

Data Sheet

PRODOPA

Methyldopa

Presentation

125mg tablet: Yellow film coated normal convex tablets, 8 mm in diameter, imprinted 'MD' over '125' on one side and 'G' on the other.

250mg tablet: Yellow film coated normal convex tablets, 10.2 mm in diameter, imprinted 'MD' over '250' on one side and 'G' on the other.

500mg tablet: Yellow film coated normal convex tablets, 12.5 mm in diameter, imprinted 'MD' over '500' on one side and 'G' on the other.

Uses

Actions

This unique antihypertensive compound, methyldopa, was derived from a fundamental research programme directed toward the synthesis of antagonists to the biochemical transformations of some aromatic amino acids to pressor amines.

The antihypertensive effect of methyldopa is probably due to its metabolism to alpha-methylnorepinephrine, which lowers arterial pressure by stimulation of central inhibitory alpha-adrenergic receptors, false neurotransmission, and/or reduction of plasma renin activity. Methyldopa has been shown to cause a net reduction in the tissue concentration of serotonin, dopamine, norepinephrine and epinephrine.

The effect of methyldopa on the balance of adrenergic amines is reversible. In the laboratory it is relatively difficult with any dosage, to evoke a paralysis of sympathetic control (i.e. nictitating membrane) as can be induced by sympathectomy, ganglion-blocking agents, or by the depleting action of excessive dosages of reserpine or guanethidine. Although the relevance of this observation may be questioned, clinical experience indicates that postural adjustments by the hypertensive patient are not as seriously embarrassed by methyldopa as by sympathectomy, ganglion-blocking agents, or guanethidine.

Laboratory demonstration of the pharmacology and safety of methyldopa is intriguing because of the close structural similarity to the naturally occurring amino acid precursors of the amines that are responsible for the adrenergic mediation of autonomic nerve impulses. For example, the acute intravenous LD₅₀ is 1,900 mg/kg in the mouse, making it less toxic than dopa. Administered orally, the acute toxicity is from 5,300 mg/kg to greater than 15,000 mg/kg, depending upon the vehicle.

Pharmacokinetics

The absorption of methyldopa shows wide individual variations. In two studies, the bioavailability of methyldopa was in the range of 8% to 62%.

Methyldopa is extensively metabolised. The known urinary metabolites are: alpha-methyldopa mono-O-sulfate 3-O-methyl-alpha-methyldopa; 3,4-dihydroxy-phenylacetone; alpha-methyldopamine; 3-O-methyl-alpha-methyl-dopamine and their conjugates.

In rats and dogs methyldopate is readily and apparently completely hydrolysed to methyldopa. Methyldopate given intravenously to dogs gave rise to relatively low and stable concentrations of methyldopa. Following intravenous use of methyldopate, the appearance of methyldopa in the urine was extended beyond that seen after an intravenous dose of methyldopa itself. These observations

indicate that methyldopate, when given intravenously, is rapidly sequestered in tissues from which methyldopa is then slowly released into the circulation.

Approximately 70% of the oral form of the medicine which is absorbed is excreted in the urine as methyldopa and its mono-O-sulfate conjugate. The renal clearance is about 130ml/min in normal subjects and is diminished in renal insufficiency. The plasma half-life of methyldopa is 105 minutes. After oral doses, excretion is essentially complete in 36 hours.

Approximately 49% of the intravenous dose of methyldopate hydrochloride is excreted in the urine as methyldopa and its mono-O-sulphate. The renal clearance of methyldopa following methyldopate hydrochloride injection is about 156 mL/min. in the normal subjects and is diminished in renal insufficiency. Following methyldopate hydrochloride injection the plasma half-life of methyldopa is 90-127 minutes. Approximately 17% of a dose of methyldopate hydrochloride given to normal subjects appears in plasma as free methyldopa.

With oral therapy, once an effective dosage range is attained, a smooth blood pressure response occurs in most patients in 12 to 24 hours. Since methyldopa has a relatively short duration of action, withdrawal is followed by return of hypertension, usually within 48 hours. This is not complicated by an overshoot of blood pressure.

Methyldopate when given intravenously in effective doses, causes a decline in blood pressure that may begin in 4 to 6 hours and last 10 to 16 hours after injection. The delayed effect may reflect storage and biotransformation to methyldopa.

Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Indications

Hypertension (mild, moderate or severe).

