

PHYSICIANS CIRCULAR

Tablets
Aldomet[®]
(methyldopa, USP)

ALDOMET[®] (methyldopa, USP) 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 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 rennin 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 man, the antihypertensive activity appears to be due solely to the *L*-isomer.

INDICATION

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

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

ALDOMET may also be used concomitantly with MODURETIC*[†] (hydrochlorothiazide and amiloride) or beta(-)blocking agents, such as BLOCADREN*[†] (timolol maleate,). Many patients can be controlled with one tablet of MODURETIC and 500 mg of ALDOMET administered once daily.

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

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

ADULTS

The usual starting dosage of ALDOMET is 250 mg 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 3 g.

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

Many patients experience sedation for two or three days when therapy with ALDOMET 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 10mg/kg of body weight daily in two to four doses. The daily dosage then is increased or decreased until an adequate response is achieved. The maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less.

CONTRAINDICATIONS

ALDOMET 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 PRECAUTIONS).
- ◆ on therapy with monoamine oxidase (MAO) inhibitors.

PRECAUTIONS

Acquired hemolytic anemia has occurred rarely in association with methyldopa therapy. Should clinical symptoms indicate the possibility of anemia, hemoglobin and/or hematocrit determinations should be performed. If anemia is present, appropriate laboratory studies should be done to determine if hemolysis is present. Evidence of hemolytic anemia is an indication for discontinuation of the drug. Discontinuation of methyldopa alone, or the initiation of adrenocortical steroids, usually results in a prompt remission of anemia. 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%. A positive Coombs test rarely occurs in the first six months of therapy with methyldopa, and it 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 1 g of methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of the drug.

Should the need for transfusion arise, prior knowledge of a positive Coombs reaction will aid in evaluation of the crossmatch. Patients with a positive Coombs test at the time of crossmatch may exhibit an incompatible minor crossmatch. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with such blood which is otherwise compatible in the major crossmatch may be

carried out. However, if positive, the advisability of transfusion with blood compatible in the major crossmatch should be determined by a hematologist or expert in transfusion problems.

Rarely, reversible reduction of the white blood count with a primary effect on the granulocytes has been seen. The granulocyte count returned promptly to normal on discontinuance of the drug. 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 drug 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 drug 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. A paradoxical pressor response has been reported with intravenous methyldopate HCl.

Patients may require reduced doses of anesthetics when on therapy with ALDOMET. If hypotension does occur during anesthesia, 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.

INTERFERENCE WITH LABORATORY TEST

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 recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methaldopa 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.

USE IN PREGNANCY

ALDOMET has been used under close medical and obstetric supervision for the treatment of hypertension during pregnancy. There was no clinical evidence that ALDOMET caused fetal 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 fetal harm appears remote. In clinical studies, treatment with ALDOMET has been associated with an improved fetal 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 fetal injury cannot be excluded, and the use of the drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risk.

NURSING MOTHERS

Methyldopa appears in breast milk. Therefore, caution should be exercised if ALDOMET is given to a breast feeding mother.

DRUG INTERACTIONS

LITHIUM

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

OTHER ANTIHYPERTENSIVE DRUGS

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

IRON

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

MONOAMINE OXIDASE (MAO) INHIBITORS

See CONTRAINDICATIONS.

SIDE 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.

Significant side effects due to ALDOMET have been infrequent and this agent is usually well tolerated.

The Following reactions have been reported:

CENTRAL NERVOUS SYSTEM

Sedation (usually transient), headache, asthenia or weakness, paresthesias, parkinsonism, Bell's palsy, involuntary choreoathetotic movements. Psychic disturbances including nightmares, impaired mental acuity and reversible mild psychoses or depression. Dizziness, light-headedness, and symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure).

CARDIOVASCULAR

Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

GASTROINTESTINAL

Nausea, vomiting, distention, constipation, flatus, diarrhea, colitis, mild dryness of mouth, sore or “black” tongue, pancreatitis, sialoadenitis.

HEPATIC

Liver disorders including hepatitis, jaundice, abnormal liver function tests.

HEMATOLOGIC

Positive Coombs test, hemolytic anemia, bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia, eosinophilia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

ALLERGIC

Drug-related fever and lupus-like syndrome, myocarditis, pericarditis.

DEMATOLOGIC

Rash, as in eczema or lichenoid eruption, toxic epidermal necrolysis.

OTHER

Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, hyper-prolactinemia, amenorrhea, impotence, decreased libido, mild arthralgia, with or without joint swelling, myalgia.

OVERDOSAGE

Acute overdosage may produce acute hypotension with other responses attributable to brain and gastrointestinal malfunction (excessive sedation, weakness, bradycardia, dizziness, light-headedness, constipation, distention, flatus, diarrhea, 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 drugs (e.g., levarterenol, epinephrine, ARAMINE[®] (metaraminol bitartrate,)) may be indicated. Methyldopa is dialyzable.

AVAILABILITY

ALDOMET[®] 250 mg is blister packs of 100's (10 x 10 strips).

Each film coated tablet contains 250mg Methyldopa, USP.