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The Prescription of Allopurinol in a Tertiary Care Centre: Appropriate Indications and Dose Adjustment

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Abstract

Objective: To determine the appropriateness (both indications and adequate dosage regimen via creatinine clearance estimation) of allopurinol by physicians of different specialties in a tertiary care centre.

Patients and methods: In this cross sectional study computerized clinical records of 156 adult patients who were prescribed allopurinol from 12th November to 11th December, 2011 were retrieved from Al Hada Hospital Taif Saudi Arabia. Main outcome variables were appropriate indications of allopurinol, prescribing physician's specialty, and dosage of allopurinol. The prescribed dosages were categorized into correct and incorrect dose adjustments based on creatinine clearance estimation. The SPSS version 16 was utilized for data analyses.

Results: The mean (\pm SD) age was 58.15 (\pm 14.99) years. There were 105 (67.3%) males and 51 (32.7%) females with male to female ratio being 2:1. Allopurinol was frequently prescribed by nephrologists and family physicians in this study. Out of 156 patients, 46 (29.5%) patients received allopurinol with appropriate indications. Eighty-five (54.5%) patients were received allopurinol without dose adjustment based on their creatinine clearance estimation; among them, 21 (13.5%) received allopurinol with appropriate indications.

Conclusion: The inappropriate use of allopurinol (both the indication and prescribed dosage) is still a major problem in a large tertiary care centre. Furthermore, the specialty of physicians is also a contributory factor in this inappropriateness.

Keywords: allopurinol, gout, hyperuricemia, drug prescription, indication

Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 2012;5 53–57

doi: [10.4137/CMAMD.S9803](https://doi.org/10.4137/CMAMD.S9803)

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Introduction

Allopurinol is the frequently prescribed pharmacological agent in the management of gout and hyperuricemia.^{1,2} It reduces the serum uric acid levels by inhibiting the xanthine oxidase enzymes, which is responsible for the synthesis of uric acid.³ In addition to gout and hyperuricemia, it has been utilized for prevention of tumor lysis syndrome⁴ and renal stones diseases (urate stones and recurrent calcium oxalate stones associated with urinary uric acid excretion more than 800 mg/day).⁵ Despite this clinical utility, severe hypersensitivity reactions may occur with allopurinol, which although less common, is associated with significant morbidity and mortality.⁶ Hence, appropriate dose regimen is imperative in the prevention of this fatal outcome.

A number of factors have been discovered to demonstrate the appropriate usage of this drug in clinical practice in order to prevent potential adverse outcomes. Hande et al⁷ first demonstrated the relationship between allopurinol dose and pre-existing renal impairment in the development of hypersensitivity syndrome and suggested guidelines for the adequate dose based on creatinine clearance. Since then most medical practitioners have followed these proposed guidelines. Stamp and colleagues⁸ emphasized the significance of creatinine clearance in the prediction of the adequate dose of allopurinol. For the purpose of this study appropriate dose calculation of the drug was based on validated quality indicators developed to assess the quality of allopurinol prescribing practices.^{9,10}

Apart from creatinine clearance estimation, physician's specialty is also a contributing factor in inadequate prescription of allopurinol. Athisakul et al¹¹ highlighted the role of different physicians in determination of indication and prescribed dosage in a large tertiary care hospital. They observed both poor adherence to the current dosing guidelines for allopurinol according to creatinine clearance and prescription of this drug in various inappropriate indications by doctors from different specialties. In spite of these causative factors, the prescribed doses of allopurinol in clinical practice by medical practitioners still diverge from the approved guidelines.¹² This necessitates the further exploration of these contributory factors in order to establish the improper usage of this commonly prescribed medicine in clinical practice. Therefore, this study aimed to determine

the appropriateness (both in terms of indications and adequate dosage regimen via creatinine clearance estimation) of utilizing allopurinol by doctors of different specialties in a tertiary care centre.

Methodology

This retrospective study was conducted at Al Hada Hospital Taif Saudi Arabia. Computerized clinical records of all adult patients, who were prescribed allopurinol, visiting outpatient clinic from 12th November to 11th December 2011 were retrieved.

A proforma was designed to document findings which included patient's demographics (name, age and gender), serum uric acid levels (in millimole/L), comorbidities (diabetes, hypertension, chronic liver disease, cerebrovascular accidents, osteo- and rheumatoid arthritis, ischemic heart disease, hypothyroidism, and polycythemia vera), indications of allopurinol usage (gout, uric acid and recurrent calcium oxalates stones, tumor lysis syndrome, hyperuricemia, and hyperuricosuria), prescribing doctor's specialty, and dosage of allopurinol. The prescribed dosages were categorized into correct and incorrect dose adjustments based on validated quality indicators developed to assess the quality of allopurinol prescribing practices.^{9,10}

For the purpose of this study following two quality indicators were used:

