010640-10

METHIMAZOLE TABLETS, USP
R01/12

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METHIMAZOLE TABLETS, USP

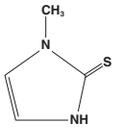
Rx only

DESCRIPTION

Methimazole (1-methylimidazole-2-thiol) is a white, crystalline substance that is freely soluble in water. It differs chemically from the drugs of the thiouracil series primarily because it has a 5- instead of a 6-membered ring.

Each tablet contains 5 or 10 mg (43.8 or 87.6 µmol) methimazole, an orally administered antithyroid drug. Each tablet also contains lactose monohydrate, magnesium stearate, corn starch, and talc.

The molecular weight is 114.17, and the molecular formula is $C_4H_6N_2S$. The structural formula is as follows:



CLINICAL PHARMACOLOGY

Methimazole inhibits the synthesis of thyroid hormones and thus is effective in the treatment of hyperthyroidism. The drug does not inactivate existing thyroxine and tri-iodothyronine that are stored in the thyroid or circulating in the blood nor does it interfere with the effectiveness of thyroid hormones given by mouth or by injection.

Methimazole is readily absorbed in the gastrointestinal tract, metabolized in the liver, and excreted in the urine.

INDICATIONS AND USAGE

Methimazole is indicated:

- In patients with Graves' disease with hyperthyroidism or toxic multinodular goiter for whom surgery or radioactive iodine therapy is not an appropriate treatment option
- To ameliorate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy

CONTRAINDICATIONS

Methimazole is contraindicated in the presence of hypersensitivity to the drug or any of the other product components.

WARNINGS

Congenital Malformations

Methimazole readily crosses placental membranes and can cause fetal harm, particularly when administered in the first trimester of pregnancy. Rare instances of congenital defects, including aplasia cutis, craniofacial malformations (facial dysmorphism; choanal atresia) and gastrointestinal malformations (esophageal atresia with or without tracheoesophageal fistula; umbilical abnormalities) have occurred in infants born to mothers who received methimazole during pregnancy. If methimazole is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be warned of the potential hazard to the fetus.

Since the above congenital defects have been reported in offspring of patients treated with methimazole, it may be appropriate to use other agents in pregnant women requiring treatment for hyperthyroidism, particularly during organogenesis, in the first trimester of pregnancy. If methimazole is used, the lowest possible dose to control the maternal disease should be given.

Agranulocytosis

Agranulocytosis is a potentially life-threatening adverse reaction of methimazole therapy. Patients should be instructed to immediately report to their physicians any symptoms suggestive of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and aplastic anemia (pancytopenia) may also occur. The drug should be discontinued in the presence of agranulocytosis, aplastic anemia (pancytopenia), ANCA-positive vasculitis, hepatitis, or exfoliative dermatitis, and the patient's bone marrow indices should be monitored.

Liver Toxicity

Although there have been reports of hepatotoxicity (including acute liver failure) associated with methimazole, the risk of hepatotoxicity appears to be less with methimazole than with propylthiouracil, especially in the pediatric population. Symptoms suggestive of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc) should prompt evaluation of liver function (bilirubin, alkaline phosphatase) and hepatocellular integrity (ALT, AST). Drug treatment should be discontinued promptly in the event of clinically significant evidence of liver abnormality including hepatic transaminase values exceeding 3 times the upper limit of normal.

Hypothyroidism

Methimazole can cause hypothyroidism necessitating routine monitoring of TSH and free T4 levels with adjustments in dosing to maintain a euthyroid state. Because the drug readily crosses placental membranes, methimazole can cause fetal goiter and cretinism when administered to a pregnant woman. For this reason, it is important that a sufficient, but not excessive, dose be given during pregnancy (see Precautions, Pregnancy).

PRECAUTIONS

General

Patients who receive methimazole should be under close surveillance and should be cautioned to report immediately any evidence of illness, particularly sore throat, skin eruptions, fever, headache, or general malaise. In such cases, white-blood-cell and differential counts should be obtained to determine whether agranulocytosis has developed. Particular care should be exercised with patients who are receiving additional drugs known to cause agranulocytosis.

Laboratory Tests

Because methimazole may cause hypoprothrombinemia and bleeding, prothrombin time should be monitored during therapy with the drug, especially before surgical procedures.

Thyroid function tests should be monitored periodically during therapy. Once clinical evidence of hyperthyroidism has resolved, the finding of a rising serum TSH indicates that a lower maintenance dose of methimazole should be employed.

Drug Interactions

Anticoagulants (oral) - Due to potential inhibition of vitamin K activity by methimazole, the activity of oral anticoagulants (e.g., warfarin) may be increased; additional monitoring of PT/INR should be considered, especially before surgical procedures.

β-adrenergic blocking agents - Hyperthyroidism may cause an increased clearance of beta blockers with a high extraction ratio. A reduced dose of beta-adrenergic blockers may be needed when a hyperthyroid patient becomes euthyroid.

