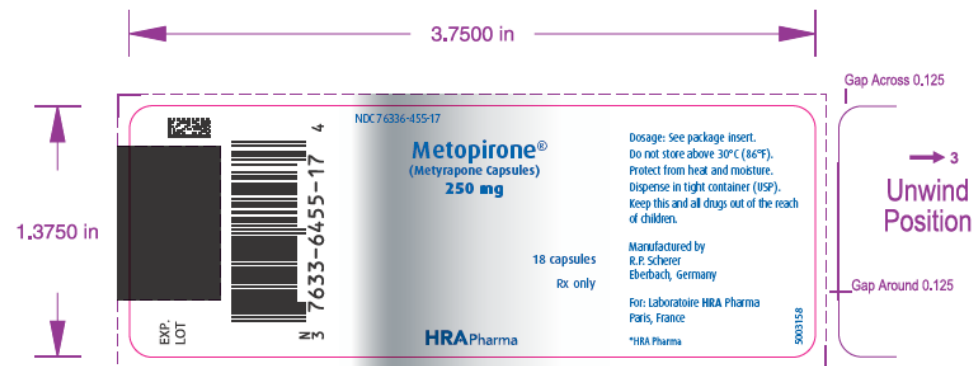


HRA Pharma	(b) (4)	
PRODUIT	METOPIRONE	
CODE ARTICLE	MOCK-UP	
TYPE	ÉTIQUETTE	
DOSAGE	250 mg	
PRÉSENTATION	18 capsules	
PAYS	USA	
FORMAT	95,25 x 34,925 mm	
FABRICANT	-	
Codes sur Pli	-	
Ref. PLAN	-	
COULEURS : 3	(b) (4)	
POLICE(S)	Dax	
CORPS minimum	5 pts	
LOGICIEL	Illustrator CS5	
CODE BARRES	Laetus	-
DATE	20/08/2013	
VERSION	4	



Metopirone[®]

(Metyrapone Capsules)

250 mg

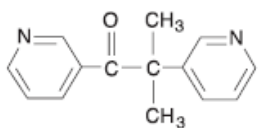
Diagnostic Test of Pituitary Adrenocorticotrophic Function

Rx only

Prescribing Information

DESCRIPTION

Metopirone (metyrapone Capsules) 250 mg is an inhibitor of endogenous adrenal corticosteroid synthesis, available as 250-mg capsules for oral administration. Its chemical name is 2-methyl-1, 2-di-3-pyridyl-1-propanone, and its structural formula is



Metyrapone is a white to light amber, fine, crystalline powder, having a characteristic odor. It is sparingly soluble in water, and soluble in methanol and in chloroform. It forms water-soluble salts with acids. Its molecular weight is 226.28.

Inactive Ingredients. Polyethylene glycol, glycerin, gelatin, sodium ethyl hydroxybenzoate, sodium propyl hydroxybenzoate, ethyl vanillin, 4-methoxyacetophenone, titanium dioxide, red ink.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The pharmacological effect of Metopirone is to reduce cortisol and corticosterone production by inhibiting the 11-beta-hydroxylation reaction in the adrenal cortex. Removal of the strong inhibitory feedback mechanism exerted by cortisol results in an increase in adrenocorticotrophic hormone (ACTH) production by the pituitary. With continued blockade of the enzymatic steps leading to production of cortisol and corticosterone, there is a marked increase in adrenocortical secretion of their immediate precursors, 11-desoxycortisol and desoxycorticosterone, which are weak suppressors of ACTH release, and a corresponding elevation of these steroids in the plasma and of their metabolites in the urine. These metabolites are readily determined by measuring urinary 17-hydroxycorticosteroids (17-OHCS) or 17-ketogenic steroids (17-KGS). Because of these actions, Metopirone is used as a diagnostic test, with urinary 17-OHCS measured as an index of pituitary ACTH responsiveness. Metopirone may also suppress biosynthesis of aldosterone, resulting in a mild natriuresis.

Pharmacokinetics

The response to Metopirone does not occur immediately. Following oral administration, peak steroid excretion occurs during the subsequent 24-hour period.

Absorption

Metopirone is absorbed rapidly and well when administered orally as prescribed.

Peak plasma concentrations are usually reached 1 hour after administration. After administration of 750 mg, mean peak plasma concentrations are 3.7 µg/mL, falling to 0.5 µg/mL 4 hours after administration. Following a single 2000-mg dose, mean peak plasma concentrations of metyrapone in plasma are 7.3 µg/mL.

