METHYLDOPA (Systemic)

Category

Antihypertensive.

Indications

Accepted

Hypertension (treatment)¾Methyldopa is indicated in the treatment of moderate to severe hypertension , including that complicated by renal disease.
Methyldopate may be used intravenously in the treatment of hypertensive crises 1, 14.

However, because of its slow onset of action, methyldopate is generally not recommended as sole initial therapy in hypertensive crises.

Pharmacology/

Mechanism of action/Effect:

The exact mechanism of antihypertensive action has not been conclusively demonstrated 13.

However, the major antihypertensive effect appears to result from conversion to alpha-methylnorepinephrine, a potent alpha-2 adrenergic agonist 13, 18, 19, 20.

Alpha-methylnorepinephrine acts centrally to stimulate alpha receptors 16, 17, 20.

This results in a decrease in sympathetic outflow and decreased blood pressure 19.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to sulfites may be sensitive to some methyldopa products because of the sulfite preservatives present.

Tumorigenicity

No evidence of a tumorigenic effect was seen in mice given doses up to 1800 mg per kg of body weight (mg/kg) per day (30 times the maximum recommended human dose) for 2 years or in rats given doses up to 240 mg/kg per day (4 times the maximum recommended human dose) for 2 years 13.

Mutagenicity

Methyldopa was not mutagenic in the Ames test with or without metabolic activation 13.

There was no increase in chromosomal aberration or sister chromatid exchanges in Chinese hamster ovary cells 13.

Pregnancy/Reproduction

Fertility¾Methyldopa did not affect fertility in male and female rats given doses of 100 mg/kg per day (1.7 times the maximum daily human dose). However, at doses of 200 mg/kg and 400 mg/kg per day (3.3 and 6.7 times the maximum daily human dose) methyldopa decreased sperm count, sperm motility, the number of late spermatids, and the male fertility index. 13

Pregnancy¾Methyldopa crosses the placenta 1, 13.

Adequate and well-controlled studies of methyldopa use in pregnant women during the first and second trimesters have not been done. Studies of methyldopa use in pregnant women during the third trimester have not been associated with adverse effects 1, 13.

Studies in rabbits at doses of 200 mg/kg per day (3.3 times the maximum daily human dose), mice at doses of 1000 mg/kg per day (16.6 times the maximum daily human dose), and rats at doses of 100 mg/kg per day (1.7 times the maximum daily human dose) showed no adverse effects 13.

FDA Pregnancy Category B. 13

Breast-feeding

Methyldopa is distributed into breast milk 1, 2.

However, problems in humans have not been documented.

Pediatrics

Appropriate studies on the relationship of age to the effects of methyldopa have not been performed in the pediatric population. However, pediatrics-specific problems that would limit the usefulness of this medication in children are not expected.

Geriatrics

Although appropriate studies on the relationship of age to the effects of methyldopa have not been performed in the geriatric population, the elderly may be more sensitive to the hypotensive 1 and sedative effects. In addition, elderly patients are more likely to have age-related renal function impairment, which may require lower doses in patients receiving methyldopa.

Dental

Use of methyldopa may decrease or inhibit salivary flow, thus contributing to the development of caries, periodontal disease, oral candidiasis, and discomfort.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Alcohol or

Central nervous system (CNS) depression-producing medications (See Appendix II)

(concurrent use may enhance the CNS depressant effects of either these medications or methyldopa)

Anticoagulants, coumarin- or indandione-derivative

(concurrent use with methyldopa may increase the anticoagulant effect of these medications; adjustment of anticoagulant dosage based on prothrombin-time determinations is recommended)

Antidepressants, tricyclic

(may reduce antihypertensive effects of methyldopa; the patient should be carefully monitored to confirm that the desired effect is being obtained)

Anti-inflammatory drugs, nonsteroidal (NSAIDs), especially indomethacin

(antihypertensive effects of methyldopa may be reduced when it is used concurrently with these medications; indomethacin, and possibly other NSAIDs, may antagonize the antihypertensive effect by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention; the patient should be carefully monitored to confirm that the desired effect is being obtained)

