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AUDIT OF PRESCRIPTIONS OF GOUT AND HYPERURICAEMIA :A THREE CENTRE STUDY FROM EASTERN INDIA

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ABSTRACT

Aims: To evaluate the prescription pattern in cases of gout and hyperuricaemia.

Settings and Design: Prescriptions of gout and hyperuricaemia were audited by one Rheumatologist & one Physician in first centre and two physicians in the second centre and one physician in the third centre.

Methods and Material: 150 prescriptions were audited in the first centre and 100 were audited in the second centre and 50 prescriptions were audited in the third centre. The period of audit was from 01 Jul 2016 to 30 Jun 2017.

Results: A total of 300 prescriptions were audited. They included 280 males and 20 females. These included 289 patients who had suffered an acute attack of gouty arthritis (monoarticular or polyarticular). 11 patients had only hyperuricaemia but no attack of gouty arthritis.Age ranged from 32 to 81 years.It was observed that 244 (81.33 %) patients were prescribed only NSAID's for duration of 2 to 15 days.

Conclusions: It was observed that in some of patients of gouty arthritis, Tab Allopurinol and Tab Febuxostat are being prescribed during acute attack of gouty arthritis. This is an inappropriate practice. In addition, dietary advice was rendered to patients to stop pulses, milk and milk products and certain vegetables which is incorrect and not evidence based.

KEYWORDS :

Introduction:

Gout is a disorder of purine metabolism.As a result of hyperuricaemia, there is a deposition of uric acid crystals in joints which leads to occurrence of acute gouty arthritis.Involvement of the first metatar sophalangeal joint is the hallmark of this disease. The disease can manifest as recurrent attacks of acute arthritis or as polyarticular joint disease. It can also manifest as chronic tophaceous gout. It can cause renal calculi and also cause renal involvement in the form of interstitial nephritis. It is more common in men. The incidence of gout has increased in recent decades leading to increased health care burden.

Acute attack of Gout is classically treated with non-steroidalanti-inflammatory drugs (NSAID's), colchicine and corticosteroids. Intraarticular steroids can also be used to treat single joint involvement. Patients who have recurrent attacks (usually 2 or more attacks per year) are started on urate lowering therapy (ULT). Urate lowering therapies include xanthine oxidase inhibitors (allopurinol, febuxostat), uricosuric agents (probenecid ,sulfinpyrazone) and uricases (pegloticase). ULT decreases the level of serum uric acid in the blood. Usually the starting dose of allopurinol is 100 mg daily which is escalated every 2-3 weeks titrating with serum uric acid levels. Although there have been a number of guidelines for the management of gout, yet the management of gout remains suboptimal.

European League Against Rheumatism (EULAR), British Society of Rheumatology (BSR), and American College of Rheumatology (ACR) have published guidelines for the management of gout. These guidelines have stressed on the need of titrating ULT to achieve a serum urate target below 300 – 360 µ /L(5-6 mg/ dl).

Subjects and Methods:

Prescriptions of gout and hyperuricaemia were audited by one Rheumatologist in first centre and two physicians in the second centre and one physician in the third centre. 150 prescriptions were audited in the first centre and 100 were audited in the second centre and 50 prescriptions were audited in the third centre. The period of audit was from 01 Jul 15 to 30 Jun 16. These prescriptions were written by General practitioners, physicians, orthopedic surgeons, general surgeons and specialists in physical medicine and rehabilitation. The prescriptions were audited keeping in mind the parameters as have been shown in Table 1.

SL NO	PARAMETERS
1.	Age
2.	Sex
3.	Height (in cms)
4.	Weight(in kgs)
5.	If weight not recorded is mention of obese/ overweight done
6.	BP(in mmHg)
7.	Serum Uric acid (in mg/dl)
8.	Blood Urea (in/dl)
9.	Serum Creatinine (in mg/dl)
10.	Blood sugar (Fasting & Postprandial)
11.	Blood Sugar (Random)
12.	Lipid profile
13.	USG Kidney ureter and bladder

Results:

A total of 300 prescriptions were audited. They included 280 males and 20 females. These included 289 patients who had suffered an acute attack of gouty arthritis (monoarticular or polyarticular). 11 patients had only hyperuricaemia but no attack of gouty arthritis. Height of the patient was recorded in only 12 patients. Weight was recorded in 36 patients. Body mass index (BMI) was endorsed in only 07 patients. However, as both height & weight were recorded in 12 patients, BMI was available in 12 patients. Weight was recorded in 36 patients out of which 10 were recorded obese. However, in 66 patients it was endorsed that patient was over weight(37) or obese(29) but weight of these 66 patients was not recorded.

