The safety and efficacy of benzbromarone in gout in Aotearoa New Zealand

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Abstract

Background: Benzbromarone is a potent uricosuric, but is not widely available due to concerns about hepatotoxicity. In Aotearoa New Zealand benzbromarone has been available since April 2013, subject to funding restrictions, for patients with inadequate urate-lowering response or intolerance to allopurinol and probenecid.

Aim: The aim of this study was to assess the safety and efficacy of benzbromarone in a real-life setting.

Methods: All patients who received funding for benzbromarone from 1/4/2013 to 30/9/2014 were identified. Prescribers were sent a questionnaire for each individual. Information on demographics, efficacy of previous urate-lowering drugs and reasons for discontinuation were collected. Specific information about the dose, effect on serum urate, adverse effects and liver function tests after commencing benzbromarone was recorded.

Results: Completed questionnaires were returned for 123/164 (75%) patients. Mean (SD) serum urate prior to benzbromarone was 0.57 (0.12) mmol/l and estimated glomerular filtration rate (eGFR) 50.3 (22.8) ml/min/1.73m^2. The median dose of benzbromarone was 100mg/day (25-200mg/day). Six months after commencing benzbromarone, mean (SD) serum urate was 0.35 (0.12) mmol/l. Benzbromarone related adverse events included rash (n=4), diarrhoea (n=9), nausea (n=6), and urate stones (n=3). Liver function tests abnormalities were uncommon and tended to be mild. There were 14 patient deaths; none were considered related to benzbromarone. Allopurinol had been prescribed prior to benzbromarone in 117/123 patients; median maximum allopurinol dose was 200mg/day (range 25-600mg/day), and 19% patients received allopurinol >300mg/day.

Conclusions: Benzbromarone provides useful urate-lowering efficacy and does not appear unsafe in patients with gout. Urate-lowering therapy prescribing requires further optimisation.

Key words: gout, benzbromarone, urate lowering therapy

Introduction

Benzbromarone is a potent uricosuric agent that was first introduced in the 1970's for the management of gout. Benzbromarone is metabolised in the liver by cytochrome P450 to 6-hydroxybenzbromarone. Both parent drug and this metabolite are potent inhibitors of the renal tubular urate-anion exchanger URAT1 [1] and GLUT9 [2]. Despite its urate-lowering efficacy, benzbromarone is not widely available due to concerns over serious hepatotoxicity. The estimated incidence of hepatotoxicity is 1:15,000 but may be higher in some populations [3], Although hepatotoxicity appears to be rare especially with doses ≤100mg daily, it can be fatal. In 2003 Sanofi-Synthelabo, which supplied most of Europe, withdrew benzbromarone from the market, although it is still available from other companies in a number of countries. It has been suggested that there was insufficient evidence to support this withdrawal and a risk-benefit assessment concluded that its withdrawal was not in the best interest of patients with gout [3].

Sustained reduction of serum urate (SU) to <0.36mmol/l, and <0.30mmol/l if tophi are present, is recommended for successful long-term management of gout [4]. Current gout guidelines recommend xanthine oxidase inhibitors (XOI), which decrease uric acid production as the first line urate lowering therapy [4-6]. The XOI allopurinol is most commonly used as it is widely available and significantly less expensive than the newer XOI febuxostat. Gout management guidelines all recommend uricosuric therapy as second-line, with both the British and European guidelines suggesting either probenecid in the setting of normal kidney function or benzbromarone for those with kidney impairment.

In Aotearoa New Zealand benzbromarone is not registered, but has been funded at a national level since April 2013 by the Pharmaceutical Management Agency (PHARMAC), the New Zealand Government agency that decides which medicines are subsidised. Funding of benzbromarone is provided subject to "Special Authority" funding criteria for patients with gout who have failed to achieve a SU <0.36mmol/l despite allopurinol at least 600mg daily in combination with probenecid up to 2gm daily. Prior to 2013 benzbromarone was funded only on a named patient basis. We undertook a national study to assess the safety and efficacy of benzbromarone in Aotearoa New Zealand since national funding began.

Methods

The study was approved by the Southern Health and Disability Ethics Committee of New Zealand (ref 14/STH/116). In order to obtain benzbromarone for an individual patient the prescriber must apply for a unique Special Authority approval number. All Special Authority approvals for benzbromarone were identified by PHARMAC from 1 April 2013 until 30 September 2014. Prescribers were provided with the patient's unique identifying National Health Index (NHI) number and were asked to complete a de-identified standardised case record form for each individual patient. Completed forms were returned to the research team. Data were collected between 30 April 2015 and 31 August 2015.