Appetite suppressants, with the exception of fenfluramine

(concurrent use may decrease the hypotensive effects of methyldopa)

Bromocriptine

(methyldopa may increase serum prolactin concentrations and interfere with effects of bromocriptine; dosage adjustment of bromocriptine may be necessary)

Fenfluramine

(concurrent use may increase the hypotensive effects of methyldopa)

Haloperidol

(concurrent use of haloperidol with methyldopa may cause unwanted mental effects such as disorientation and slowed or difficult thought process)

Hypotension-producing medications, other (See Appendix II) 1, 13

(hypotensive effects may be potentiated when these medications are used concurrently with methyldopa; although some antihypertensive and/or diuretic combinations are frequently used for therapeutic advantage, dosage adjustments may be necessary during concurrent use)

Levodopa

(concurrent use with methyldopa may alter the antiparkinsonian effects of levodopa and may also produce additive toxic CNS effects such as psychosis)

Lithium

(concurrent use with methyldopa may increase the risk of lithium toxicity, even though serum lithium concentrations remain within the recommended therapeutic range 4, 13)

>> Monoamine oxidase (MAO) inhibitors, including furazolidone, procarbazine, and selegiline

(methyldopa may cause hyperexcitability in patients receiving MAO inhibitors; headache, severe hypertension, and hallucinations have been reported 13)

Sympathomimetics, such as:
>> Cocaine
Dobutamine
Dopamine
Ephedrine
Epinephrine
Mephentermine
Metaraminol
Methoxamine
>> Norepinephrine
>> Phenylephrine or
Phenylpropanolamine

(concurrent use with sympathomimetic pressor amines may decrease the hypotensive effect of methyldopa and potentiate the pressor effect of these medications; if concurrent use of cocaine, norepinephrine, or phenylephrine is indicated, caution is required, and only very small initial doses should be administered)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Aspartate aminotransferase (AST [SGOT]) measurement, serum, using colorimetric methods 1, 13

(methyldopa may interfere with measurement of AST)

Creatinine measurement, serum, using the alkaline picrate method 1, 13

(methyldopa may interfere with measurement of serum creatinine)

Urinary catecholamine measurement

(methyldopa may produce falsely elevated results since it causes fluorescence at the same wavelengths as catecholamines; methyldopa does not interfere with urinary vanillylmandelic acid [VMA] determinations 1, 13)

Urinary uric acid measurement, using the phosphotungstate method 1, 13

(methyldopa may interfere with measurement of urinary uric acid)

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) 1 and

Alkaline phosphatase 1 and

Aspartate aminotransferase (AST [SGOT]) 1 and

Bilirubin 1

(serum concentrations may be increased, indicating possible hepatotoxicity 1, 13)

Blood urea nitrogen (BUN) and

Potassium and sodium, serum and

Prolactin, serum and

Uric acid, serum

(concentrations may be increased)

Positive direct antiglobulin (Coombs') tests

(may be produced in 10 to 20% of patients on prolonged methyldopa therapy and usually occur after 6 to 12 months of therapy; rarely, these are associated with hemolytic anemia; the positive Coombs' test may not revert to normal until weeks or months after methyldopa is discontinued; less frequently, a positive indirect Coombs' test may occur, which may interfere with crossmatching of blood; lowest incidence is with daily doses of 1 gram or less 1, 13)

Prothrombin time 1

(may be prolonged indicating possible hepatotoxicity 13)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Hepatic disease, active, such as acute hepatitis and active cirrhosis 1, 13

Risk-benefit should be considered when the following medical problems exist

Cerebrovascular disease, severe bilateral

(rarely, involuntary choreoathetotic movements have been observed during methyldopa therapy 1)

Coronary insufficiency, including angina pectoris

(may be aggravated 1, 13)

>> Hemolytic anemia, autoimmune, history of

>> Hepatic disease, history of, in conjunction with past use of methyldopa 1, 13

Hepatic function impairment 1

(reduced biotransformation; lower doses may be required)

Mental depression, history of

Parkinson's disease

(may be exacerbated)

>> Pheochromocytoma 1

(interference with tests for catecholamines; in addition, pressor responses have been reported)

