Drugs 14: 349-366 (1977)

Benzbromarone: A Review of its Pharmacological Properties and Therapeutic Use in Gout and Hyperuricaemia

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Summary

Synopsis: *Benzbromarone[1] is a benzofuran derivative which lowers serum urate and increases urinary urate excretion in normal, hyperuricaemic and gouty subjects. In open short- and long-term studies benzbromarone reduced serum uric acid levels by one-third to one-half and maintained its effectiveness for periods of up to 8 years. Single-dose experimental studies have shown benzbromarone to have a urate-lowering effect similar to that of a therapeutic dose of probenecid or sulphinpyrazone, but unlike these drugs benzbromarone can be administered in a once daily regimen. In 2 short-term comparative therapeutic trials in a small number of patients with hyperuricaemia, 80mg of micronised benzbromarone daily was at least as effective as 1000mg of probenecid or 300mg of allopurinol daily in lowering serum uric acid levels. Side-effects during benzbromarone administration are usually mild and primarily gastrointestinal in nature.*

Pharmacodynamic Studies: In studies in rats, benzbromarone decreased the reabsorption of uric acid injected into the proximal tubule but had no effect on excretion of distally-injected urate. In man, therapeutic doses of benzbromarone reduced serum uric acid levels in normal or hyperuricaemic individuals by one-third to one-half, with a concurrent rise in urinary uric acid excretion. In addition to uricosuric activity, an effect on enzymes involved in purine metabolism and an increase in faecal urate excretion have been proposed as the mechanisms of the lowering effect of benzbromarone on serum uric acid. Some urate-lowering effect has occurred in a small number of anephric patients, supporting the possible existence of an extrarenal mechanism of action. Further systematic studies are needed however, to confirm this. A dose of 80mg of micronised or 100mg of non-micronised benzbromarone has about the same effect on serum urate and urinary urate excretion as 1 to 1.5g of probenecid or 400 to 800mg of sulphinpyrazone. The duration of activity of a single dose is up to 48 hours and benzbromarone can thus be administered in a once daily dose, unlike other uricosuric drugs.

As with other uricosuric agents, concomitant administration of pyrazinamide or aspirin decreases the effectiveness of benzbromarone, but studies of the extent of this decrease in activity have produced variable results, depending on the dosages of the inhibiting drugs.

Pharmacokinetic Studies: Absorption of benzbromarone after oral dosing is affected by the particle size of the preparation administered; 100mg of a standard non-micronised dose showing the same bioavailability as about 80mg of micronised drug. About 50% of a single, non-micronised dose is absorbed and dehalogenated in the liver to form bromobenzarone and benzarone, which retain part of the activity of the parent compound. Excretion occurs primarily via the bile and faeces and to a lesser extent in the urine.

Therapeutic Trials: Although benzbromarone has undergone only limited direct comparative trials with other uricosuric agents, it is nevertheless an effective urate-lowering drug. In open studies, serum uric acid levels have been decreased by one-third to one-half in hyperuricaemic and gouty patients and maintained at the lower levels for periods of up to 8 years. Most tophaceous deposits either disappeared or were reduced in size after several months of therapy. In 2 short-term comparative studies, 80mg of micronised benzbromarone daily was at least as effective as 1000mg of probenecid or 300mg of allopurinol daily in lowering serum uric acid levels of a smaller number of patients with hyperuricaemia.

The effectiveness of benzbromarone is reduced in patients with impaired renal function and most authors consider the drug to be ineffective if the glomerular filtration rate is below 20ml per minute. Although a standard dose (100mg/day, non-micronised) has reduced serum urate to some extent in a few treated patients with severe renal dysfunction, increased doses, which may lead to troublesome side-effects, have usually been required to achieve adequate results.

Side-effects were usually mild, diarrhoea being reported in about 3 to 4% of patients. As with other uricosuric drugs, joint pains, acute attacks of gout and urinary urate precipitation

1 'Desuric', 'Uricovac' (Labaz); 'Minuric' (Reckitt-Labaz); 'Narcaricin' (Heumann).

can occur if colchicine cover, urinary pH adjustment and adequate fluid intake are not provided, particularly during initial treatment stages. A severe skin rash, in a patient with impaired renal function and a history of allergies, and allergic conjunctivitis have been reported in isolated instances.

Another benzofuran derivative, benziodarone, with a structure similar to benzbromarone, markedly enhances the effect of warfarin and some other oral coumarin and indanedione anticoagulants. Thus, although potentiation of oral anticoagulants did not occur in a few patients who have received concomitant therapy with benzbromarone, until further studies are available benzbromarone should be administered with caution to patients receiving anticoagulant therapy.

Dosage: Most gouty or hyperuricaemic patients with normal renal function have been optimally controlled on 40 to 80mg of micronised or 100 to 200mg of non-micronised benzbromarone administered once daily. As with other uricosuric agents, colchicine (0.5mg twice daily) should be administered concurrently for the first few months, until serum uric acid levels are reduced, to prevent joint pain or the precipitation of acute attacks of gout. Adequate fluid intake and maintenance of urinary pH at 6.3 to 6.7 will minimise the risk of urinary urate precipitation.

1. Animal Pharmacodynamic Studies

Benzbromarone, a benzofuran derivative (fig. 1), is recommended for the treatment of gout and hyperuricaemia. In animal studies, benzbromarone decreased the reabsorption of uric acid in the proximal tubule of rats. *In vitro* evidence of inhibition of xanthine oxidase and nucleotide dehydrogenases has been shown with high concentrations of the drug, but these findings appear to be of little significance in man.

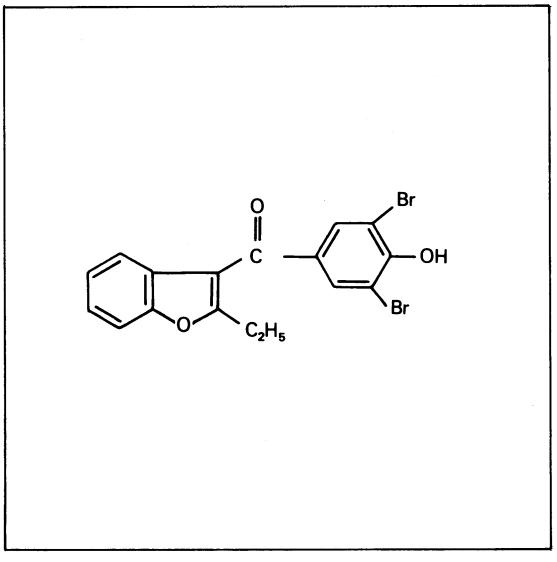

Fig. 1. Chemical structural formula of benzbromarone [2-ethyl-3-(4-hydroxy-3,5-dibromobenzoyl)-benzofuran].

1.1 Effect on Urate Transport in the Kidney

Both benzbromarone and its iodinated predecessor, benziodarone, inhibited urate reabsorption in the proximal tubule of rats when administered in an intravenous dose of 10mg/kg (Kramp, 1973; Kramp and Lenoir, 1975). When carbon-14-labelled urate was injected into proximal convulutions, total urinary recovery of radioactivity was significantly higher in treated rats than in the control group (83 to 88% versus 72 to 83%), but urinary urate excretion after distal injection of uric acid was not affected by either drug.

