Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients

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Abstract In 2003, the uricosuric drug benzbromarone was withdrawn from the market. The first alternative drug of choice was the xanthine oxidase inhibitor allopurinol. The purpose was to (1) investigate the efficacy of allopurinol (standard dosage) compared with previous treatment with benzbromarone; and (2) investigate the combination therapy allopurinol-probenecid as an effective alternative treatment compared with previous benzbromarone treatment. A prospective, open study was carried out in a cohort of 51 gout patients who discontinued benzbromarone therapy because of market withdrawal. Patients were given 200–300 mg allopurinol (stage 1). When allopurinol failed to attain the target serum urate (sUr) levels ≤ 0.30 mmol/l, probenecid 1,000 mg/day was added (stage 2). Treatment with benzbromarone monotherapy (range: 100–200 mg/day; mean 138 mg/day) resulted in 92% of patients reaching target levels sUr ≤ 0.30 mmol/l with a decrease of 61[11]% compared to baseline. In stage 1, 32 patients completed treatment with allopurinol monotherapy (range 200–300 mg/day; mean 256 mg/day), which resulted in 25%

of patients attaining sUr target levels. Decrease in sUr levels was 36[11]%, which was significantly less compared to treatment with benzbromarone ($p < 0.001$). In stage 2, 14 patients received allopurinol-probenecid combination therapy, which resulted in 86% of patients attaining target sUr levels (after failure on allopurinol monotherapy), which was comparable to previous treatment with benzbromarone ($p = 0.81$). Decrease in sUr levels was 53[9]% (CI 95%: 48–58%), which was a non-significant difference compared to previous treatment with benzbromarone ($p = 0.23$). Benzbromarone is a very effective antihyperuricemic drug with 91% success in attainment of target sUr levels ≤ 0.30 mmol/l. Allopurinol 200–300 mg/day was shown to be a less potent alternative for most selected patients to attain target sUr levels (13% success). In patients failing on allopurinol monotherapy, the addition of probenecid proves to be an effective treatment strategy for attaining sUr target levels (86% success).

Keywords Allopurinol · Benzbromarone · Gout · Probenecid · Hyperuricemia

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Introduction

In 2003, benzbromarone was withdrawn from the European market [1]. The reason for the withdrawal was the risk of fulminant hepatitis according to the information given by the manufacturer. Since the introduction of benzbromarone in the early 1970s, three cases of severe hepatitis have been published [2–4]. On the other hand, benzbromarone seems well tolerated in general use [5] in contrast to allopurinol, which causes frequently (2–5%) allergic skin reactions. The uncertainty remains whether the efficacy-safety balance of

benzbromarone really is unfavourable, compared to the other antihyperuricemic drugs available like allopurinol, probenecid and sulphinpyrazone [6]. In Europe, benzbromarone was available only as a prescription uricosuric drug in a limited number of countries. In the Netherlands, the only registered alternative for patients with chronic gout was allopurinol, a uricostatic drug acting by inhibition of xanthine oxidase.

The goal of antihyperuricemic treatment is to reduce the serum urate (sUr) level below the threshold of supersaturation to allow the dissolution of existing monosodium urate (MSUr) crystals in the joints and to stop the deposition of new crystals [7–11]. The solubility of urate in joint fluids is influenced by temperature, pH, concentration of cations, level of articular dehydration and the presence of nucleating agents such as insoluble collagens, chondroitin sulphate and non-aggregated proteoglycans [1].

The treatment goal of antihyperuricemic therapy is usually supposed to reach sUr levels below 0.36 mmol/l [8–10]. It is shown that recurrent gouty attacks are better prevented

[12, 13] and that tophi dissolve more quickly [14] in the presence of sUr levels ≤ 0.30 mmol/l, compared with levels 0.30–0.36 mmol/l. Thus, we aimed the sUr treatment goal for gout patients at ≤ 0.30 mmol/l.