Renal function impairment

(increased sensitivity to effects of methyldopa, possibly due to accumulation of the sulfate conjugate; lower doses may be required 1, 13)

Sensitivity to methyldopa 1, 13

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Antinuclear antibody (ANA) titer 6 and

Complete blood counts 6 and

Lupus erythematosus cell preparations 6

(may be indicated if patient develops arthralgia, continued malaise, or other symptoms of systemic lupus erythematosus (SLE)-like syndrome 6)

Blood cell counts, including hematocrit, hemoglobin, or red cell count 1, 13

(recommended prior to initiation of therapy to establish a baseline for determination of development of hemolytic anemia; may also be required at periodic intervals during therapy)

>> Blood pressure measurements

(recommended at periodic intervals in patients being treated for hypertension; selected patients may be trained to perform blood pressure measurements at home and report the results at regular physician visits)

Direct Coombs' test 1, 13

(recommended before initiation of treatment and after 6 and 12 months of treatment 1, 13)

Hepatic function determinations

(recommended at baseline and at periodic intervals during therapy, especially during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs 1, 13)

Side/Adverse Effects

Note: Darkening of urine on exposure to air, caused by breakdown of methyldopa or its metabolites, may occur rarely 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Edema, peripheral 1, 13 (swelling of feet or lower legs)
Incidence less frequent

Drug fever 1, 13 (fever, shortly after onset of therapy); mental status changes 1 (mental depression or anxiety, nightmares or unusually vivid dreams)

Note: Drug fever usually occurs within the first 3 months of therapy and is sometimes accompanied by eosinophilia or hepatic function test changes 1, 13.

The hepatic reaction to methyldopa appears to be immunologic or hypersensitive in nature 1, 13.

Incidence rare

Cholestasis 1, 13 or hepatitis and hepatocellular injury 1, 13 1, 13 (dark or amber urine; pale stools; yellow eyes or skin); colitis 1, 13 (severe or continuing diarrhea or stomach cramps); hemolytic anemia, autoimmune 13 (continuing tiredness or weakness after having taken this medication for several weeks); leukopenia, reversible 1, 13 , or granulocytopenia, reversible 1, 13; myocarditis 1, 13 (fever, chills, troubled breathing, and fast heartbeat); pancreatitis 1, 13 (severe stomach pain with nausea and vomiting); systemic lupus erythematosus (SLE)-like syndrome 1, 5, 6, 13 (general feeling of discomfort or illness or weakness; joint pain; skin rash or itching); thrombocytopenia 1

Note: Hemolytic anemia occurs in less than 5% of patients showing a positive Coombs' test.
Rarely, fatal hepatic necrosis has been reported 1, 13.

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent¾more than 5%Drowsiness 1, 13; dryness of mouth 1, 13; headache 13

Note: Drowsiness is especially likely to occur at initiation of therapy and after dosage increases. 13

Incidence less frequent or rare

Decreased sexual ability or interest in sex¾more common in men than in women 1, 3; diarrhea 1; hyperprolactinemia 1, 13 (swelling of breasts or unusual milk production); nausea or vomiting 1; orthostatic hypotension 1, 13 (dizziness or lightheadedness when getting up from a lying or sitting position); paresthesias 1, 13 (numbness, tingling, pain, or weakness in hands or feet); sinus bradycardia 1, 13 (slow heartbeat); stuffy nose 1, 13

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (See Poison Control Center Listing).
Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Bradycardia; constipation; diarrhea; dizziness; flatus; gastric distention; hypotension, acute; lightheadedness; nausea; sedation, excessive; vomiting; weakness
Treatment of overdose

To decrease absorption¾
If clinically indicated and ingestion is recent, gastric lavage or emesis may reduce absorption 13.

Specific treatment¾

Management is mostly symptomatic and supportive 13.

This includes particular attention to heart rate and cardiac output, blood volume, electrolyte balance, paralytic ileus, urinary function, and cerebral activity 13.