Data collection included patient demographics, previous urate lowering therapies and SU response, laboratory variables including liver function and SU before and six months after benzbromarone, adverse effects with benzbromarone and reasons for discontinuation of benzbromarone. Liver function test (LFT) abnormalities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Where the patient had died, the

prescriber was contacted by telephone to ascertain cause of death, comorbidities and urate lowering therapy at time of death.

Mean pre and post SU were compared using paired t-tests and the proportions of patients achieving target SU were compared between drugs using McNemar's chi^2 test.

Results

There were 164 unique Special Authority approvals for benzbromarone during the period 1/4/2013 to 30/9/2014. Case record forms were returned for 131/164 (76.8%). In eight cases the forms were blank, leaving 123/164 (75%) in the final analysis. Those completing the form were primary care physicians (n=55), rheumatologists (n=58), general physicians (n=3), and nephrologists (n=2).

Demographics

Of the 123 patients for whom data was returned, 85 (69.1%) were male, 70 (56.9%) were New Zealand European and 46 (37.4%) were Māori or Pacific Island. The mean (SD) duration of gout was 15 (9.4) years and tophi were present in 70 (56.9%). Mean (SD) SU prior to any ULT was 0.61 (0.11) mmol/l (range 0.36-0.94 mmol/l; n=106).

Urate lowering therapy prior to benzbromarone

Allopurinol was prescribed prior to benzbromarone prescription in 117/123 patients; in the remaining six, allopurinol was not prescribed due to concomitant azathioprine therapy. The median maximum allopurinol dose was 200 mg/day (range 25-600 mg/day; n=72) and only 14/72 (19%) patients received >300 mg/day allopurinol. Mean (SD) SU on maximum allopurinol dose was 0.46 (0.11) mmol/l (range 0.29-0.74 mmol/l; n=59). Twelve patients

(20%) achieved SU <0.36mmol/l with allopurinol. In the 55 patients who had a SU before and during allopurinol therapy available, the mean (SD) SU pre allopurinol was 0.61 (0.12) mmol/l and on maximum dose of allopurinol was 0.46 (0.11) mmol/l ($p<0.001$).

In the entire group the reasons for allopurinol discontinuation were rash or allergy (n=56), ongoing gout flares (n=7), failure to reach target SU (n=106), renal impairment (n=8) and not tolerated but not otherwise specified (n=41). Of the twelve patients who had SU<0.36 mmol/l reasons for discontinuation were rash (n=5), gout flares (n=1), failure to reach target SU (n=2, both patients had tophi), and not tolerated but not otherwise specified (n=5).

Probenecid use was reported for 59/123 (47.9%) patients, and for 11/123 (8.9%) no data on probenecid was recorded. Kidney impairment was stated as the reason for not prescribing probenecid in 25/53 (47%) who did not receive probenecid. The median maximum probenecid dose was 1000 mg/day (n=45) with a mean (SD) SU 0.49 (0.12) mmol/l (range 0.23-0.73 mmol/l) (n=38) on maximum probenecid dose. Only 5/38 (13%) achieved SU<0.36 mmol/l. For the 32 patients who had a SU on no ULT and during probenecid therapy available, the mean (SD) SU pre ULT was 0.62 (0.11) mmol/l and on maximal dose probenecid was 0.50 (0.11) mmol/l ($p<0.001$). In the entire group who received probenecid, reasons for stopping were failure to reach target SU (n=53), rash/allergy (n=5), gout flares (n=1), kidney function deterioration (n=1), drug intolerance not otherwise specified (n=23), and one patient achieved target SU but developed kidney stones.

There were only ten patients who received combination probenecid and allopurinol therapy. In this combination group five received 500mg/day of probenecid and five received 1000 mg/day. Median allopurinol dose was 400 mg/day (range 50 – 600mg/day) and mean (SD) SU on combination therapy was 0.47 (0.09) mmol/l (range 0.37-0.69 mmol/l).

Benzbromarone efficacy

The mean (SD) age at time of starting benzbromarone was 65.3 (14.3) years. Mean (SD) SU prior to benzbromarone was 0.57 (0.12) mmol/l (range 0.28-0.94 mmol/l; n=116). Mean (SD) creatinine was 135.5 (49.8) mmol/l (n=113) and eGFR 50.3 (22.8) ml/min/1.73m^2 (n=112). The median dose of benzbromarone was 100mg/day (range 25-200 mg/day) (n=109).

