

Probenecid

Probenecid 500mg tablet

Presentation

A yellow film coated, capsule-shaped, tablet imprinted "DAN DAN" and "5347".

Therapeutic Class

PROBENECID is a uricosuric and renal tubular blocking agent.

Indications

Gout:

PROBENECID is an effective uricosuric agent for the treatment of hyperuricaemia in all stages of gout and gouty arthritis, except a presenting acute attack.

Asymptomatic hyperuricaemia seems to occur in a significant percentage of relatives of gouty patients. PROBENECID may be given prophylactically to these persons to forestall acute gouty attacks and urate deposition in tissues.

By virtue of its effective uricosuric activity, PROBENECID may be used to control the hyperuricaemia induced or aggravated by the many diuretics employed for the treatment of oedema and hypertension (e.g. thiazides and similar diuretics).

β-lactam Antibiotic Therapy:

PROBENECID is indicated for the elevation and prolongation of plasma levels by whatever route the antibiotic is given. A two- to fourfold increase in plasma levels has been demonstrated for penicillin G, or V, the synthetic penicillins, ampicillin, methicillin, oxacillin, cloxacillin, nafcillin, carbenicillin and for the cephamycin, cefoxitin sodium, and the cephalosporins, cephalothin, cephalexin and cephaloglycin.

Dosage and Administration

PROBENECID is available as tablets for oral use, each containing 500mg of probenecid.

Gout:

Therapy with PROBENECID should not be initiated until an acute gouty attack has subsided. However, if an acute attack is precipitated during therapy, the medicine may be continued without changing the dosage, and therapeutic doses of colchicine, indomethacin or other appropriate therapy should be given to control the acute attack.

The recommended dosage for adults is 250mg (1/2 tablet) twice a day for one week, followed by 500mg (1 tablet) twice a day thereafter.

Some degree of renal impairment is common in patients with gout; therefore, a daily dosage of 1000mg may be adequate for many patients. If necessary, however, the daily dosage may be increased every four weeks by increments of 500mg (within tolerance, and usually not beyond 2000mg daily) if symptoms of gouty arthritis are not controlled or the 24-hour urate excretion is not above 700mg.

PROBENECID may not be effective in chronic renal insufficiency particularly when the glomerular filtration rate is 30ml/minute or less.

Gastric intolerance may be indicative of overdosage, and may be corrected by reducing the dosage without losing the therapeutic response.

PROBENECID should be continued at a dosage that will maintain a normal serum uric acid level. When acute attacks have been absent for six months or more and serum uric acid levels remain within normal limits, the daily dosage of PROBENECID may be decreased by 1 tablet every 6 months to a minimum effective dosage. The maintenance dosage should not be reduced to the point where serum uric acid levels tend to rise.

Therapy of Gonorrhoea

For the treatment of uncomplicated gonorrhoea in men or women, a single 1000mg dose of PROBENECID (2 tablets) may be given with adequate doses of oral ampicillin, intramuscularly injected aqueous procaine penicillin G or cefoxitin. If oral ampicillin is used, PROBENECID should be administered simultaneously. If a parenteral antibiotic is administered, the dose of PROBENECID should be given preferably at least 30 minutes before the injection.

β-Lactam Antibiotic Therapy (General)

The recommended dosage for adults is 2000mg (4 tablets) daily in divided doses, reduced in older patients suspected of having renal impairment. Because of its mechanism of action, probenecid is not recommended for concurrent use with a β-lactam antibiotic in the presence of known renal impairment.

The recommended dosage for children two years of age or older is 25mg/kg (or 0.7g/square metre body surface) of body weight initially, followed by 40mg/kg (or 1.2g/square metre body surface) daily in divided doses every six hours. The adult dosage, however, is recommended for children weighing more than 50kg (110 lbs).

The phenolsulfonphthalein (PSP) excretion test may be used to determine the effectiveness of probenecid in retarding penicillin excretion and maintaining therapeutic levels. The renal clearance of PSP is reduced to about one-fifth of the normal rate when dosage of PROBENECID is adequate.