In an isolated organ experiment, benzbromarone was less potent than sulphinpyrazone and more potent than probenecid in inhibiting uric acid uptake by separated rabbit renal tubules. 50% inhibition occurred with 0.02, 0.18 and 0.26 mM concentration of sulphinpyrazone, benzbromarone and probenecid, respectively (Kippen et al., 1977). At very high drug

concentrations (about 0.5 mM), benzbromarone and sulphinpyrazone were approximately equipotent, both resulting in about 80% inhibition of uric acid uptake.

1.2 Effect on Enzymes Involved in Purine Metabolism

Inhibition of xanthine oxidase has been demonstrated in isolated rat liver preparations, but inhibition *in vivo* has not been shown (see Kramer and Muller, 1973). Since there appears to be no correlation between the inhibitory effect of a chemical on xanthine oxidase *in vitro* and hypouricaemic activity in man (Mertz, 1969), the significance of this *in vitro* finding is doubtful (see section 2.3).

A high dose of benzbromarone (100mg/kg) administered to rats for 3 to 12 days had no influence on the activity of adenine- and hypoxanthine-guanine-phosphoribosyltransferase in liver or erythrocytes (Becher, 1977).

2. *Human Pharmacodynamic Studies*

The uricosuric activity of the benzofuran derivatives has been studied since 1965 when benziodarone was reported to reduce serum uric acid levels and to increase urinary uric acid excretion. Subsequent studies showed that benzbromarone had a similar uricosuric activity, both in gouty and non-gouty subjects.

In normal or hyperuricaemic subjects, benzbromarone increases urinary uric acid excretion shortly after an oral dose and reduces serum uric acid by one-third to one-half after single or repeat doses. A dose of 80mg of a micronised and 100mg of a non-micronised preparation of benzbromarone have equal urate-lowering activity, and are about equipotent with 1 to 1.5g of probenecid or 400 to 800mg of sulphinpyrazone. Most investigators report a decreased effectiveness in the presence of renal dysfunction and the drug is not recommended when the glomerular filtration rate is below 20ml per minute.

The effect of concomitant administration of aspirin or of pyrazinamide on the urate-lowering and uricosuric activity of benzbromarone has not been unequivocally established, but as with other uricosuric agents it appears that pyrazinamide may block its activity while low doses of aspirin reduce its effect on renal clearance of uric acid by up to 50%.

Benzbromarone lowers serum uric acid levels through its uricosuric activity. Although some evidence supporting additional mechanisms (effect on enzymes involved in purine metabolism, increased faecal urate excretion) has been reported, further studies are required to clarify if these effects consistently occur, and if they contribute significantly to the urate-lowering action in man.

2.1 Effect on Serum Uric Acid Levels

Single oral doses or once daily repeated doses of benzbromarone reduce serum uric acid levels in normal and hyperuricaemic persons on a dose-related basis. 100mg of a non-micronised or 80mg of a micronised preparation lowers serum uric acid by 33 to 59%, with an accompanying increase in urinary uric acid excretion.

In 5 metabolically normal subjects, a single 10mg dose of micronised benzbromarone showed no urate-lowering activity while 20, 40 and 80mg doses caused a dose-related decrease in serum uric acid, the highest dose resulting in a 34% reduction 24 hours after administration (Jain et al., 1974). Onset of activity appeared between 3 and 4 hours with maximum effect at 24 hours (fig. 2). Similarly, in another study in normal subjects (30) using non-micronised benzbromarone, a single 100mg oral dose reduced serum uric acid from a mean of 5.28 to 3.51mg/100ml (a reduction of 34%) within the first 24 hours. A gradual rise then occurred over several days with original levels reached again by the end of the fourth day. Reduced serum uric acid levels were accompanied by an increase in urinary urate excretion

Table I. Effects of single doses of benzbromarone (100mg) and probenecid (1.5g) administered to one patient 8 days apart (Zollner et al., 1970)

	Benzbromarone	Probenecid
Uric acid clearance[1]	13.3ml/min	12.85ml/min
Urinary uric acid excretion[1]	13.62mg	13.36mg
Plasma uric acid[1]	3.28mg/100ml	3.38mg/100ml

1 Average values of several determinations.

which returned to pre-test levels after 4 to 5 days (Zollner et al., 1970a). Repeat doses of 100mg daily for 6 to 10 days reduced serum uric acid levels by up to 60% in the first 5 days.

In 50 hyperuricaemic or gouty patients, 5 to 14 consecutive daily doses of 20, 40 or 80mg of micronised benzbromarone reduced serum uric acid by 19%, 32 to 41%, and 50 to 59% respectively (Lee, 1977a).

2.1.1 Duration of Action

The duration of activity of a single dose of benzbromarone is up to 48 hours, probably due to a slow rate of elimination and/or active metabolites,

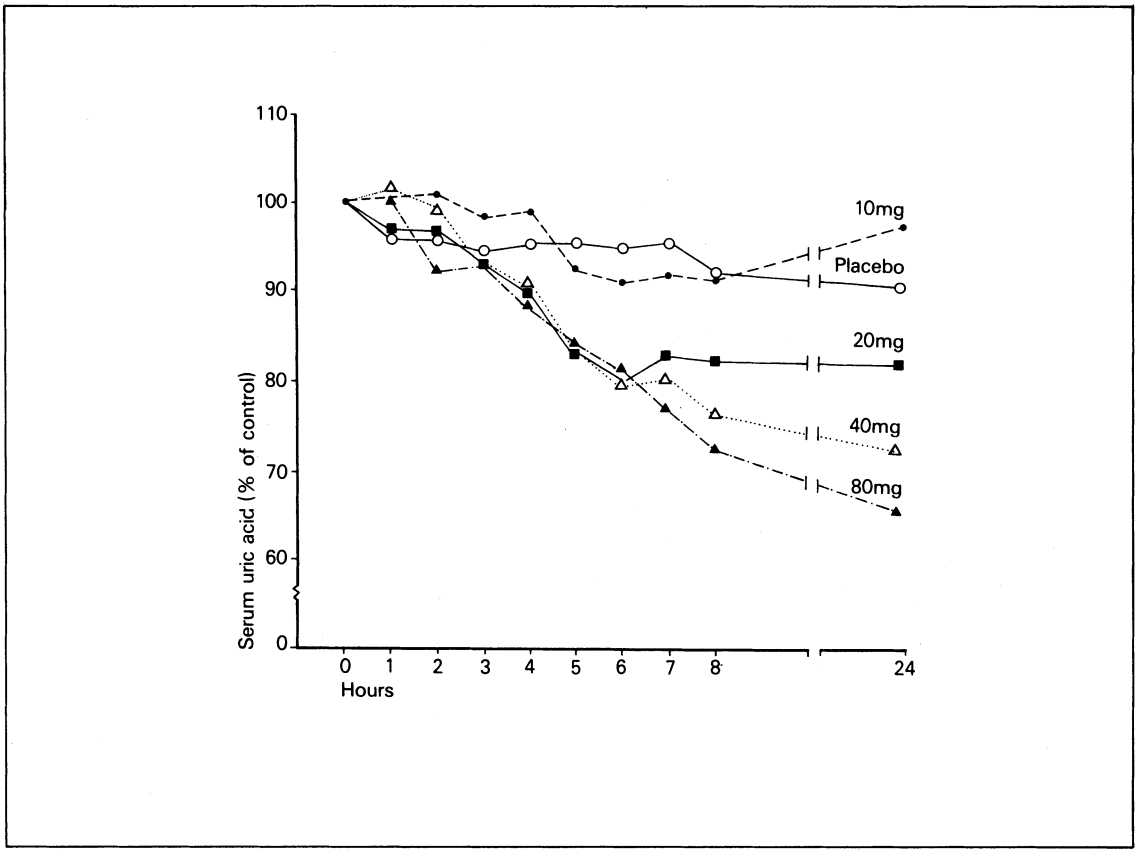

Fig. 2. Effect of single oral doses of benzbromarone and placebo on mean serum uric acid presented as a percentage of mean pretreatment control for each period in normal subjects (after Jain et al., 1974).

bromobenzarone and benzarone, which have been shown to have uricosuric activity (Jain et al., 1974; Broekhuysen et al., 1972; Zollner and Grobner, 1971).