Metabolism

The major biotransformation is reduction of the ketone to metyrapol, an active alcohol metabolite. Eight hours after a single oral dose, the ratio of metyrapone to metyrapol in the plasma is 1:1.5. Metyrapone and metyrapol are both conjugated with glucuronide.

Excretion

Metyrapone is rapidly eliminated from the plasma. The mean \pm SD terminal elimination half-life is 1.9 ± 0.7 hours. Metyrapol takes about twice as long as metyrapone to be eliminated from the plasma. After administration of 4.5 g metyrapone (750 mg every 4 hours), an average of 5.3% of the dose was excreted in the urine in the form of metyrapone (9.2% free and 90.8% as glucuronide) and 38.5% in the form of metyrapol (8.1% free and 91.9% as glucuronide) within 72 hours after the first dose was given.

INDICATIONS AND USAGE

Metopirone is a diagnostic drug for testing hypothalamic-pituitary ACTH function.

CONTRAINDICATIONS

Metopirone is contraindicated in patients with adrenal cortical insufficiency, or hypersensitivity to Metopirone or to any of its excipients.

WARNINGS

Metopirone may induce acute adrenal insufficiency in patients with reduced adrenal secretory capacity.

PRECAUTIONS

General

Ability of adrenals to respond to exogenous ACTH should be demonstrated before Metopirone is employed as a test. In the presence of hypo- or hyperthyroidism, response to the Metopirone test may be subnormal.

Since Metopirone may cause dizziness and sedation, patients should exercise caution when driving or operating machinery.

Laboratory Tests

See INTERPRETATION.

Drug Interactions

Drugs affecting pituitary or adrenocortical function, including all corticosteroid therapy, must be discontinued prior to and during testing with Metopirone.

The metabolism of Metopirone is accelerated by phenytoin; therefore, results of the test may be inaccurate in patients taking phenytoin within two weeks before.

A subnormal response may occur in patients on estrogen therapy.

Metopirone inhibits the glucuronidation of acetaminophen and could possibly potentiate acetaminophen toxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity and reproduction studies in animals have not been conducted.

Metopirone was not mutagenic with or without metabolic activation in three strains of bacteria.

Pregnancy Category C

A subnormal response to Metopirone may occur in pregnant women. Animal reproduction studies have not been conducted with Metopirone. The Metopirone test was administered to 20 pregnant women in their second and third trimester of pregnancy and evidence was found that the fetal pituitary responded to the enzymatic block. It is not known if Metopirone can affect reproduction capacity. Metopirone should be given to a pregnant woman only if clearly needed.

Animal reproduction studies adequate to evaluate teratogenicity and postnatal development have not been conducted with Metopirone.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Metopirone is administered to a nursing woman.

Pediatric Use

See DOSAGE AND ADMINISTRATION.

Geriatric Use

Clinical studies of Metopirone did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Cardiovascular System: Hypotension.

Gastrointestinal System: Nausea, vomiting, abdominal discomfort or pain.

Central Nervous System: Headache, dizziness, sedation.

Dermatologic System: Allergic rash.

Hematologic System: Rarely, decreased white blood cell count or bone marrow depression.

OVERDOSAGE

Acute Toxicity

One case has been recorded in which a 6-year-old girl died after two doses of Metopirone, 2 g.

Oral LD₅₀ in animals (mg/kg): rats, 521; maximum tolerated intravenous dose in one dog, 300.

Signs and Symptoms

The clinical picture of poisoning with Metopirone is characterized by gastrointestinal symptoms and by signs of acute adrenocortical insufficiency.

Cardiovascular System: Cardiac arrhythmias, hypotension, dehydration.

Nervous System and Muscles: Anxiety, confusion, weakness, impairment of consciousness.

Gastrointestinal System: Nausea, vomiting, epigastric pain, diarrhea.

Laboratory Findings: Hyponatremia, hypochloremia, hyperkalemia.

Combined Poisoning

In patients under treatment with insulin or oral antidiabetics, the signs and symptoms of acute poisoning with Metopirone may be aggravated or modified.

Treatment

There is no specific antidote. Besides general measures to eliminate the drug and reduce its absorption, a large dose of hydrocortisone should be administered at once, together with saline and glucose infusions.

Surveillance: For a few days blood pressure and fluid and electrolyte balance should be monitored.