Sympathomimetic agents may be indicated 13.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Methyldopa (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to methyldopa
Breast-feeding¾Distributed into breast milk
Use in the elderly¾Increased sensitivity to hypotensive and sedative effects
Other medications, especially MAO inhibitors
Other medical problems, especially active hepatic disease, history of hepatic disease associated with methyldopa, history of autoimmune hemolytic anemia, or pheochromocytoma
Proper use of this medication

Possible need for control of weight and diet, especially sodium intake

>> Patient may not experience symptoms of hypertension; importance of taking medication even if feeling well

>> Does not cure, but helps control hypertension; possible need for lifelong therapy; checking with physician before discontinuing medication; serious consequences of untreated hypertension

Compliance with therapy; taking medication at the same times each day to maintain the therapeutic effect

>> Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
Precautions while using this medication

Making regular visits to physician to check progress

>> Not using other medications, especially nonprescription sympathomimetics, unless ordered by physician

>> Reporting fever to physician

Caution if any kind of surgery (including dental surgery) or emergency treatment is required

>> Caution when driving or doing things requiring alertness, because of possible drowsiness

Caution when getting up suddenly from a lying or sitting position

Possible dryness of mouth; using sugarless candy or gum, ice, or saliva substitute for relief; checking with physician or dentist if dry mouth continues for more than 2 weeks

Caution if any laboratory tests required; possible interference with test results

Side/adverse effects

Signs of potential side effects, especially edema, drug fever, mental status changes, cholestasis, hepatitis, hepatocellular injury, colitis, hemolytic anemia, leukopenia, granulocytopenia, myocarditis, pancreatitis, SLE-like syndrome, and thrombocytopenia

General Dosing Information

If methyldopa is added to a thiazide diuretic regimen, the dosage of the thiazide need not be changed 1, 13.

If methyldopa is to be given with other antihypertensives, the initial dosage of methyldopa for an adult should be limited to 500 mg daily 1, 13.

Any increase in dosage should be initiated with the evening dose of methyldopa to minimize the effects of sedation 1, 13.

Tolerance to methyldopa may develop within 2 or 3 months after initiation of therapy as a result of fluid retention and expanded plasma volume 13.

Adding a diuretic or increasing the dosage of methyldopa may restore control 13.

Addition of thiazide diuretics to the regimen is recommended if therapy has not been started with a thiazide or if a daily dose of 2 grams of methyldopa does not maintain control 1, 13.

If orthostatic hypotension occurs, dosage reduction is recommended 1.

Recent evidence suggests that withdrawal of antihypertensive therapy prior to surgery is not necessary, but that the anesthesiologist must be aware of such therapy.
It is recommended that methyldopa be discontinued if Coombs' positive hemolytic anemia occurs 1, 13.

Although the anemia usually remits promptly, corticosteroids may be administered if necessary 1, 13.

If this effect is shown to be due to methyldopa, therapy with the drug should not be reinstituted 1, 13.

If a blood transfusion is needed in a patient receiving methyldopa, both a direct and indirect Coombs' test are recommended 1.

If hemolytic anemia is not present, usually only the direct Coombs' test will be positive, which will not interfere with typing or positive crossmatching 1, 13.

However, a positive indirect Coombs' test may interfere with the major crossmatch, and a hematologist or transfusion expert will be needed 1.

It is recommended that methyldopa be withdrawn if fever, abnormal liver function tests, or jaundice occurs 1, 13.

If these effects are shown to be due to methyldopa, therapy with the drug should not be reinstituted 1, 13.

For parenteral dosage forms only

Intramuscular or subcutaneous administration is not recommended because of unreliable absorption. Following stabilization of blood pressure using intravenous methyldopate, the patient should be transferred to methyldopa tablets at the same dosage as was used parenterally 14.

Oral Dosage Forms

METHYLDOPA ORAL SUSPENSION USP

Usual adult dose

Antihypertensive¾
Initial: Oral, 250 mg two or three times a day for two days, the dosage then being adjusted, preferably at intervals of not less than two days, until the desired response is obtained 1, 13.

Maintenance: Oral, 500 mg to 2 grams a day, divided into two to four doses 1, 13.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose and may require a lower dose to prevent syncope.