The amount of urate in the body depends on dietary intake, synthesis and excretion. Hyperuricemia results from the overproduction of urate (10%), from the underexcretion of urate (90%) or often a combination of the two [7]. Therefore, theoretically, the urate balance, in terms of the ratio of overproduction and underexcretion of urate, may be clinically important for the rational choice of a uricostatic drug, a uricosuric drug or a combination of both. However, there are no trials to support or refute this theory [6]. From observational studies, it is concluded that benzbromarone 75–120 mg/day is very effective in the control of hyperuricemia, better than allopurinol 300–450 mg/day [5, 15, 16].

We carried out an observational study to evaluate the effectiveness of allopurinol monotherapy and combination therapy of allopurinol with the uricosuric drug probenecid

Fig. 1 Flow of participants through each stage of the study. GFR Glomerular filtration rate

in underexcretor-type and overproducer-type gout patients previously treated with benzbromarone. Because allopurinol is reported to be less potent than benzbromarone in lowering sUr, we investigated the combination allopurinol–probenecid as an alternative treatment when allopurinol failed.

Materials and methods

A prospective, open label study was carried out in patients who had to discontinue benzbromarone therapy and contacted the rheumatology department in the period July–December 2003. The inclusion criteria were the following: (1) diagnosis of gout proven by presence of MSUr crystals in the synovial fluid [17] or otherwise complying with the American Rheumatism Association criteria [18]; (2) pre-treatment with benzbromarone monotherapy of 100–200 mg/day for at least 2 months with available sUr efficacy results; (3) no relevant liver disease and (4) no relevant renal disease, defined as glomerular filtration rate (GFR) $>50 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$.

Before entering the study, liver function, serum creatinine (sCr), sUr, urinary creatinine excretion (uCr) and urinary urate excretion (uUr) on unrestricted purine diet were measured after benzbromarone was stopped for at least 1 month. GFR was estimated from the simplified Modification of Diet in Renal Disease (MDRD) formula [19, 20]. Underexcretion of urate was defined as a urate clearance (ratio uUr/sUr) $<6.0 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ [21]. Results of pre-treatment with benzbromarone were collected from the patient's chart.

In stage 1, patients were given allopurinol with a maximum of 200–300 mg once a day in a step-up dosage scheme; maximum dosage prescribed depended on kidney function, tolerability and prescriber's preference. When the treatment goal of $\text{sUr} \leq 0.30 \text{ mmol/l}$ was not reached with allopurinol after 2 months, patients were included in stage 2, and probenecid 500 mg twice daily was added to allopurinol. Each treatment regimen was evaluated after a treatment period of >2 months, and sCr, sUr, uCr and uUr were measured. Prophylaxis of gouty episodes with colchicine was prescribed to all patients until target sUr level was reached ($\text{sUr} \leq 0.30 \text{ mmol/l}$).

Table 1 Demographic data, baseline urate characteristics and previous results attained with benzbromarone of patients enrolled in stage 1 (allopurinol treatment) and enrolled in stage 2 (allopurinol–probenecid treatment)

	Stage 1 ^a Allopurinol ($n=50$)	Stage 2 ^a Allopurinol–probenecid ($n=14$)
Demographics		
Age (years)	57 [9]	55 [8]
Male gender (%)	94	93
Tophaceous gout (%)	24	14
GFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)		
50–80 (%)	57	50
>80 (%)	43	50
History of allopurinol use (%)	20	14
Baseline urate characteristics		
Baseline sUr (mmol/l), range	0.55 [0.08], 0.41–0.69	0.54 [0.08], 0.42–0.68
Baseline uUr (mmol/day), range	3.7 [1.3], 1.6–6.8	3.8 [1.7], 1.6–6.8
Baseline UrCl (ml/min), range	4.8 [1.9], 1.8–11.2	5.0 [2.5], 1.8–10.4
Underexcretor-type (%)	95	92
Previous benzbromarone results ^b		
Dosage benzbromarone (mg/day)	139 [49]	143 [51]
Benzbromarone sUr (mmol/l), range	0.21 [0.07], 0.09–0.38	0.23 [0.06], 0.14–0.31
Treatment goal reached		
sUr $\leq 0.30 \text{ mmol/l}$ (%)	92	93
sUr $\leq 0.36 \text{ mmol/l}$ (%)	98	100
Benzbromarone ΔsUr (%)	–61 [11]	–58 [8]
Benzbromarone uUr (mmol/day), range	5.0 [1.7], 2.4–8.5	5.3 [1.7], 2.4–8.0
Benzbromarone UrCl (ml/min), range	16.2 [4.6], 6.2–24.5	16.3 [4.9], 6.2–22.2

