Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout

F Perez-Ruiz, A Alonso-Ruiz, M Calabozo, A Herrero-Beites, G García-Erauskin, E Ruiz-Lucea

Abstract

***Objectives*—To study the efficacy of allopurinol and benzbromarone to reduce serum urate concentrations in patients with primary chronic gout.**

***Methods*—Prospective, parallel, open study of 86 consecutive male patients with primary chronic gout. Forty nine patients (26 normal excretors and 23 under excretors) were given allopurinol 300 mg/day and 37 under excretors benzbromarone 100 mg/day. After achieving steady plasma urate concentrations with such doses, treatment was then adjusted to obtain optimal plasmatic urate concentrations (under 6 mg/dl).**

***Results*—Patients receiving allopurinol 300 mg/day showed a mean reduction of plasmatic urate of 2.75 mg/dl (from 8.60 to 5.85 mg/dl) and 3.34 mg/dl (from 9.10 to 5.76 mg/dl) in normal excretors and under excretors respectively. Patients receiving benzbromarone 100 mg/day achieved a reduction of plasmatic urate of 5.04 mg/dl (from 8.58 to 3.54 mg/dl). Fifty three per cent of patients receiving allopurinol and 100% receiving benzbromarone achieved optimal plasma urate concentrations at such doses. The patients with poor results with allopurinol 300 mg/day achieved a proper plasma urate concentration with allopurinol 450 to 600 mg/day, the mean final dose being 372 mg/day. Renal fuction improved and no case of renal lithiasis was observed among benzbromarone treated patients, whose mean final dose was 76 mg/day.**

***Conclusion*—Benzbromarone is very effective to control plasma urate concentrations at doses ranging from 50 to 100 mg/day. Uricosuric treatment is a suitable approach to the treatment of patients with gout who show underexcretion of urate.**

(*Ann Rheum Dis* 1998;**57**:545–549)

Rheumatology Section
F Perez-Ruiz
A Alonso-Ruiz
M Calabozo
E Ruiz-Lucea

and Nephrology Division
G García-Erauskin

Hospital de Cruces, Pais Vasco, Spain
Rehabilitation Division, Hospital de Gorliz, Pais Vasco, Spain
A Herrero-Beites

Correspondence to:
Dr F Perez-Ruiz, Sección de Reumatología, Hospital de Cruces, Pza de Cruces sn, 48903 Barakaldo, Vizcaya, Spain.

Accepted for publication
8 July 1998

The clinical manifestations of gout are linked to the formation of monosodium urate (MSU) crystals, which are both responsible for the inflammatory manifestations as well as the joint damage produced by tophi. The aim of antihyperuricaemic treatment in chronic gout is to reduce plasma urate concentrations below the threshold of supersaturation of the extracellular tissue to stop the deposition of MSU crystals and allow the dissolution of existing ones. This is clearly stated in most textbooks and reviews published during the past 50 years.[1–7]

The evidence of when to start urate lowering drug (ULD) treatment is conflicting: most authors support that ULD treatment should be considered after a first episode,[3] some advocate that only patients who suffer more than four episodes/year should be given ULDs,[8] and others that such a decision should be on an individual patient basis.[9] However, most authors agree that patients with chronic gouty arthritis with or without articular or soft tissue tophi should be given ULDs.[2–7 9–11] Recently, Ferraz and O'Brien have shown that "ULD treatment is cost effective, and cost saving in patients that present 2 or more recurrent attacks per year".[11] Three questions arise then for physicians and patients: which drug? (should be prescribed), how much? (should plasma urate be lowered), and how long? (should it remain low)?

Despite the fact that benzbromarone and allopurinol have been available for the treatment of gout for more than 20 years in Europe, we could not find a comparative study in the literature (MEDLINE search). This study was carried out to compare the efficacy of allopurinol and benzbromarone, in lowering plasma urate concentrations below those considered therapeutic for the dissolution of MSU crystals in tissues,[12–16] using a pathogenic approach.

