The Efficacy of Combined Low Dose of Allopurinol and Benzbromarone Compared to Standard Dose of Allopurinol in Hyperuricemia

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Objective : *To compare the efficacy of combined low dose of hypouricemic drugs (Allopurinol 100 mg and benzbromarone 20 mg; Allomaron) and standard dose 300 mg of allopurinol in hyperuricemia.*
Material and Method : *A prospective, open study of 94 hyperuricemic patients was done at King Chulalongkorn Memorial Hospital. Each group of 47 patients was given a combined low dose of hypouricemic drugs (Allopurinol 100 mg and benzbromarone 20 mg; Allomaron) and a standard dose 300 mg of allopurinol. Serum uric acid was measured before and 4 weeks after receiving the drugs. The efficacy was measured from the difference of the level of serum uric acid before and after receiving the drugs.*
Results : *The patients receiving the combined low dose of hypouricemic drugs and standard dose of allopurinol showed a mean reduction of serum uric acid of 2.5 $\pm$ 3.4 mg/dl and 4.1 $\pm$ 2.7 mg/dl consecutively. There was a statistically significant difference between the 2 groups (P = 0.010).*
Conclusion : *This study demonstrates that the efficacy of standard dose 300 mg of allopurinol is superior to a combined low dose of allopurinol and benzbromarone in lowering the level of serum uric acid level.*

Keywords : *Allopurinol, Benzbromarone, Allomaron, Hyperuricemia*

J Med Assoc Thai 2004; 87(9): 1087-91

Hyperuricemia is a common problem in clinical practice. It is defined as serum uric acid level of more than 7.0 mg/dl in men or more than 6.0 mg/dl in women. The incidence of hyperuricemia varies from 2-7 percent based on a study population[1,2], and 13-28 percent in routinely screened hospitalized patients[3,4].

Hyperuricemia may occur in a wide variety of conditions, genetic or acquired, metabolic or renal, symptomatic or asymptomatic. Most patients with hyperuricemia are asymptomatic and never develop gout. The risk of gout increases with an increasing serum uric acid level. In patients with a serum uric acid level of more than 10 mg/dl, the 5-year prevalence of gout is 30 percent, in those with a level less than 7 mg/dl, the prevalence is 0.6 percent[5]. Hyperuricemia is frequently associated with other metabolic perturbations, such as hypertension, dyslipidemia, type 2 diabetes mellitus, renal disease, and obesity. Whether hyperuricemia plays a causal role or is an epiphenomenon is currently unknown. One previous study showed an increased risk ratio for death from all causes in patients with an elevated serum uric acid level[6]. The lowering of the serum uric acid is necessary in patients with clinical symptoms associated with hyperuricemia and occasionally in certain asymptomatic subjects.

The serum uric acid may be diminished by drugs which act either by decreasing the production of uric acid (Xanthine oxidase inhibitors e.g. allopurinol) or by increasing its renal excretion (Uricosuric drugs e.g. probenecid, sulfinpyrazone, and benzbromarone). Allopurinol has been widely used in clinical practice because it has been used for a long time and can be used conveniently with a once daily dosage. The dose of allopurinol may vary from 100 to 900 mg/day, but the regularly prescribed dose is 300 mg/day in normal renal function[7,8]. Probenecid has a short half life and multiple drugs interaction. Sulfinpyrazone has a short half life and some serious

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side effects such as blood dyscrasia. Benzbromarone can be administered in a once-a-day schedule, and previous reports showed it to be more effective than allopurinol in lowering serum uric acid[9-12]. A combination of xanthine oxidase inhibitors and uricosuric drugs has been occasionally used in hyperuricemia. A fixed combination of allopurinol 100 mg and benzbromarone 20 mg (Allomaron) has been available more than 20 years, but there has been no report in the English literature in the aspect of comparison of the efficacy with a standard dose of allopurinol. This study aimed to compare the efficacy of the fixed combination of allopurinol 100 mg and benzbromarone 20 mg (Allomaron) to a standard dose of 300 mg of allopurinol.

Material and Method

A prospective, open, clinical trial was carried out in patients consecutively who came to the out-patient rheumatology clinic, King Chulalongkorn Memorial Hospital. The following conditions had to be met for the patients to be considered for inclusion in the study.

- Age 15 years old or more.
- Serum uric acid level above 7 mg/dl.
- Serum creatinine less than 1.5 mg/dl.
- No significant liver disease.
- Absence of concomitant diseases or treatments known to cause hyperuricemia.
- Absence of concomitant drugs known to have uriccosuric effect or interfere with the efficacy or metabolism of allopurinol or benzbromarone (such as salicylates, diuretics, amiodarone, or pyrazinamide etc.)

The exclusion criteria included pregnancy, abnormal liver function test, leucopenia (white blood cell count less than 4000 cells/mm^3), history of sensitivity to allopurinol or benzbromarone.

