# Ten years' experience with benzbromarone in the management of gout and hyperuricaemia

A. MASBERNARD, C. P. GIUDICELLI


## Summary

The results over 10 years in 200 patients (103 with gout and 97 with hyperuricaemia) treated with benzbromarone 75 - 120 mg/d are reported.

The average stable decrease in the serum uric acid level was 54%. The severity and incidence of articular manifestations in the patients with gout were reduced by 75% before the end of the 1st year of treatment; relapses were very uncommon in the following years. In all cases tophaceous deposits disappeared within 6 - 18 months. Adequate fluid intake and alkalinization of urine effectively contributed to a low incidence of urinary incidents (3%), although 35% of the patients were over-excretors of urate before treatment and 33% had a previous history of urolithiasis or associated urinary problems. The drug was well tolerated by 96% of the patients. Renal tolerance has been demonstrated by routine urinalysis and functional tests, as has the long-term safety of the drug with regard to the liver, nervous system and eyes. The biological and clinical results suggest that benzbromarone should be considered as the drug of choice in the majority of gouty and hyperuricaemic patients.


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The effective treatment of gouty arthritis can be achieved only by a stable, persistent lowering of the serum urate level. Gout is not an isolated event. It results from as many as 10 - 20 years of asymptomatic hyperuricaemia, the correction of which prevents long-term damage to the osteo-articular, renal and vascular systems. While very useful in treating the acute gouty episode, colchicine and anti-inflammatory agents have no effect on the cause of the disease and its insidious progression to joint, soft-tissue, kidney and arterial lesions.

Reduction of serum uric acid levels below a saturation threshold of 6,4 mg/dl can be achieved by decreasing the synthesis of uric acid (using xanthine oxidase inhibitors) or by increasing the renal excretion of uric acid, which is the more logical approach in that only about 20% of patients produce excessive uric acid, the remaining 80% or so suffering some impairment in normal renal excretion of this waste product.

Allopurinol has been widely used for many years. It lowers serum urate levels by 30 - 35%; side-effects are reported in 15 - 20% of patients, and may be sufficiently severe to warrant discontinuation of therapy in 12% or more.

Probenecid, given in two or three evenly spread doses because of its short half-life, lowers serum urate levels by an average of 33%. Side-effects are not uncommon and certain toxic manifestations lead to discontinuation of therapy in up to one-third of patients. Probenecid also interferes with the renal excretion of certain other drugs.

Sulphinpyrazone has a similar hypo-uricaemic action. Side-effects, including blood dyscrasias, can lead to discontinuation of therapy in some 25% of patients. The drug also potentiates the action of anticoagulants. Additionally, both probenecid and sulphinpyrazone induce a paradoxical uric acid retention when given in low dosage, and are antagonized by acetylsalicylic acid.

Such limitations in hypo-uricaemic activity, possible side-effects and possible interference with concomitant medication led to a search for more active and better tolerated compounds. Among the benzofuran group benziodarone proved to be an effective agent and benzbromarone was shown to have equally potent biological activity and clinical efficacy.

Benzbromarone (or 2-ethyl-3(4-hydroxy-3,5-dibromo-benzoyl)-benzofuran) was found experimentally to be a potent inhibitor of renal urate reabsorption and to have significant hypo-uricaemic and uricosuric activity in both non-gouty and gouty subjects at doses of 25 mg/d and more. The European studies were confirmed 7 years later by American authors. The onset of uricosuric action is rapid. Urinary uric acid excretion peaks at about 5 hours and excretion is prolonged over 15-21 hours. Some metabolites of the drug participate in this prolongation of uricosuric activity. The action is unaffected by urinary pH. Impaired renal function reduces uricosuric activity, which nevertheless persists providing creatinine clearance remains above 15-20 ml/min. The biological effect of 100 mg benzbromarone has been shown to be equivalent to that of 1,5 g probenecid and greater than that of 300 mg allopurinol.

Aspirin given simultaneously with benzbromarone slightly reduces its uricosuric action, while both pharmacological studies and clinical experience show that the drug fully reverses the hyperuricaemic effect of thiazide diuretics. Unlike probenecid, benzbromarone does not interfere with the tubular secretion of organic acids and has no effect on the urinary excretion of penicillin. Renal excretion of electrolytes, the glomerular filtration rate and renal function are unaffected, as demonstrated by both specific experimentation and long-term clinical observation.