Dosage and Administration

ORAL THERAPY

General:

Methyldopa is largely excreted by the kidney and patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower doses.

Withdrawal of methyldopa is followed by return of hypertension usually within 48 hours. This is not complicated by an overshoot of blood pressure.

Therapy with methyldopa may be initiated in most patients already on treatment with other antihypertensive agents.

Methyldopa may also be used concomitantly with amiloride/hydrochlorothiazide tablets or beta-blocking agents, such as timolol maleate. Many patients can be controlled with one tablet of amiloride 5mg/hydrochlorothiazide 50mg and 500mg of methyldopa administered once daily.

When methyldopa is given to patients on other antihypertensives, the dose of these agents may need to be adjusted to effect a smooth transition. Terminate these antihypertensive medications gradually if required (see manufacturers' recommendations on stopping these medicines)

Following such previous antihypertensive therapy, the initial dose of methyldopa should be limited to not more than 500mg daily and increased as required at intervals of not less than 2 days.

Adults:

The usual starting dosage of methyldopa is 250mg two or three times a day in the first 48 hours. The daily dosage then may be increased or decreased, preferably at intervals of not less than two days, until an adequate response is achieved. The maximum recommended daily dosage is 3g.

When methyldopa 500mg is added to 50mg of hydrochlorothiazide, the two agents may be given together once daily.

Many patients experience sedation for two or three days when therapy with methyldopa is started or when the dose is increased. When increasing the dosage, therefore, it may be desirable to increase the evening dose first.

Children:

Initial dosage is based on 10 mg/kg of body weight daily in two or four doses. The daily dosage then is increased or decreased until an adequate response is achieved. The maximum dosage is 65 mg/kg or 3.0g daily, whichever is less.

Contraindications

Methyldopa is contraindicated in patients:

- with active hepatic disease, such as acute hepatitis and active cirrhosis
- with hypersensitivity (including hepatic disorders associated with previous methyldopa therapy) to any component of these products (see Warnings and Precautions)
- on therapy with monoamine oxidase (MAO) inhibitors
- depression

'Prodopa' is not recommended for the treatment of phaeochromocytoma (see "Warnings and Precautions").

Warnings and Precautions

Acquired haemolytic anaemia has occurred rarely in association with methyldopa therapy. Should clinical symptoms indicate the possibility of anaemia, haemoglobin and /or haematocrit determinations should be performed. If anaemia is present, appropriate laboratory studies should be done to determine if haemolysis is present. Evidence of haemolytic anaemia is an indication for discontinuation of the medicine.

Discontinuation of methyldopa alone or the initiation of adrenocortical steroids usually results in a prompt remission of anaemia. Rarely, however, fatalities have occurred. Some patients on continued therapy with methyldopa develop a positive direct Coombs test. The incidence of positive Coombs test as reported by different investigators has averaged between 10 and 20 percent. A positive Coombs test rarely occurs in the first six months of therapy with methyldopa, and if not encountered within 12 months, is unlikely to develop with continued administration. This phenomenon is also dose-related with the lowest incidence occurring in patients receiving 1g of methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of the medicine.

Should the need for transfusion arise, prior knowledge of a positive Coombs reaction will aid in evaluation of the cross match. Patients with a positive Coombs test at the time of cross match may exhibit an incompatible minor cross match. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with such blood which is otherwise compatible in the major cross match may be carried out. However, if positive, the advisability of transfusion with blood compatible in the major cross match should be determined by a haematologist or expert in transfusion problems.

Rarely, a reversible reduction of the white blood cell count with a primary effect on the granulocytes has been seen. The granulocyte count returned promptly to normal on discontinuance of the medicine. Reversible thrombocytopenia has occurred rarely.

Occasionally, fever has occurred within the first 3 weeks of administration of methyldopa. In some cases this fever has been associated with eosinophilia or abnormalities in one or more liver function tests. Jaundice, with or without fever, may occur also, with onset usually within the first 2 or 3 months of therapy. In some patients, the findings are consistent with those of cholestasis. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy performed in several patients with liver dysfunction showed a microscopic focal necrosis compatible with medicine hypersensitivity.

A determination of hepatic function and a white cell and differential blood count should be done at intervals during the first 6-12 weeks of therapy, or whenever an unexplained fever may occur. If fever, abnormalities in liver function tests, or jaundice appear, therapy with methyldopa should be stopped.

