Observations and Effects of Educational Consults on Allopurinol Prescribing

J.W. Devlin, N. Bellamy and C.D. Bayliff

ABSTRACT

Allopurinol has been used in the management of hyperuricemic states for several years. Despite its efficacy for these indications, recent concerns have been raised regarding the unnecessary morbidity and mortality occasionally associated with its inappropriate use. In an effort to assess the utilization of allopurinol, a concurrent drug utilization review was undertaken. Fifty patients who were prescribed allopurinol were entered into the study and underwent health record review and patient interview, to determine appropriateness of therapy and the need for educational intervention. A number of inconsistencies with regard to established guidelines were identified. As well, 11 of 50 patients (22%) required intervention because of either lack of indication or excessive dose. Fifty-five percent of the educational interventions, performed by the pharmacist, were accepted as written. The current utilization of allopurinol at our facility differs susbstantially from guidelines developed for optimal utilization of allopurinol. Further, a pharmacy based intervention program can improve prescribing practices of allopurinol.

Key Words: *allopurinol, drug utilization review, intervention*

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RÉSUMÉ

On emploie l'allopurinol pour traiter l'hyperuricémie depuis plusieurs années. Récemment, malgré l'efficacité du médicament, on a exprimé des inquiétudes quant à la morbidité et à la mortalité occasionnellement associées à un emploi inapproprié. Pour les vérifier, on a effectué une étude sur l'emploi simultané de médicaments. Ont participé à cette étude 50 malades à qui on avait prescrit de l'allopurinol. On a passé leurs dossiers de santé en revue et on les a interrogés afin de déterminer si le traitement était approprié et si des mesures éducatives se justifiaient. Plusieurs divergences ont été révélées par rapport aux directives établies. En outre, il a fallu intervenir auprès de 11 patients (22%) parce que le traitement n'était pas indiqué ou parce que le dosage était excessif. Cinquante-cinq pour cent (55%) des interventions éducatives des pharmaciens ont été acceptées. À l'heure actuelle, la prescription de l'allopurinol dans notre établissement s'écarte sensiblement des directives élaborées pour garantir l'utilisation optimale du médicament. De plus, un programme d'intervention développé par le pharmacien peut améliorer les pratiques concernant l'utilisation de l'allopurinol.

Mots clés: *allopurinol, revue de l'utilisation de médicament, intervention*

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INTRODUCTION

Although a major advance in the pharmacotherapy of hyperuricemia and hyperuricemic states, the utilization of allopurinol remains problematic despite 30 years of clinical experience.[1] Some years ago, Deyo et al noted that compliance to allopurinol in an arthritis clinic was only 63.5 percent.[2] More recent surveys in Canada,[3] Australia,[4] and New Zealand[5] indicate that family physicians are more liberal in their use of allopurinol, but are less likely to cover the introduction of the agent with

prophylactic nonsteroidal anti-inflammatory drugs or colchine, to titrate the dose against the serum uric acid, or to adjust the dose according to serum creatinine. Formal chart reviews conducted in a group general practice in Australia also discovered cases in which allopurinol had been introduced and monitored in a sub-optimal manner.[6] Other investigators have raised concern regarding the unnecessary morbidity and mortality occasionally associated with the inappropriate use of allopurinol to treat hyperuricemic states.[7] Indeed,

Singer et al observed that only 13 percent of patients had legitimate indications for the use of allopurinol.[7] The most substantial toxicities occur due to the development of the allopurinol hypersensitivity syndrome. This syndrome tends to occur with high doses of allopurinol and has been associated with several factors including underlying renal impairment, advanced age and concomitant thiazide diuretic use.[8] Each of these factors plays a role in elevating the serum concentration of allopurinol's active metabolite, oxypurinol, con-

tributing to the development of the syndrome. These concerns have prompted several authors to urge that caution be used when prescribing the drug, especially in patients with identified risk factors.[3-8]