2.1.2 Comparison with Other Uricosuric Agents

Probenecid and Sulphinpyrazone: The uricosuric effect of a single, non-micronised, 100mg dose of benzbromarone was compared with that of 1.5g of probenecid in the same normal volunteer, the drugs being given 8 days apart (Zollner et al., 1970). 9 hours after ingestion, serum uric acid was 2.30mg/100ml and 2.35mg/100ml after benzbromarone and probenecid, respectively. Effects on uric acid clearance and urinary uric acid excretion were likewise similar for the 2 drugs (table I). In 22 hyperuricaemic or gouty patients, 40 to 80mg of micronised benzbromarone similarly reduced serum urate levels or produced the same degree of uricosuria as 1 to 1.5g of probenecid or 400 to 800mg of sulphinpyrazone (Lee, 1977a; Yu, 1976).

Benziodarone: In 8 hyperuricaemic patients who had been receiving long-term treatment with benziodarone, substitution of the same dose of benzbromarone resulted in a similar though slightly smaller reduction in serum uric acid, and lower urinary uric acid clearance (Masbernard and Francoz, 1969). Similar findings resulted when the order of substitution was reversed. Thus, Zollner et al., (1970a) observed a slightly greater uricosuric effect with a single 100mg dose of benziodarone than with an equal dose of benzbromarone in the period immediately following administration to the same patient. In another study in which single 100mg doses of benzbromarone and benziodarone were administered 8 days apart to 14 subjects (7 healthy volunteers, 7 patients with hyperuricaemia), both drugs had a similar effect on serum uric acid (32 to 36% decrease), urinary uric acid excretion (increased about 200%), and uric acid clearance (increased about 300%) [Masbernard and Vaccon, 1970].

2.2 Effect on Xanthine Oxidase

Benzbromarone very weakly inhibits human xanthine oxidase *in vitro*, but does not appear to have inhibitory activity *in vivo*.

Benzbromarone inhibited xanthine oxidase from human liver on a non-competitive basis with an inhibition constant about 170 times that of allopurinol (competitive inhibition) and about 17,000 times that oxypurinol, an allopurinol metabolite (Sinclair and Fox, 1975; Spector, 1977). No increase in urinary xanthine or hypoxanthine, as occurs in man with xanthine oxidase inhibition, was demonstrable for 22 hours after a single 160mg (micronised) dose of benzbromarone (Sinclair and Fox, 1975).

2.3 Mechanism of Urate-Lowering Activity

The mechanism of the serum uric acid lowering effect of benzbromarone appears to be due to its uricosuric activity. Although some authors have demonstrated a significant effect on enzymes involved in purine metabolism, others have reported the opposite and thus no definite conclusions can be drawn from studies available at present. Experimental evidence supporting an increase in faecal excretion of uric acid during benzbromarone therapy has also been reported. Some urate-lowering activity in a small number of anephric patients (see section 4.3) supports the possible existence of an extrarenal mechanism of action (i.e. other than increased uricosuria) but further systematic investigation is needed to confirm this.

Greiling (1969) postulated that the reduction in oxypurine excretion which he observed after benziodarone administration (and which has since been reported following benzbromarone; Sinclair and Fox, 1975) was dependent upon activation of the enzyme hypoxanthine-guanine-phosphoribosyl transferase, with a resultant increase in inosine-5-monophosphate concentration and inhibition of uric acid synthesis via a feedback mechanism. Muller et al., (1975) demonstrated that uric acid synthesis was in-

hibited in the red blood cells of gouty patients receiving 300mg per day of benzbromarone, and the activity of adenine- and hypoxanthine-guanine-phosphoribosyl transferase were increased significantly (by 30 and 15% respectively) after 1 week of such treatment. Other authors however found no changes in phosphoribosylpyrophosphate levels in erythrocytes (Sorensen and Levinson, 1976) or in the activity of phosphoribosyltransferases (Sorensen and Levinson, 1976; Becher, 1977; Cartier et al., 1977) when benzbromarone was administered to hyperuricaemic or healthy subjects for periods of up to 1 year.

Muller et al., (1975) reported a 50% increase in urinary excretion of allantoin, a bacterial breakdown product of intestinally-excreted uric acid. Allantoin is reabsorbed and excreted via the kidneys, and increased urinary levels may thus indicate enhanced intestinal excretion of uric acid.

Other authors however consider that the only significant mode of action of benzbromarone is as a uricosuric agent which inhibits reabsorption of uric acid in the proximal tubule or in Henle's loop (Politta et al., 1973; Sorensen and Levinson, 1976; Sinclair and Fox, 1975).

2.4 Effect of Aspirin Administration on Uricosuric Activity

As with other uricosuric agents, the effectiveness of benzbromarone was reduced during concomitant administration of aspirin, particularly low doses, but studies of the extent of this reduction have produced varying results depending on the dosage of aspirin used.

In a single healthy subject, the urate-lowering effect of benzbromarone was decreased by the admin-