If related to methyldopa the temperature and abnormalities in liver function characteristically have reverted to normal when the medicine was discontinued. Methyldopa should not be reinstated in such patients. Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction.

Patients may require reduced doses of anaesthetics when on methyldopa. If hypotension does occur during anaesthesia, it usually can be controlled by vasopressors. The adrenergic receptors remain sensitive during treatment with methyldopa.

Dialysis removes methyldopa; therefore, hypertension may recur after this procedure.

Rarely, involuntary choreoathetotic movements have been observed during therapy with methyldopa in patients with severe bilateral cerebrovascular disease. Should these movements occur, therapy should be discontinued.

“Prodopa” should be used with extreme caution in patients, or in near relatives of patients, with hepatic porphyria.

Interference with Laboratory Tests:

Methyldopa may interfere with the measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric method. Interference with spectrophotometric methods for SGOT analysis has not been reported.

Since methyldopa will cause fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high concentrations of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma.

It is important to recognise this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa does not interfere with measurement of VMA (vanillylmandelic acid) by those methods which convert VMA to vanillin. Methyldopa is not recommended for the treatment of patients with pheochromocytoma.

Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites.

Pregnancy and Lactation

Methyldopa has been used under close medical and obstetric supervision for the treatment of hypertension during pregnancy. There was no clinical evidence that methyldopa caused foetal abnormalities or affected the neonate.

Published reports of the use of methyldopa during all trimesters indicate that if this drug is used during pregnancy the possibility of foetal harm appears remote. In clinical studies, treatment with methyldopa has been associated with an improved foetal outcome. The majority of the women in these studies were in the third trimester when methyldopa therapy was begun.

Methyldopa does cross the placental barrier and appears in cord blood.

Although no obvious teratogenic effects have been reported, the possibility of foetal injury cannot be excluded and the use of the medicine in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Nursing Mothers: Methyldopa appears in breast milk. Therefore, caution should be exercised if methyldopa is given to a breast feeding mother.

Animal Toxicology:

Subacute oral toxicity studies in dogs indicated no pertinent histopathologic changes when methyldopa was administered in dosages up to 2,000 mg/kg/day for four weeks, although inanition was observed at the maximal dosage. Chronic oral toxicity studies conducted for long periods at dosages up to and including 1,800 mg/kg/day for rats, 1,350 mg/kg/day for dogs and 1,000 mg/kg/day for monkeys elicited no histopathologic or chemical changes of clinical significance. The mechanism of the development of a positive Coombs test has been under study in several species of animals, including primates. The results indicate that a positive direct Coombs test of unknown etiology has been observed occasionally in dogs and rats at high doses of methyldopa. Further, in one dog, anaemia and arrest of erythropoietic maturation at the prorubricyte-rubricyte level occurred during two periods of treatment with methyldopa at doses of 1,000 mg/kg/day and one period of treatment at doses of 20 mg/kg/day. On each occasion, withdrawal of the medicine was followed by a return of the haemoglobin to pre-test levels. No evidence of tumorigenic effect was seen when methyldopa was given for two years to mice at doses up to 1,800 mg/kg/day or to rats at doses up to 240 mg/kg/day (30 and 4 times the maximum recommended human dose in mice and rats, respectively, based on a patient weight of 50kg).

Methyldopa was not mutagenic in the Ames Test and did not increase chromosomal aberration or sister chromatid exchanges in Chinese hamster ovary cells. These *in vitro* studies were carried out both with and without exogenous metabolic activation.

Fertility was unaffected when methyldopa was given to male and female rats at 100 mg/kg/day (1.7 times the maximum daily human dose based on a patient weight of 50kg). Methyldopa decreased sperm count, sperm motility, the number of late spermatids, and the male fertility index when given to male rats at 200 and 400 mg/kg/day (3.3 and 6.7 times the maximum daily human dose based on a patient weight of 50kg).

Reproduction studies performed with methyldopa at oral doses up to 1,000 mg/kg in mice, 200 mg/kg in rabbits, and 100 mg/kg in rats revealed no evidence of harm to the foetus. These doses are 16.6 times, 3.3 times, and 1.7 times, respectively, the maximum daily human dose based on a patient weight of 50kg.

Adverse Effects

The following reactions have been reported:

Cardiac disorders: Bradycardia, aggravation of angina pectoris, myocarditis, pericarditis.