Six patients were documented to have never commenced benzbromarone and were excluded from all subsequent analysis leaving a total of 117 patients included in the analysis. The majority of patients (n=79) started benzbromarone after April 2013 although patients who had been on this medicine prior to that and subsequently received a Special Authority approval were included (n=33). Six months after commencing benzbromarone, mean (SD) SU was 0.35 (0.12) mmol/l (range 0.11-0.67 mmol/l; n=99) (Figure 1). In the 97 patients for whom data were available before and after prescription of benzbromarone, the mean (SD) SU pre benzbromarone was 0.56 (0.12) mmol/l and six months post benzbromarone was 0.34 (0.11) mmol/l $p<0.001$. Serum urate increased or did not change on benzbromarone in 10/97 (10%) patients suggesting non-adherence. Target SU (<0.36 mmol/l) was achieved in 62/117 (62.6%) of patients receiving benzbromarone, a significantly higher percentage than on allopurinol or probenecid (Figure 2).

Benzbromarone safety

Benzbromarone-related adverse events were rash in four patients, diarrhoea in nine, nausea in six, and urate stones in three patients. Prescribers were specifically asked if there had been

any abnormal liver function tests and to provide the laboratory values. Abnormal LFTs were reported in 24/117 (20.5%) patients, details of specific LFT abnormalities according to CTCAE guidelines are outlined in Table 1.

At the time of the study, 67/117 (57.3%) of patients remained on benzbromarone; 49/117 (41.9%) were no longer taking it and the status of one patient was unknown. Reasons for discontinuation are outlined in Table 2. Fourteen patients had died at the time of the study, of these six were taking benzbromarone at the time of death. The mean age of the patients who died was 76 years (range 58-86 years). Of the fourteen patients who died, two had been changed to febuxostat prior to death. In no case did the prescriber attribute cause of death to benzbromarone. Co-morbidities and cause of death are outlined in Table 3. Compared with corresponding age/sex-congruent life table estimates, excess risks of death did not seem dissimilar to that expected with other series of patients with severe gout observable in other places [7]. However, this must be tempered by possible under-identification of deaths and over-estimation of person-time benzbromarone use in our study.

Effect of ULT in patients with impaired kidney function

Renal impairment was common, with 22/112 (19.6%) patients having eGFR <30mls/min/1.72m^2, 55/112 (49.1%) eGFR >30-59 mls/min/1.72m^2 and 35/112 (31.3%) eGFR >60mls/min/1.72m^2. With each drug there was no statistically significant difference in the number of patients who achieved SU<0.36mmol/l based on eGFR. However, at each eGFR numerically more people on benzbromarone achieved SU<0.36 mmol/l, compared with the other two allopurinol and probenecid (Figure 3).

Discussion

This study has demonstrated that benzbromarone is an effective urate lowering drug in patients with gout. As expected for a drug that is funded for patients who have failed both allopurinol and probenecid, it is used in patients with long-standing and severe disease. While some liver function abnormalities were recorded, these were generally mild with no CTCAE grade 3 or 4 elevations in liver transaminases. A number of patients who had been prescribed benzbromarone died. None of the reported deaths were attributed to benzbromarone and none were due to hepatotoxicity.

An important aspect of this study was analysis of urate-lowering therapies used prior to benzbromarone. In Aotearoa New Zealand, allopurinol is approved up to a dose of 900mg daily and probenecid to 2000mg daily (typically 1000mg bd). Allopurinol 600mg daily and probenecid are currently pre-requisites for the special authority funding of benzbromarone in Aotearoa New Zealand. In our study, the majority of patients had not received more than 300mg daily of allopurinol and probenecid doses were also low. Furthermore, the majority of patients who discontinued allopurinol and probenecid did so because of failure to reach target serum urate. It is well documented that many patients do not achieve target serum urate with low doses of allopurinol (≤300mg/day) [8]. At least some of the reluctance to use higher doses of allopurinol is due to concerns of adverse effects in those with kidney disease. Restricting the dose of allopurinol based on kidney function is associated with failure to reach target serum urate [9]. However, there is increasing evidence that use of allopurinol in doses >300mg/day irrespective of kidney function is safe [10]. While larger clinical trials are pending, the American College of Rheumatology currently recommends that allopurinol can be increased above 300mg/day even in those with kidney impairment with appropriate patient education and monitoring of liver function tests and kidney function [4].

In our study, another reason for stopping allopurinol, probenecid and benzbromarone was ongoing gout flares. Gout flares are common after commencing urate lowering therapy and even after target serum urate is achieved and sustained gout attacks may continue for 12-18 months [8, 11]. Therefore, gout attacks occurring during these periods do not represent failure of urate lowering therapy. Rather, it is important that patients' expectations about when gout attacks will cease are managed with appropriate counselling. In addition, adequate prophylaxis against gout attacks needs to be given with a non-steroidal anti-inflammatory, colchicine or corticosteroid. The American College of Rheumatology recommends prophylaxis for at least 6 months [4]. Collectively, our data suggest that further education for clinicians managing gout is required with an emphasis on dosing of different urate lowering therapies to achieve target serum urate, appropriate prophylaxis against gout attacks when commencing urate lowering therapy, time until gout attacks will cease after achieving target serum urate and ensuring patient understanding about the rationale for urate-lowering therapy.