Contraindications

Hypersensitivity to any component of this product.

PROBENECID is not recommended for persons with known blood dyscrasias or uric acid kidney stones, nor for children under two years of age.

Therapy with PROBENECID should not be started until an acute gouty attack has subsided.

Warnings and Precautions

Use with caution in patients with a history of peptic ulcer.

The appearance of hypersensitivity reactions requires cessation of therapy with PROBENECID.

If PROBENECID is given with methotrexate, the dosage of methotrexate should be reduced and serum levels may need to be monitored (see INTERACTIONS).

Haematuria, renal colic, costovertebral pain, and formation of urate stones associated with the use of probenecid in gouty patients may be prevented by alkalinisation of the urine and a liberal fluid intake. Sufficient sodium bicarbonate (3g to 7.5g daily) or potassium citrate (7.5g daily) is recommended to maintain an alkaline urine. With such quantities of alkali, the acid-base balance of the patient should be watched.

Alkalinisation of the urine is recommended until the serum acid level returns to normal (upper normal limit in males is about 6mg/100ml and in females, it is about 5mg/100ml) and tophaceous deposits disappear, i.e., during the period when urinary excretion of urates is at a high level. After the miscible pool of uric acid decreases to normal (about 1g) and deposited urates are resorbed and eliminated, alkalinisation of the urine probably is unnecessary, since the urinary urate concentration is lower and less likely to cause crystallisation.

Exacerbation of gout during therapy with PROBENECID may occur; in such cases, a therapeutic dosage of indomethacin, colchicine or other appropriate therapy should be added.

Use in Pregnancy

Probenecid crosses the placental barrier and appears in cord blood. The use of any medicine in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards.

Nursing Mothers

It is not known whether the medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when PROBENECID is administered to a nursing mother.

Teratogenicity

Reproduction studies in the rabbit and the rat at doses up to 10 times the recommended human dose have shown no evidence of teratogenic effects to the foetus due to probenecid.

Because animal reproduction studies are not always predictive of human response, PROBENECID should be used during pregnancy only if clearly needed.

Adverse Effects

Headache, gastrointestinal symptoms (e.g. anorexia, nausea, vomiting), urinary frequency, hypersensitivity reactions (including anaphylaxis, dermatitis, pruritus, urticaria, fever and Stevens-Johnson syndrome), sore gums, flushing, alopecia, dizziness, and anaemia have occurred; also haemolytic anaemia which in some instances could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells. Toxic epidermal necrolysis has been reported rarely after combination therapy of colchicine and probenecid. Nephrotic syndrome, leukopaenia, hepatic necrosis, and aplastic anaemia occur rarely.

In gouty patients exacerbation of gout, and uric acid stones with or without haematuria, renal colic, or costovertebral pain, have been observed.

Laboratory Tests

A reducing substance may appear in the urine of patients receiving PROBENECID which may produce a false-positive Benedict's test leading to the possibility of a false diagnosis of glycosuria. However, this disappears with discontinuance of therapy.

Falsely high readings for theophylline have been reported in an in vitro study, using the Schack and Waxler technique, when therapeutic concentrations of theophylline and PROBENECID were added to human plasma.

Interactions

In patients on PROBENECID the use of acetylsalicylic acid in either small or large doses is contraindicated because it antagonises the uricosuric action of probenecid. In patients on probenecid who require a mild analgesic agent the use of paracetamol rather than small doses of salicylates would be preferred.

Caution should be used if PROBENECID is administered simultaneously with methotrexate. PROBENECID has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

PROBENECID increases the mean plasma elimination half-life of a number of other medicines which can lead to increased peak plasma concentrations. These medicines include acetaminophen, naproxen, indomethacin, ketoprofen, meclufenamate, lorazepam, rifampin, acyclovir, ganciclovir and zidovudine. The clinical significance of this effect on plasma elimination half-life is not known; however, adjustment in the usual dosage of these medicines may be required.

