Comparative Study of Allopurinol and Uralyt-4 in patients with Hyperuricemia in Diyala Governorate

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Summary:

Background: Hyperuricemia represents a major public health problem; approximately most population has hyperuricemia, serum uric acid ≥6.5 mg/dL in women and ≥7.0 mg/dL in men. Allopurinol has been approved for the treatment of hyperuricemia patients. Epidemiological and experimental studies suggest a linkage between hyperuricemia and type of treatment.

Objective: To assess the effect of allopurinol and uralyt- 4 and mixture of two drugs (allopurinol and uralyt-4) in hyperuricemia patients

Methods: A total of 60 serum patients with history of hyperuricemia, obtained from Baladrus Hospital in Diyala governorate, were included in this study. In addition, ten normal uric acid level persons used as control group. Serum used for uric acid. We used two type of treatment to compare the effective of each one to treat patients with hyperuricemia, patients were divided into three groups first one treated with allopurinol at 300mg/day, second group treated with uralyt-4 at 10 mg/day for three time daily while the third group treated with mixture of allopurinol and uralyt-4. Level of uric acid measured after 4 weeks and 8 weeks by enzymatic colorimetric method

Results: The present study, patients had a mean age of 44.5±0.12 years, significant differences noticed between three age groups. The percentage of males equal to females. Urate concentration was more likely to be lower in patients receiving mixture of allopurinol and uralyt-4 comparing with patients receiving single drug such as allopurinol or uralyt-4. But statistical significant differences were not found among them.

Conclusion: allopurinol was effective in reducing serum urate in hyperuricemic patients with gout but combination 0f Uralyt-4 (10 mg/d) allopurinol were more efficacious compared with allopurinol (300 mg/d). The doses of allopurinol to which Uralyt-4 has been compared, although commonly prescribed, are low in the range of approved doses of allopurinol. The tolerability of Uralyt-4 for the treatment of hyperuricemia is similar to that of allopurinol.

Key word: Hyperuricemia, Allopurinol, Uralyt-4

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Introduction:

Hyperuricemia, an integral component of metabolic syndrome, is a major health problem causing gout and renal damage. Urine alkalizers such as citrate preparations facilitate renal excretion of the uric acid, but its supportive effect on xanthine oxidase inhibitors has not been tested yet [1]. Uric acid is an independent predictor of mortality and cardiovascular events in both high-risk patients, such as those with heart failure [2] and diabetes [3], and the general population [4-6]. Serum uric acid is commonly elevated in subjects with chronic kidney disease (CKD), but was historically viewed as an issue of limited interest. Recently, uric acid has been resurrected as a potential contributory risk factor in the development and progression of CKD [7]. Hyperuricemia is a common complication after kidney transplantation that may adversely affect graft survival [8].Hyperuricemia is associated with cardiovascular disease, but it is usually considered a marker rather than a risk factor. Previous studies using uric acid-lowering drugs in normouricemic animals are not suitable to answer the effect of hyperuricemia on ventricular remodeling after myocardial infarction [9].Allopurinol is a widely used urate-lowering therapy (ULT) in patients with gout and hyperuricaemia. The therapeutic aim is to lower serum urate levels and prevent the precipitation of urate crystals. Clinical studies have shown that maintaining serum uric acid levels - 6.0 mg dl-1 (or - 0.36 m mol l-1) results in a reduction in the incidence of gout flares, decreased numbers of urate crystals in aspirated fluid from joints and reductions in size and number of tophi [10-12]. Allopurinol improves endothelial function, defects in which are known to be associated with progression of cardiovascular disease [13]. This drug is usually well tolerated and lowers serum urate in the order of 20%. However, despite allopurinol-associated urate lowering, recurrent attacks may still occur. Furthermore, hypersensitivity rashes can be problematic, despite attempts at desensitization. Additional urate-lowering therapies may therefore be required. Alternative drugs for preventing gout include the uricosuric agentssulphinpyrazone,

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limited by its side-effect profile, and benzbromarone and probenecid, the availabilities of which are restricted in certain European countries.So this study designs to investigate the effect of Allopurinol and Uralyt-4 and mixture of both of them in patients with hyperuricaemia and study the correlation with age and gender

Patients and Methods:

Patients and samples: The study included 60 serum patients with a history of hyperuicemia that were selected from the Baladrus hospital in Diyala Governorate, during the period from January 2012 till May 2013. Patients gender included 30 males (50%) and 30 females (50%), age ranged from 40-65 years with a mean age of 44.5±0.12. All patients had high level of serum uric acid by used enzymatic colorimetric method. Normal serum specimens were obtained from ten healthy looking controls group of the same age groups as control group used for compared.