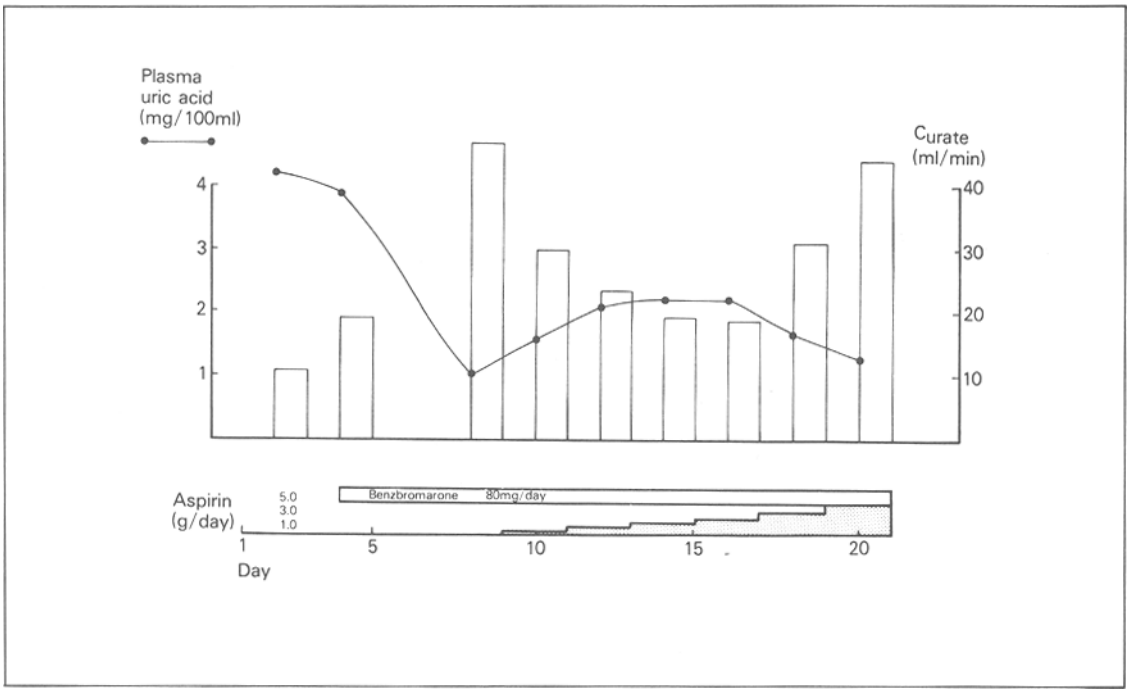

Fig. 3. Effect of varying doses of aspirin on benzbromarone-induced uricosuria in a single patient (urate clearance represented by open bars) [after Sorensen and Levinson, 1976].

istration of graded-doses of aspirin when tested over a period of several weeks; the maximum inhibitory dose of aspirin being taken as 2600mg daily (fig. 3; Sorensen and Levinson, 1976). When this dose was subsequently administered to 29 normal subjects receiving daily doses of 40 or 80mg of micronised benzbromarone, 58 to 80% of the urate-lowering effect was retained (Lee, 1977a; Sorensen and Levinson, 1976). Other authors, however have reported a more significant inhibition of urate-lowering activity, as reflected in uric acid clearance, in a short-term study using a lower dose of aspirin. Thus, in 6 gouty patients a single 600mg dose of aspirin reduced the peak ratio of urate to creatinine clearance achieved with a 160mg dose (micronised) of benzbromarone by about one-half (23% versus 12%; Sinclair and Fox, 1975).

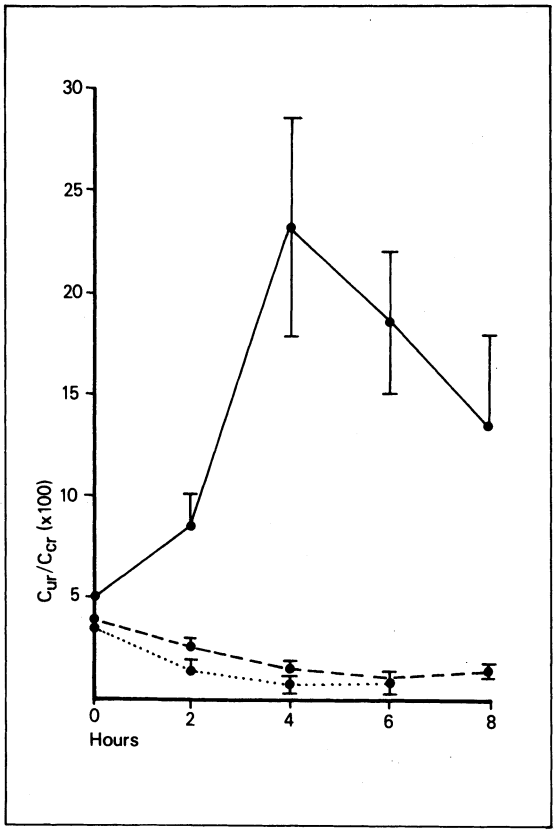

Fig. 4. Effect of benzbromarone alone and benzbromarone plus pyrazinamide on urinary uric acid excretion. Benzbromarone 160mg micronised dose in 6 patients (——); pyrazinamde 3g dose in 5 patients (.....); both drugs together in 5 patients (- - - -) [after Sinclair and Fox, 1975].

2.5 Activity in Patients Receiving Pyrazinamide

The extent of the loss of activity of benzbromarone in patients receiving pyrazinamide, an antituberculosis drug known to raise serum uric acid levels by inhibition of tubular secretion, cannot be clearly determined from studies available at present. Some authors have reported a complete loss of activity during concurrent administration, as with other uricosuric drugs, but in 1 study benzbromarone lowered serum urate in tuberculosis patients being treated with pyrazinamide.

Kropp (1970) administered a low daily dose of benzbromarone (50mg non-micronised) for 8 to 10 days to 10 patients receiving pyrazinamide 35mg/kg/day as treatment for tuberculosis. Plasma uric acid was reduced in all patients (mean reduction 24.3%), and returned to normal levels in 4 of the 10 patients. In the presence of a slightly higher dose of pyrazinamide (3g), however, a single high dose of benzbromarone (160mg micronised) had no uricosuric effect in 5 patients with gout (Sinclair and Fox, 1975; fig. 4), and other authors refer to unpublished data showing a loss of activity of benzbromarone during concurrent pyrazinamide administration (Sorensen and Levinson, 1976).

2.6 Effect on Lipid and Triglyceride Metabolism

Many patients with gout and hyperuricaemia also present with hyperlipidaemia and hypercholesterolaemia (Bresnik and Muller, 1974). A correlation between lipid, carbohydrate and purine metabolism which implicates fatty acid breakdown as one of the causative factors of increased uric acid synthesis, and therefore of gout, has been described by

Greiling (1969). Thus, the effect of agents used in the treatment of gout on lipid and triglyceride metabolism is of interest.

Benzbromarone does not appear to significantly affect lipid metabolism in usual therapeutic doses. Although 2 studies have reported increases in blood free fatty acids and triglycerides after very large daily doses (400 to 600mg/day, non-micronised; see Kramer and Muller, 1973; Bresnik and Muller, 1974), other authors have not seen a significant effect on lipid metabolism during treatment with usual doses of 50 to 200mg daily (Arcoraci, 1975; Begemann and Neu, 1975; Bresnik and Muller, 1974; Mertz et al., 1970; Ravera, 1975).

3. Pharmacokinetic Studies

Absorption of benzbromarone from the gastrointestinal tract appears to be partially dependent upon the particle size of the drug; micronised preparations being absorbed faster and more completely than preparations with a larger particle size. The major metabolite benzarone, and other metabolite bromobenzarone, possess uricosuric activity. The bile and faeces are the principal routes of excretion.

3.1 Absorption

In single-dose, oral bioavailability studies in 26 normal subjects, 100mg of non-micronised benzbromarone was equivalent to 80mg of a micronised preparation (Lee, 1977a). About 50% of a single, oral, non-micronised dose of 100mg is absorbed (Broekhuysen et al., 1972). In another single-dose study using 40mg of micronised drug, peak serum concentrations were reached at 2 hours in 6 of 9 patients (mean concentration 1.21μg/ml), at 4 hours in 2 patients and at 8 hours in 1 patient (Yu, 1976). Maximum uricosuria did not correspond with peak serum levels (fig. 5).

