REGITINE®
phentolamine mesylate

NAME OF THE DRUG

Active ingredient: phentolamine mesylate
Chemical Name: 2-([N-(m-Hydroxyphenyl)p-toluidino]-methyl)-2-imidazoline methanesulfonate
Molecular Weight: 377.5
Molecular Formula: C\textsubscript{17}H\textsubscript{19}N\textsubscript{3}O·CH\textsubscript{3}SO\textsubscript{3}H
CAS Number: 65-28-1
Chemical Structure:

\[
\begin{array}{c}
\text{H} \\
\text{CH}_2\text{N}\text{N} \\
\text{CH}_3 \cdot \text{CH}_3\text{SO}_3\text{H}
\end{array}
\]

DESCRIPTION

Phentolamine mesylate is a white, slightly hygroscopic, odourless crystalline powder with a bitter taste. Melting point 177° to 181°C. It is soluble 1:1 in water, 1:5 in alcohol and 1:700 in chloroform. Aqueous solutions have a pH of about 5.

Each Regitine ampoule contains 10 mg phentolamine mesylate in 1 mL water for injections. The solution is clear and colourless, and contains bioactive excipients sodium metabisulphite (E223) and glucose - anhydrous (see PRESENTATION AND STORAGE CONDITIONS).

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: \(\alpha\)-adrenergic receptor blocker; ATC code: C04A B01:

Phentolamine is a competitive non-selective \(\alpha_1\)- and \(\alpha_2\)-adrenergic receptor blocker of relatively short duration of action. It causes vasodilatation and a fall in blood pressure resulting from the blockade of both post-junctional vascular \(\alpha_1\)- and \(\alpha_2\)-adrenoceptors. It also antagonises the vasoconstrictor response to noradrenaline and adrenaline infusions. Enhanced neural release of noradrenaline due to presynaptic \(\alpha_2\)-blockade may contribute to the positive inotropic and chronotropic effects of Regitine on cardiac muscle.
The administration of Regitine intravenously to man produces transient falls in mean systemic vascular resistance and mean systemic arterial pressure as a result of dilatation in the arterial as well as in the venous vascular bed. These effects of Regitine are accompanied by tachycardia, triggered by the baroreceptor reflex system and the autonomic nervous system.

When patients with phaeochromocytoma are submitted to surgery to remove the tumour, a sudden severe rise in blood pressure is likely to occur during induction of anaesthesia and during manipulation of the tumour. This is the result of excessive circulating catecholamines secreted by the tumour. The extreme pressor effect produced may be counteracted by the administration of Regitine. After removal of the tumour, hypotension may occur, which may be counteracted by ceasing administration of Regitine and giving plasma volume expanders.

**Pharmacokinetics**

**Elimination:**
Regitine has a half-life in the blood of 19 minutes after intravenous administration. Approximately 13 % of a single intravenous dose appears in the urine as unchanged drug.

**Distribution:**
Phentolamine is bound to an extent of 54 % to proteins of human serum in the concentration range of 0.02 to 109 micrograms/mL.

**INDICATIONS**

- Management of hypertensive episodes that may occur in patients with phaeochromocytoma, for example during preoperative preparation and surgical manipulation.
- Diagnosis of phaeochromocytoma by Regitine blocking test if other more specific tests are not available.

**CONTRAINDICATIONS**

- Known hypersensitivity to phentolamine and related compounds.
- Known hypersensitivity to sulphites.
- Hypotension
- Myocardial infarction, history of myocardial infarction, coronary insufficiency, angina, or other evidence of coronary artery disease.
- Regitine should not be used in patients with renal impairment, since no pharmacokinetic studies with Regitine have been performed in such patients and little is known about the fate of Regitine in these circumstances.
PRECAUTIONS

General

Use of the Regitine blocking test:
For screening tests in patients with hypertension, the generally available urinary assay of catecholamines or other biochemical assays have largely replaced the Regitine and other pharmacological tests for reasons of accuracy and safety. Therefore, the Regitine blocking test is not the procedure of choice and should be used only when these other specific tests are not available.