DOSAGE AND ADMINISTRATION

Single-Dose Short Test

This test, usually given on an outpatient basis, determines plasma 11-desoxycortisol and/or ACTH levels after a single dose of Metopirone. The patient is given 30 mg/kg (maximum 3 g Metopirone) at midnight with yogurt or milk. The same dose is recommended in children. The blood sample for the assay is taken early the following morning (7:30-8:00 a.m.). The plasma should be frozen as soon as possible. The patient is then given a prophylactic dose of 50 mg cortisone acetate.

Interpretation

Normal values will depend on the method used to determine ACTH and 11-desoxycortisol levels. An intact ACTH reserve is generally indicated by an increase in plasma ACTH to at least 44 pmol/L (200 ng/L) or by an increase in 11-desoxycortisol to over 0.2 μ mol/L (70 μ g/L). Patients with suspected adrenocortical insufficiency should be hospitalized overnight as a precautionary measure.

Multiple-Dose Test

Day 1: Control period - Collect 24-hour urine for measurement of 17-OHCS or 17-KGS.

Day 2: ACTH test to determine the ability of adrenals to respond - Standard ACTH test such as infusion of 50 units ACTH over 8 hours and measurement of 24-hour urinary steroids. If results indicate adequate response, the Metopirone test may proceed.

Day 3-4: Rest period.

Day 5: Administration of Metopirone: Recommended with milk or snack.

Adults: 750 mg orally, every 4 hours for 6 doses. A single dose is approximately equivalent to 15 mg/kg.

Children: 15 mg/kg orally every 4 hours for 6 doses. A minimal single dose of 250 mg is recommended.

Day 6: After administration of Metopirone - Determination of 24-hour urinary steroids for effect.

Interpretation

ACTH Test

The normal 24-hour urinary excretion of 17-OHCS ranges from 3 to 12 mg. Following continuous intravenous infusion of 50 units ACTH over a period of 8 hours, 17-OHCS excretion increases to 15 to 45 mg per 24 hours.

Metopirone

Normal response: In patients with a normally functioning pituitary, administration of Metopirone is followed by a two- to four-fold increase of 17-OHCS excretion or doubling of 17-KGS excretion.

Subnormal response: Subnormal response in patients without adrenal insufficiency is indicative of some degree of impairment of pituitary function, either panhypopituitarism or partial hypopituitarism (limited pituitary reserve).

1. *Panhypopituitarism* is readily diagnosed by the classical clinical and chemical evidences of hypogonadism, hypothyroidism, and hypoadrenocorticism. These patients usually have subnormal basal urinary steroid levels. Depending upon the duration of the disease and degree of adrenal atrophy, they may fail to respond to exogenous ACTH in the normal manner. Administration of Metopirone is not essential in the diagnosis, but if given, it will not induce an appreciable increase in urinary steroids.

2. *Partial hypopituitarism* or limited pituitary reserve is the more difficult diagnosis as these patients do not present the classical signs and symptoms of hypopituitarism.

Measurements of target organ functions often are normal under basal conditions. The response to exogenous ACTH is usually normal, producing the expected rise of urinary steroids (17-OHCS or 17-KGS).

The response, however, to Metopirone is *subnormal*; that is, no significant increase in 17-OHCS or 17-KGS excretion occurs.

This failure to respond to metyrapone may be interpreted as evidence of impaired pituitary-adrenal reserve. In view of the normal response to exogenous ACTH, the failure to respond to metyrapone is inferred to be related to a defect in the CNS-pituitary mechanisms which normally regulate ACTH secretions. Presumably the ACTH secreting mechanisms of these individuals are already working at their maximal rates to meet everyday conditions and possess limited "reserve" capacities to secrete additional ACTH either in response to stress or to decreased cortisol levels occurring as a result of metyrapone administration.

Subnormal response in patients with Cushing's syndrome is suggestive of either autonomous adrenal tumors that suppress the ACTH-releasing capacity of the pituitary or nonendocrine ACTH-secreting tumors.

Excessive response: An excessive excretion of 17-OHCS or 17-KGS after administration of Metopirone is suggestive of Cushing's syndrome associated with adrenal hyperplasia. These patients have an elevated excretion of urinary corticosteroids

under basal conditions and will often, but not invariably, show a "supernormal" response to ACTH and also to Metopirone, excreting more than 35 mg per 24 hours of either 17-OHCS or 17-KGS.

HOW SUPPLIED

Capsules 250 mg -- soft gelatin, white to yellowish-white, oblong, opaque, imprinted HRA on one side in red ink.

Bottles of 18.....NDC 76336-455-17

Do not store above 30°C (86°F).

Protect from moisture and heat.

Dispense in tight container (USP).

5003157

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMESH RAGHAVACHARI
09/05/2013