Recently, Zell and Carmichael reviewed the pharmacy records of 286 out-patients on allopurinol.[9] Only 45 had a definite indication for allopurinol as defined by their pharmacy and therapeutics committee. The investigators observed that physicians did not use diagnostic tests optimally; did not attempt to modify risk factors for gout; and did not use less expensive alternative therapy such as uricosuric drugs, even when these would have been appropriate. Given the disconcerting nature of these observations, we have conducted a drug utilization review (DUR) of allopurinol in the in-patient population of a Canadian teaching hospital. DUR is a structured process by which actual prescribing practices and drug use are assessed against predetermined standards.[10] The use of DURs to assess and improve utilization and prescribing practices in other disease states is well documented.[11-15] The objectives of our study were two-fold: to assess physicians' prescribing practices of allopurinol, and to determine if an educational program could favourably affect these practices.

METHODS

Fifty consecutive patients receiving allopurinol upon admission to Victoria Hospital, London who were identified through the unit dose drug distribution system were included in the survey. Patients were excluded if they were deemed unable to participate in the interview process; if they were admitted to intensive care areas; or if they were under the age of 18 years. Demographic data, biochemical and laboratory profiles, and infor-

mation on allopurinol dose, duration and effectiveness of therapy, as well as information regarding concomitant medications were collected on a previously developed and pretested form (Appendix I). Data were obtained from a combination of a review of the health record and a patient interview.

Patient information was collected and judged to either meet the criteria or to fail to do so. For purposes of this DUR, therapy which failed to meet the criteria necessitating an intervention by the pharmacist occurred when:
1. the indication for therapy as identified by Singer et al[7] was lacking or
2. the prescribed dose was 50 percent or more of that recommended by Cameron et al.[16]

If therapy was judged to meet the criteria, nothing further was done. When the criteria were not met, an educational consult was attached to the front of the patient's health record. (See Appendix II). This consult gave a brief patient history, identified the need for change, and suggested the appropriate therapeutic change. The consult was adjusted depending on whether there was a lack of indication or the dose was excessive. The outcome of these patient consultations was determined by further review of the health record for each patient at the time of discharge, including a review of the discharge summary.

Descriptive statistics were calculated for relevant variables and are expressed as mean ± standard deviation unless otherwise stated. The relationships between dose and patient age, serum urate, serum creatinine and calculated creatinine clearance[17] were determined utilizing least squares linear regression analysis.[18]

This project was approved by the Ethics Review Board for Health Science Research involving Hu-

man Subjects at the University of Western Ontario and informed consent was obtained from each patient prior to participation.

RESULTS

Over a seven week period from April 20, 1989 to June 8, 1989, 50 consecutive patients admitted to hospital and eligible for study were surveyed. Four other patients who received allopurinol during this period were excluded; two because the patient was unable to participate in the interview process, in one case due to a reduced level of consciousness, and in the other case due to a language barrier. In two other patients, allopurinol therapy was discontinued prior to interview.

The mean age of the patients was 69.8 ± 9.3 years (range: 46 to 91 years). There were 40 males and 10 females. The average allopurinol dose prescribed was 248.0 ± 89.1 mg/day (range: 50 - 600 mg/day). Fifty-six percent of patients were receiving 300 mg/day. No relationship was found between age and allopurinol dose (r=0.004). The indications for allopurinol were: history consistent with gout (42 patients); renal calculi (3); prevention of hyperuricemia in association with treatment of malignant disease (3); indeterminate (2). None of the patients were admitted because of their gout.

The mean duration of allopurinol therapy was 9.1 ± 7.7 years (range: one month to 30 years). Fifty-four percent of patients started to receive allopurinol for gout or renal stones after their first attack. Sixty percent of patients had not had a recurrence since starting allopurinol therapy. When patients were questioned regarding the use of other drugs to control acute gout, allopurinol was the sole agent used in 50 percent of cases. Sixty-two percent of the patients (25 males and 6 females) had a serum urate measurement per-

formed. The mean serum urate level in males was 313.2 ± 99.8 μmol/L and in females was 392.3 ± 164.69 μmol/L. Seven percent of these patients had a serum urate less than or equal to 200 μmol/L and 32 percent had a serum urate less than or equal to 250 μmol/L (normal range: 150 - 360 μmol/L (females); 150-475 μmol/L (males)). No relationship was found between serum urate and allopurinol dose (r=0.032) in the male population. However, a weak positive relationship was found in the female patients (r=0.64).