Methods

A prospective, parallel, open study was carried out in patients consecutively referred to a hospital rheumatology unit. The following conditions had to be met for the patients to be considered for inclusion in the study: (1) the 1977 ARA criteria for the classification of gout[17]; (2) the patient not to have received urate lowering treatment one month before entering the study; (3) absence of concomitant treatment or disease known to cause hyperuricaemia; (4) avoidance of drugs known to have uricosuric effect or interfere with the efficacy or metabolism of allopurinol or benzbromarone (such as salicylates, diuretics or amiodarone); (5) no significant liver disease or renal disease (clearance of creatinine should be over 60 ml/min/1.73m^2).

Before entering the study all patients had complete blood cell count, liver function, plasmatic urate (Pur), plasmatic creatinine (Pcr), clearance of creatinine (Ccr), clearance of urate (Cur), and urinary uric acid excretion (24 h Uur) on unrestricted purine diet. Ccr, Cur, and 24 h Uur were calculated using a 24 hour urine

sample and normalised for a body surface area of 1.73 m^2. Plasmatic and urinary uric acid determinations were performed by uricase method (Boehringer-Manheim). Prophylaxis of gouty episodes was prescribed to all patients: colchicine 1 mg/day (or diclofenac 50 mg/day when a previous history of adverse effects or intolerance to colchicine was present) up to three months after an optimal level of Pur was achieved.

Patients were asked to avoid alcoholic beverages and take a normocaloric, unrestricted purine diet. A hypocaloric diet (2000 kcal/day) was prescribed to patients who were overweight. Alcohol intake and being overweight have been shown to correlate to poor control of plasma urate concentrations.[18 19] The Cur was considered normal when it exceeded 6 ml/min/1.73m^2 [20 21] and patients were classified as normoexcretors (overproducers) when they showed Cur 6ml/min/1.73m^2, and as underexcretors when Cur<6ml/min/1.73m^2. Patients showing overproduction were given allopurinol 300 mg orally once a day. Also patients with underexcretion of urate were treated with allopurinol 300 mg/day who showed: (1) prominent soft tissue tophi; (2) a history of possible nephrolithiasis; (3) 24 h Uur over 700 mg/day despite Cur < 6 ml/min. The rest of the patients with underexcretion of urate were given benzbromarone 100 mg orally once a day. Patients treated with benzbromarone were encouraged to obtain diuresis of over 1 ml/min throughout the study (urine output was checked in each control visit), but no alkali was initially prescribed.

Measurements of Pur, Pcr, Cur, Ccr, 24 h Uur in 24 hour urine samples, and liver tests were performed every three months. Complete blood cell counts were made at least twice a year. The presence of uric acid crystals was investigated in urine samples from patients treated with benzbromarone. Urate lowering treatment was considered steady when Pur did not differ by more than 1 mg/dl in two consecutive measurements. Once a steady Pur level was achieved, a first analysis of data was performed. Allopurinol and benzbromarone doses were adjusted to achieve optimal Pur concentrations—that is, under 6.0 mg/dl, (357 μmol/l)[6 14–16] in all patients and to avoid 24 h Uur concentrations higher than 1000 mg/day (5.95 mmol/l) in the patients treated with benzbromarone to minimise the risk of urolithiasis.

Statistic analysis was made with a statistic microcomputer program EPI INFO 6.0.[20] Results were studied with one way analysis of variance, *t* test, paired *t* test, and non-parametric tests (Wilcoxon and Mann-Whitney) when necessary. Results from parametric tests are expressed as mean (SD).

Results

Ninety one patients entered the study. Five were excluded during follow up because of poor compliance with treatment (two patients), loss of follow up (two patients) or persistent alcohol intake (one patient). Eighty six men were available for the analysis of results. All of them fulfilled ARA criteria for the classification of gout[17] and 64 of 86 (74.4%) showed MSU crystals in synovial fluid samples or in material aspirated from tophi. Tophi were observed in 33 of 86 patients (38.4%). Mean age was 52.5 (9.6) years (range 32 to 76) and time from onset of the symptoms of gout was 8.3 (6.7) years (range 1–30). Twenty three patients (26.7%) were classified as normoexcretors and 63 (73.3%) as underexcretors. Twenty six underexcretors were given allopurinol (12 had prominent tophi, eight had a possible or proved history of renal colic, and six showed 24 h Uur from 700 to 800 mg/day). The 37 remaining underexcretors were given benzbromarone 100 mg/day. Table 1 shows general data, renal function tests, and renal uric acid results before treatment. Steady plasmatic urate concentrations were achieved between the sixth and the ninth month measurements in all patients.