The lowering of the serum urate level caused by benzbromarone appears to be due solely to its uricosuric activity. It does not affect salivary, gastric and biliary excretion of uric acid or its intestinal elimination. The absence of any enzymatic effects of benzbromarone was confirmed by studies carried out in 10 of our patients on benzbromarone 200 mg/d for 2 weeks.

By 1967 clinical studies of benzbromarone in gout had been conducted in several European countries and in Japan. By 1975 large, controlled studies had been completed in North America on 325 patients. The authors reported their clinical experience in Canada,[1,2] France,[3] and Greece, while recently Matzkies and co-workers[4,5] reported on the remarkable efficacy of doses of

**Department of Nephrology and Haemodialysis Unit, Postgraduate Teaching Army Hospital, Val-de-Grace, Paris, France**
A. MASBERNARD, M.D., *Professor*
C. P. GIUDICELLI, M.D., *Associate Professor*

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benzbromarone as low as 50 or even 25 mg, as well as the results of a general survey on 3 899 patients.

Our clinical experience since 1968 is based upon 200 hyperuricaemic patients treated for long periods of time. Conclusions drawn from this large group fully confirm our previous published reports.[1,2]

## Patients and methods

### Patient groups

The 200 patients studied included 103 with gouty disease, of whom 52 had articular manifestations only, 23 had additional renal colic or a history of urolithiasis, 16 had articular manifestations and tophi, and 12 had articular manifestations, tophi and previous urinary tract problems. There were also 41 patients with primary asymptomatic hyperuricaemia, 42 patients with secondary asymptomatic hyperuricaemia, and 14 with severe renal insufficiency. The ages of the 103 gouty patients (100 males and 3 females) ranged from 25 to 83 years (mean 51,9 years), and 33% had a family history of gout. Their gout had persisted for 10-40 years in 27% and for 1-5 years in 50%. Hyperuricosuria (> 700 mg/d) was not accompanied by a urinary history in 38% of cases but was associated with a urinary history in 39%. The mean uric acid clearance rate in patients with no tophi was 6,13 ml/min and 4,57 ml/min in patients with tophi. The mean urinary pH in those with no history of urinary symptoms was 5,83, and in those with a history of urinary symptoms 6,05.

Hypertriglyceridaemia , hyperlipidaemia, obesity and overt or latent diabetes were associated problems in more than 50% of the patients , 17% were hypertensive and 6 had proteinuria. Twelve patients had a mild renal deficiency, and 9 overt cirrhosis or fatty degeneration of the liver. One-third of the patients were abusing alcohol. One patient of Asiatic origin had a two-thirds deficiency in adenosine-phosphoribosyltransferase and a 50% deficiency in adenosine-deaminase.

Benzbromarone was the first antihyperuricaemic agent prescribed for 73 patients; in a further 29 cases it was substituted for previous less active or less well-tolerated medication (i.e. 20 had been on benziodarone, 1 on probenecid and 8 on allopurinol).

**Primary asymptomatic hyperuricaemia.** No previous treatment with diuretics or anti-inflammatory agents or renal insufficiency could be considered responsible for the biological disorder in these 41 patients, associated as in the gouty patients with a noticeable lowering in urate clearance rate (mean 5,73 ml/min, with 62% of the patients below 6,2 ml/min). The 37 male and 4 female patients (mean age 42,8 years) had the same high incidence of associated metabolic disorders as the gouty subjects and could be considered as being in the 'pre-gouty stage' of their purine disorder.

**Secondary asymptomatic hyperuricaemia.** In these 42 patients (37 males and 5 females, average age 45 years) the condition was related to diuretic or anti-inflammatory therapy and/or to a nephropathy (i.e. nephrotic syndrome, lupus nephropathy, membranous glomerulopathy, etc). Before treatment, the urate clearance rate averaged 5,35 ml/min and 74% of the patients had a uric acid clearance rate less than the normal value minus 1 SD. Benzbromarone replaced benziodarone in 2 cases and allopurinol in 1.