When radiolabelled benzbromarone purified by repeat crystallisation (large particle size) was administered orally, peak blood levels occurred 5 to 6 hours after a single 100mg dose. During repeat administration of 100mg daily for 14 days (non-micronised drug), blood radioactivity rose sharply for the first 2 days to a level corresponding to 2.1μg/ml of benzbromarone, then rose more gradually to a peak of 3.4μg/ml at day 12 (Broekhuysen et al., 1972).

3.2 Metabolism and Excretion

Following absorption, the drug undergoes extensive dehalogenation in the liver to form bromobenzarone and benzarone which are partially conjugated with glucuronic acid. 12 hours after inges-

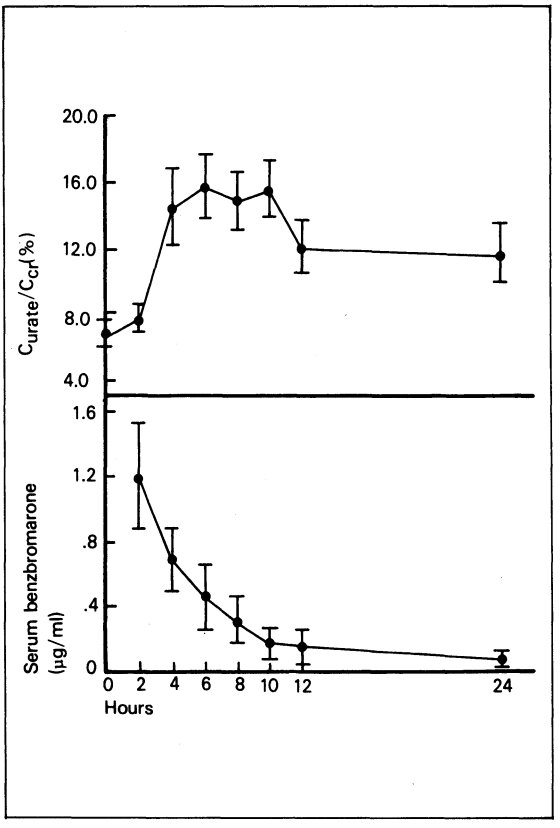

Fig. 5. Serum levels of drug and ratio of urate to creatinine clearance after a single 40mg micronised dose of benzbromarone in 9 patients with gout (after Yu, 1976).

tion, approximately 75% of the absorbed drug has been converted to benzarone, whch has uricosuric activity as has bromobenzarone (Broekhuysen et al., 1972).

Excretion of benzbromarone is via the urine, bile and faeces. Following a single oral dose of 100mg of labelled drug (non-micronised), 6% of the radioactivity was recovered in the urine, 27% in the faeces and 49% in the bile (Broekhuysen et al., 1972).

4. Therapeutic Trials

Although comparative trials with standard uricosuric drugs have been limited to 2 short-term studies in a few patients, benzbromarone is nevertheless an effective urate-lowering agent.

In uncontrolled short- and long-term studies it has reduced serum uric acid levels by one-third to one-half in hyperuricaemic or gouty patients and maintained the lower levels for treatment periods of up to 8 years. In most patients with tophaceous deposits, tophi either disappeared or were reduced in size after several months of therapy. In 2 short-term controlled studies involving a small number of patients with hyperuricaemia, 80mg of micronised benzbromarone daily for 5 to 7 days was at least as effective as 1000mg of probenecid or 300mg of allopurinol daily. Daily doses of 40 to 80mg of micronised benzbromarone have been about as effective as 100mg of a non-micronised preparation. Side-effects were primarily gastrointestinal in nature although joint pains, acute attacks of gout, and urate precipitation in the urine may occur, as with other uricosuric drugs, if appropriate precautions are not taken (see sections 5 and 7). Isolated cases of allergic reactions (severe skin rash, allergic conjunctivitis) have also been reported.

4.1 Short-Term Studies

Benzbromarone has reduced serum uric acid levels by about one-half in short-term studies in hyperuricaemic or gouty patients.

In a study involving 54 hyperuricaemic and 12 normal subjects who were treated with 100mg benzbromarone and 1mg of colchicine daily, a similar uricosuric effect was found in both groups. Serum uric acid was reduced by a mean of 55% after 1 week of therapy. Urinary clearance of uric acid levels at the end of 1 week increased by an average of 308% after 24 hours and remained above (188%) pre-treatment levels at the end of 1 week (Charbonnet and Rossier, 1973).

A 46 ± 14% reduction in serum uric acid levels after 5 days of treatment with 100mg daily of benzbromarone was reported by Mertz (1969) in 23 hyperuricaemic patients, 7 of whom presented with gout. Similarly, Ravera (1975) reported a rapid and constant lowering of serum uric acid in 23 hyperuricaemic patients, 5 of whom had gout, who were treated with benzbromarone 200mg daily for 4 days then 100mg daily for 10 days. A reduction in serum uric acid following 100mg benzbromarone for 6 to 15 days occurred in 9 hyperuricaemic patients treated by Matzkies et al., (1976) and in 22 patients treated by Barrachero et al., (1973).

In 2 hyperuricaemic patients (1 with gout) who responded poorly to extended therapy with a relatively low dose of allopurinol (200mg daily), treatment with benzbromarone 100mg a day resulted in a reduction in serum uric acid levels within 1 month from 11.2 to 4.6mg/100ml in the patient with gout, and from 9.1 to 4.0mg/100ml in the asymptomatic patient (Allwright, 1974).

Other authors have reported a 33 to 70% decrease in serum uric acid levels after 1 to 3 weeks of treatment with 40mg of micronised and 25 to 200mg of non-micronised benzbromarone daily (Arcoraci, 1975; Begemann and Neu, 1975; Kotzaurek and Hueber, 1968; Lee, 1977a; Matzkies and Berg, 1977; Matzkies et al., 1977; Yu, 1976).

4.2 Medium and Long-Term Studies

In 2 long-term studies involving a total of over 500 gouty or hyperuricaemic patients, benzbro-

marone decreased mean serum uric by 36 to 50% with continued effectiveness for up to 8 years. Treatment was well tolerated, the drug being discontinued due to side-effects in less than 5% of patients.

Masbernard and Giudicelli (1976) treated 81 patients with gout and 62 with hyperuricaemia for periods of up to 8 years (mean treatment periods were 4 and 2.5 years, respectively). Treatment with a non-micronised preparation was started at 50mg per day, gradually increased to not more than 200mg per day and then slowly decreased to about 100mg daily after several years. Mean serum uric acid decreased from 8.35 to 4.2mg/100ml after a few days, then stabilised at about 4.0mg/100ml. Urinary uric acid excretion and uric acid clearance rose from 658mg/day and 5.66ml/minute to stable levels of about 974mg/day and 15 to 21ml/minute, respectively. In 23 patients with tophaceous deposits marked regression of tophi was noted after 6 to 12 months treatment and was verified radiologically. In 61 patients with gout who had not received previous treatment, the calculated 'index of severity' of gout (the number of attacks per year times the severity, graded 1 to 4) decreased from 13.2 before treatment to 2.5 after the first year of therapy with benzbromarone. Diarrhoea was reported in 3.9% of patients, and treatment was discontinued due to adverse reactions in 4.5% of patients (diarrhoea and a severe skin reaction in 1 patient with renal dysfunction and a history of allergies). No changes occurred in liver function, EEG patterns or ophthalmic tests. There was no evidence of proteinuria and renal function was unchanged in 21 patients treated for more than 5 years.