1. 'IF a gout patient is receiving an initial prescription for allopurinol AND has significant renal impairment (defined as a serum creatinine ≥ 2 mg/dl or measured/estimated creatinine clearance ≤ 50 mL/min) THEN the initial daily allopurinol dose should be less than 300 mg per day BECAUSE the risk of allopurinol-related toxicity is increased in the presence of significant renal impairment in gout patients given a daily allopurinol dose equal to or exceeding 300 mg. and
2. IF a patient has asymptomatic hyperuricaemia characterized by (1) no prior history of gouty arthritis or tophaceous deposits AND (2) no prior history of nephrolithiasis or hyperuricosuria AND (3) no ongoing treatment of malignancy THEN urate-lowering therapies should NOT be initiated BECAUSE there is currently no widely accepted indication for the treatment of asymptomatic hyperuricaemia.^{9,10}



The creatinine clearance was calculated using Cockcroft-Gault equation.¹³

All statistical analyses were performed using statistical package SPSS for Windows program (version 16, SPSS Inc, Chicago, IL, USA). Quantitative data were expressed as mean \pm SD (standard deviation). Frequencies and percentages were utilized to expressed categorical data.

Results

Allopurinol was prescribed to 156 patients during the study period with mean (\pm SD) age of 58.15 (\pm 14.99) years. There were 105 (67.3%) males and 51 (32.7%) females with male to female ratio being 2:1. The mean (\pm SD) serum uric acid levels of study participants were 0.43 (\pm 0.12) millimole/L. The associated medical illnesses of patients are shown in Table 1. Allopurinol was administered at a dosage of 100 mg/day, 150 mg/day, 200 mg/day and 300 mg/day to 88 (56.4%), 01 (0.6%), 03 (1.9%) and 64 (41%) patients, respectively.

Table 2 demonstrates the details of the physicians who prescribed allopurinol, indications and dose adjustment according to creatinine clearance of the patients. Allopurinol was most commonly prescribed by nephrologists followed by family physicians in this study. Out of 156 patients, allopurinol was given with appropriate indications in 46 (29.5%) patients. Among them, gout was the most frequent indication followed by uric acid stones (Fig. 1). None of the patients in this study received allopurinol for recurrent calcium oxalate stones and hyperuricosuria. This indication of hyperuricosuria is important as not a single physician order for uric acid excretion in our review. We do not know the exact cause however this was probably related to poor adherence to guidelines or poor knowledge.

Table 1. Co-morbidities of patients (n = 156).

Co-morbidities	n (%)
Diabetes mellitus	74 (47.4)
Hypertension	88 (56.4)
Chronic renal disease	65 (41.7)
Cerebrovascular accidents	05 (3.2)
Osteoarthritis	21 (13.5)
Rheumatoid arthritis	02 (1.3)
Ischemic heart disease	36 (23.1)
Hypothyroidism	10 (6.4)
Polycythemia vera	05 (3.2)

Note: Data is shown in number followed by percentages in parentheses.

Eighty-five (54.5%) patients in this study received allopurinol without dose adjustment for their creatinine clearance. Only twenty-one (13.5%) of these patients received allopurinol with appropriate indications. Among them, twelve patients received allopurinol prescribed by nephrologists.

Discussion

The results revealed that nephrologists prescribed allopurinol in majority of patients. Allopurinol was given with appropriate indication in 46 (29.5%) patients. Furthermore, dose adjustment according to creatinine clearance was not carried out in 85 (54.5%) patients; among them, 21 (13.5%) received allopurinol with appropriate indications.

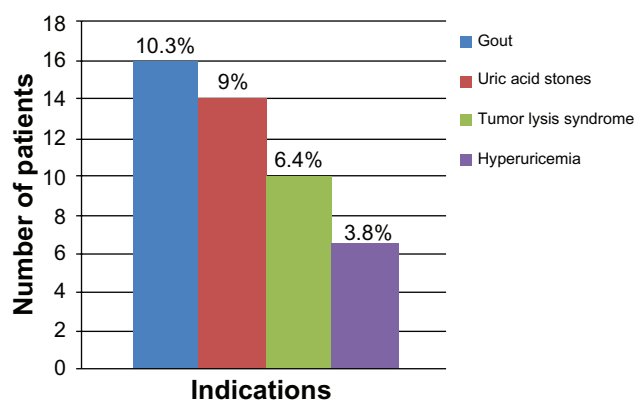
Allopurinol is the most commonly prescribed medication for the treatment of gout and hyperuricemia but has been associated with severe adverse reactions that can lead to death.¹⁴ A 10 years observational survey at the dermatology department of Cagliari (Italy), allopurinol was the causative drug in 84 of 780 cases (10.7%) of cutaneous adverse drug reaction.¹⁵ Most of the allopurinol prescriptions were inappropriate without dose adjustment in this survey. Hence, this determines the improper usage of allopurinol in clinical practice. The current study also showed the administration of allopurinol in several non-indications (70.5%). In a review of 28 patients with hypersensitivity syndrome associated with allopurinol by Lee et al,⁶ only ten (36%) received this drug with clear indications. The current study also demonstrates appropriate indications in 29.5% of patients, which is nearly comparable to the Lee et al study. Therefore, these literature reviews conclude that medical practitioners mostly prescribe allopurinol irrationally with no clear indications. Another important finding of this study is that physicians prescribe it for all patients with asymptomatic mildly elevated uric acid level. The current recommendation for the treatment of asymptomatic hyperuricemia is that it should be treated if the level of uric acid is very high (Male: 713 micromol/L and Female: 595 micromol/L).^{16,17} In the current study, the mean uric acid level was 430 (\pm 120) micromol/L; which clearly point out the trend of treating uric acid at much lower level to the current recommendations. Hyperuricosuria can be treated if the uric acid excretion is >1100 mg or 6,5 mmol/day; failed to dietary restriction to lower it less than 1000 mg or 5.9 mmol/L.^{16,17}