This retrospective study has a number of limitations. Although the response rate to this study was high at 75%, the data provided was not complete for all responses. Furthermore, due to the de-identification of individual patient data, we were not able to independently verify the data provided. There may have been responder bias since responses were not provided for one quarter of patients prescribed benzbromarone. Deaths may have been under-identified due to the incomplete response rate and the study design, noting that we did not specifically ask whether patients were alive, rather whether patients were continuing to receive benzbromarone and if not, the reason for discontinuing benzbromarone. Furthermore, it was

not possible to determine when benzbromarone was discontinued prior to death in a number of patients.

This nationwide study suggests that, in population settings, benzbromarone provides useful urate-lowering efficacy and does not appear unsafe for patients with gout as a third-line urate-lowering drug. This study has highlighted a number of areas of gout management that require improvement, specifically optimal dosing of available urate-lowering drugs and recognition that gout flares do not necessarily represent lack of urate-lowering efficacy.

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Figure legends

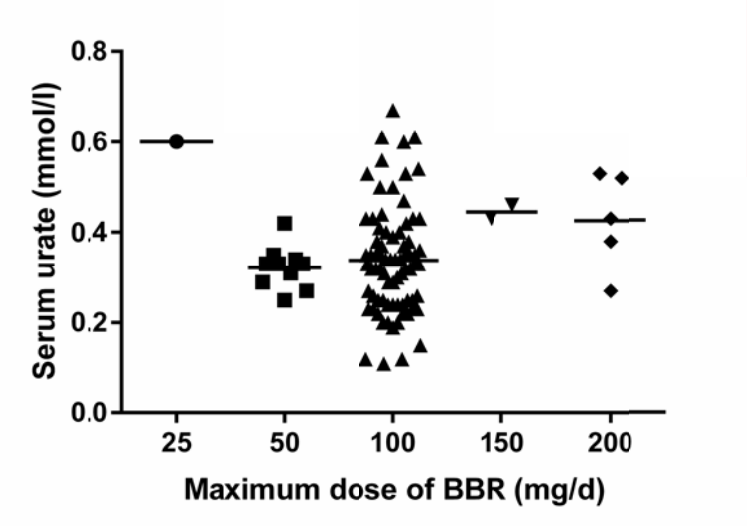

Figure 1: Serum urate concentrations after six months of benzbromarone.

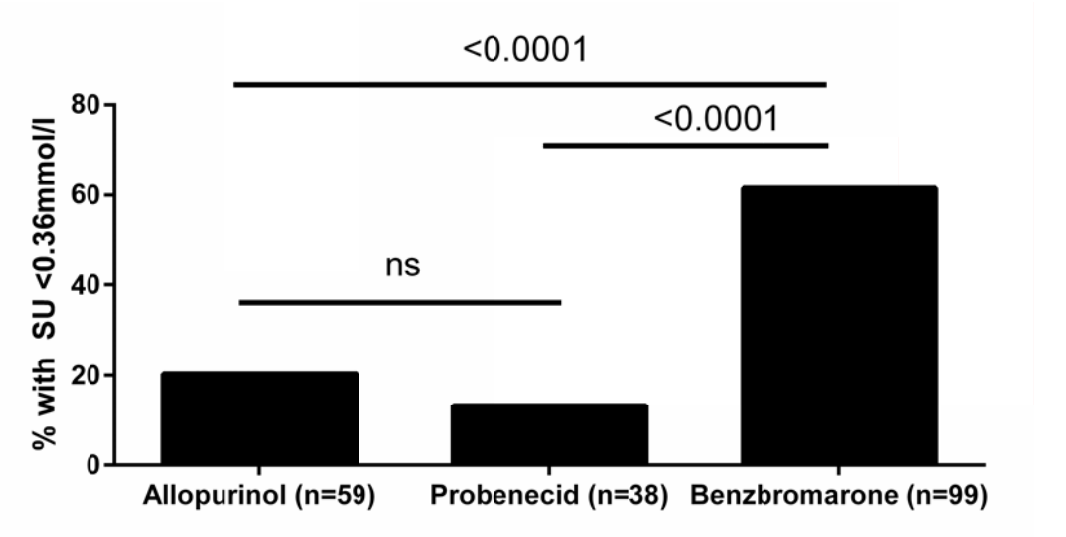

Figure 2: Percentage of patients achieving target with allopurinol, probenecid or benzbromarone.

