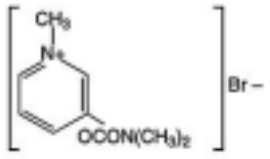
MESTINON®

(pyridostigmine bromide)

INJECTABLE

DESCRIPTION: Mestinon (pyridostigmine bromide) is an orally active cholinesterase inhibitor. Chemically, pyridostigmine bromide is 3-hydroxy-1-methylpyridinium bromide dimethylcarbamate. Its structural formula is:



Each mL contains 5 mg pyridostigmine bromide compounded with 0.296 parabens (methyl and propyl) as preservatives, 0.0296 sodium citrate and pH adjusted to approximately 5.0 with citric acid and, if necessary, sodium hydroxide.

ACTIONS: Mestinon facilitates the transmission of impulses across the myoneural junction by inhibiting the destruction of acetylcholine by cholinesterase. Pyridostigmine is an analog of neostigmine (Prostigmin®) but differs from it clinically by having fewer side effects. Currently available data indicate that pyridostigmine may have a significantly lower degree and incidence of bradycardia, salivation and gastrointestinal stimulation. Animal studies using the injectable form of pyridostigmine and human studies using the oral preparation have indicated that pyridostigmine has a longer duration of action than does neostigmine measured under similar circumstances.

INDICATIONS: Mestinon Injectable is useful in the treatment of myasthenia gravis and as a reversal agent or antagonist to nondepolarizing muscle relaxants such as curariform drugs and gallamine triethiodide.

CONTRAINDICATIONS: Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

WARNINGS: Mestinon Injectable should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of Mestinon are administered, as during reversal of muscle relaxants, the prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

As is true of all cholinergic drugs, overdosage of Mestinon may result in cholinergic crisis, a state characterized by increasing muscle weakness which, through involvement of the muscles of respiration, may lead to death.

Myasthenic crisis due to an increase in the severity of the disease is also accompanied by extreme muscle weakness and thus may be difficult to distinguish from cholinergic crisis on a symptomatic basis. Such differentiation is extremely important, since increases in doses of Mestinon or other drugs in this class in the presence of cholinergic crisis or of a refractory or "insensitive" state could have grave consequences. Osserman and Genkins' indicate that the two types of crisis may be differentiated by the use of Tensilon© (edrophonium chloride) as well as by clinical judgment The treatment of the two conditions obviously differs radically. Whereas the presence of *myasthenic* crisis requires more intensive anticholinesterase therapy, *cholinergic crisis,* according to Osserman and Genkins[1] calls for the prompt withdrawal of all drugs of this type. The immediate use of atropine in cholinergic crisis is also recommended. A syringe containing 1 mg of atropine sulfate should be immediately available to be given in aliquots intravenously to counteract severe cholinergic reactions.

Atropine may also be used to abolish or obtund gastrointestinal side effects or other muscarinic reactions; but such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis.

For detailed information on the management of patients with myasthenia gravis, the physician is referred to one of the excellent reviews such as those by Osserman and Genkins[2] Grob[3] or Schwab.[4,5]

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgment, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Usage in Pregnancy: The safety of Mestinon during pregnancy or lactation in humans has not been established. Therefore, use of Mestinon in women who may become pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

PRECAUTION: Pyridostigmine is mainly excreted unchanged by the kidney.6,7,8 Therefore, lower doses may be required in patients with renal disease, and treatment should be based on titration of drug dosage to effects.?

ADVERSE REACTIONS: The side effects of Mestinon are most commonly related to over-dosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine, but for reasons shown in the preceding section the expedient is not without danger. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION: *For Myasthenia Gravis: To* supplement oral dosage, pre- and postoperatively, during labor and postpartum, during myasthenic crisis, or whenever oral therapy is impractical, approximately 1130th of the oral dose of Mestinon may be given parenterally, either by intramuscular or *very slow* intravenous injection. *The patient must be closely observed for cholinergic reactions, particularly if the intravenous route is used.*

For details regarding the management of myasthenic patients who are to undergo major surgical procedures, see the article by Foldes.[9]

Neonates of myasthenic mothers may have transient difficulty in swallowing, sucking and breathing. Injectable Mestinon may be indicated - by symptomatology and use of the Tensilon© (edrophonium chloride) test - until Mestinon Syrup can to taken. To date the world literature consists of less than 100 neonate patients.[10] Of these only 5 were treated with injectable pyridostigmine, with the vast majority of the remaining neonates receiving neostigmine. Dosage requirements of Mestinon Injectable are minute, ranging from 0.05 mg to 0.15 mg/kg of body weight given intramuscularly. It is important to differentiate between cholinergic and myasthenic crises in neonates. (See WARNINGS.)

Mestinon given parenterally 1 hour before completion of second stage labor enables patients to have adequate strength during labor and provides protection to infants in the immediate postnatal state. For further information on the use of Mestinon Injectable in neonates of myasthenic mothers, see the article by Namba.[10]

Note: For information on a diagnostic test for myasthenia gravis, and on the evaluation and stabilization of therapy, please see product information on Tensilon® (edrophonium chloride).

For Reversal of Nondepolarizing Muscle Relaxants: When Mestinon Injectable is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) also be given intravenously immediately prior to the Mestinon. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Usually 10 or 20 mg of Mestinon will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported. For additional information on the use of Mestinon for antagonism of nondepolarizing muscle relaxants see the article by Katz" and McNall.12

Failure of Mestinon Injectable to provide prompt (within 30 minutes) reversal may occur, eg, in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

HOW SUPPLIED: Mestinon is available in 2-mL ampuls (boxes of 10) (NDC 0187-3011-10).

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Manufactured for ICN Pharmaceuticals Inc.
Costa Mesa, CA 92626
by Hoffmann-La Roche Inc.
Nutley, N.J. 07110

13-06-74725-0995 Revised: September 1995

13-20-74725-0995 Printed in U.S.A.