Before entering the study, history and physical examination was done in all patients, and blood samples were drawn before and 4 weeks after treatments to assess serum uric acid, complete blood count (CBC), blood urea nitrogen (BUN), creatinine (Cr), and liver function test (serum alanine amino-transferase and serum aspartate aminotransferase). Every patient had no acute arthritis at least 1 week before entering the study. The patients who already took hypouricemic drugs were asked to stop the drugs for at least one month before entering the study. The patients were randomized into 2 groups. One group received allopurinol 300 mg once a day (Allopurinol group) and the other received one tablet of fixed combined low dose of allopurinol 100 mg and benzbromarone 20 mg (Allomaron) once a day (Combined low dose group). Each group received the drug for one month, and blood samples were drawn again at the same laboratory as checked before. Colchicine 0.6 mg/day was prescribed to all of the patients for prophylaxis of an attack of acute gouty arthtritis.

Statistical analysis was made with a statistical microcomputer program SPSS 7.5. Descriptive statistics were used to characterize the patients. Results are presented as mean, standard deviation (SD), and percent. Difference in the means of variable between the two treatment groups was assessed by unpaired t-test.

Results

Ninety four patients were enrolled and completed the study. Each group had 47 patients. Mean age $\pm$ SD of the allopurinol and combined low dose groups were 59.2 $\pm$ 11.0 (range 33-79) years and 54.1 $\pm$ 12.17 (range 31-80) years consecutively. There were 44 (94%) and 41 (91%) male patients in the allopurinol and combined low dose group consecutively. All of the patients in the allopurinol group had symptomatic hyperuricemia while 41 (91%) were symptomatic in the combined low dose group, but there was no significant statistical difference between the 2 groups. Duration of hyper-uricemia before being enrolled in the study was 62.4 $\pm$ 40.5 (range 12-120) and 64.1 $\pm$ 86.4 (range 0.1-312) months in the allopurinol and the combined low dose group consecutively. Table 1 shows the data of age, sex,

Table 1. Characteristics of all patients and comparison between allopurinol and combined low dose groups

Characteristics	Allopurinol	Combined low dose	P value
Number	47	47	-
Age in years			
mean $\pm$ SD	59.2 $\pm$ 11.0	54.1 $\pm$ 12.7	0.001
Sex			
Male (%)	94	91	NS
Female (%)	6	9	
Type of hyperuricemia			
Symptomatic (%)	100	87	NS
Asymptomatic (%)	0	13	
Duration of hyperuricemia (months)	62.4 $\pm$ 40.5	64.1 $\pm$ 86.4	NS

type and duration of hyperuricemia between the two groups.

There was no significant difference in mean serum uric acid before starting the treatments in the allopurinol (10.4 ± 1.9, range 7.3-16.1 mg/dl) and combined low dose (9.6 ± 3.7, range 7.6-18.7 mg/dl) groups. The mean serum uric acid after the treatments were 6.3 ± 1.2 (range 3.4-8.7) mg/dl and 7.2 ± 1.8 (4.3-10.0) mg/dl in the allopurinol and the combined low dose groups respectively. The mean difference of serum uric acid before and after the treatments were 4.1 ± 2.4 (range 0.9-12.7) mg/dl and 2.5 ± 3.4 (range 0.6-9.2) mg/dl in the allopurinol and the combined low dose groups respectively. There was a significant difference (P = 0.010) in the efficacy in lowering uric acid levels comparatively between the two groups. The results are shown in Table 2.

None of the patients had an acute attack of arthritis during and one month after the study. There were no clinical adverse drug reactions. Only two patients in the allopurinol group and one patient in the combined low dose group showed a slight increase in serum alanine aminotransferase and serum aspartate aminotransferase but the levels increased less than twice the normal limits. CBC and BUN/Cr were within normal limits after the treatments.

Table 2. Serum uric acid levels before and after treatment with allopurinol and combined low dose

Serum uric acid levels (mg/dl)	Allopurinol	Combined low dose	P value
Before treatment	10.4 ± 1.9	9.6 ± 3.7	NS
After treatment	6.3 ± 1.2	7.2 ± 1.8	-
Difference between before and after treatment	4.1 ± 2.4	2.5 ± 3.4	0.010

Discussion

Oral hypouricemic drugs have been used for lowering serum uric acid for a long time. Xanthine oxidase inhibitors and uricosuric drugs are two groups of oral hypouricemic drugs. Allopurinol has been widely used in clinical practice since 1963. It is a potent inhibitor of uric acid synthesis. The dosage can vary from 100-900 mg/day. A previous study showed that a dose of 300 mg/day of allopurinol reduced serum uric acid to normal values in 85 percent of patients with hyperuricemia and gout, and in some patients a dose of 100-200 mg/day was adequate[7]. Benzbromarone is a very potent uricosuric drug that is widely used outside the U.S. Its mechanism of action is similar to that of probenecid and sulfinpyrazone, but is much more effective in renal insufficiency than either of the other uricosuric drugs. The medication is administered in a once-a-day schedule, with the dose ranging from 20-120 mg[13-15].