Table 2. Details of allopurinol prescribed by physicians, indication and dose adjustment.⁹

	Numbers of allopurinol prescription	Appropriate indications		Inappropriate indications	
		Correct dose adjustment n (%)	Incorrect dose adjustment n (%)	Correct dose adjustment n (%)	Incorrect dose adjustment n (%)
Rheumatologists	02	02 (100)	0 (0)	0 (0)	0 (0)
Family physicians	33	02 (6.1)	02 (6.1)	20 (60.6)	09 (27.3)
Nephrologists	86	10 (11.6)	12 (14)	19 (22.1)	45 (52.3)
Internists (general physicians)	14	04 (28.6)	01 (7.1)	03 (21.4)	06 (42.9)
Oncologists	08	04 (50)	03 (37.5)	1 (12.5)	0 (0)
Urologists	08	03 (37.5)	02 (25)	02 (25)	01 (12.5)
Cardiologists	04	0 (0)	0 (0)	01 (25)	03 (75)
Endocrinologists	01	0 (0)	01 (100)	0 (0)	0 (0)
Total	156	25 (16)	21 (13.5)	46 (29.5)	64 (41)

No single physician order for uric excretion in our review which probably related to poor adherence to guidelines or poor knowledge.

In addition to inappropriate indications, prescribed dosing guidelines based on creatinine clearance are also obligatory for the prevention of fatal adverse outcomes of the allopurinol, as previously mentioned by Hande and associates in their case series.⁷ Since then, a large body of literature has been published to emphasize this fact.^{8,11,18,19} The dose adjustment of allopurinol according to creatinine clearance prevents the severe toxicity associated with over dosage, as previously mentioned by Perez-Ruiz and co-workers.²⁰ Despite this, a wide diversity in allopurinol doses has been observed from the approved guidelines.¹² In this study, eighty-five (54.5%) patients received allopurinol without dose adjustment for their creatinine clearance.

**Figure 1.** Indications of allopurinol.

Athisakul et al¹¹ in their study also demonstrated a significant number of patients who were received allopurinol without dose adjustment.

Although improper indications and inadequate dose adjustment of allopurinol are considered to be fundamental factors in inappropriate prescriptions, consideration of physicians' specialty also has pivotal role in this inappropriateness. A limited study has been conducted in this regard. Athisakul et al¹¹ showed that internists prescribed this medicine with proper indications to majority of patients (70.8%) in a tertiary care centre. Gout was the main indication of its usage in their study. Out of this, 61 (63.5%) patients received corrected dose adjustment based on their creatinine clearance. The administration of allopurinol with both inappropriate indications and dose adjustment was given by family physicians, orthopedists, and other specialists in their study. In the current study, gout was the main indication followed by uric acid stones for allopurinol therapy. This is the main explanation of the major proportion of allopurinol prescriptions by nephrologists in this hospital. Another possible reason for the prescription of allopurinol by nephrologists is publication of new epidemiological data that claims that lowering uric acid level may decrease progression of renal failure and degree of hypertension.²¹ The family physicians in the current study were responsible for improper prescription of allopurinol in terms of adequate indications, which is nearly similar to the results of Athisakul et al study.¹¹



There are few limitations of this study. Firstly, the decline in serum uric acid levels with corrected dose adjustment of allopurinol was not evaluated by authors. Secondly, the side effects of allopurinol (with or without dose adjustment) were not delineated in this study.

Conclusion

The inappropriate use of allopurinol (both the indication and prescribed dosage) is still a major problem in a large tertiary care centre. Main reason of inappropriate prescription is use of allopurinol even to patient with asymptomatic mild hyperuricemia. Furthermore, the specialty of physicians is also a contributory factor in this inappropriate prescription.

Author Contributions

Analysed the data: ABJ, AHS, ASW, AG, AR. Wrote the first draft of the manuscript: ABJ, AHS, ASW, AG, AR. Contributed to the writing of the manuscript: ABJ, AHS, ASW, AG, AR. Agree with manuscript results and conclusions: ABJ, AHS, ASW, AG, AR. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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