Forty-six percent of patients had a serum creatinine measurement with a mean of 123.7 ± 71.9 μmol/L. The mean calculated creatinine clearance was 1.0 ± 0.44 mL/sec. No relationship was found between either serum creatinine (r=0.026) or calculated creatinine clearance (r=0.016) and dose.

Fifty percent of our patients were receiving thiazide diuretics and 35 percent were receiving low dose aspirin (≤650 mg per day).

Eleven patients (22 percent) of the 50 assessed required an educational consult, due to a lack of indication in three cases or due to excessive dose in eight cases (See Table I).

Of the 11 educational consults, six were successful in achieving a change in drug therapy; that is, either allopurinol was stopped or the dose was decreased. Of these 11 cases, seven were admitted under medical services and four under surgical services. Six of seven educational consults admitted under a medical specialist were accepted. None of the four surgical education consults resulted in any change in therapy.

DISCUSSION

Although the majority of patients with asymptomatic hyperuricemia, gouty arthritis and urate nephro-

Table I: Comparison of Allopurinol Use in the Ontario Gout Survey (OGS) and Drug Utilization Review

Parameter	OGS[3]	DUR
Commenced after first attack	27%	54%
Dose adjusted according to serum urate	60%	No relationship between serum urate and dose
Dose adjusted according to serum creatinine or creatinine clearance	54%	No relationship between serum creatinine/creatinine clearance and dose
Risk of drug interaction with diuretic appreciated	92%	50% of patients received these potential interactants
Risk of drug interaction with low dose ASA appreciated	31%	35% of patients received these potential interactants

lithiasis likely receive appropriate therapy, problems in the utilization of drugs used to treat these conditions remain. Whether the data are collected by postal questionnaire[3-5] or chart review,[2,6,7,9] on in-patients or out-patients[6,9] suboptimal prescribing practices have been detected. While certain general trends emerge, most of which point to unnecessary treatment and excessive dosage, a number of discrepancies in the findings of various investigators also emerge (See Table I). While only 27 percent of general practitioners in the Ontario Gout Survey (OGS)[3] indicated that they would prescribe allopurinol after the first attack of gout, double that number of patients in this study (54 percent) indicated that they had been prescribed the drug after their first gout attack. Although allopurinol has no anti-inflammatory activity and its introduction may indeed aggravate an acute attack of gout, 50 percent of patients in our study indicated that allopurinol was the sole agent used during their very first attack. Clearly, this is at variance with current recommendations[19] and practice.[3-5.]

With regard to adjusting the dose according to the serum urate concentration or renal function, 60 percent and 54 percent of family physicians respectively in the OGS indicated that they would adjust the dose according to these para-

meters. However, in our study we found no relationship between either of these parameters and allopurinol dosage. Indeed, several patients received doses in excess of that recommended (See Table II). Finally, with regard to modifying risk factors for hyperuricemia, 92 percent of family physicians were aware of the potential for thiazides to aggravate the hyperuricemic state and 31 percent were aware of the potential for A.S.A. to do the same. Despite this, 50 percent of patients in our study were receiving thiazide diuretics and 35 percent were receiving low dose A.S.A. (≤ 650 mg per day) in addition to allopurinol.

While there may be many reasons for these discrepant findings, some of which relate to the utilization of different research techniques, it should be noted that many patients in the present study had received allopurinol for long periods of time and may have originally been prescribed the drug at a time prior to awareness of the aforementioned information. Drug prescribing habits may also be, in part, a function of year of graduation from medical school.[20] To our knowledge, this issue has never been directly addressed in the area of prescribing of musculoskeletal agents. It is of interest, however, that in the OGS, those physicians who recommended the use of phenylbutazone as the drug of first