After treatment with initial doses (fig 1), patients taking allopurinol 300 mg/day, overproducers and underexcretors, showed a reduction of mean Pur from 8.60 mg/dl (512 μmol/l) to 5.85 mg/dl (348 μmol/l) and from 9.10 mg/dl (541 μmol/l) to 5.76 mg/dl (344 μmol/l) respectively. The percentage of reduction from initial Pur was 31.69% for overproducers and 36.26% for underexcretors. There was no difference in the efficacy of allopurinol whether it was used in normoexcretors or underexcretors. Cur remained unchanged and 24 h Uur decreased in both groups, but was much lower in patients with underexcretion (fig 1).

Table 1 Data for before and after treatment

	Overproducers Allopurinol (n=23) (Group 1)	*Underexcretors Allopurinol (n=26) (Group 2)*	*Underexcretors Benzbromarone (n=36) (Group 3)*	*p Value (for intergroup comparisons)*
Age (y)	51.4 (8.2)	53.8 (6.4)	53.1 (19.8)	NS
Onset (y)	9.7 (6.3)	7.9 (5.7)	8.3 (7.5)	NS
Tophi (%)	43.4	46.1	31.4	NS
iPur (mg/dl)	8.60 (0.92)	9.10 (1.36)	8.58 (1.36)	NS
fPur (mg/dl)	5.85 (0.87)***	5.76 (1.33)***	3.54 (1.21)***	1 and 2 *v* 3 <0.001
Red Pur (%)	31.69 (9.31)	36.26 (13.08)	58.27 (14.48)	1 and 2 *v* 3 <0.001
iCcr (ml/min)	116 (22)	108 (21)	87 (22)	1 and 2 *v* 3 <0.05
fCcr (ml/min)	119 (23)	110 (22)	104 (22)**	NS
iCur (ml/min)	6.71 (0.70)	4.52 (1.05)	3.89 (1.15)	2 *v* 3 NS
fCur (ml/min)	6.60 (1.30)	4.98 (1.56)	18.43 (9.31)***	2 *v* 3 <0.001
i24 h Uur (mg)	831 (113)	584 (132)	474 (132)	1 *v* 2 and 3 <0.01
f24 h Uur (mg)	559 (145)**	404 (125)**	819 (190)***	1 and 2 *v* 3 <0.001

iPur = initial plasmatic urate; fPur = final plasmatic urate; red Pur (%) = percentage of reduction from initial plasmatic urate (red Pur = (iPur−fPur)/iPur×100). iCcr = initial clearance of creatinin; fCcr = final clearance of creatinin; iCur = initial clearance of urate; fCur = final clearance of urate; i24 h Uur = initial 24 h urinary excretion of urate; f24 h Uur = final 24 h urinary excretion of urate. **Final *v* initial values p<0.01. ***Final *v* initial values p<0.001. Data shown as mean (SD).

Patients taking benzbromarone 100 mg/day showed a decrease of mean Pur from 8.58 mg/dl (510 μmol/l) to 3.54 mg/dl (211 μmol/l). The percentage of reduction from initial Pur was 58.27%. Mean 24 h Uur after treatment was 819 mg/day (4.87 mmol/day), ranging from 586 to 1106 mg/day (3.48 to 6.58 mmol/day). There was no difference in 24 h Uur in patients with or without tophi: 814 (178) mg/day *v* 821 (199) (4.84 (1.06) and 4.88 (1.18) mmol/day respectively). Cur increased from 3.89 ml/min to 18.43 ml/min. There was a significant difference (p=0.039) in the efficacy of benzbromarone in patients with lower initial Ccr (nine patients with Ccr from 60 to 70 ml/min) compared with those patients with higher initial Ccr (28 patients): they showed a mean reduction of Pur of 4.12 (1.66) mg/dl (245 (98) μmol/l) and 5.35 (1.69) mg/dl (318 (100) μmol/l), respectively. No patient showed uric acid crystals on urine samples and no case of kidney stones was observed.

