Metopirone®
(metyrapone)

NAME OF THE DRUG

Active ingredient: metyrapone
Chemical names: 2-methyl-1,2-di-3-pyridyl-1-propanone
CAS number: 54-36-4
Molecular weight: 226.27
Molecular formula C_{14}H_{14}N_{2}O
Chemical structure:

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\text{Chemical structure image}
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DESCRIPTION

Metopirone is supplied as soft gelatin capsules each containing 250 mg of metyrapone. It also contains sodium ethyl hydroxybenzoate, ethyl vanillin, gelatin, glycerol, acetanisole, macrogol 400, macrogol 4000, sodium propyl hydroxybenzoate, titanium dioxide, and water – purified as excipients.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic agent, test for pituitary function.
ATC code: V04CD01

Metopirone inhibits reversibly the biosynthesis of cortisol, corticosterone, and aldosterone in the adrenal cortex by blocking enzymatic 11-beta-hydroxylation in the steroid ring. In the normal person, a compensatory increase in ACTH release follows and the secretion of 11-desoxycortisol, 11-desoxycorticosterone and 17-hydroxycorticoids is markedly accelerated.

Pharmacokinetics

Metyrapone is rapidly absorbed after administration by mouth and is also rapidly eliminated from the plasma. Peak concentrations are usually attained in plasma 1 hour after ingestion of Metopirone. Following a dose of 750mg, the mean peak concentration is 3.7ug/mL and decreases to a mean value of 0.5ug/mL 4 hours after ingestion. The elimination half-life of metyrapone from plasma is 20 to 26 minutes.
Metyrapol (reduced metyrapone) is the principal active metabolite. The metyrapone / metyrapol ratio in the plasma 8 hours after a single oral dose is 1/1.5.

Following a total dosage of 4.5g metyrapone (750mg every 4 hours), the quantities excreted in the urine 72 hours after the first dose averaged 5.3% of the total dosage in the form of metyrapone (9.2% in free form and 90.8% conjugated with glucuronic acid) and 38.5% in the form of metyrapol (8.1% in free form and 91.9% conjugated with glucuronic acid).

**INDICATIONS**

**Diagnostic Use**
- For the diagnosis of latent ACTH deficiency such as in cases of known pituitary dysfunction or of a suspected pituitary tumour, as well as before and after surgical intervention in the region of the pituitary; and, to assess the degree of ACTH suppression during or after glucocorticoid therapy.
- For the differential diagnosis of states of adrenocortical hyperfunction in Cushing's Syndrome.

**CONTRAINDICATIONS**

- Adrenocortical insufficiency
- Hypersensitivity to metyrapone or to any of the excipients.

**PRECAUTIONS**

Since the Metopirone test yields satisfactory results only if the adrenal cortex is still capable of responding normally to ACTH, it may be advisable to ascertain responsiveness to exogenous ACTH administration before a diagnostic test with Metopirone is undertaken because Metopirone may induce acute adrenal insufficiency in patients with reduced adrenal secretory capacity as well as in patients with gross hypopituitarism.

Long-term treatment with Metopirone can cause hypertension due to excessive secretion of desoxycorticosterone.

In cases where adrenocortical or anterior pituitary function is more severely impaired, Metopirone may provoke transient adrenocortical insufficiency. This can be rapidly overcome by administering a corticosteroid.
Patients with liver cirrhosis often show a delayed response to Metopirone, because the liver damage results in a slower breakdown of cortisol.

In cases of thyroid hypofunction, the urinary steroid excretion may rise only sluggishly or not at all, in response to Metopirone.

Patients with ectopic Cushing’s syndrome are at risk for opportunistic infections such as *Pneumocystis Jirovecii* pneumonia during Metopirone treatment.

**Effect on Ability to Drive and Use Machines**
Since Metopirone may cause dizziness and sedation, patients should exercise caution when driving or operating machinery.

**Genotoxicity, carcinogenicity and teratogenicity**
No studies for genotoxicity or carcinogenicity have been performed with Metopirone. Animal reproduction studies, adequate to evaluate teratogenicity and postnatal development, have not been conducted.

**Use in Pregnancy**
Safety in pregnancy has not been established; therefore the drug should not be used in pregnant women unless it is urgently indicated and the expected benefits outweigh any potential risk.

**Use in Lactation**
It is not known if the active substance of Metopirone passes into the breast milk, hence nursing mothers should refrain from breast feeding their infants during treatment with Metopirone.

**Interactions with Other Drugs**
Before performing the Metopirone tests, drugs influencing pituitary or adrenocortical function must be withdrawn.