Digitalis glycosides - Serum digitalis levels may be increased when hyperthyroid patients on a stable digitalis glycoside regimen become euthyroid; a reduced dosage of digitalis glycosides may be needed.

Theophylline - Theophylline clearance may decrease when hyperthyroid patients on a stable theophylline regimen become euthyroid; a reduced dose of theophylline may be needed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2 year study, rats were given methimazole at doses of 0.5, 3, and 18 mg/kg/day. These doses were 0.3, 2, and 12 times the 15 mg/day maximum human maintenance dose (when calculated on the basis of surface area). Thyroid hyperplasia, adenoma, and carcinoma developed in rats at the two higher doses. The clinical significance of these findings is unclear.

Pregnancy Category D

Due to the rare occurrence of congenital malformations associated with methimazole use, it may be appropriate to use other agents in pregnant women requiring treatment for hyperthyroidism, particularly in the first trimester of pregnancy (during organogenesis).

Patients should be advised that if they become pregnant or intend to become pregnant while taking an antithyroid drug, they should contact their physician immediately about their therapy.

In many pregnant women, the thyroid dysfunction diminishes as the pregnancy proceeds; consequently, a reduction in dosage of anti-thyroid therapy may be possible. In some instances, use of anti-thyroid therapy can be discontinued 2 or 3 weeks before delivery. Because the drug readily crosses placental membranes, methimazole can cause fetal goiter and cretinism when administered to a pregnant woman. For this reason, it is important that a sufficient, but not excessive, dose be given during pregnancy. (See **WARNINGS**.)

Nursing Mothers

Methimazole is excreted into breast milk. However, several studies found no effect on clinical status in nursing infants of mothers taking methimazole, particularly if thyroid function is monitored at frequent (weekly or biweekly) intervals. A long-term study of 139 thyrotoxic lactating mothers and their infants failed to demonstrate toxicity in infants who are nursed by mothers receiving treatment with methimazole.

Pediatric Use

Because of postmarketing reports of severe liver injury in pediatric patients treated with propylthiouracil, methimazole is the preferred choice when an antithyroid drug is required for a pediatric patient. (See **DOSAGE AND ADMINISTRATION**.)

ADVERSE REACTIONS

Major adverse reactions (which occur with much less frequency than the minor adverse reactions) include inhibition of myelopoieses (agranulocytosis, granulocytopenia, thrombocytopenia, and aplastic anemia), drug fever, a lupuslike syndrome, insulin autoimmune syndrome (which can result in hypoglycemic coma), hepatitis (jaundice may persist for several weeks after discontinuation of the drug), periarteritis, and hypoprothrombinemia. Nephritis occurs very rarely.

Minor adverse reactions include skin rash, urticaria, nausea, vomiting, epigastric distress, arthralgia, paresthesia, loss of taste, abnormal loss of hair, myalgia, headache, pruritus, drowsiness, neuritis, edema, vertigo, skin pigmentation, jaundice, sialadenopathy, and lymphadenopathy.

OVERDOSAGE

Signs and Symptoms

Symptoms may include nausea, vomiting, epigastric distress, headache, fever, joint pain, pruritus, and edema. Aplastic anemia (pancytopenia) or agranulocytosis may be manifested in hours to days. Less frequent events are hepatitis, nephrotic syndrome, exfoliative dermatitis, neuropathies, and CNS stimulation or depression.

No information is available on the median lethal dose of the drug or the concentration of methimazole in biologic fluids associated with toxicity and/or death.

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is the certified Regional Poison Control Center. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in the patient.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's medical status.

DOSAGE AND ADMINISTRATION

Methimazole is administered orally. The total daily dosage is usually given in 3 divided doses at approximately 8-hour intervals.

Adults

The initial daily dosage is 15 mg for mild hyperthyroidism, 30 to 40 mg for moderately severe hyperthyroidism, and 60 mg for severe hyperthyroidism, divided into 3 doses at 8-hour intervals. The maintenance dosage is 5 to 15 mg daily.

Pediatric

Initially, the daily dosage is 0.4 mg/kg of body weight divided into 3 doses and given at 8-hour intervals. The maintenance dosage is approximately 1/2 of the initial dose.

HOW SUPPLIED

Methimazole Tablets, USP 5 mg - white to off-white, round, flat-faced, bevelled-edged tablets, scored with "EM" 5 on one side and plain on the other.

They are available in:

Bottles of 100	NDC 49884-640-01
Bottles of 500	NDC 49884-640-05

Methimazole Tablets, USP 10 mg - white to off-white, round, flat-faced, bevelled-edged tablets, scored with "EM" 10 on one side and plain on the other.

They are available in:

Bottles of 100	NDC 49884-641-01
Bottles of 500	NDC 49884-641-05

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Dispense in tight, light-resistant container.

Manufactured and Distributed by:
PAR PHARMACEUTICAL COMPANIES, INC.
Spring Valley, NY 10977

Revised: 01/12

OS640-01-1-10