The mean reduction of Pur was greater in patients taking benzbromarone than that achieved in the 49 patients with allopurinol: from 8.58 to 3.54 mg/dl (5.04 mg/dl, 299 (93) μmol/l) and from 8.86 to 5.80 mg/dl (3.0 6mg/dl, 182 (71) μmol/l) (p<0.001), respectively. The percentage of reduction of Pur was also different: 58.27% *v* 34.53% (p<0.001), respectively.

None of the 37 patients taking benzbromarone 100 mg/day failed to achieve Pur concentrations below 6 mg/dl while 23 of 49 (47%) patients taking allopurinol 300 mg/day showed Pur concentrations over 6 mg/dl (p<0.0001). Sixteen of these 23 patients (32%) ranged from 6 to 7 mg/dl and seven of them (15%) showed Pur concentrations over 7.0 mg/dl. Patients with final Pur concentrations above 6 mg/dl

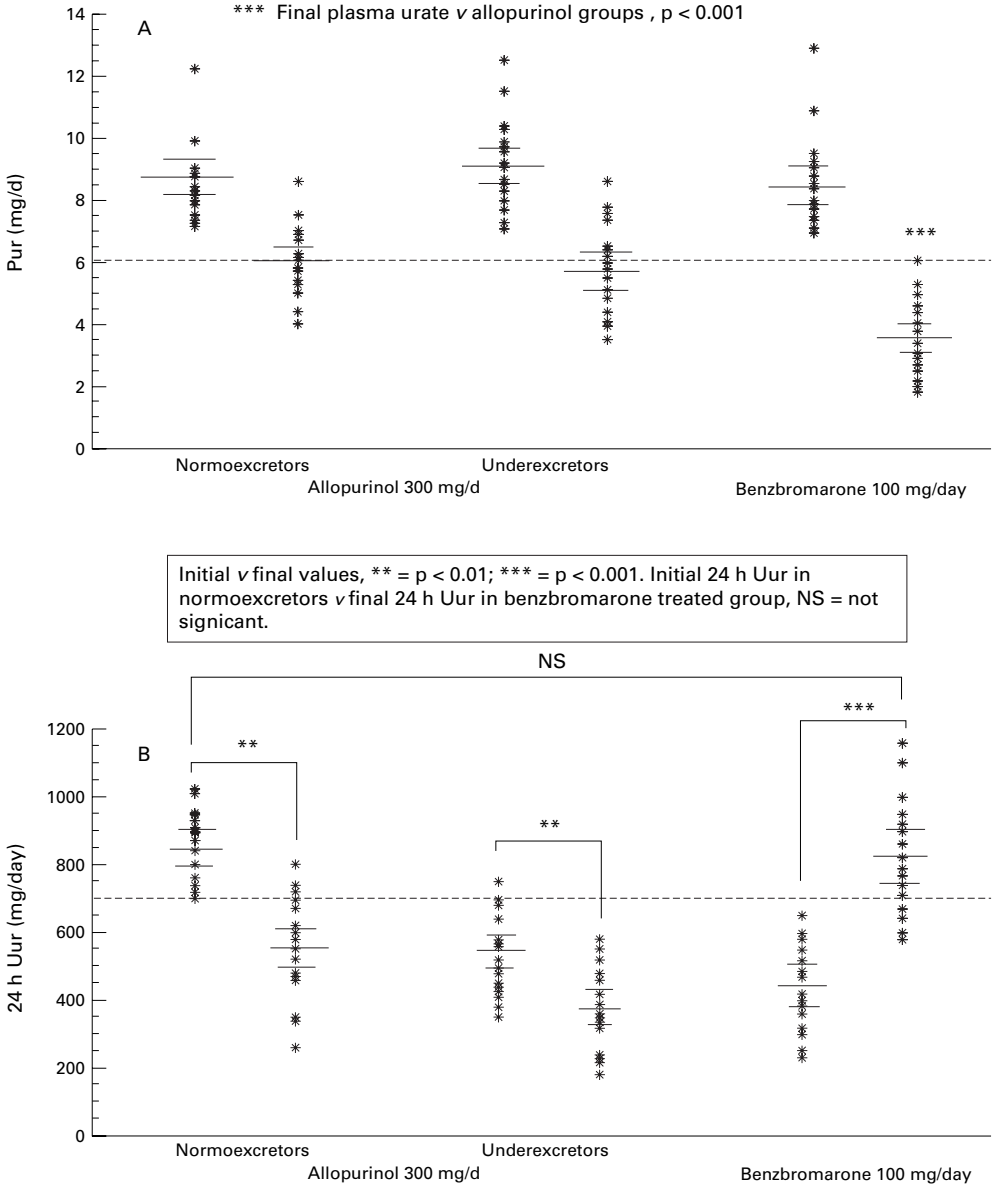

Figure 1 Initial and final plasma urate (Pur) (fig 1A) and 24 hour urinary urate (24 h Uur) (fig 1B) after standard doses of urate lowering drugs (allopurinol 300 mg/day or benzbromarone 100 mg/day). Note that the mean initial 24 h Uur in normoexcretors is not different to the mean final 24 h Uur from underexcretors treated with benzbromarone. Bars indicate the mean and the 95% confidence limits.

showed an initial mean Pur value of 9.15 mg/dl (544 μmol/l) while patients with final Pur concentrations below 6 mg/dl showed an initial mean Pur value of 8.46 mg/dl (503 μmol/l) (p=0.019).

After the initial trial with standard doses of ULDs, doses were adjusted to maintain Pur under 6.0 mg/dl . The dose of allopurinol had to be increased up to 450 mg/day in 21 patients, up to 600 mg/day in two patients and it could be reduced to 200 mg/day in two patients. Therefore, the mean dose to obtain Pur concentrations under 6.0 mg/dl was 372 mg/day. Benzbromarone could be reduced to 50 mg/day in 18 of 37, the mean final dose being 76 mg/day. The overall mean follow up was 12.5 (2.6) months (12.4 (2.9) for normoexcretors, 12.0 (2.8) for underexcretors taking allopurinol, and 12.1 (2.1) for underexcretors taking benzbromarone.