BP was recorded in 130 out of 300 patients. Out of these 130 patients, 56 patients were known hypertensive on anti-hypertensive treatment and 74 patients were detected to be hypertensive during examination. In 12 prescriptions, it was recorded that blood pressure was normal. However in these patients recorded of BP was not present. In 158 patients, no record or mention of BP was made. The anti-hypertensive drugs prescribed included ACE inhibitors, angiotensin receptor blockers (ARB's), beta blockers & calcium channel blocker. In 02 patients thiazide diuretic were used.

Table 2 : Age distribution of patients

Age group	Number of patients
30-40	76
40-50	114
50-60	54
60-70	44
70-80	22
>80	1

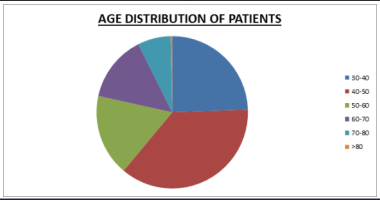
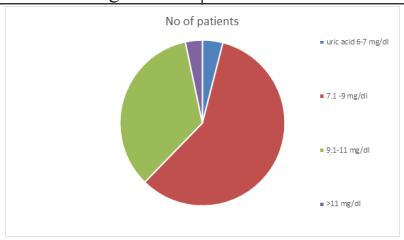


Table 3 Serum Uric Acid Levels In 300 Patients

Serum Uric Acid Levels	Number Of Patients
6 to 7 mg %	12
7.1 to 9 mg%	175
9.1 to 11 mg%	103
More than 11 mg%	10



Serum uric acid levels were done in all 300 patients. 11 patients had asymptomatic hyperuricaemia. 289 patients had suffered at least one attack of acute gout (monoarticular or polyarticular Gout). 23 patients were having tophi which was recorded in documents. Serum uric acid was between 6 to 7 mg/dl in 12 patients. In 175 patients, serum uric acid was between 7.1 to 9 mg/dl.In 103 patients, serum uric acid was between 9.1 to 11 mg/dl.In 10 patients, serum uric acid was recorded to be more than 11 mg/dl. There were 28 patients who had gout for more than one year and in these serial levels were available. Table 2 shows the level of serum uric acid.

Blood sugar (Fasting & Postprandial) was done in 230 out of 300 patients and 16 were found to be diabetic while 02 patients had impaired GTT. It was also observed that in 07 patients, Blood sugar (Random) levels were recorded and they were normal in all these 07 patients. Also, in 03 patients, Blood sugar levels were not endorsed but it was mentioned on record that these 03 patients were diabetic.

Blood urea/BUN levels and serum creatinine were done in 216 patients and it was observed that 27 patients had elevated serum creatinine levels.

Lipid profile was recorded in 163 patients. In 40 patients only serum cholesterol was done. In 163 patients whose lipid profile was done, raised low density lipoprotein (LDL) levels alone were found in 29 patients and raised triglyceride levels alone were found in 09 patients. In 11 patients both LDL levels and triglyceride levels were raised. In 40 patients whose serum cholesterol alone was done, 11 were found to have raised serum cholesterol levels. Ultrasonogram (USG) to see for kidney, ureter & bladder area was done in 44 patients. 07 patients had renal/ ureteric calculi.

As regards therapy of acute gout, out of 278 patients of gouty arthritis, it was observed that 244 patients were prescribed only NSAID's for duration of 2 to 15 days. In 18 patients only oral or injectable steroids were given and in 14 patients both NSAID's and oral steroids were given. In 02 patients, NSAID's and Tab colchicine were given.

In 14 patients, Tab Allopurinol or Tab Febuxostat was started during acute attack of Gout. Out of these 14 patients, in 8 patients, Tab Allopurinol 300 mg per day was started. In 02 patients, Tab Allopurinol 200 mg per day was started. In 2 patients Tab Allopurinol 100 mg per day was started. In 01 patient, Tab Febuxostat 80 mg per day was started and in 01 patient, Tab Febuxostat 40 mg daily was started. In 11 patients with hyperuricaemia, Tab Allopurinol (100-300 mg per day) or Tab Febuxostat (40-80 mg per day) were started even though these patients had no attack of gouty arthritis. It was also observed that 178 patients were advised to avoid red meat and 156 patients were advised to avoid alcohol.

In addition, 17 patients were advised to avoid pulses, milk and milk products. In 05 prescriptions, a list of many vegetables were given which were to be avoided by the patients that included Brinjal, cauliflower and beans.

Discussion:

Gout is known to humankind since the fifth century B.C. Leeuwenhoek in (1679) first described crystals in a patient of chronic tophaceous gout, which were identified as uric acid. Acute gouty arthritis was recognized by Hippocrates and he described it as 'the unwalkable disease'. Gout was known as the king of the diseases and disease of the kings(2). It was likely because as rich could afford for binge alcohol drinking and lifestyle that helps in the causation.