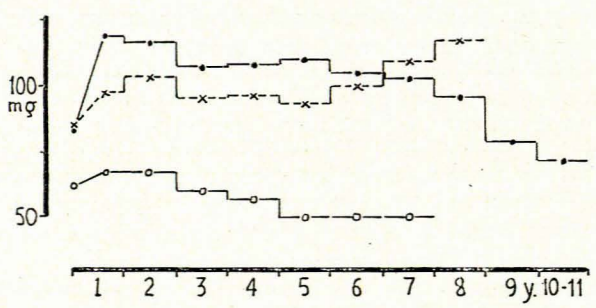


**Fig. 1. Mean daily dosage of benzbromarone in patients treated for gout (●), primary (°) or secondary (x) latent hyperuricaemia.**

**Severe renal insufficiency.** In 12 patients severe renal insufficiency (mean serum creatinine level 6,1 mg/dl) was responsible for the hyperuricaemia and was treated with benzbromarone. Two other patients, who required regular haemodialysis , also received the drug.

### Dosage

Benzbromarone was administered orally in regular increments followed by progressively tapered doses (Fig. 1). After the 8th year of treatment the dosage could be reduced further without serum uric acid levels rising above 5 mg/dl, even in patients with previous tophi. From the 5th year of treatment all patients with primary latent hyperuricaemia could be treated with benzbromarone 50 mg/d. In several cases of secondary asymptomatic hyperuricaemia due to renal deterioration following the natural course of the underlying nephropathy, the dosage had to be increased.

In patients with severe renal impairment and in rare cases in the other groups, benzbromarone was given in higher doses (up to 300 mg/d). Dosages of 50 and 100 mg were given as a single dose in the morning; patients receiving 150 or 200 mg/d were given 100 mg in the morning and the balance (50 or 100 mg) in the evening. Serum uric acid levels remained stable throughout the day.

### Duration of treatment

**Gout.** Patients in this group were treated for up to 10 years 8 months (mean 5 years 1 month); 29 patients received benzbromarone for more than 5 years.

**Primary asymptomatic hyperuricaemia.** These patients were treated for up to 8 years and 5 months (mean 3 years 1 month); 15 patients received benzbromarone for more than 3 years.

**Secondary asymptomatic hyperuricaemia.** These patients were treated for up to 9 years (mean 3 years 4 months); 15 patients received benzbromarone for more than 3 years.

**Severe renal insufficiency .** Patients were treated for up to 4 months (mean 35 days).

### Associated measures

Of prime importance and aimed at preventing articular flare-ups and urinary symptoms are associated measures including: (*i*) prophylactic colchicine (1 mg/d) for 2-3 months or even longer (in gouty patients); (*ii*) adequate fluid intake (2 l/d) divided throughout the day; and (*iii*) alkalinization (or, better, neutralization) of the urine with oral sodium bicarbonate, mineral soda, sodium, or potassium citrate preparations.

The importance of adequate fluid intake and alkalinization of the urine cannnot be over-emphasized in patients with a history of urolithiasis or urate over-production and when environmental factors (uncontrolled diet, excessive perspiration) tend to increase uric acid excretion or reduce urine output. During the 1st year of treatment we found that restriction of the intake of purine and alcoholic beverages was desirable; after a year's successful treatment this becomes superfluous and can be abandoned without detriment.

## Follow-up

All patients were seen more frequently at the beginning of treatment and then at least every 4 months; at each visit the serum urate level was determined, 24-hour urinary urate excretion and clearance and the urinary pH measured, and the urine examined for crystals, erythrocytes and leucocytes. Renal function and the blood picture were studied at least once a year. When articular abnormalities or tophi had been found initially joint radiographs were repeated.

Extensive investigations into the effects of benzbromarone on the liver, nervous system and eyes were also performed.

# Results

## Biological

In all the patients benzbromarone produced a dramatic fall in serum uric acid levels, which then remained fairly stable (Fig. 2) and far below the 'safety level' of 5 mg/dl (Table I). In a few rare cases the serum urate levels were found to be slightly above 6 mg/dl, but this was probably due to poor compliance. There was no significant difference between patients with or without tophi as regards final serum urate levels. The sustained uricosuric action of benzbromarone is shown by the persistent elevation of urinary urate excretion (27 - 40% above the initial level). Correspondingly a sustained elevated uric acid clearance rate (mean + 180%) was calculated throughout the period of treatment in all the patients. A high urine output (2 l/d) contributes to the uricosuric efficacy of the drug.

In patients with severe renal insufficiency daily doses of 100, 200 and 300 mg benzbromarone reduced the serum uric acid levels only by 23%, 27% and 46% respectively, enhanced urinary urate excretion by only 3%, 27% and 33% and increased urate clearance by less than 90%. The drug was ineffective in the 2 patients undergoing regular haemodialysis.