In a second long-term multi-investigator study, 408 gouty or hyperuricaemic patients were treated with 40 or 80mg of micronised benzbromarone daily; 337 patients receiving treatment for longer than 6 months and 171 patients for over 1 year (Lee, 1977a). 323 of 326 patients available for long-term evaluation retained throughout their treatment period the lower serum urate levels achieved in the first few weeks (mean reduction 35.5%; range 15 to 48%). Uric acid levels in the remaining 3 patients, who received 40mg benzbromarone daily, showed a systematic upward trend throughout the study. There were a total of 219 acute gout attacks during the study compared with 346 during a similar period before treatment. Tophi in 22 of 29 patients either disappeared or decreased in size, while tophi in 7 patients were unchanged. 10 patients (2.5%) discontinued the drug due to intolerance (1 renal calculi, 3 renal colic, 5 diarrhoea, 1 acute gout attack). Diarrhoea or 'loose bowels' occurred in 2.7% of patients during the trial, with renal calculi, renal colic, sandy urine and nausea reported in a small number of patients. No consistent changes occurred in ECG or ophthalmological tests.

A number of additional studies (table II) have demonstrated a decrease in serum uric acid levels of about 50% during benzbromarone therapy. Side-effects were primarily gastrointestinal in nature, with joint pains or acute attacks of gout occurring frequently (12 to 29%) if initial colchicine cover was not provided but infrequently if this precaution was taken.

4.3 Comparisons with Other Urate-Lowering Drugs

The relative effectiveness of benzbromarone in lowering serum uric acid, compared with probenecid, another uricosuric agent, or allopurinol, a xanthine oxidase inhibitor, remains to be firmly established in 'longer-term', well-controlled studies involving a larger number of patients with gout or hyperuricaemia. In 2 short-term comparative studies involving small numbers of patients, benzbromarone (80mg micronised) was as active (1 study) or more active than (1 study) probenecid (1000mg) and allopurinol (300mg) after 5 to 7 days of treatment. The 2 studies were of similar design, but in one all drugs were given in a once daily dosage, while in the other benzbromarone was given once daily and probenecid and allopurinol were given in divided doses. Nevertheless, the response to probenecid and allopurinol was identical in both trials; the difference in results arising from a greater response to

Table II. Medium- and long-term therapeutic trials of benzbromarone in patients with gout or hyperuricaemia and normal renal function

Author	Number of patients	Daily dose[1]	Trial period (months)	Mean serum uric acid (mg/100ml)			Side-effects
				initial	final	% decrease	
Bresnik and Muller (1974)	20	600mg x 2wk then 100mg	6	8.8	4.9	44%	Gastrointestinal (10%)
Broll et al (1975)	34	100-200mg	6	7.1	4.2	41%	Diarrhoea (9%)
Famaey and Vandenabeele (1970)	40	100-300mg	2	8.6	3.8	56%	Gastrointestinal (7.5%)
Hartung (1972)	53	100mg	6-9	7-14	<6	50%[2]	
Lee (1977a)	408	40 or 80mg (micronised)	1-24+	—	—	36%	Diarrhoea (2.7%) Renal colic or calculi (2.2%) Sand urine (1.2%) Nausea (0.5%)
Masbernard and Francoz (1969)	25[7]	50-200mg	3.6	8.2	3.4	58%	Diarrhoea (3%)
Masbernard and Giudicelli (1976)	143	50-200mg	30-48[3]	8.4	3.7-4.0	52-56%	Joint pains (12%)[4] Diarrhoea (3.9%)
Masbernard et al. (1971)	15[7]	150-200mg	12-36	8.0	3.4-3.8	53-58%	Joint pains (23%)[4] Sand urine (5%) Renal colic (5%)
Sorensen and Levinson (1976)	7	40 or 80mg (micronised)	6-12	9.8	5.2	47%	Acute gout attack (29%)[4] Renal colic (14%)
Sternon et al. (1967)	24	50-300mg	0.1-5	8.4	3.8	55%	Gastrointestinal (12%) Conjunctivitis (4%)
Van Bogaert (1969)	23	100-300mg	6-7[5]	7.2	3.3	54%	
Zollner et al. (1971)	85	50-150mg	6+	—	—	—[6]	Gastrointestinal (11%) Renal colics (5%) Temporary impotence (5%)

1 All doses except 40 and 80mg/day are non-micronised; 40 and 80mg doses are a micronised preparation.
2 Per cent reduction reported for 5 patients only.
3 Mean treatment periods for hyperuricaemic and gouty patients, respectively.
4 Primarily in patients who did not receive initial colchicine cover.
5 Results given after 4 months treatment.
6 Data not given. Serum uric acid was reduced to <6mg/100ml in all patients during treatment.
7 These patients also included in Masbernard and Giudicelli (1976).

benzbromarone in one of the studies. In both comparisons, the maximum effect of benzbromarone occurred by the fourth day, while the response to allopurinol (and to probenecid in 1 study) was still increasing when the studies were terminated.

Thus, in a randomised, crossover study in 6 patients with hyperuricaemia, 80mg of micronised benzbromarone administered once daily was compared with 500mg of probenecid twice daily and 100mg of allopurinol 3 times daily (Lee, 1977b). Patients were hospitalised during the 5-day drug administration periods, and a placebo was administered twice daily for 5 days before the study and for 4 days between drug treatments. The mean serum uric acid level decreased from 8.97mg/100ml (pretreatment placebo period) to 5.32mg/100ml after benzbromarone (41% decrease), 6.36mg/100ml after probenecid (29% decrease), and 6.52mg/100ml after allopurinol (27% decrease). The maximum response to benzbromarone and probenecid was reached after the third day, while the response to allopurinol was still increasing after the fourth day (fig. 6), the last day for which data was provided. The control serum uric acid level before probenecid treatment (7.80mg/100ml) was lower than that before benzbromarone (9.35mg/100ml) or allopurinol