GFR Glomerular filtration rate, sUr serum urate, uUr urate excreted in urine, UrCl urate clearance

^a Data shown as mean[standard deviation] and range, unless stated otherwise

^b Latest results before benzbromarone withdrawal

Table 2 Effectiveness of allopurinol (stage 1) and allopurinol–probenecid combination therapy (stage 2)

	Stage 1 ^a Allopurinol (<i>n</i> =32)	Stage 2 ^a Allopurinol–probenecid (<i>n</i> =14)
Dosage allopurinol (mg/day)	256 [50]	243 [51]
Dosage probenecid (mg/day)	–	1,000
sUr reached (mmol/l), range	0.36 [0.07], 0.24–0.57	0.25 [0.04], 0.20–0.35
ΔsUr (%) from baseline	–36 [11]	–53 [9]
ΔsUr (%) from allopurinol monotherapy	–	–33 [10]
ΔsUr (%) from benzbromarone monotherapy	+78 [60]	+19 [43]
uUr (mmol/day), range	2.3 [0.8], 0.8–4.3	3.1 [0.9], 1.5–4.4
UrCl (ml/min), range	4.4 [1.3], 2.3–7.7	8.8 [2.4], 4.5–13.9
Treatment goal reached		
sUr ≤ 0.30 mmol/l (%)	25	86
sUr ≤ 0.36 mmol/l (%)	53	100

sUr Serum urate, uUr urate excreted in urine, UrCl urate clearance

^aData shown as mean[standard deviation] and range, unless stated otherwise

Fig. 2 Box-plot diagram for sUr results of stage 1, *n*=32 (**a**) and stage 2, *n*=14 (**b**). Open circle Outlying value

Primary endpoints for stages 1 and 2 were the percentage of patients attaining sUr target ≤ 0.30 mmol/l and the relative decrease in sUr attained with each treatment regimen.

Statistical Package for the Social Sciences (SPSS) 14.0 for Windows was used for data collection, data validation, data selection and statistical analysis. Student's two-sided paired *t* test and chi-squared test were used to compare the effectiveness of benzbromarone, allopurinol and allopurinol–probenecid therapy. Yates's continuity correction was used where appropriate. Normality was verified with Kolmogorov–Smirnov analysis. A *p* value <0.05 is considered statistically significant.

Results

Ninety patients made an appointment with the rheumatology department because of benzbromarone withdrawal. Fifty patients (55%) were assigned to stage 1 treatment and received allopurinol 200–300 mg/day (Fig. 1). Table 1 shows demographic data, urate results on benzbromarone therapy and urate results at baseline >4 weeks after discontinuation of benzbromarone therapy. Thirty-two patients (64%) completed stage 1 and were included in the analysis. Eight patients attained target serum levels on allopurinol 200–300 mg/day and completed the study. Fourteen patients were assigned to and completed the combination therapy allopurinol–probenecid 500 mg twice daily (stage 2) and were included in the analysis.

Urate results after allopurinol (stage 1) and allopurinol–probenecid (stage 2) treatment are presented in Table 2 and Fig. 2. With allopurinol monotherapy, the sUr reached was 0.36 [0.07] mmol/l, and eight (25%) patients reached target sUr ≤ 0.30 mmol/l. Compared to treatment with benzbromarone

marone 100–200 mg/day, significantly less patients attained target sUr levels ($p<0.001$). With allopurinol–probenecid, sUr reached was 0.25 [0.04] mmol/l, and 12 (86%) patients reached target sUr after failure on allopurinol monotherapy. No significant difference was found compared to treatment with benzbromarone ($p=0.81$).

Using allopurinol monotherapy, sUr decreased 36[11]% compared to baseline. This was significantly less than relative sUr decrease attained with benzbromarone in this group ($p<0.001$). With allopurinol–probenecid treatment, sUr decreased 53[9]% (CI 95%: 48–58%), which did not significantly differ from benzbromarone ($p=0.23$).