There are guidelines for the diagnosis and treatment of gout. However it is easy to infer from our study that the guidelines are usually not followed.(3)Despite well established guidelines it has been seen that gout is not well managed on many occasions and guidelines are not strictly adhered to, especially by primary care physician.(4-7) Mostly because of poor awareness, lack of adequate patient education about risk factors and non-adherence to urate lowering therapy(8). On many instances disease management is directed primarily towards control of acute attacks only. Such lapses in the management can result in precipitations or prolongation acute gout attacks.(9) In one of the recent studies on prescribing pattern for gouty arthritis (10)looking at predictors of adherence in gout patients consisted of majority of elderly women with the mean age of around 79 yrs.

Gout is classically diagnosed and managed as a chronic inflammatory condition primarily affecting joints, however its association with metabolic syndrome and increased cardiovascular risk is well established. (11) In addition to the cardiovascular risk gout is also implicated in the increased risk of diabetes mellitus (12) . The chronic inflammatory process of gouty arthritis seems to promote the diabetogenic state in these patients. (13)It is seen in our study that not many doctors gave much importance to recording blood pressure, weight, lipid levels and blood sugar levels. Thus many doctors were treating gout more likely as a joint disorder and not looking into the bigger picture of metabolic syndrome. It is needless to say this calls for strict adherence to guidelines and treating gout in totality. It is imperative that weight and BP be recorded, blood sugar and lipid profile be noted and appropriate advice initiated. Thus the management of gout patients should start from patient education, weight loss (14) and control of other risk factors.

The underlying pathophysiologic process can be distinguished into phases of asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. Hyperuricemia is typically defined as increased serum uric acid levels more than 6.8 mg/dl. Although hyperuricemia is a predisposing factor (15) for both gout and uric acid renal calculi but it is important to distinguish between "asymptomatic hyperuricemia "and clinical gout. A study involving around 2000 healthy men were followed with serial uric acid levels and clinical examination for almost 15 years found annual rate of gouty arthritis to be less than 5 % with serum uric acid levels of 9 mg/dl or more and only 0.5 % for uric acid levels between 7.0 to 8.9 mg/dl (15).All cases of hyperuricemia need not be treated with urate lowering therapy. (16). Those not accompanied with musculoskeletal complains should be monitored with diet and life style modification.

EULAR guidelines recommend allopurinol as a cost effective ,first line agent for urate lowering therapy in patients with normal renal function (18). Allopurinol therapy significantly reduces serum uric acid levels,(19) reduced episodes of acute flare (20) and decrease in tophus (21).

In our study we observed that in some cases the physicians had targeted serum uric acid levels diligently and made efforts to bring them down below 6.0 mg/dl. However a large number of doctors tent to start with a dose of 300 mg per day of allopurinol.

More appropriately, allopurinol should be started with 100 mg daily and gradually increased every 2 to 4 weeks to a target serum uric acid (22, 23).Although allopurinol can be given as high as 800 mg daily dose, however in most instances dosage exceeding 300 mg daily dose is not used.(24). The gradual up-titration of allopurinol prevents acute attacks of gout which occur when serum uric acid levels fall rapidly due to mobilization of urate from tissue deposits. (25). It is important to concurrently use other agents like naproxen and colchicine to reduce acute flares after initiating ULTs.

Allopurinol is the most commonly used urate lowering agent, however caution needs to be exercised while prescribing in patients with renal impairment. There is a risk of allopurinol hypersensitivity syndrome that occurs more often in presence of azotemia due to increased concentration of a metabolite, oxypurinol.(26)Previous studies reported inappropriately higher allopurinol doses in patients with renal insufficiency, 47 % in elderly adults and 39% in adults. Our study also observed that blood urea and serum creatinine levels were done in only

20 % of patients whose prescription has been audited. One of the difference may be that our population was younger. However it is imperative that the renal function be assesses in gout and dosage modification in patients with azotemia.(26, 27) This was assessed in same cases where dosage of allopurinol has been reduced in our study on observing presence of azotemia.In one of the recently published large series systematic review on allopurinol hypersensitivity, including over 800 cases published between January 1950 and December 2012 indicated that factors associated with AH, such as concomitant diuretic use, pre-existing renal impairment and recent initiation of allopurinol. (28)Another risk factor was the HLA-B*5801 status in causing allopurinol induced Steven Johnson syndrome and toxic epidermal necrolysis, this becomes significant in Asian populations where there is a higher carriage rate of the allele.(29-31)

Allopurinol can induce bone marrow suppression if co administered with agents- azathioprine or 6 mercaptopurine. (32)It can also increase the drug levels of warfarin and cyclosporine mandating close monitoring.