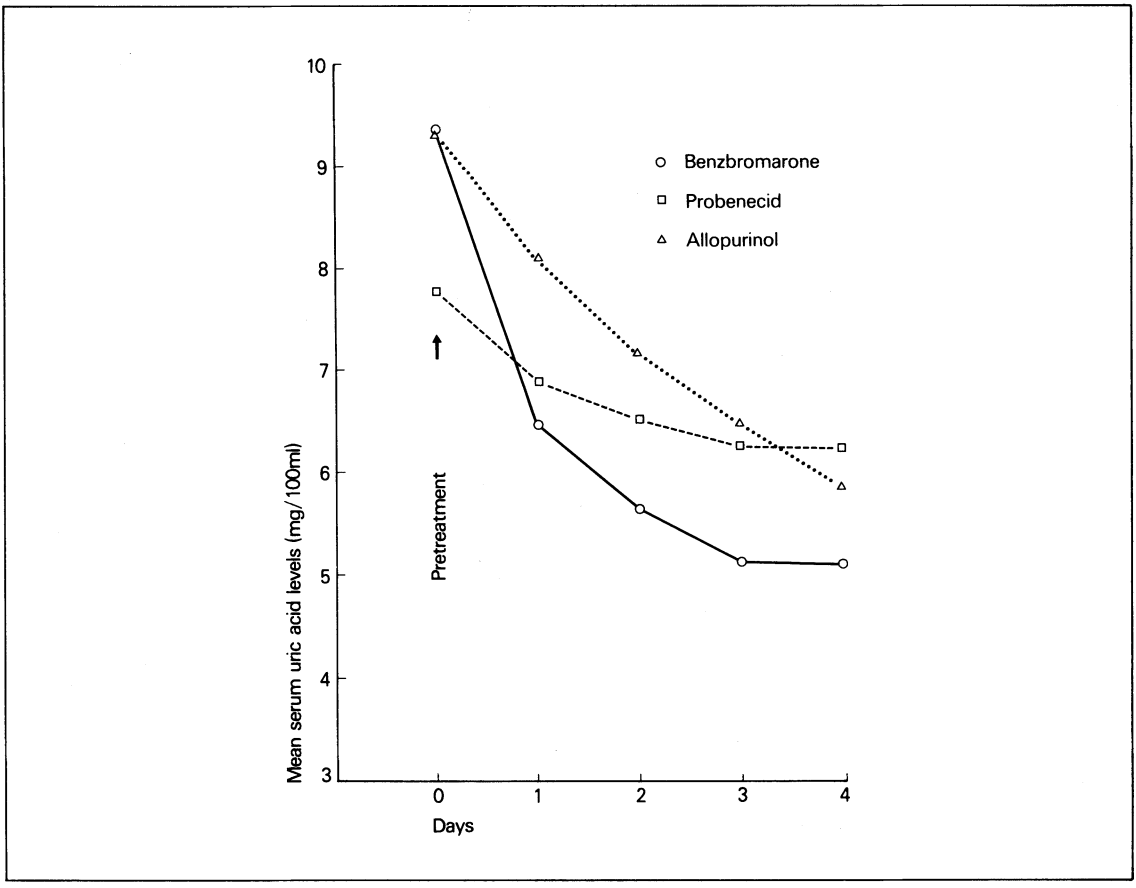

Fig. 6. Mean serum uric acid levels in 6 patients with hyperuricaemia during treatment with benzbromarone (80mg micronised, once daily), probenecid (500mg twice daily) and allopurinol (300mg, 3 times daily) [Lee, 1977b].

(9.33mg/100ml), probably due to a carry-over effect from the allopurinol period which preceeded probenecid in 4 of the 6 patients. Thus, the 4-day placebo period between drugs was insufficient to allow the effects of allupurinol to dissipate.

In a similarly designed study, using a longer placebo period between drug treatments, all 3 drugs were approximately equieffective. 80mg of micronised benzbromarone, 1000mg of probenecid, and 300mg of allopurinol were administered once daily for 7 days to 6 patients with hyperuricaemia (Lee, 1977c). The study was preceeded by a 14-day placebo period (1 tablet daily) and each drug administration period was separated from the next by a 7-day placebo period. The mean serum uric acid level decreased from 9.59mg/100ml (pretreatment placebo period) to 6.20mg/100ml after benzbromarone (35% decrease), 6.68mg/100ml after probenecid (30% decrease), and 7.01mg/100ml after allopurinol (27% decrease). While the maximum response to benzbromarone appeared to occur by the fourth day, the response to allopurinol and probenecid was still increasing on the fifth day, the last day for which individual data was provided (fig. 7.)

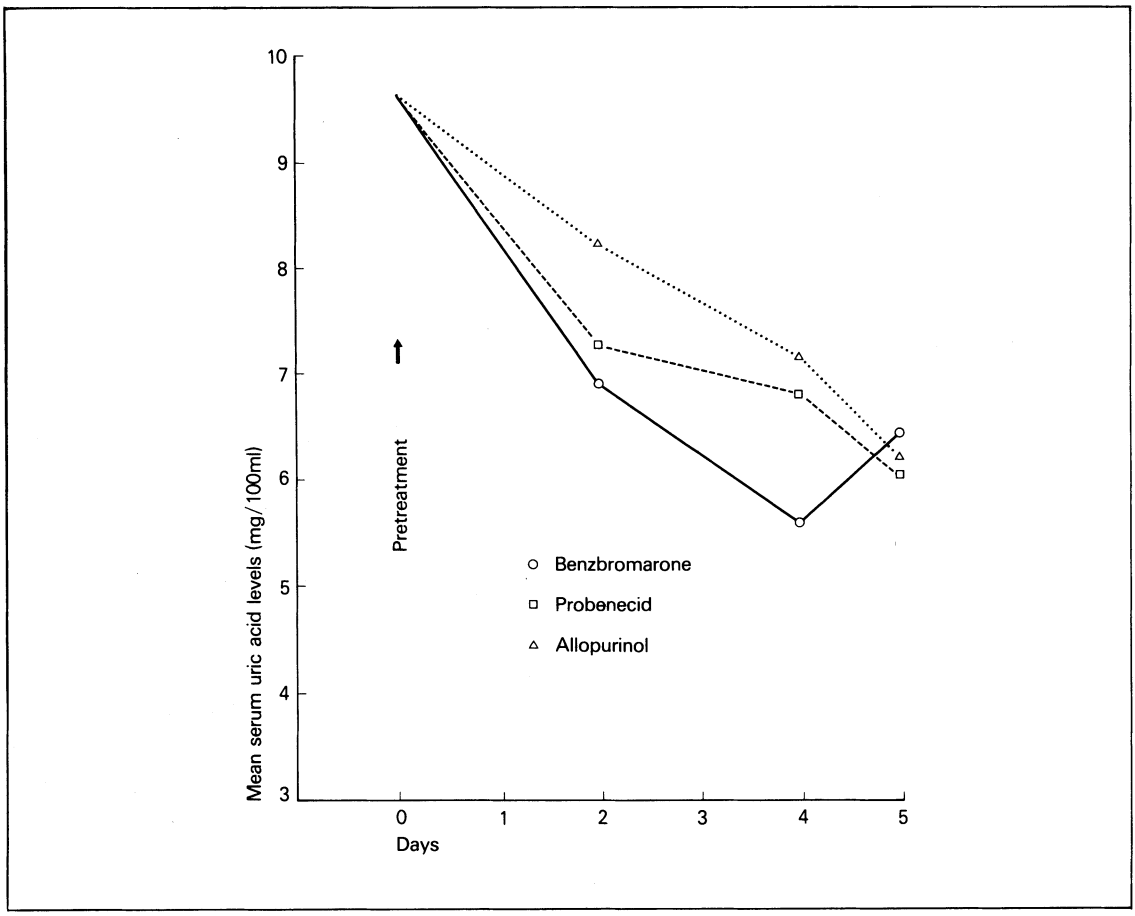

Fig. 7. Mean serum uric acid levels in 6 patients with hyperuricaemia during treatment with benzbromarone (80mg micronised, once daily), probenecid (1000mg once daily) and allopurinol (300mg once daily) [Lee, 1977c].

4.4 Effectiveness in Patients with Renal Dysfunction

The effectiveness of the traditional uricosuric drugs is reduced in the presence of renal dysfunction, and the potential complications of increased urinary uric acid excretion in such patients may outweigh the benefits. Thus, allopurinol is usually considered the preferred treatment in patients with significantly reduced renal function and hyperuricaemia requiring drug treatment (Hart, 1976).