Table II: Summary of Educational Consults

Patient	Intervention Type: Dose (D) or Indication (I)	Patient History	Recommendation	Surgery (S) Medicine (M)	Outcome: Change (C) No Change (NC)
1.	D	300 mg/day CrCl=0.48 mL/sec (on thiazide)	decrease dose to 100 mg/day	M	C
2.	I	300 mg/day Pt has rec'd no chemo for 3 years. Still on allopurinol for tumour lysis.	discontinue therapy	M	C
3.	D	300 mg/day CrCl=0.42 mL/sec (on thiazide)	decrease dose to 100 mg/day	M	NC
4.	I	300 mg/day Pt never had an attack but family history positive for gout	discontinue therapy	S	NC
5.	I	50 mg/day Pt had never experienced a gouty attack and had no idea why he was taking this drug	discontinue therapy	S	NC
6.	D	600 mg/day CrCl=0.25 mL/sec	decrease dose to 100 mg/day	M	C
7.	D	200 mg/day CrCl=0.33 mL/sec (on thiazide)	decrease dose to 100 mg/day	S	NC
8.	D	200 mg/day CrCl=0.42 mL/sec	decrease dose to 100 mg/day	M	C
9.	D	300 mg/day CrCl=0.49 mL/sec (on furosemide)	decrease dose to 100 mg/day	M	C
10.	D	200 mg/day CrCl=0.32 mL/sec	decrease dose to 100 mg/day	M	C
11.	D	300 mg/day CrCl=0.36 mL/sec	decrease dose to 100 mg/day	S	NC

(CrCl = creatine clearance)

choice in the treatment of acute gout, were among the oldest physicians in the group surveyed.[3]

In our study an educational intervention was only attempted for two specific issues involving utilization: 1) no indication for the drug and, 2) dose in excess of that recommended for renal function. These criteria may be considered liberal since results of synovial fluid analysis were not available. As a result, any complaint of acute joint pain was accepted as an indication for allopurinol. Hence,

our methodology likely underestimates the amount of inappropriate use due to a lack of indication. Using a patient interview and health record review, we found 6 percent of patients did not have an appropriate indication for allopurinol. This contrasts with the work of Zell and Carmichael in which 82 percent of patients had no indication for allopurinol.[9] The discrepancy between these two estimates is likely due to differences in research methodology. Specifically, Zell required that very

stringent criteria be fulfilled before allopurinol use was deemed appropriate, while we were much more liberal.

In our study, a total of 11 educational consults were made: three for a lack of indication and eight for excessive dosing. Of these, one educational intervention in the first group and five educational interventions in the second group were successful in correcting the defined deficiencies (See Table II). Like Day et al,[21] we have observed that some patients in a teaching hospital, given allopurinol for a variety of indications, may be exposed to excessive daily doses. Of the 11 educational consults made, all six which were successful in achieving either discontinuation of allopurinol therapy or dose reduction occurred in patients admitted under medicine and whose care was being supervised by consultants in general internal medicine. It is equally noteworthy that none of the four educational consults provided to patients admitted under surgical consultants resulted in any change in therapy (p = .015, Fisher's Exact test). This dichotomy may reflect the greater familiarity of physicians with the issues once they are brought to their attention, or indicate a propensity for surgeons to delegate the responsibility back to the referring physician for management following discharge.

The major limitation of our study was the reliance on a patient interview to determine some of the information on allopurinol use. A patient interview was incorporated into our study design due to poor documentation in the health record regarding the indication for and duration of allopurinol use. In an attempt to minimize the bias of interview, we were very liberal in considering appropriateness. For example, any acute joint pain was considered to be gout. By using such liberal criteria, we believe we have underestimated the amount of

inappropriate prescribing of allopurinol.