Usual adult prescribing limits

3 grams a day 1, 13.

Usual pediatric dose

Antihypertensive¾
Oral, initially 10 mg per kg of body weight or 300 mg per square meter of body surface, divided into two to four doses, the dosage then being adjusted, preferably at intervals of not less than two days, until the desired response is obtained, but not exceeding 65 mg per kg of body weight or 3 grams daily, whichever is less. 13

Strength(s) usually available

U.S.¾50 mg per mL (Rx)[Aldomet (alcohol 1%) (benzoic acid) (sodium bisulfite) (sugar) (polysorbate)]

Canada¾Not commercially available.

Packaging and storage:

Store below 26 °C (79 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container. Protect from freezing.

Auxiliary labeling:

· Shake well before using.
· May cause drowsiness.
· Do not take other medicines without your doctor's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

METHYLDOPA TABLETS USP

Usual adult dose

Antihypertensive¾
Initial: Oral, 250 mg two or three times a day for two days, the dosage then being adjusted, preferably at intervals of not less than two days, until the desired response is obtained 13.

Maintenance: Oral, 500 mg to 2 grams a day, divided into two to four doses 13.

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose and may require a lower dose to prevent syncope.

Usual adult prescribing limits

3 grams a day 13.

Usual pediatric dose

Antihypertensive¾
Oral, initially 10 mg per kg of body weight or 300 mg per square meter of body surface, divided into two to four doses, the dosage then being adjusted, preferably at intervals of not less than two days, until the desired response is obtained, but not exceeding 65 mg per kg of body weight or 3 grams daily, whichever is less 13.

Strength(s) usually available

U.S.¾125 mg (Rx)[Aldomet (without sodium metabisulfite preservative)] [Generic] (with or without sodium metabisulfite preservative)

250 mg (Rx)[Aldomet (without sodium metabisulfite preservative)] [Generic] (with or without sodium metabisulfite preservative)

500 mg (Rx)[Aldomet (without sodium metabisulfite preservative)] [Generic] (with or without sodium metabisulfite preservative)

Canada¾125 mg (Rx)[Aldomet] [Apo-Methyldopa] [Dopamet] [Novomedopa] [Nu-Medopa]

250 mg (Rx)[Aldomet] [Apo-Methyldopa] [Dopamet] [Novomedopa] [Nu-Medopa]

500 mg (Rx)[Aldomet] [Apo-Methyldopa] [Dopamet] [Novomedopa] [Nu-Medopa]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· May cause drowsiness.
· Do not take other medicines without your doctor's advice.

Note: Check refill frequency to determine compliance in hypertensive patients.

Parenteral Dosage Forms

METHYLDOPATE HYDROCHLORIDE INJECTION USP

Usual adult dose

Antihypertensive¾
Intravenous infusion, 250 to 500 mg in 100 mL of 5% dextrose injection, administered slowly over a thirty- to sixty-minute period, every six hours if necessary. 12

Note: Geriatric patients may be more sensitive to the effects of the usual adult dose and may require a lower dose to prevent syncope.

Usual adult prescribing limits

1 gram every 6 hours. 14

Usual pediatric dose

Antihypertensive¾
Intravenous infusion, 20 to 40 mg per kg of body weight in 5% dextrose injection, administered slowly over a thirty- to sixty-minute period, every six hours if necessary, but not exceeding 65 mg per kg of body weight or 3 grams daily, whichever is less 14.

Strength(s) usually available

U.S.¾50 mg per mL (Rx)[Aldomet (sodium bisulfite) (methylparaben) (propylparaben)] [Generic] (may contain sodium metabisulfite, methylparaben, propylparaben)

Canada¾50 mg per mL (Rx)[Aldomet (sodium bisulfite) (methylparaben) (propylparaben)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

References

Note: All references used in the development and earlier revisions of this monograph have not yet been incorporated into the computer database and, therefore, are not listed below. Citations for information not yet referenced in the monograph will be provided upon request.

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10 Methyldopate HCl injection package insert (Quad¾US), Rec 10/86.

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12 Aldomet injection package insert (MSD¾US), Rev 3/90, Rec 4/92.

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