Use with caution in the following circumstances

Cardiac effects:
Monitoring of the blood pressure is necessary for appropriate selection of patient, dosage and duration of therapy. Myocardial infarction, cerebrovascular spasm and cerebrovascular occlusion have been reported to occur following the administration of Regitine, usually in association with marked hypotensive episodes.

Tachycardia and cardiac arrhythmias may occur with the use of Regitine.

Hypersensitivity to sulphites:
The presence of sulphites in Regitine ampoules can lead, especially in patients with bronchial asthma, to isolated hypersensitivity reactions, which may become manifest as an acute asthma attack, or shock, or clouding of consciousness.

Gastrointestinal effects:
Due to its stimulatory effect on the gastro-intestinal tract, including gastric secretion, Regitine should be used with caution in patients with gastritis or peptic ulcer.

Effects on ability to drive or use machines:

Regitine may cause central nervous symptoms (see "Adverse reactions") which may impair the patient's reactions. Patients must therefore be warned against engaging in activities that require quick reactions, such as driving motor vehicles and operating machines.

Carcinogenicity / mutagenicity

Experimental data have established that phentolamine lacks mutagenic potential in bacteria, and does not induce chromosomal aberrations in mammalian somatic cells in vivo. Long-term carcinogenicity studies have not been conducted with phentolamine.
Use in pregnancy (Category B1)

Animal studies have established that phentolamine lacks embryotoxicity and teratogenic activity in mice (at doses up to 150 mg/kg), rats (up to 450 mg/kg) and rabbits (up to 100 mg/kg).

As a general rule no drugs should be taken during the first three months of pregnancy, and the benefits and risks of taking drugs should be carefully considered throughout the whole pregnancy.

Experience with Regitine in pregnant women is not available. Do not use in pregnancy unless treatment is considered essential.

Use in lactation

No information is available as to whether or not phentolamine passes into human milk. For safety reasons, it is not recommended to use Regitine during lactation.

Interactions with other drugs

Regitine may augment the hypotensive effect of other antihypertensive agents. Antipsychotics may enhance the hypotensive effect of α-adrenergic blocking agents. The hypertensive effects of dopamine may be counteracted by phentolamine.

Nonselective beta-agonists
Due to blockade of vasoconstrictor alpha receptors by phentolamine, concurrent use of agents with nonselective beta-agonist properties (i.e. adrenaline, isoprenaline) can produce additive lowering of blood pressure.

ADVERSE REACTIONS

The following adverse reactions have been observed.

Frequency estimates: very common ≥ 10 %
common ≥ 1 % to < 10 %
uncommon ≥ 0.1 % to < 1 %
rare ≥ 0.01 % to < 0.1 %
very rare < 0.01 %

Cardiovascular system:
Very common: orthostatic hypotension, tachycardia
Common: acute or prolonged hypotensive episodes, myocardial infarction
Uncommon: angina, cardiac arrhythmias.

Central nervous system:
Common: dizziness, weakness, cerebrospasm, cerebrovascular occlusion

Gastro-intestinal tract:
Common: nausea, vomiting, diarrhoea, aggravation of peptic ulcer, abdominal pain.

Other organ systems:
Common: nasal stuffiness, flushing
Uncommon: chest pain

DOSAGE AND ADMINISTRATION

Management of hypertensive episodes in patients with phaeochromocytoma:
For the management of hypertensive crises that arise before surgery or during induction of anaesthesia, intubation, or surgical removal of tumour, 2 to 5 mg of Regitine is injected intravenously and repeated if necessary, monitoring the blood pressure response. For children, use the minimum effective dose e.g. 1 mg for a child over 8 years old.

Diagnosis of phaeochromocytoma - Regitine blocking test:
The test is most reliable in detecting phaeochromocytoma in patients with sustained hypertension and least reliable in those with paroxysmal hypertension. False-positive tests may occur in patients with hypertension without phaeochromocytoma.