Figure 3 shows cumulative probability plots of target sUr selected and percentage of treatment success found in stages 1 and 2 for selected target sUr and different treatment regimens.

Discussion

First of all, this study shows that benzbromarone is a very potent antihyperuricemic drug; in this cohort of patients using benzbromarone 100–200 mg/day, more than 90% of the patients have optimal sUr levels. With allopurinol standard dosage 200–300 mg/day, comparable effectiveness cannot be achieved for this group. The average allopurinol dosage (mean 243 mg/day) might be considered relatively low; however, (1) no efficacy data on allopurinol ≥ 600 mg/day are available in the literature; (2) dosages >300 mg/day are generally not advised because of increased risk of adverse drug reactions [22]; (3) benzbromarone (mean 138 mg/day) and probenecid (1,000 mg/day) could also be dosed higher.

It must be noted that every patient in this study was previously treated with benzbromarone, thereby introducing the possibility to overestimate the percentage of responders

Fig. 3 Cumulative probability plot of selected target sUr concentration and success of attainment of selected target sUr for stage 1, $n=32$ (a) and stage 2, $n=14$ (b). Filled triangle Benzbromarone, filled square allopurinol, open circle allopurinol–probenecid, open square no medication, sUr serum urate

to benzbromarone. Furthermore, a dropout occurred in stage 1 of 38%, which may have influenced the outcome. The relatively high dropout rate was mainly due to the design of the study (cohort) in combination with the sudden need for alternative treatment. On the other hand, we found a mean relative decrease in sUr of 61% for benzbromarone and 36% for allopurinol, which corresponds well with values published in the literature of 54–58% for benzbromarone 80–125 mg/day and 27–44% for allopurinol 300 mg/day in patients not previously treated with benzbromarone [5, 15, 16, 23, 24].

This cohort consisted of more than 90% patients of uric acid underexcretor type. From a pathogenic point of view, it is suggested that allopurinol, as an inhibitor of uric acid production, would be more effective in overproducer-type gout. However, this is not supported by clinical data [15]. Previous findings indicate that even in patients with apparently high uUr, there is a relative underexcretion of urate [25]. Thus, when treatment goals are not achieved with allopurinol in this group of patients, combination with a uricosuric drug (e.g. benzbromarone, probenecid) might be very useful.

Adding probenecid to allopurinol contributed an additional 33[10]% (CI 95%: 28–38%) decrease in sUr on average, resulting in reaching the target sUr for most patients (87% success). Thus, in finding an appropriate alternative therapy for benzbromarone, adding probenecid to allopurinol was proven to be an effective strategy. An interaction between allopurinol and probenecid is described in the literature [26], resulting in an increased clearance of oxipurinol, the active metabolite of allopurinol. However, our data do not support this finding to be clinically important, as the addition of probenecid to allopurinol decreased sUr with 31% on average.

In stage 1, five patients (10%) stopped allopurinol therapy because of adverse events related to allopurinol. Reported events were rash, pruritus, diarrhoea, nausea and dizziness, which are all well-known side effects of allopurinol. Becker et al. [23] found a similar rate (12%) of adverse events related to allopurinol.

There are few therapeutic options available to lower sUr to target levels other than the drugs used in this study. The uricosuric drug sulphinpyrazone is not widely used due to its adverse effects profile [27]. Minor additive serum-lowering effects may be achieved by losartan or fenofibrate [27, 28]. The uricostatic febuxostat may be available soon. Recently, it was shown that when using febuxostat 80–120 mg/day, 47–66% of the patients reached sUr levels ≤ 0.30 mmol/l compared to 13% with allopurinol 300 mg/day [23]. A new promising treatment option for patients with severe tophaceous gout is the development of recombinant uricase [29, 30] and pegylated recombinant uricase. Uricase-based drugs are potentially very effective but also very expensive drugs, so further (pharmacoeconomic) studies on optimizing antihyper-

uricemic therapy with old (out of patent) drugs, like benzbromarone, are warranted. At this moment, benzbromarone seems to be the most effective antihyperuricemic drug, and from our point of view, availability of benzbromarone in other countries would make treatment of difficult gout more successful [31].

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