JA Singh et al(33) found deficiencies in the quality of care provided to veterans with diagnosis of gout. They observed that deficiencies were most prominent in laboratory monitoring for efficacy and side effects, but were also remarkable for dose adjustments for renal failure. They observed that for 22% of their patients with real insufficiency received higher that recommended allopurinol doses, similarto the 25 % non-compliance rate found in earlier studies.

Febuxostat, a non-purine analogue is a potent and selective xanthine oxidase inhibitor used as ULT in patients of gout specially who are intolerant to allopurinol. (34). It is used in usual dosage of 40 to 80 mg daily orally to as high as 80 to 120 mg daily in case of persistently elevated uric acid levels even after two weeks of therapy. The primary mode of elimination is hepatic hence it should be used with great caution in cases of liver impairment.

The other group of drugs- uricosuric agents which include probenecid ,sulfinpyarazaone are efficacious in patient whom uric acid excretion is less than 800 mg/day. However their benefits are negated in presence of renal insufficiency.(35) Their action is by inhibition or renal tubular urate reabsorption and promoting renal urate elimination. (36)Uricosurics can be used as useful adjuncts to xanthine oxidase therapy. (37)
It is apt to conclude that the prescriber must check urea and creatinine levels and adjust dosage of allopurinol after seeing azotemia otherwise patient will develop adverse effects of allopurinol which are uncalled for.

The earlier recommendations for management of gout were issued 10 yrs ago by European league against rheumatism (EULAR). The first recommendation by the American college of rheumatology were published in 2012. In between, British Society for Rheumatology (BSR) published recommendation in 2007. The editorial has highlighted that the main problem with various recommendations is not in their content, but in their implementation. The recommendation needs to be disseminated to health care workers and implemented in day to day practice.

The serum uric acid above which crystals form is the saturation point of uric acid that varies with the temperature, the lowest value being 360 mmol/L (6.0 mg/dl). If the saturation threshold is reached ,uric acid crystallize and the monosodium urate crystals , called tophi can deposit in joints , tendons, cartilage and surrounding tissues with an inflammatory response.(38)This value therefore is targeted when uric acid levels in the blood falls below 360 mmol/L(6.0) mg/dl) , microcrystals dissolve.(39)Evidence also indicates that targeting and maintaining uric acid levels below 6.0 mg/dl may result in depletion of total uric acid body stores. (40)However on the other hand uric acid levels can be normal or even low in almost one third of patients presenting as acute attacks (41).

Colchicine is a useful drug in management of acute gout. Even in our study colchicine has been used in acute attacks of gout as a single agent or in combination with NSAID's. (25). Colchicine in low dosage is recommended in treatmentof acute attack of gout. Oral colchicine therapy is one of the preferred first line treatment for acute gouty attacks in new ACR recommendations. Recent evidence suggests that that low-dose colchicine in patients with a history of coronary heart disease could reduce the incidence of major cardiovascular events.(42) Long term adherence is crucial for the best results in gout .(43) Physicians must educate patients effectively and elaborate lyabout the drugs used and the principles of management of gout. These can have remarkable results.A pilot study done in Nottingham, UK involved one hour of patient information before starting allopurinol. This was followed by telephone or face to face interviews with ameans to improve patient adherence. After 1 year, 92 % of patient achieved target serum uric acid levels < 6 mg /dl and 85 % had levels <5 mg/dl . This study emphasizes that gout can be successfully controlled, not by using new drugsbut by having physicians and nurses spend enough time educating the patients. In our study also many patients had been explained well about adherence to allopurinol therapy and advice about diet was given effectively to them. However, strict adherence to therapy is crucial. (46)

Limitation of our study-

Our study was observational cross-sectional study. It did not have follow up of patients unlike other studies which had followed up patients for a long period of time. But nevertheless it gave an insight into the prescription practice of doctors in eastern India and lacunae which prevail and considering lack of data in this field a study of this nature will prove useful.

Conclusion

It was observed that in some of patients of gouty arthritis, allopurinol and febuxostat are being prescribed during acute attack of gouty arthritis. This is inappropriate practice. In addition, dietary advice was rendered to patients to stop pulses, milk and milk products and certain vegetables which is incorrect and not evidence based. Also, starting Tab Allopurinol and Tab Febuxostat in asymptomatic hyperuricaemia is also not supported by evidence. BP recording was not done routinely. Weight was also not recorded usually. It was observed that a sizable number of patients were evaluated for blood sugar levels, blood urea, serum creatinine and lipid profile. USG Abdomen to see for renal calculi was however not done in majority of patients.Recording of blood pressure,height and weight of the patient also needs to be recorded regularly.

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