Contemporary Themes

Committee on the Review of Medicines

RECOMMENDATIONS ON PHENYLBUTAZONE, OXYPHENBUTAZONE, FEPRAZONE, ALLOPURINOL, COLCHICINE, PROBENECID, AND SULPHINPYRAZONE

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Three years ago the Committee on the Review of Medicines began a review for the Medicines Commission of the drugs which were already on the market. The first set of its recommendations was published last year (17 September, p 758). Further recommendations are published below.

Phenylbutazone

Indications. Rheumatoid arthritis, osteoarthrosis, ankylosing spondylitis and gout, osteoarthrosis of the spine and degenerative disc disease presenting as lumbago, sciatica, or radiculitis. Prolapsed intervertebral disc. Reiter's disease and other seronegative (non-rheumatoid) arthropathies. Bone pain associated with Paget's disease and secondary neoplasm. Moderate to extensive superficial thrombophlebitis.

Dosage. ADULTS: Oral 400-600 mg daily initially, 200-300 mg daily maintenance, maximum 800 mg in acute gout. Rectal: 250-500 mg daily by suppository. Intramuscular injection: 600 mg every 2-3 days. CHILDREN: 5-10 mg/kg daily (orally).

Contraindications. Where danger of cardiac decompensation exists. Renal or hepatic disease including recent hepatitis. History of peptic ulceration, blood dyscrasia, known sensitivity to pyrazoles.

Precautions. History of dyspepsia. Concurrent therapy with other plasma protein-binding drugs—for example, oral anticoagulants, oral hypoglycaemic agents—may necessitate a modification in dosage.

Warnings and adverse effects. Gastrointestinal intolerance and bleeding. Blood dyscrasias may occur suddenly even after a small dose, particularly in the elderly. Blood count should be monitored both before and regularly during treatment. Associated risks of phenylbutazone therapy should always be weighed against the severity of the patient's condition and the expected clinical effect.

Oxyphenbutazone

Indications. Rheumatoid arthritis, osteoarthrosis, ankylosing spondylitis and gout. Osteoarthrosis of the spine and degenerative disc disease presenting as lumbago, sciatica, or radiculitis. Reiter's disease and other seronegative (non-rheumatoid) arthropathies. Bursitis and synovitis associated with recognised rheumatic diseases. Inflammation of certain ocular diseases, including uveitis, scleritis, keratitis, and postoperative inflammation. Prevention and treatment of severe postoperative inflammation and swelling, particularly in relation to faciomaxillary, ophthalmic, laryngeal, and plastic surgery. Swelling and pain due to *serious* sprains, strains, fractures, and contusions. Moderate to extensive superficial thrombophlebitis.

Dosage. ADULTS: Oral 400-600 mg daily for the initial 48 hours, 200-300 mg daily maintenance. Rectal: 250-500 mg daily by suppository. CHILDREN: 5-10 mg/kg daily (orally).

Contraindications. Where danger of cardiac decompensation exists. Renal or hepatic disease including recent hepatitis. History of peptic ulceration, blood dyscrasia, known sensitivity to pyrazoles.

Precautions. History of dyspepsia. Concurrent therapy with other plasma protein-binding drugs—for example, oral anticoagulants, oral hypoglycaemic agents—may necessitate a modification in dosage.

Warnings and adverse effects. Gastrointestinal intolerance and bleeding. Blood dyscrasias may occur suddenly even after a small dose, particularly in the elderly. Blood count should be monitored both before and regularly during treatment. Associated risks of oxyphenbutazone therapy should always be weighed against the severity of the patient's condition and the expected clinical effect.

Feprazone

Indications. Rheumatoid arthritis, osteoarthrosis.

Dosage. 200-600 mg daily. The maintenance dose should be reduced in patients with renal impairment. Paediatric usage not established.

Contraindications. Where danger of cardiac decompensation exists. Hepatic disease including recent hepatitis. History of peptic ulceration, blood dyscrasia, drug rash, or known sensitivity to pyrazoles.

Precautions. Concurrent therapy with plasma protein-binding drugs—for example, oral anticoagulants and oral hypoglycaemic agents—may necessitate a modification in dosage.

Warnings and adverse effects. Since blood dyscrasias occur with the other pyrazole drugs, blood count should be monitored both before and regularly during treatment.

Allopurinol

Indications. Gout: primary hyperuricaemia. Secondary hyperuricaemia: prophylaxis of uric acid and calcium oxalate stones.

Dosage. ADULTS: Initial dosage 100-200 mg, maintenance dosage 200-600 mg daily, rarely to 900 mg daily. Maximum single dose 300 mg. CHILDREN: 10-20 mg/kg body weight daily. Individual dose levels should be reduced as necessary to maintain normal serum urate concentrations. Overlap of treatment when changing from uricosuric therapy to allopurinol is recommended for one to three weeks to ensure a continuous hypouricaemic effect. Allopurinol administration should precede treatment with cytotoxic drugs. DOSE RECOMMENDED IN PRESENCE OF IMPAIRED RENAL FUNCTION: Impaired renal function may prolong drug action. Serum urate concentrations should be monitored and the dose adjusted accordingly. The following dose recommendation is for adults:

Creatinine clearance

Over 20 ml/min—standard dose

10-20 ml/min—100-200 mg daily

2-10 ml/min—100 mg daily or less frequently.

USE IN RENAL DIALYSIS: Allopurinol and its metabolites are removed by renal dialysis. If frequent dialysis is required, an alternative schedule of 300-400 mg after each dialysis with none in the interval is suggested.

Contraindications. Acute gout.

Precautions. Treatment should not be started during or immediately after an acute attack of gout. Administration during pregnancy. Reduce the dosage of allopurinol in patients with renal or hepatic disease. Reduce the dosage of 6-mercaptopurine and azathioprine if used concurrently with allopurinol.