Since PROBENECID decreases the renal excretion of conjugated sulfonamides, plasma concentrations of the latter should be determined from time to time when a sulfa medicine and PROBENECID are coadministered for prolonged periods. PROBENECID may prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycemia.

The uricosuric action of PROBENECID is antagonised by pyrazinamide.

In animals, the renal tubular reabsorption of erythromycin is inhibited by probenecid and the renal excretion of sodium acetrizoate is decreased.

Because of its mechanism of action, PROBENECID is not recommended in conjunction with a β -lactam antibiotic in the presence of known renal impairment.

In addition to its effect on the excretion of uric acid, the β -lactam antibiotics (other than cephaloridine) PROBENECID decreases the urinary excretion of p-aminosalicylic acid (PAS), p-aminohippuric acid (PAH), phenolsulfonphthalein (PSP), pantothenic acid, 17-ketosteroids, sodium iodomethamate and related iodinated organic acids, PROBENECID decreases both hepatic and renal excretion of sulfobromophthalein (BSP). The renal tubular reabsorption of phosphorus is inhibited in hypoparathyroid but not in euparathyroid individuals.

Overdosage

In the event of overdosage, symptomatic and supportive measures should be employed along with gastric lavage. If signs of central nervous excitation are present, a short-acting barbituate may be given parentally.

Actions

Probenecid is a uricosuric and renal tubular blocking agent designed for maintenance treatment of gout and gouty arthritis. Probenecid inhibits the tubular reabsorption of urate, thus increasing urinary excretion of uric acid and decreasing serum uric acid levels. This action is reversible upon withdrawal of the medicine and is demonstrable in normal individuals as well as in patients under treatment. Effective uricosuria will reduce the miscible urate pool, retard urate deposition, and promote resorption of urate deposits.

PROBENECID Tablets, used by most physicians as the uricosuric agent of choice, is effective for the treatment of gout and gouty arthritis. By inhibiting the renal tubular reabsorption of urates, it increases the urinary excretion of uric acid and decreases serum uric acid levels.

Despite pronounced uricosuric activity, time is required to achieve clinical results. Acute attacks of gout may occur during the early phase of probenecid therapy in spite of the return to normal of the serum uric acid level. However, with continued use for some months, attacks of acute gout become less frequent and less intense.

As urate deposits in periarticular and articular structures are reabsorbed, joint pain is relieved, greater articular mobility is achieved, and further joint destruction may be averted. Patients have an increased feeling of well-being, and, in some instances, are able to carry on their normal activities after years of incapacitation.

PROBENECID may have a favourable effect on the gouty kidney. As urate deposits are mobilised, renal function may improve and further destructive changes may be prevented.

PROBENECID is also a valuable adjuvant to anti-infective therapy with the β -lactam antibiotics (other than cephaloridine) and p-aminosalicylic acid. PROBENECID interferes with the renal tubular excretion of these substances and thus increases and prolongs their plasma concentrations - an important consideration when treating conditions requiring intensive therapy.

Pharmacokinetics

Onset and Duration of Action in Usual Doses

Peak plasma levels are reached in 2 to 4 hours. The plasma half-life of probenecid is between 6 and 12 hours.

Absorption

Probenecid is completely absorbed after oral administration.

Metabolism

The plasma half-life of probenecid is between 6 and 12 hours. Between 85 to 95% of the medicine is bound to plasma protein, largely to albumin. The major metabolite, probenecid acyl glucuronide accounts for close to 50% of the dose. Approximately equal amounts (10 to 15%) of mono-n-propyl, secondary alcohol and carboxylic acid metabolites are excreted. The primary alcohol metabolite is not found in measurable amounts.

Excretion

Urine - Following oral administration, 75 to 88% of the dose is found in the urine. Urinary excretion of unchanged probenecid is dependent on both the pH and flow rate of urine.

Pharmaceutical Precautions

Store at controlled room temperature 15°C -30°C.

Medicine Classification

Prescription Medicine

Package Quantities

PROBENECID 500mg tablets are available in containers of 100 and 1000.

Further Information

Nil

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