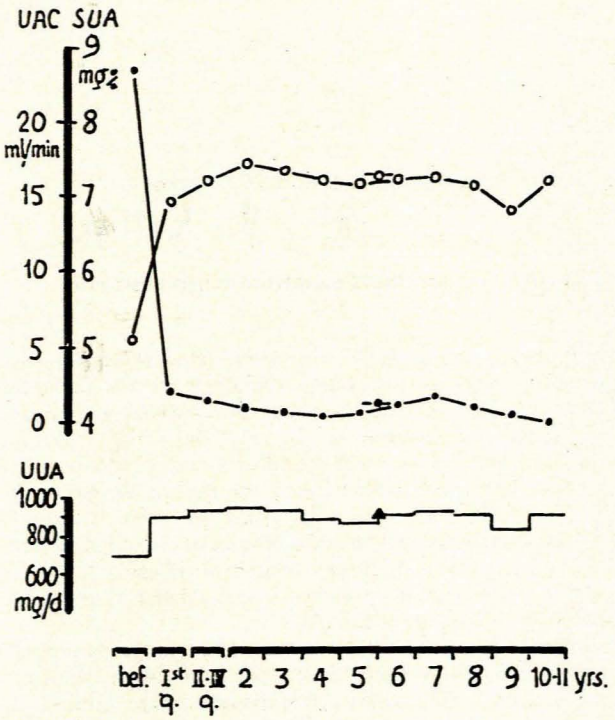


**Fig. 2. Serum uric acid level (SUA), urinary uric acid excretion (UUA) and uric acid clearance (UAC) in 186 hyperuricaemic patients before and on long-term treatment with benzbromarone (—●— = mean SUA ($N = 1929$); —o— = mean UAC ($N = 1569$); ▲ = means UUA ($N = 1784$) during treatment).**

## Clinical

Only after a sufficient duration of therapy can clinical results be appreciated. Fig. 3 demonstrates how the clinical course of gout can be dramatically changed by rationally controlled treatment with benzbromarone. We calculated the so-called 'index of severity' of gout in 73 patients given benzbromarone as the first drug of choice by multiplying the yearly incidence of the articular attacks (here the mean was 3 before treatment) by the severity of each attack, quoted from 1 to 3 according to intensity and duration. It can be seen that the index falls from 9 before treatment with benzbromarone to less than 4 during the first 3 months of treatment, and then to less than 2 during the following 9 months. During the first 3 months of treatment 18 of 73 patients (24%) experienced frank or moderate attacks of gout, represented below the curve by black, open or half symbols according to severity. Frank attacks became more rare from the first months onwards, as did the total number of articular manifestations . Five of the episodes of slight articular pain were precipitated by the discontinuation of colchicine, and some were related to an increase in the daily dose of the uricosuric drug. Initial flare-ups were more frequent in patients treated with higher and more rapidly increased doses, but were not more severe in the patients with tophi. Some of these articular manifestations were provoked by the same precipitating factors as before treatment; this justifies compliance with the dietary restrictions during the first 10-12 months of treatment, as discussed previously.

After 1 year of treatment we observed only very rare, transient and slight articular manifestations — 1 frank attack in the 4th year after over-indulgence in alcohol, 1 slight attack in another patient in the 6th year after a banquet, and 3 episodes of mild joint pain, brought about by decreasing the daily dosage of benzbromarone and remitting spontaneously within several days.

Parallel with this we noted in all cases a rapid and marked improvement in any other atypical muscular, tendinous and

**TABLE I. SERUM URIC ACID LEVEL, URINARY EXCRETION AND CLEARANCE BEFORE AND DURING LONG-TERM TREATMENT WITH BENZBROMARONE**

| | Serum uric acid level (mg/dl) | | | Urinary uric acid level (mg/d) | | | Uric acid clearance rate (ml/min) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | During | % | Before | During | % | Before | During | % |
| **G** | **8,6** ($N = 74$) | **4,12** ($N = 1264$) | **—52** | **678** ($N = 74$) | **917** ($N = 1173$) | **+35** | **5,67** ($N = 74$) | **16,45** ($N = 167$) | **+194** |
| **PLHU** | **8,43** ($N = 41$) | **3,95** ($N = 288$) | **—53** | **687** ($N = 41$) | **876** ($N = 274$) | **+ 27** | **5,73** ($N = 41$) | **16,96** ($N = 225$) | **+ 196** |
| **SLHU** | **9,09** ($N = 37$) | **4,91** ($N = 359$) | **—46** | **646** ($N = 37$) | **904** ($N = 344$) | **+40** | **5,32** ($N = 37$) | **14,41** ($N = 266$) | **+171** |

G = gout; PLHU = primary latent hyperuricaemia; SLHU = secondary latent hyperuricaemia.

