# PRESCRIBING INFORMATION

**METHYLDOPA**

**Methyldopa Tablets USP**

**125 mg, 250 mg and 500 mg**

**Antihypertensive**

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## PHARMACOLOGY:

Methyldopa is an aromatic-amino acid decarboxylase inhibitor; it inhibits the decarboxylation of dopa, thereby interfering with the formation of dihydroxyphenethylamine (dopamine), a precursor of norepinephrine. It also inhibits the formation of serotonin from 5-hydroxytryptophane. While the inhibition of decarboxylation by methyldopa has been successfully demonstrated in man, the useful effect on blood pressure has not yet been shown definitely to result from this biochemical effect, and is more likely due to a central effect.

Only the levoisomer (methyldopa) has the ability to inhibit dopa decarboxylase and to deplete animal tissues of norepinephrine. In man, the antihypertensive activity appears to be due solely to the levoisomer. Approximately twice the dosage of the racemate is required for equal antihypertensive effects.

Methyldopa has been shown to influence the balance of physiologically important amines in various tissues. Thus, this compound can be shown to cause a net reduction in the tissue concentration of serotonin, norepinephrine, or epinephrine that varies from tissue to tissue. The effect on norepinephrine is apparently related to formation of alpha-methylnorepinephrine, a metabolite of methyldopa, which displaces norepinephrine from adrenergic neurons. Laboratory evidence indicates that alpha-methylnorepinephrine may be involved in the antihypertensive action of methyldopa by becoming a substitute transmitter at sites in the CNS responsible for the control of hemodynamic function. Normal or elevated plasma renin activity may be decreased by methyldopa.

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 of 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.

Methyldopa is well absorbed on oral administration to man and laboratory animals. It has no direct effect on cardiac or renal functions.

Methyldopa has a close structural similarity to the naturally occurring amino acid precursors of the amines that are responsible for the adrenergic mediation of autonomic nerve impulses.

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 1 dog, anemia and arrest of erythropoietic maturation at the prorubricyte-rubricyte concentration occurred during 2 periods of treatment with methyldopa at doses of 1000 mg/kg/day, and-1 period of treatment at doses of 20 mg/kg/day. On each occasion, withdrawal of the drug was followed by a return of the hemoglobin to pretest concentrations.

## INDICATIONS:

The treatment of arterial hypertension. May be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper response in patients with hypertension of various severity.

May be employed as the initial agent in the treatment of hypertension in those patients for which treatment should not be started with a diuretic.

## CONTRAINDICATIONS:

Active hepatic disease, such as acute hepatitis and active cirrhosis. If previous methyldopa therapy has been associated with liver disorders or hemolytic anemia (see Precautions). Hypersensitivity to methyldopa.

## PRECAUTIONS:

With prolonged methyldopa therapy, 10 to 20% of patients develop a positive direct Coombs test which usually occurs between 6 and 12 months of methyldopa therapy. Lowest incidence is at a daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, the physician should determine whether hemolytic anemia exists, and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test, there is less often a positive indirect Coombs test which may interfere with cross-matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may

be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy.

If Coombs positive hemolytic anemia occurs, the cause may be methyldopa, and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If hemolytic anemia occurs, the drug should not be reinstituted.

When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after the methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Occasionally, fever has occurred within the first 3 weeks of methyldopa therapy, associated in some cases with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time and bromsulphalein retention. Jaundice, with or without fever, may occur with onset usually within the first 2 to 3 months of therapy. In some patients the findings are consistent with those of chloestasis.

Rarely, fatal hepatic necrosis has been reported after use of methyldopa. These hepatic changes may represent hypersensitivity reactions. Periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy, or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients. Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction.

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 drug. Rare cases of granulocytopenia have been reported. In each instance, upon stopping the drug, the white cell count returned to normal. Reversible thrombocytopenia has occurred rarely.

When methyldopa is used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed closely to detect side

reactions or unusual manifestations of drug idiosyncrasy. A paradoxical pressor response has been reported with i.v. methyldopate.

Use in pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Though no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction.

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

Since methyldopa causes fluorescence in urine samples at the same wave lengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa does not interfere with measurement of VMA (vanillylmandelic acid), a test for pheochromocytoma, 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.

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

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

Hypertension has recurred occasionally after dialysis in patients given methyldopa because the drug is removed by this procedure.

## ADVERSE EFFECTS:

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

CNS: sedation, headache, asthenia or weakness, dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements, psychic disturbances including nightmares and reversible mild psychoses or depression, toxic encephalopathy.

Cardiovascular: bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by the use of a diuretic (Discontinue methyldopa if edema progresses or if signs of heart failure appear).

Gastrointestinal: nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or ··black·· tongue, pancreatitis, sialadentis.

Hepatic: abnormal liver function tests, jaundice, liver disorders.

Hematologic: positive Coombs test, hemolytic anemia, leukopenia, granulocytopenia, thrombocytopenia.

Allergic: drug-related fever, myocarditis.

Other: nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

**OVERDOSE:**

Symptoms: Acute overdosage may produce acute hypotension bradycardia, dizziness, with other major responses attributable to brain and gastrointestinal malfunction (excessive sedation, weakness, lightheadedness, constipation, distention, flatus, diarrhea, nausea, vomiting).

Potentiation of antihypertensive action may occur in combination therapy with other antihypertensives.

Chronic overdosage may produce hypotension and syncope, especially in the presence of advanced arteriosclerosis.

Treatment: Discontinue the drug. If 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 symptomatic treatment with special attention to cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function, and cerebral activity. Administration of sympathomimetic drugs may be indicated.

## DOSAGE:

Adults: The usual starting dosage is 250 mg 2 or 3 times a day in the first 48 hours. The daily dosage then may be increased or decreased, preferably at intervals of not less than 2 days, until an adequate response is achieved. To minimize the sedation, start dosage increases in the evening. By adjustment of dosage, morning hypotension may be prevented without sacrificing control of afternoon blood pressure.

When methyldopa is given to patients on other antihypertensives, the dose of the agents may need to be adjusted to effect a smooth transition. When methyldopa is added to a thiazide, the dosage of thiazide usually need not be changed. A thiazide may be added at any time during methyldopa therapy and is recommended if therapy has not been started with a thiazide or if effective control of blood pressure cannot be maintained on 2 g of methyldopa daily. When methyldopa is given with antihypertensives other than thiazides, its initial dosage should be limited to 500 mg daily in divided doses.

The usual daily maintenance dosage of methyldopa is 500 mg to 2 g in 2 to 4 doses. Although occasional patients have responded to higher doses, the maximum recommended daily dosage is 3 g.

Studies suggest that once optimum dosage is ascertained, the antihypertensive effect can be maintained by giving the same total daily dose once every 24 hours.

Occasionally, tolerance may occur, usually between the second and third month of therapy. Adding a diuretic or increasing the dosage of methyldopa frequently will restore effective control of blood pressure.

Smaller doses may be needed in patients with impaired renal function or in older patients with an increased sensitivity or an advanced arteriosclerotic vascular disease (see Precautions).

Children: Initial dosage is based on 10 mg/kg daily in 2 to 4 doses. The daily dosage then is increased or decreased until an adequate response is achieved. The maximum dosage is 65 mg/kg or 3 g daily, whichever is less.

## SUPPLIED:

Each yellow film-coated tablet contains methyldopa 125, 250, or 500 mg.
Supplied in bottles of 100 or 1000.