Study design: The patients divided into three groups according to type of therapy, first group (A) each patients had been received allopurinol at dose 300 mg/daily. Second group (B) each patients had been received uralyate-4 at a dose 10 mg / three time daily, while the last group (C) each patients had been received allopurinol and uralyt-4 together.Clinical and biochemical assessments were performed: (I) without any therapy, (II) after 4 weeks of once-daily therapy with allopurinol at 300 mg for group A, three times daily of uralyt-4 at a dose 10 mg for group B and mixture of the two therapy for group C, (III) after 8 weeks of receiving the therapy for each group.Blood sample was drawn by vein puncture using disposable 5 ml syringe, then the blood transferred into plain plastic test tube and left to clot at room temperature, then spun at 3500 rpm using ordinary centrifuge. Finally the sera were collected and labeled and stored at -20 ˚C for subsequent analysis, enzymatic colorimetric method used for measuring uric acid. Preparation of three tubes, first one blank tube contains only 1.0 ml of RI. Mono reagent, the second is sample tube which contains 1.0 ml of RI. Mono reagent and 25 µl serum patients while the third tube is CAL. Standard which contains1.0 ml of RI. Mono reagent and 25 µl CAL. Standard, mixed and incubated for 10 minutes at room temperature. This process was done in dark room, and then the absorbance (A) of the samples and the standard was read at 520 nm against the reagent blank. Samples with concentrations higher than 20 mg/dl was diluted 1:5 with saline and assayed to be multiplied by a factor of 5 used specific law to find the value.

Statistical analysis: was performed using the t-test with Fischer exact test for quantitative parameters such as age of patients, also used chi-Squared test for qualitative parameters, such as gender and others.

Results:

Patients details: Sixty cases of hyperuricemic patients with gout, 30 males (50%) and 30 females 50%), the percentage of males was equal to females. Age of patients with gout and hyperuricemia ranged from 40 to 65 years. Mean age of patients was (44.5 years). When comparing with healthy control group was (53.41 years) as show in Table (1), there was a highly significant difference (P<0.0005) noticed between both groups.

Table(1): Mean age distribution among patients with gout and hyperuricemia.

Studied groups	Number	Age Range			(t-test)/ P-value*
		Mean	Mini	Maxi	
Control	10	53.41±0.36	40	65	31.92
Hyperuricemic patients	60	44.5±0.12	40	65	54.88

*Highly significant (P<0.0005)

As showen in (Table 2) a significant difference was noticed betweenthree age groups, 51-60 years was the highest percentage (40%), while 61-70 years was the lower percent (23.3%).

Table (2): Distribution of patients with gout and hyperuricemia according to their age strata.

Age stratum	Number	Percentage	Comparison of Significance	
			Chi^2-value	Sig.
40-50	22	36.6%	Sig. 4.800	P<0.0005
51-60	24	40%		
61-70	14	23.3%		
Total	60	100%		

*Significant (P<0.0005)

Statistical analysis showed no significant difference (P>0.05) between gender and urate concentration as shown in table (3)

Table (3): Level of uric acid (mg/dL) of gout and hyperuricemic patients and control.

Study group	Male	Female	Comparison of Significance	
			P-value	Sig.
Control (10)	5.26	4.13	0.016	Non. Sig.
Patients(60)	8.50	8.04		

*Non-significant (P>0.05)

There were 60 study subjects of these 20 were on allopurinol treatment, 20 were on uralyat-4 and 20 patients were on mixture of (allopurinol and uralyat-4) as shown in table 4.The results of statistical analysis showed no significant differences (P>0.05)

between gender and types of treatments after 4 weeks of treatment.

Table (4): Effect of allopurinol, uralyt-4 and mixture of (allopurinol and uralyt-4) on level of uric acid(mg/dL) after 4 weeks of treatment.