Although standard doses of benzbromarone administered for up to 6 months have reduced serum urate to some extent in patients with mild to severe renal dysfunction without causing adverse effects, increased dosage is usually required to obtain an adequate response. In severe renal impairment (glomerular filtration rate less than 20ml per minute), the drug is considered ineffective by most authors.

Koethe et al., (1973) treated 45 patients with hyperuricaemia and renal dysfunction (serum creatinine 0.8 to 10.8mg/100ml; mean 3mg/100ml), 6 patients requiring chronic peritoneal dialysis, and 3 patients on long-term haemodialysis, with 100mg of non-micronised benzbromarone daily for up to 6 months. Serum uric acid was reduced by a lesser amount (23 to 25%) in those patients who required dialysis treatment than in patients whose renal dysfunction was less severe (39% reduction). Blood creatinine and urea levels were not significantly altered during benzbromarone administration. In shorter-term (1 to 4 weeks) fixed-dose studies, a 100mg daily dose (non-micronised) reduced serum uric acid by 35 to 38% in 38 patients with mild to moderate renal insufficiency (serum creatinine range of 1.9 to 6.4mg/100ml) compared with a 55% reduction in 60 patients with normal renal function (Begemann and Neu, 1975; Charbonnet et al., 1973). The same daily dose (100mg) decreased serum urate by 10 and 23% in 2 anephric patients with hyperuricaemia who were treated with benzbromarone for 1 month (Bec et al., 1977). No increase in the dialysis of urate occurred during the study period.

Masbernard and Giudicelli (1976) found that a dose of 300mg of benzbromarone (non-micronised) per day was required to produce a 50% decrease in serum uric acid in 12 patients with moderate renal impairment (mean serum creatinine 6.1mg/100ml), while 200mg or less produced similar results in patients with normal renal function. A severe skin reaction with purpura and blistering occurred in 1 patient with decreased renal function.

Other authors report that benzbromarone is of little use in patients with hyperuricaemia and advanced renal failure, due to decreased efficacy (requiring increased dosage) and the appearance of troublesome side-effects, as well as the threat of urate precipitation in the urine (Mertz, 1969).

When the glomerular filtration rate (gfr) is below 35ml per minute, benzbromarone treatment produces less than a 40% reduction in plasma urate; when the gfr is less than 20ml per minute a reduction in plasma uric acid of 20% or less can be expected (Masbernard and Francoz, 1969) at which stage benzbromarone therapy is not recommended (Mertz, 1969; Jain et al., 1974).

4.5 Effect on Diuretic-Induced Hyperuricaemia

Benzbromarone lowers serum uric acid levels during chlorothiazide administration without affecting the diuretic activity. In 5 patients receiving chlorothiazide 1.5g daily, the addition of benzbromarone 150mg daily (non-micronised) reduced serum uric acid from 7.3 to 3.0mg/100ml without changing urinary volume or sodium excretion (Gross and Girard, 1972). Similarly, combined treatment with chlorothiazide and benzbromarone (40 or 80mg daily of a micronised preparation) in 36 metabolically normal subjects decreased serum uric acid (quantitative data not given) without affecting the activity of the diuretic (Lee, 1977a).

4.6 Use in Fasting Patients

In 2 studies on patients who have developed hyperuricaemia during severe fasting over a 21-day

period for dietary reasons, benzbromarone 100mg (non-micronised) per day (47 patients) gradually reduced serum uric acid from 7mg/100ml to 4 or 5mg/100ml by the end of the study period, while serum urate in 20 controls who did not receive uricosuric therapy gradually rose to 11 to 14mg/100ml. A higher dose (300mg per day in 11 patients) reduced serum urate levels more markedly and rapidly to 3mg/100ml within 3 days (Schmahl and Schraepler, 1975; Schraepler and Schulz, 1976).

5. *Side-effects*

Benzbromarone appears to be well-tolerated, side-effects usually being mild in nature. Discontinuation of treatment due to intolerance (usually diarrhoea) has been necessary in 2.6 to 4.5% of patients. Diarrhoea has been reported in 2.2 to 9.0% of patients, with an apparent overall incidence of about 3 to 4%. Temporary impotence in men, lasting for 4 to 6 weeks with continuing treatment, has been reported in a few patients in 1 study (Zollner et al., 1971).

A severe skin reaction has been reported in 1 patient with renal dysfunction and a history of allergies receiving 300mg benzbromarone daily, and allergic conjunctivitis during benzbromarone administration was reported in another patient.

As with other uricosuric agents, joint pains and acute attacks of gout can occur during initial treatment stages if concomitant colchicine cover is not provided, as can urinary urate precipitation with consequent renal and ureteric symptoms. Most authors thus recommend maintaining a high fluid intake and urinary output, which may also enhance the uricosuric effectiveness (Masounabe-Puyanne, 1977), and maintenance of urinary pH at 6.3 to 6.7 to increase uric acid solubility.

6. *Precautions*

Administration of benzbromarone to patients with impaired renal function should be undertaken with caution. Although some such patients have been successfully treated for up to 6 months, most investigators report a decreased effectiveness and a need for higher doses which may cause troublesome side-effects. Certainly, when the glomerular filtration rate is below 20ml per minute the drug has very limited effectiveness (Mertz, 1969; Jain et al., 1974; section 2.1.3).

7. *Drug Interactions*

Oral anticoagulants: Although in a few patients, concomitant administration of benzbromarone and nicoumalone, ethylbiscoumacetate, and phenindione has not resulted in increased anticoagulant activity (Masbernard, personal communication 1977), another benzofuran derivative, benziodarone, with a similar structure to benzbromarone, markedly increases the effects of warfarin, nicoumalone, ethylbiscoumacetate, phenprocoumon and diphenadione (Verstraete et al., 1968; Pyorala et al., 1963). A third benzofuran derivative, amiodarone, did not influence the effect of phenprocoumon (Verstraete et al., 1968). The mechanisms and determinants or oral anticoagulant interaction are complex and it seems wise that, until further studies in this area are available (particularly with warfarin which has not been administered concurrently with benzbromarone in published studies to date), patients receiving benzbromarone and oral anticoagulants should be observed closely for possible potentiation of anticoagulant activity over the first weeks of combined administration of the drugs.

Aspirin: As with other uricosuric drugs, aspirin, particularly in low doses, reduces the uricosuric activity of benzbromarone (see section 2.4).

8. *Dosage*

Since particle size affects the extent and rate of absorption (see section 3), dosage is dependent upon the

type of preparation used. A dose of 80mg of micronised drug provides the same bioavailability as a dose of 100mg of non-micronised drug. Thus, in studies using standard non-micronised formulations most gouty patients were optimally controlled on 100 to 200mg per day, while 100mg daily was usually effective in hyperuricaemic patients with normal renal function. When a micronised form of the drug is used, 40 to 80mg daily provides optimum results in most patients. Because of its prolonged duration of action, benzbromarone may be administered in a single daily dose.

As with other uricosuric agents, colchicine (0.5mg twice daily) should be administered concurrently during the initial months of therapy, until serum uric acid levels are significantly reduced, to prevent joint pain or acute attacks of gout. Adequate diuresis and maintenance of urinary pH at 6.3 to 6.7, especially during the early treatment stages, will minimise the risk of urinary urate precipitation (see section 5).

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