Preparation for the test:
Sedatives, analgesics, and all other medications except those that might be deemed essential (such as digitalis and insulin) are withheld for at least 24 hours, and preferably 48 to 72 hours, prior to the test. Antihypertensive drugs are withheld until blood pressure returns to the untreated, hypertensive level. This test is not performed on a patient who is normotensive.

Intravenous Regitine blocking test:
Procedure: the patient is kept at rest in the supine position throughout the test, preferably in a quiet, darkened room. Injection of Regitine is delayed until blood pressure is stabilised, as shown by blood pressure readings taken every 10 minutes for at least 30 minutes.

The dose for adults is 5 mg; for children 1 mg.

The syringe needle is inserted into the vein, and injection is delayed until pressor response to venepuncture has subsided.
Regitine is injected rapidly. Blood pressure is recorded immediately after injection, at 30-second intervals for the first 3 minutes, and at 60-second intervals for the next 7 minutes.

**Interpretation:**
A positive response, suggestive of phaeochromocytoma, is indicated when the blood pressure is reduced by more than 35 mm Hg systolic and by 25 mm Hg diastolic. A typical positive response is a reduction in pressure of 60 mm Hg systolic and 25 mm Hg diastolic. Usually, the maximal effect is evident within 2 minutes after injection. A return to preinjection pressure commonly occurs within 15 to 30 minutes but may occur more rapidly.

If blood pressure falls to a dangerous level, the patient should be treated as outlined under "Overdosage". A negative response is indicated when the blood pressure is raised, unchanged, or reduced by less than 35 mm Hg systolic and by 25 mm Hg diastolic after injection of Regitine. A negative response to this test does not exclude the diagnosis of phaeochromocytoma, especially in patients with paroxysmal hypertension in whom the incidence of false-negative responses is high.

**Intramuscular Regitine blocking test:**
The dose for adults is 5 mg intramuscularly; for children 3 mg. Blood pressure is recorded every 5 minutes for 30 to 45 minutes following injection. A positive response is indicated when the blood pressure is reduced by 35 mm Hg systolic and by 25 mm Hg diastolic, or more, within 20 minutes following injection.

**OVERDOSAGE**

**Symptoms:**
The main clinical manifestations of overdosage with Regitine are arterial hypotension, reflex tachycardia, cardiac stimulation, arrhythmia, increase of systemic venous capacity and possibly shock. These effects may be accompanied by headache, hyperexcitability and disturbances of vision, sweating, increased gastric motility, vomiting and diarrhoea, hypoglycaemia.

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

There is no specific antidote. No specific information for the management of acute overdosage with Regitine is available. On the basis of the pharmacological properties of Regitine, the following measures are advisable:
- Hypotension, excessive peripheral vasodilatation: Noradrenaline, in cautiously titrated continuous i.v. infusion, can be considered the physiological antagonist; the effect of Regitine may wear off in a short time, and administration of noradrenaline may have to be adjusted accordingly. When a pressor agent is used, ECG should be monitored, because major arrhythmias may occur. Alternative measures such as keeping the
patient's legs raised and administering a plasma expander should be implemented concomitantly. Do not use adrenaline since this may cause a further fall of blood pressure under the given conditions.

- Disturbances of cardiac rhythm: Adjust treatment to the nature of the arrhythmia.
- Hypoglycaemia: Provide glucose i.v. until reaction is compensated.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Aqueous injectable solution in ampoules: ampoules (1 mL) containing 10 mg phentolamine mesylate, 0.5 mg sodium metabisulphite, 35.0 mg glucose-anhydrous, and water for injections up to 1 mL; packs of five.

Storage: Store at 2°C- 8°C. Do not freeze. Protect from light. Keep out of the reach of children.

Poisons schedule: (S4) Prescription Only Medicine

SPONSOR

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