Warnings and adverse effects. May precipitate an attack of acute gout during early stages of therapy. Possible potentiation of oral anticoagulants. Fluid intake should ensure adequate urinary output. Discontinue administration on occurrence of pruritus or skin eruptions.

Colchicine

Indications. Treatment and prophylaxis of acute gout. During initial therapy with allopurinol or urocosuric drugs in chronic gout.

Dosage. Acute attack, 1 mg initially (orally) then 0·5 mg every 2-3 hours until pain is relieved or diarrhoea occurs or until a total dose of 10 mg is reached. A course of therapy should not be repeated within three days. Prophylaxis, 0·5-1·5 mg orally, nightly or alternate nights. Dosage should be increased at the earliest possible sign of an impending acute attack. Combined therapy, with allopurinol or uricosuric drugs 0·5 mg two or three times daily. Not suitable for use in children.

Contraindications. Pregnancy.

Precautions. Reduced cardiac, renal, or hepatic function.

Warnings and adverse effects. Gastrointestinal symptoms are most likely to occur in patients with peptic ulceration or spastic colon.

Probenecid

Indications. Gout and hyperuricaemia. As an adjunct to therapy with penicillins and certain cephalosporins—for example, cephalothin, cephalexin and cephaloglycin.

Dosage. URICOSURIC THERAPY: Usual adult dose 500 mg daily for one week followed thereafter by 1 g daily. Daily dosage may be increased by 500 mg every four weeks up to a maximum of 2 g daily. When acute attacks have been absent for at least six months and serum urate concentrations are normal, dosage may be reduced by 500 mg daily over a period of months to the minimum effective dose. Paediatric dosage not established. PENICILLIN AND CEPHALOSPORIN THERAPY: General, ADULTS 2 g daily. Smaller dosage for elderly patients with suspected renal impairment. CHILDREN over two years—25 mg/kg body weight (or 0·7 g/m^2 body surface) initially; followed by 40 mg/kg (or 1·2 g/m^2) daily (or adult dosage if weight is over 50 kg). Gonorrhoea—single dose of 1-2 g, with adequate doses of either oral ampicillin or ampicillin derivatives.

Contraindications. History of blood dyscrasias or uric acid stones. Acute gout. Concurrent administration of salicylates.

Precautions. Administration during pregnancy. History of peptic ulcer.

Warnings and adverse effects. In the treatment of hyperuricaemia, ensure adequate fluid intake and alkalinisation of urine. Plasma concentration of sulphonamide is increased after prolonged concurrent therapy with probenecid. Reducing substances may appear in the urine.

Sulphinpyrazone

Indications. Chronic and recurrent acute gout. Hyperuricaemia.

Dosage. 100-200 mg daily increasing to 600 mg (rarely 800 mg) daily over first week, or until serum urate concentrations are within normal limits. Subsequent dosage should be reduced as necessary to maintain normal serum urate concentrations. Sulphinpyrazone should be given daily in divided doses with meals or milk. In some cases a single dose may suffice. Paediatric usage not established.

Contraindications. Active peptic ulcer. Severe hepatic disease. Sensitivity to phenylbutazone or other pyrazoles. Concurrent administration of salicylates.

Precautions. Administration during pregnancy. Use with caution in patients with healed peptic ulcer, impaired renal function or nephrolithiasis. Concurrent therapy with other plasma protein-binding drugs—for example, anticoagulants, sulphonamides, and hypoglycaemic agents—may necessitate a modification in dosage.

Warnings and adverse effects. May precipitate an attack of acute gout. Gastrointestinal bleeding may occur. Ensure adequate fluid intake and alkalinisation of the urine during initial stages of therapy. Invalidation of results of renal function tests involving PAH, PSP, or other organic acids may occur. Blood dyscrasias may occur suddenly even after a small dose. Blood count should be monitored both before and regularly during treatment.

Letter from . . . Chicago

Oblomov's syndrome

GEORGE DUNEA

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We spent two days on the beautiful island of Fiji, with its lush tropical vegetation, its towering palm trees, and its colourful flowers. We swam in the warm ocean, lay in the sun, drank Fijian beer, and rode with the natives on the bus from Nadi to Lautoka. We owed this unexpected tropical holiday to the striking Australian air controllers, and learnt on landing at Sydney's Mascot airport (and submitting to the traditional anti-sheep-disease spraying) that the controllers had walked out because one of their "mates" had hurt his back lifting a chair at work. Unable to stand for long periods he would have accepted a lower paid clerical job, but the union insisted on retirement with full superannuation privileges; so that the man, caught between management and the unions, eventually had to resign from his job. But that was some time ago. . . .

Lately the air controllers have again been in the news, this time at Chicago's O'Hare, the world's busiest airport, where 750 000 planes land each year, and where the controllers play a perpetual game of chess in the dark, in front of a radar screen, with blips representing circling planes as chessmen. The stress and responsibility are enormous; and periodic computer failures aggravate their ulcers, headaches, insomnia, and nightmares—so that many live on aluminium hydroxide gel (Maalox) and diazepam and drink themselves to sleep, and few last longer than five years in their jobs. So they want better working conditions, more pay, fewer hours, a back-up computer, and less stress.

Teachers too think that their occupation is making them sick, at least in the Chicago public schools, where violence and lack of discipline remain unresolved issues, and where union leaders claim that the stress of teaching has caused "a major health problem." At least 12% of all teachers have ulcers, colitis, neurodermatitis, or hypertension, and many others are said to suffer from mental fatigue, anxiety, depression, low self-esteem, and lack of sociability. Administrative problems such as

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