**Observed interactions**
Anticonvulsants (e.g. phenytoin; barbiturates) psychoactive drugs (e.g.amitriptyline, chlorpromazine, and alprazolam), hormone preparations, corticosteroids, cyproheptadine, and anti-thyroid agents may exert an influence on the results of the Metopirone test.

**Anticipated interactions**
Metopirone may potentiate Paracetamol (acetaminophen) toxicity in humans.
ADVERSE REACTIONS

Adverse drug reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Blood and the lymphatic system disorders
   Not known: Bone marrow failure

Endocrine disorders
   Rare: Adrenal insufficiency

Nervous system disorders
   Common: Dizziness, sedation, headache
   Not known: Light-headedness

Vascular disorders
   Common: Hypotension
   Not known: Hypertension

Gastrointestinal disorders
   Common: Nausea, vomiting
   Rare: Abdominal pain

Skin and subcutaneous tissue disorders
   Rare: Allergic skin reactions, hirutism
   Not known: Alopecia

DOSAGE AND ADMINISTRATION

Diagnostic Agent

Short Single Dose Test (which can be carried out in ambulant patients) for the diagnosis of latent ACTH deficiency:

In the short single-dose test, 11-desoxycortisol (Compound S) and/or ACTH are determined in the plasma following a single dose of Metopirone. At around midnight the patient is given 1 to 2g of Metopirone (30mg/kg - adults or children) together with yogurt or milk. Eight hours later a sample of whole venous blood is taken, centrifuged at 4°C and the plasma deep frozen at -20°C, immediately. Afterwards a prophylactic dose of 50mg cortisone acetate should be administered.
**Assessment:**
The accepted normal values employed will depend on the method used for assaying ACTH and 11-desoxycortisol and may vary in different laboratories. A rise in plasma ACTH to at least 44 pmol/litre (200ng/litre), or in 11-desoxycortisol to over 0.2 umol/litre (70 ug/litre), usually indicates a normal ACTH reserve.

Patients in whom adrenocortical insufficiency is suspected, and who cannot be adequately supervised at home, should be hospitalised for the night as a precautionary measure.

**Multiple Dose Test (which can only be carried out in hospital) for the diagnosis of latent ACTH deficiency and the differential diagnosis of states of adrenocortical hyperfunction in Cushing's Syndrome:**
The urinary excretion of steroids is measured. After control values have first been obtained for the 24 hours preceding the Metopirone test, 500 to 750 mg Metopirone is administered every 4 hours for 24 hours, to a total of 3.0 to 4.5g. It is recommended that the capsules be taken together with milk or after a meal. All urine passed in the following 24 hours is collected and stored at -10°C until analysis is done. The effect on the urinary steroid values can be expected to reach its maximum within this 24 hour period.

**Assessment:**
- **ACTH deficiency:**
  When the anterior pituitary is functioning normally Metopirone causes a pronounced increase (to double or more) in the urinary excretion of 11-desoxycortisol and other 11-desoxycorticosteroids. The absence of such an increase indicates secondary adrenocortical insufficiency.

- **Cushing's syndrome:**
  If the urinary excretion of 11-desoxycorticosteroids increases in response to Metopirone, this indicates that excessive production of ACTH has led to adrenocortical hyperplasia (Cushing's disease). Such an increase can be taken as a sign that an autonomous cortisol-producing adrenocortical tumour is not present.

**OVERDOSAGE**

**Symptoms:**
The chief features of the clinical picture of an overdosage of Metopirone are gastro-intestinal symptoms and signs of acute adrenocortical insufficiency.

Laboratory findings: hyponatraemia, hypochloraemia, hyperkalaemia.
In patients under treatment with insulin or oral antidiabetics, the signs and symptoms of acute poisoning with Metopirone may be aggravated or modified.

**Treatment:**

Contact the Poisons Information Centre on 131 126 for advice on management.

There is no specific antidote. Besides the usual measures taken in cases of poisoning to eliminate the drug and reduce absorption, large doses of glucocorticoids, electrolyte and fluid replacement, and glucose infusions are indicated.

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

**PRESENTATION AND STORAGE CONDITIONS**

**Presentation**

Metopirone capsules 250 mg are cream coloured, soft gelatin capsules, marked CIBA and LN on reverse sides in brown ink. Each bottle contains 50 capsules.

**Storage**

Store below 30°C. Protect from moisture. Keep out of the reach and sight of children.

**POISON SCHEDULE**

(S4) Prescription Only Medicine

**NAME AND ADDRESS OF SPONSOR**

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113
® = registered trademark

**DATE OF APPROVAL**

Approved by the Therapeutic Goods Administration 20 June 1984.
Date of most recent amendment: 7 July 2011