There have been only a few studies of the combination of xanthine oxidase inhibitor and uricosuric drug in hyperuricemia[16-18]. The reason for the combination of two groups of hypouricemic drugs may be the different site of action, and may have a synergistic effect. Most of the studies are the combination of allopurinol and probenecid, or a combination of allopurinol and sulfinpyrazone[17,18].

Comparison of the efficacy of allopurinol with uricosuric drugs in lowering serum uric acid have been shown in previous studies. Allopurinol was superior to probenecid in one study[19], but there was no difference in another study[20]. Benzbromarone 100 mg/day was significantly superior to both allopurinol 300 mg/day and probenecid 1000 mg/day in one study [9]. The other studies showed that benzbromarone was more effective than allopurinol[10-20].

The present study demonstrates that hyperuricemia is more frequent in males than females. Mean age is more than 50 years old. Most of the patients were symptomatic and had a long duration of hyperuricemia. Regarding the comparative efficacy of these two groups of drugs, it has been shown that allopurinol 300 mg is significantly superior to the combined low dose of allopurinol 100 mg and benzbromarone 20 mg in lowering serum uric acid level (P = 0.010). This may be explained that the dosage of the combined low dose recommended by the pharmaceutical company may be inadequate and may be adjusted by monitoring the level of serum uric acid.

Concerning the adverse drug reactions, there were no clinical side effects in any of the patients. There was only a slight increase in serum alanine aminotransferase and serum aspartate aminotransferase but the levels increased less than twice the normal limits. However, it cannot be concluded because the duration of follow up was only one month. The increase of serum alanine aminotransferase and serum aspartate aminotransferase may come from either allopurinol or benzbromarone[8].

From the present study, the authors conclude that allopurinol 300 mg/day is superior to one tablet daily of the fixed combination of allopurinol 100 mg and benzbromarone 20 mg. However, the dosage of the drugs may be adjusted properly by monitoring the level of serum uric acid.

Acknowledgment

The authors wish to thank Dr.Wanla Kulwichit and Ms.Sujinda Jaisai for preparing the manuscript.

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ประสิทธิภาพของยาผสมขนาดต่ำของอัลโลพูรินอลกับเบนซ์โบรมาโรนเปรียบเทียบกับยาอัลโลพูรินอลขนาดมาตรฐานในผู้ป่วยที่มีระดับกรดยูริคในเลือดสูง

สมชาย อรรฆศิลป์, มนาธิป โอศิริ, อุทิศ ดีสมโชค, ยิ่งยศ อวิหิงสานนท์

วัตถุประสงค์ *: ศึกษาประสิทธิภาพในการลดระดับกรดยูริคในเลือดของยาผสมขนาดต่ำของอัลโลพูรินอล 100 มก. กับเบนซ์โบรมาโรน 20 มก.เปรียบเทียบกับยาอัลโลพูรินอลขนาดมาตรฐาน 300 มก. ในผู้ป่วยที่มีระดับกรดยูริคในเลือดสูง*

วิธีการศึกษา *: ผู้ป่วยที่มีระดับกรดยูริคในเลือดสูงจำนวน 94 ราย เข้าร่วมในการศึกษาแบบเปิดชนิดไปข้างหน้าที่โรงพยาบาลจุฬาลงกรณ์ โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มละ 47 ราย กลุ่มที่ 1 ได้รับยาผสมของอัลโลพูรินอล 100 มก. กับเบนซ์โบรมาโรน 20 มก. (ชื่อการค้าคืออัลโลมารอน) กลุ่มที่ 2 ได้รับยาอัลโลพูรินอล 300 มก. โดยทั้ง 2 กลุ่มจะได้รับยา 4 สัปดาห์ ได้ทำการตรวจระดับกรดยูริคในเลือดก่อนและหลังได้รับยาเพื่อเปรียบเทียบประสิทธิภาพในการลดระดับกรดยูริคของยาทั้ง 2 กลุ่ม*

ผลการศึกษา *: ผู้ป่วยกลุ่มที่ได้รับยาผสมของอัลโลพูรินอล 100 มก. กับเบนซ์โบรมาโรน 20 มก. มีระดับกรดยูริคในเลือดลดลง 2.5 $\pm$ 3.4 มก./ดล ในขณะที่อีกกลุ่มลดลง 4.1 $\pm$ 2.7 มก./ดล. ซึ่งมีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($P = 0.010$)*

สรุป *: การศึกษานี้พบว่ายาอัลโลพูรินอล 300 มก. มีประสิทธิภาพในการลดระดับกรดยูริคในเลือดสูงกว่ายาผสมของอัลโลพูรินอล 100 มก. กับเบนซ์โบรมาโรน 20 มก. ในผู้ป่วยที่มีระดับกรดยูริคในเลือดสูง*