Blood and lymphatic system disorders: Haemolytic anaemia, bone-marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia.

Nervous system disorders: Sedation (usually transient), headache, paraesthesia, Parkinsonism, Bell's palsy, involuntary choreoathetotic movements, impaired mental acuity, prolonged carotid sinus hypersensitivity. Dizziness, light-headedness, and symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure).

Respiratory, thoracic and mediastinal disorders: Nasal stuffiness.

Gastrointestinal disorders: Nausea, vomiting, distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or 'black' tongue, pancreatitis.

Skin and subcutaneous tissue disorders: Rash as in eczema or lichenoid eruption, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders: Lupus – like syndrome, mild arthralgia with or without joint swelling, myalgia.

Endocrine disorders: Hyperprolactinaemia.

Infections and infestations: Sialadenitis.

Vascular disorders: Orthostatic hypotension (decrease daily dosage).

General disorders and administrative site conditions: Asthenia or weakness, oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear.), drug-related fever.

Hepatobiliary disorders: Liver disorders including hepatitis, jaundice.

Reproductive system and breast disorders: Breast enlargement, gynaecomastia, amenorrhoea, lactation, impotence, failure of ejaculation.

Psychiatric disorders: Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido.

Investigations: Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, rise in blood urea.

Ability to drive and use machines: 'Prodopa' may cause sedation, usually transient, during the initial period of therapy or whenever the dose is increased. If affected, patients should not carry out activities where alertness is necessary, such as driving a car or operating machinery.

Interactions

Lithium:

When methyldopa and lithium are given concomitantly the patient should be monitored carefully for symptoms of lithium toxicity.

Other Antihypertensive Medicines:

When methyldopa is used in combination with other antihypertensive medicines, potentiation of antihypertensive action may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of medicine idiosyncrasy.

Other Classes of medicines:

The antihypertensive effect of 'Prodopa' may be diminished by sympathomimetics, phenothiazines, tricyclic antidepressants and MAOIs (see 'Contra-indications'). In addition, phenothiazines may have additive hypotensive effects.

Iron:

Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulphate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa

Overdosage

Acute overdosage may produce acute hypotension with other responses attributable to brain and gastrointestinal malfunction (excessive sedation, weakness, bradycardia, dizziness, light-headedness, constipation, distension, flatus, diarrhoea, nausea, vomiting).

In the event of overdosage, symptomatic and supportive measures should be employed. When ingestion is recent, gastric lavage or emesis may reduce absorption. When ingestion has been earlier, infusions may be helpful to promote urinary excretion. Otherwise, management includes special attention to cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity.

Sympathomimetic medicines (e.g. levarterenol, epinephrine, metaraminol bitartrate) may be indicated. Methyldopa is dialysable.

The oral LD50 of methyldopa is greater than 1.5g/kg in both the mouse and the rat.

Pharmaceutical Precautions

Store at or below 25 C. Protect from light.

Medicine Classification

Prescription Medicine.

Package Quantities

125mg tablets in bottles of 100's and 500's

250mg tablets in bottles of 100's and 500's

500mg tablets in bottles of 100's

Further Information

Methyldopa is an effective antihypertensive agent that reduces both supine and standing blood pressure. Symptomatic postural hypotension, exercise hypotension and diurnal blood pressure variations rarely occur. By adjustment of dosage, morning hypotension can be prevented without sacrificing control of afternoon blood pressure.

Methyldopa has no direct effect on cardiac function and usually does not reduce glomerular filtration rate, renal blood flow or filtration fraction. Cardiac output usually is maintained without cardiac acceleration. In some patients, the heart rate is slowed.

Because of its relative freedom from adverse effects on kidney function, methyldopa can be of benefit in the control of high blood pressure, even in the presence of renal impairment. It may help arrest or retard the progression of renal function impairment and damage due to sustained elevation of blood pressure.

Normal or elevated plasma renin activity may decrease in the course of methyldopa therapy.

The ability to inhibit dopa decarboxylase and to deplete animal tissues of norepinephrine resides solely in the L-isomer (methyldopa). In humans, the antihypertensive activity appears to be due solely to the L-isomer.

Excipients:

Ethylcellulose, guar gum, Opadry yellow, sodium starch glycollate, anhydrous citric acid, disodium edentate, colloidal silicon dioxide and magnesium stearate.

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