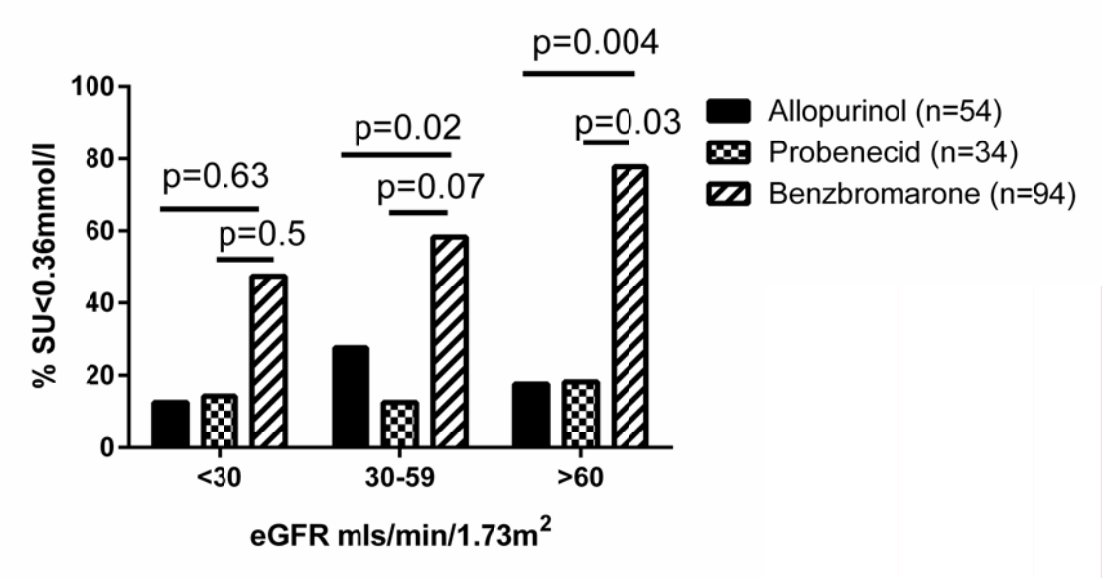

Figure 3: Percentage of patients achieving target SU (<0.36mmol/l) based on eGFR

Table 1: Laboratory values in those with reported liver function test abnormalities. Of 117 patients on benzbromarone, liver function test abnormalities were reported in 24 patients.

Laboratory test	Number patients with paired data	Number abnormal as per CTCAE	Grade* 1	Grade* 2	Grade* 3
Aspartate aminotransferase (AST, upper limit of normal 40 IU/L)	12				
Pre benzbromarone		3	3		
Post benzbromarone		4	4		
Alanine aminotransferase (ALT, upper limit of normal 45 U/L)	21				
Pre benzbromarone		3	3		
Post benzbromarone		5	5		
Alkaline phosphatase (ALP, upper limit of normal 150 U/L)	18				
Pre benzbromarone		3	3		
Post benzbromarone		4	3	1	
Gamma-glutamyltransferase (GGT, upper limit of normal 50 U/L)	23				
Pre benzbromarone		14	10	2	2
Post benzbromarone		14	7	4	3

***CTCAE Grades:** ALT/AST grade 1: - >ULN – 3xULN, grade 2: >3 – 5 x ULN, grade 3: >5 – 20 x ULN

*GGT/ALP grade 1: >ULN – 2.5 x ULN, Grade 2: >2.5 – 5 x ULN, grade 3: >5 – 20 x ULN

Table 2: Reasons for discontinuing benzbromarone.

Reasons for stopping	Number
Adverse effect (rash, diarrhoea, nausea)	13
Lack of efficacy	5
Renal impairment	4
Non adherence/patient choice	15
Tophi resolved	1
Changed to febuxostat	7
Still having gout flares	5 (4/5 at target)
No recent gout attacks	1
Kidney stone	2
Unknown	2
Deceased	14

Table 3: Comorbidities and cause of death in the 14 patients who had died.

Comorbidities	**Number**
Cardiovascular disease	10/12
Diabetes	5/12
Hypertension	11/12
Obesity	2/10
Chronic kidney disease	12/12
Hyperlipidaemia	8/11
Causes of death	
Infection	3
Malignancy	2
Cardiac disease	3
Stroke	2
Fractured neck of femur with acute kidney failure	1
End stage kidney disease	1
During surgery for mitral valve replacement	1
Abdominal aortic aneurysm rupture	1