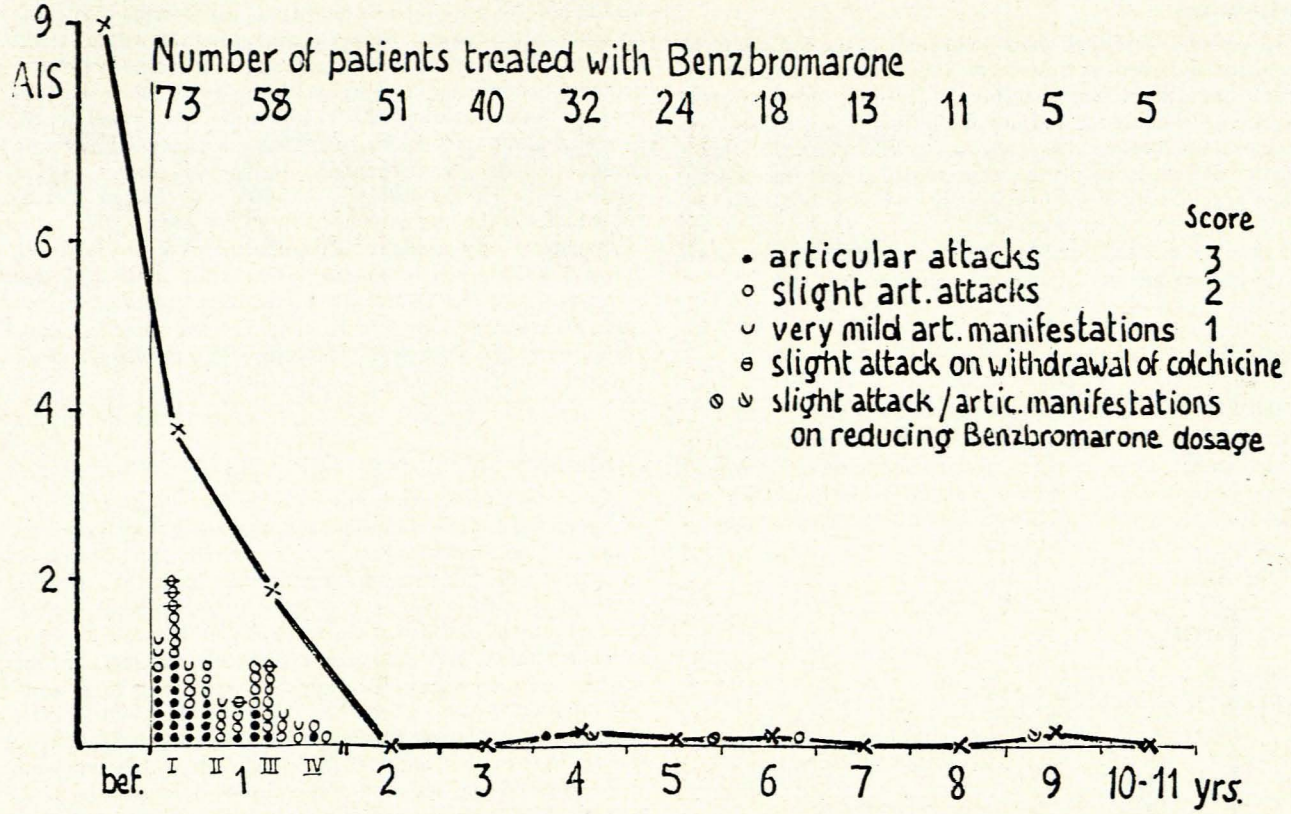


**Fig. 3. Articular index of severity = 9 (3 x 3) = an average of 3 articular attacks every year before treatment. The 73 patients had not previously been treated with serum uric acid-lowering agents.**

periarticular complaints present. In all the 28 patients with initial urate deposits tophi were fully resorbed within 6-18 months, and in all cases radiographs showed an improvement in bony and articular lesions, which tended to become more sharply limited and to give place to calcification within 1 year.