The mean Ccr increased in all groups after treatment, but differences were only significant in those patients treated with benzbromarone (from 87 (22) ml/min to 104 (22) ml/min, p< 0.001).There was not a single case of withdrawal because of adverse reactions either to allopurinol or to benzbromarone. Two patients taking allopurinol showed a slight increase in serum alanine aminotransferase (less than twice the normal limits) and one patient taking benzbromarone suffered diarrhoea with concommitant administration of colchicine that subsided after colchicine discontinuation.

Discussion

This study shows that benzbromarone is very useful for the control of hyperuricaemia using doses ranging from 50 to 100 mg/day. It also shows that 47% of our patients taking allopurinol did not achieve optimal Pur concentrations with 300 mg/day despite alcohol abstinence and weight reduction. Previous studies showed that poor control of uricaemia is common,[23–27] and it may result in radiological progression of bony lesions,[23] increased size of tophi,[23] and frequent recurrence of gouty bouts and tophi after withdrawal of urate lowering treatment.[24 25 27]

Although most standard sources of information recommend uricosurics to correct hyperuricaemia in underexcretors,[5–8 29 30] this approach is not a common practice in more recent studies.[23–26] Epidemiological studies show that only 2–15% of patients with gout were taking uricosuric drugs.[30–32] It may be because uricosurics such as probenecid or sulphinpyrazone have to be given in a twice daily regimen and have little efficacy in patients with low Ccr, and that patients taking uricosurics should be monitored to avoid the risk of renal stones. Although benzbromarone showed a little lower efficacy in patients with the lowest Ccr, an important reduction of Pur (of 4.12 mg/dl) was observed in these patients.