CONCLUSION

This drug utilization review, like other cross-sectional surveys has detected a significant degree of inappropriate allopurinol therapy. We are particularly concerned by the large number of patients treated with allopurinol after their very first attack of gout; by patients whose allopurinol dosage was not adjusted according to either serum urate or serum creatinine; and by those patients who received concomitant low dose A.S.A. or thiazide diuretic therapy. It appears from international surveys[3-5] that the majority of physicians are aware of many of these therapeutic concerns; yet, chart reviews indicate that theory is not always put into practice. It also appears that physicians are much more likely to respond to the recommendations of an educational consult than their colleagues in surgical disciplines. This DUR highlights the extent of inappropriate allopurinol therapy which may result in increased patient moribidity and health care costs. Given that allopurinol treatment is often prescribed life-long, these latter costs may be significant. Finally, it appears that an educational program based on a DUR has the potential to modify prescribing behaviour in receptive physicians. ☒

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Appendix I

ALLOPURINOL UTILIZATION REVIEW

1. Patient Data:

   Name _____ Age _____ Sex _____ Weight _____

   Hospital File No. _____ Admission Date _____ Discharge Date _____

   Diagnosis (1) _____ Concurrent _____

        (2) _____ Medications _____

        (3) _____   _____

        (4) _____   _____

   Dose of allopurinol _____

2. Indication for allopurinol

   (1) _____ documented history of gout as per medical history

   (2) _____ signs/symptoms of gout

    pain _____ swelling _____ redness _____ explosive onset _____

    fever _____ severity in peripheral joints _____

   (3) _____ identification of crystals of monosodium urate in aspirated synovial fluid

   (4) _____ tumour lysis

   (5) _____ urinary excretion of uric acid greater than 5 mmol/d on a diet with rigid purine restriction

   (6) _____ recurrent (uric acid) renal calculi

   (7) _____ hyperuricemia: males greater than 480 μmol/L
             females greater than 390 μmol/L

   (8) _____ development of tophi

3. Laboratory Data:

Date	Serum Uric Acid	Serum Creatinine	Urine 24 h Uric Acid Excretion
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

4. Duration of Therapy

   _____ < 1 week   _____ 1 year to < 3 years

   _____ 1 week to 6 months _____ 3 to < 5 years

   _____ 6 months to < 1 year _____ > 5 years

5. Symptomatic Effectiveness

   a) _____ number of attacks per year prior to commencing allopurinol
     (If started after first attack, check here _____)

   b) _____ number of attacks in first year since starting allopurinol

   c) _____ Have you ever taken another drug for gout?

      Yes _____   No _____

    If yes, when did you start taking it? _____

    Did you use it intermittently during an acute <u>attack</u> of gout, or take it continuously every day? _____

    _____ any drugs taken for gout since starting allopurinol?

      Drug   **Date**

      _____ _____

      _____ _____

Appendix II

<div style="border:1px solid black; padding:1em;">

<div align="center">**EDUCATIONAL CONSULT**</div>

THIS IS NOT A PERMANENT PART OF THE PATIENT RECORD

ATTENTION — MEDICAL/SURGICAL ATTENDING STAFF   **Date** _____

In conjunction with Dr. N. Bellamy of the Department of Medicine, an audit of allopurinol use is being completed at **Victoria Hospital** by the Department of Pharmacy Services.

Indications for use of allopurinol have been recently outlined in the OMA's Drug Report (Number 26, July 1988) and include:

(1) tophaceous gout

(2) major urate (as uric acid) overproduction (ie. urinary excretion more than 5 mmol/d of urate on a diet with rigid purine restriction)

(3) frequent gouty attacks unresponsive to prophylactic colchicine when urocosuric agents cannot be used due to intolerance, lack of efficacy, renal insufficiency, or poor patient compliance

(4) recurrent urate renal calculi

(5) recurrent calcium oxalate renal calculi when associated with hyperuricosuria

(6) prevention of acute urate nephropathy in patients receiving cytotoxic therapy for neoplastic disease

_____ , a patient on your service, has received allopurinol for approximately _____ years.

In renal insufficiency allopurinol dosing should be adjusted as follows:

	Cr/Cl (mL/sec)	Allopurinal dose
_____	0	100 mg thrice weekly
_____	0.17	100 mg on alternate days
_____	0.33	100 mg daily
_____	0.67	150 mg daily
_____	1.0	200 mg daily
_____	2.0	300 mg daily

(Cameron et al, BMJ 1987; 294:1505)

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