Articular manifestations were never observed in the patients with asymptomatic hyperuricaemia, even at the beginning of treatment. In 2 patients with soft-tissue urate deposits due to prolonged diuretic therapy benzbromarone induced a total resorption of the tophi within less than 1 year, although the diuretic therapy was continued.

In patients with severe renal impairment benzbromarone therapy was too brief to assess its possible beneficial effect.

## Tolerance

In 7 patients (3,5%) gastro-intestinal disturbances, including diarrhoea, occurred between 2 weeks and 15 months of beginning treatment. Diarrhoea subsided spontaneously within a few days of cessation of the drug.

In 1 allergic patient (0,5%) with severe renal insufficiency we observed a severe pustulous and petechial skin reaction in the 3rd week of treatment (300 mg/d), which subsided within a few days of cessation of treatment. In all the other patients benzbromarone was very well tolerated in every way.

Routine follow-up demonstrated the innocuousness of the drug. Particular attention was paid to renal tolerance. Proteinuria remained unchanged or absent in 116 of 134 patients (87%) and improved or disappeared in 8 others (6%). In 10 transient or intermittent proteinuria was related to associated diabetes, hypertension or lithiasis.

Similarly, microscopic haematuria, which was rarely present, did not become more common during treatment. As shown in Table II, renal function parameters did not change significantly over the 10 years of treatment in the patients with gout and primary latent hyperuricaemia or in those with severe renal disease, who were given rather higher doses for up to 3 months. Most of the patients with secondary asymptomatic hyperuricaemia had a causal renal disease, the spontaneous course of which was seemingly not influenced by the uricosuric drug.

**TABLE II. RENAL FUNCTION BEFORE AND DURING LONG-TERM TREATMENT WITH BENZBROMARONE FOR GOUT/PRIMARY LATENT HYPERURICAEMIA AND SHORT-TERM TREATMENT IN PATIENTS WITH SEVERE RENAL INSUFFICIENCY**

| | Serum urea level (mg/dl) | | Urea clearance rate (ml/min) | | Serum creatinine level (mg/dl) | | Creatinine clearance rate (ml/min) | |
|---|---|---|---|---|---|---|---|---|
| | Before | During | Before | During | Before | During | Before | During |
| **Long-term treatment (G, PLHU)** | **34 (*N* = 123)** | **36,2 (*N* = 729)** | **48 (*N* = 97)** | **49,4 (*N* = 404)** | **1,14 (*N* = 104)** | **1,14 (*N* = 499)** | **98,4 (*N* = 97)** | **98,9 (*N* = 434)** |
| **Short-term treatment (SRI)** | **128 (*N* = 11)** | **109 (*N* = 29)** | **16,6 (*N* = 6)** | **16,6 (*N* = 10)** | **6,2 (*N* = 9)** | **6,2 (*N* = 21)** | **17 (*N* = 6)** | **20 (*N* = 9)** |

G = gout; PLHU = primary latent hyperuricaemia; SRI = severe renal insufficiency.

The lack of hepatic side-effects was convincingly demonstrated in 111 patients (80 treated for more than 1 year) by routine studies of liver function and enzyme levels and by liver echography in 45 cases. Three patients suffered from viral hepatitis during treatment, and recovered without sequelae. No abnormalities which could have been attributed to a toxic effect of benzbromarone on the haemopoietic system were observed. Some of our patients were treated simultaneously with antimetabolites; none of them revealed any potentiating effect of benzbromarone on the haematological toxicity of the immunosuppressive drugs.

Deleterious effects of benzbromarone on the nervous system (EEG, nerve conduction velocity, resistance to ischaemia) or the eyes (lens and cornea) were not observed in 26 of our patients on long-term treatment. No abnormal psychiatric manifestations pointing to chronic bromide toxicity were noted.

## Adverse reactions to treatment

Our patients did not fully escape the two dangers of any uricosuric therapy, articular flare-ups and urolithiasis. Of the 30 articular attacks observed in the first 3 months of treatment only 20 had no obvious precipitating cause and were therefore probably or possibly due to treatment. Twelve of them (in 7 patients) were frank gouty attacks. In the patients previously treated with a less potent hypo-uricaemic agent a progressive substitution of benzbromarone succeeded in avoiding any rapid lowering in serum uric acid levels and hence avoided articular incident.