Allopurinol	*Uralyt-4*	*Mixture (A & U)*	P-value
Male 5.73	6.08	4.84	
Female 5.01	5.26	4.36	0.001
Total 60(100%)			

*Non-significant (P>0.05)

Urate concentration was more likely to be lower in patients receiving mixture of Allopurinol and uralyt-4 comparing with patients receiving single drug such as allopurinol or uralyt-4. However statistical significant differences were not found among them as shown in Table (5).

Table (5): Effect of allopurinol, uralyt-4 and mixture of (allopurinol and uralyt-4) on level of uric acid mg/d after 8 weeks of treatment.

Allopurinol		*Uralyt-4*	*Mixture (A & U)*	P-value
Male	4.89	5.48	4.26	
Female	4.27	5.11	3.62	1.80
Total 60(100%)				

*Non-significant (P = 1.80)

Discussion:

In this study it was found that allopurinol used to treat hyperuricemic patients with gout is associated with reduced urate concentration. This finding was in agreement with others which indicated that allopurinol decreased serum uric acid levels by inhibiting the enzyme xanthine oxidase [15]. A study performed by Wei *et al*., (2011) suggested that high dose allopurinol may be associated with reduced risk of mortality and cardiovascular events through its patho-physiological pathology [16]. However, it is not clear whether this finding extends to all patients on allopurinol [17]. More recently, Luk *et al*. reported a significant survival benefit of allopurinol treatment in hyperuricaemic patients [18]. We also observed this benefit in results of this study. Another study had done by Kelley (1975) indicated that a reduction in the serum urate concentration in hyperuricemic subjects can be achieved by increasing the renal excretion of uric acid, by inhibiting its synthesis, or by a combination of both modalities. The three most commonly used hypouricemic drugs are probenecid, sulfinpyrazone and allopurinol. Each drug has been considered in detail with regard to its mechanism of action, metabolism, diverse metabolic effects, side effects and interaction with other drugs [19]. The present study was a performed on all patients having elevated urate concentration, to determine the effect of allopurinol and uralyt-4 and mixture of both of them after 4 and 8 weeks. This is the first time that combinations between two drugs (allopurinol and uralyt-4) are used in hyperuricaemic patients. Many study performed by use different drugs such as study done by Feher *et al*., (2003), who assessed the short urate-lowering effect of fenofibrate in men on long term allopurinol therapy for hypericaemia and got [14]. This combination may be related with treatment of uric acid is not always benign. For example, allopurinol therapy can be associated with fatal Stevens-Johnson syndrome, and, while screening for HLA-B68 may allow the elimination of subjects at highest risk for this condition [20], this procedure is rarely done. Allopurinol may also accumulate in subjects with a low eGFR. The new xanthine oxidase inhibitor, febuxostat does not appear to be associated with Stevens-Johnson-syndrome to date, and its dosage does not need to be modified in chronic kidney disease. It may also be more effective at lowering the uric acid level in the setting of CKD [21].Another study had done by Becker *et al.* (2010), who comprised 1072 patients with gout, serum uric acid >8 mg/dL and either normal serum creatinine or serum creatinine 1.5-2 mg/dL. Patients were randomized to febuxostat (up to 240 mg/day) and allopurinol (100-300 mg/day) and indicate no difference in side effects between the groups but low dose should be initiated and the dosage increased slowly over 4-8 weeks [22]. The results of present study revealed that serum uric acid levels were significantly decreased in subjects treated with allopurinol and uralyt-4 but combination of these two drugs showed a more powerful effect to reduce urate level than if either drug was used alone. This may be related with the effect of uralyt-4 (potassium sodium hydrogen citrate) it's used to treat many diseases due to no side effects have so far been reported, but not recommend for patients with acute or chronic renal failure, metabolic alkalosis and chronic urinary tract infections with urea-splitting bacteria. In conclusion, allopurinol was effective in reducing serum urate in hyperuricemic patients with gout but combination of uralyt-4 (10 mg/day) and allopurinol were more efficacious compared with allopurinol (300 mg/day) alone. Further investigation is needed with large sample size and study the correlation with certain risk factors, such as lifestyle, i.e. body mass index, infection with other disease to clarify this issue.

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