI. Allopurinol-induced DRESS syndrome. Indian J Pharmacol 2012 May; 44(3): 412–414.