Adverse reactions to treatment were rare in our patients (Table III) despite the fact that a high proportion were urate over-excretors or had a history of renal colic.

**TABLE III. ADVERSE REACTIONS IN 20 OUT OF 200 PATIENTS TREATED WITH BENZBROMARONE OVER A 10-YEAR PERIOD**

| Adverse reaction | Incidence | Percentage |
|---|---|---|
| **Diarrhoea** | **7** | **3,5** |
| **Allergy** | **1** | **0,5** |
| **Urinary sand** | **4** | **1,5** |
| **Renal colic** | **2** | **1,0** |
| **Urate lithiasis** | **4** | **1,5** |
| **Oxalate lithiasis** | **3** | **1,5** |
| **Phosphate lithiasis*** | **1** | **0,5** |
| **No adverse reactions** | **180** | **90,0** |
| **Total number of patients** | **200** | **100,0** |

Two patients experienced two adverse reactions.
*This patient had an associated primary hypercalciuria.

Urate crystals in sediment did not become more frequent during treatment. In those patients who experienced urinary problems during treatment the urinary pH did not increase in spite of the neutralizing preparations prescribed (were they in fact taken?), whereas the urinary pH did increase in the patients who did not have any urinary symptoms during treatment with benzbromarone. Two of the 4 episodes of 'sandy urine' and 3 of the 4 of urate lithiasis were associated with insufficient hydration and/or neutralization or urine. Two patients suffered from renal colic following a train journey, but did not pass stones. The overall incidence of urate lithiasis is therefore only 2%, and it does not exceed 3% if we consider that the 2 latter cases were perhaps related to urate concretions. Uric acid excretion and clearance was not significantly greater in patients who had urinary incidents than in the others. A history of urolithiasis is an essential determinant of the urinary risk of treatment: there was only 1 episode of sandy urine in the 68 gouty patients without any history of urinary symptoms, but 2 such episodes, 2 of urate stone, 1 of renal colic and 1 of oxalate lithiasis among the 35 patients who had had urinary problems before treatment. The mean dosage of benzbromarone was slightly higher (142 mg/d) in the patients who experienced such incidents than in the whole group during the first 4 years of treatment (114 mg/d).

## Discussion

The long-term administration of benzbromarone confirmed earlier findings from pharmacological studies and short-term clinical trials. Benzbromarone is a uricosuric agent with a continuous, uniform and potent efficacy which reduces serum uric acid levels by 46 - 54% in normal doses, as well as reducing the urate pool. The half-life of the drug enables single daily doses to be administered.

Biological data collected from our patients are very similar to those published by other authors. The superiority of benzbromarone to probenecid and sulphinpyrazone is obvious, and its greater antihyperuricaemic potency relative to that of allopurinol has also constantly been documented experimentally and clinically.

From a clinical viewpoint all authors have observed the unequivocal benefits of treatment with benzbromarone within a few months. Clinical results appear better than those obtained with the two previously used uricosuric agents, probenecid and sulphinpyrazone.

While we did not observe any attacks after 1 year of treatment with benzbromarone, Serre *et al.* noted gouty attacks in 20% of a large group of patients treated with probenecid for 2 - 3 years and in some 10% of those treated for 4 - 9 years. Effective reduction of tophi took place in some 25 - 36% of these patients.

Allopurinol possesses a more limited clinical action. Of 110 patients treated by Serre *et al.* for up to 4 years, 26 (24%) still experienced attacks and 'a reduction of tophi was noted in 19 out of the 81 tophic patients'. Even in the most severe and tophaceous forms of gout, benzbromarone brought about a total and constant disappearance of joint pains.

Articular attacks were not observed in the 41 patients with primary asymptomatic hyperuricaemia treated for up to 7 years and whose history and clinical and biological characteristics strongly suggested that they were 'pre-gouty' subjects. The value of benzbromarone in our patients with secondary asymptomatic hyperuricaemia is not so clear; associated and/or causal disease interfered and often determined the clinical course and outcome. Many authors, however, believe that associated hyperuricaemia may worsen the course of the the underlying nephropathy and that of hypertension, and should therefore be treated routinely. Further, in this group gouty manifestations which could have occurred in the absence of treatment were not observed. In the patients with severe renal impairment treatment was too short for any valid conclusions to be drawn from the data obtained.