Relative underexcretion of urate has been reported in 80 to 90% of the patients with primary gout[29 33 34] so uricosuric treatment would seem to be a more pathogenic approach to the treatement of hyperuricaemia for most of the patients with gout, as suggested by Wolfe *et al*.[30] We use Cur together with 24 h Uur to classify patients for uricosuric treatment because Cur reflects renal handling of urate.[35] Uricosurics were the first ULDs used: cincophen and salycilates were used more than 50 years ago[1] and proved to be useful, but toxicity was a serious concern.[1 36] Benzbromarone is a benzofuran that produces a uricosuric effect by inhibiting postsecretory tubular resorption of urate.[37] A few reports of trials using single therapy with benzbromarone are available from the literature in the past 20 years.[38 40] In two series (using doses that ranged from 50 to 150 mg/day), the average reduction of Pur concentration ranged from 54% to 63% and the mean Pur was under 5 mg/dl.[38 39] Benzbromarone has also been shown to be useful and well tolerated in renal transplant recipients with gout secondary to cyclosporin-A treatment with the patients showing low renal function (near to 40 ml/min) and the interaction between azathioprine and allopurinol in patients with a renal transplant being avoided.[40]

Our approach to avoid renal complications of uricosuric treatment is the following: (1) to select patients with low Cur and 24 h Uur, (2) to indicate allopurinol as the first drug to be used in patients with a history of kidney lithiasis or prominent tophi, and (3) to monitor urinary uric acid concentration and pH during treatment, the most important factors involved in uric acid lithogenesis,[41] and modify them (with higher fluid intake and/or urine alkalinisation) to avoid risk of lithiasis.

Allopurinol is actually the most commonly ULD prescribed.[30–32] Although the modal value of the dose of allopurinol is 300 mg/day (range 100 to 900 mg/day),[32] 47% of our patients taking allopurinol, as in other studies,[42] did not achieve optimal Pur concentrations with 300 mg/day. By contrast, the mean dose selected by the WHO is 400 mg/day[43] closer to the 372 mg/day mean dose that our patients needed to obtain Pur values under 6 mg/dl.

Clearance of creatinine increased in all groups after treatment, and significantly in patients taking benzbromarone. This increase is thought to be related to the avoidance of NSAIDs after successful control of hyperuricaemia and gouty bouts in all patients and because patients with the lower renal function (on benzbromarone) were probably more prone to achieve amelioration of renal function than patients in the other groups, whose renal function was higher initially.

Both allopurinol and benzbromarone have a good safety profile, but only when prescribed to patients with symptomatic hyperuricaemia.[44] The dose should be adjusted to obtain Pur < 6 mg/dl (357 μmol/l) if possible.[14 15] Also, patients taking allopurinol with renal insufficiency or concommitant diuretic treatment have a higher risk of developing severe toxicity,[45] and additional caution should be taken in patients taking concommitant azathioprine treatment.[46] Benzbromarone is also a safe drug.[39] As it is conjugated in the liver and excreted to the bile, caution should be taken in patients with hepatobiliary diseases although a recent report suggests that benzbromarone does not seem to cause short-term changes in

liver function in patients with liver cirrhosis with mild to moderate liver failure (Child's stages A and B).[47]

Recurrent, but self limited, hepatic toxicity has been reported in a 68 year old woman taking benzbromarone.[48] Subfulminant hepatitis has been reported in four patients taking high doses (300 mg/day) of benzarone—an analogue of benzbromarone—to treat peripheral vascular insufficiency.[49 50] Three of four patients were over 65 years and two were taking thyroid hormones. Liver toxicity appeared after six weeks to four months from the onset of benzarone treatment. Three fatalities occurred. On the other hand, Mastbernard *et al*[39] did not find any significant liver toxicity in 29 patients who were treated with benzbromarone for more than five years and up to 10 years. Monitoring of liver function tests during follow up should be recommended, especially if high doses of benzbromarone are prescribed or other benzofurans (such as amiodarone) are concommitantly used.

In conclusion, benzbromarone is very effective for the control of hyperuricaemia in patients with chronic gout. The mean dose of allopurinol needed to obtain optimal control of uricaemia was closer to that recommended by WHO than to that recommended in current literature. Uricosuric drugs (such as benzbromarone 50–100 mg/day) should be considered for patients with underexcretion of urate, except for patients with previous nephrolithiasis as uricosuric treatment is a more physiological approach to the treatment of gout in these patients.

The authors thank Dr Eliseo Pascual, from Alicante University, for reviewing the manuscript and for his interesting suggestions. This work has not been supported by any grant either from the pharmaceutical industry, private or public institutions.

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