Progressively increased dosage and the prophylactic administration of colchicine for the first weeks or months of treatment was useful in helping to reduce the incidence of joint attacks. The incidence of urinary symptoms was as low as 2 - 3% in our group and far below those of 21% reported by Serre *et al.* in patients treated with probenecid and 18% observed by Yu *et al.* in patients treated with sulphinpyrazone. This is particularly significant since 35% of our patients had a previous history of urinary symptoms and 19 - 44% of patients were found to have hyperuricosuria prior to treatment. Furthermore, our findings show that a history of urolithiasis, even if it increases the risk of recurrence during uricosuric therapy, does not absolutely

contraindicate low-dose, well-controlled benzbromarone therapy.

General tolerance of benzbromarone is very good, as has been demonstrated by all authors. In only 3,5% of our patients did diarrhoea necessitate the interruption of treatment; this figure is similar to that in the American co-operative study (3,4%). This side-effect is not severe and is strictly transient, but unfortunately precludes continuation of treatment.

The renal, hepatic and haematological safety of benzbromarone deserves stressing. The drug can be administered for prolonged periods of time to patients who frequently have associated kidney or liver diseases or impairment. Our results confirm those of other authors. Benzbromarone can safely be administered to patients with renal or hepatic disease. The prolonged excretion of increased amounts of uric acid does not alter tubular function, which on the contrary is certainly endangered by interstitial deposits due to chronic hyperuricaemia. Benzbromarone also does not affect carbohydrate metabolism in diabetic patients.

The absence of interference with other drugs makes benzbromarone especially useful in treating hyperuricaemic patients, who often require associated therapy such as analgesics, anticoagulants, antidiabetics or antihypertensive drugs, and even antimetabolites in some nephropathies.

In the light of our long-term results and those obtained during the last 10 years from more than ten countries, we can state that this benzofuran derivative is an important addition to the antihyperuricaemic armamentarium, and that improved therapeutic results and tolerance as well as a reduction in side-effects can be expected.

In our opinion, however, some absolute or relative contraindications to benzbromarone still exist, and can be summarized as follows: (*i*) severe renal insufficiency with a serum creatinine level greater than 4 ml/dl; (*ii*) enormous overproduction and overexcretion of uric acid due to enzymatic deficiency, a haemopathy or drastic weight reduction; and (*iii*) renal and urinary lesions and malformation with obstacle(s) to urine outflow and urine stasis — hydronephroses, polycystic renal disease, spongy kidney, ureteric strictures, obstructions and dilatations must be excluded.

Besides these absolute contraindications some relative ones should be considered and the indications thoroughly weighed against possible risks. A history of previous renal colic is not a contraindication to benzbromarone; however, frequent and/or recent attacks, depending on their severity, may necessitate caution in prescribing, especially if there is associated hyperuricaemia or hypercalciuria. In any event one must be aware of the increased risk, as demonstrated by our patients, and be cautious in terms of dosage, in neutralizing the urine, and in ensuring that the patient will maintain an adequate fluid intake. In the presence of such relative contraindications and in patients in whom an additional increase in urate excretion is feared, low doses of benzbromarone (20 - 25 mg) and allopurinol (100 mg), recently shown by Mertz[6] to be both safe and efficacious, may be considered.

When used alone, the usual effective dose of benzbromarone lies between 50 and 100 mg/d. Only in patients with tophi is an increase to 150 mg/d necessary; this should be maintained for 1-2 years in order to induce a greater blood-tissue concentration gradient of uric acid and thus to accelerate the resorption of the tophaceous deposits. In patients with asymptomatic hyperuricaemia with no renal function impairment who are not taking any associated hyperuricaemic drug, 50 mg/d is usually sufficient. It is advisable to reiterate the absolute necessity of increasing dosage gradually at the beginning of treatment, particularly in patients who have a marked articular over-reactivity, a history of renal colic, very acid urine or a poor urine output.

Because of its biological and clinical profile, good long-term tolerance and the low incidence of side-effects, it seems logical and reasonable to consider benzbromarone as the first drug of choice in the treatment of gout, this 'prototype of the diseases due to deposits',[7] where the underexcretion of uric acid plays a dominating role. Benzbromarone gently corrects the causative underlying retention, and, in the majority of patients with gout and all the more in those with tophi, low uric acid clearance or 'pre-gouty' hyperuricaemia, fulfils the desired criteria both of efficacy and safety and helps to prevent attacks and renal impairment and to prolong the life of such patients in a state of comfort and health.

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