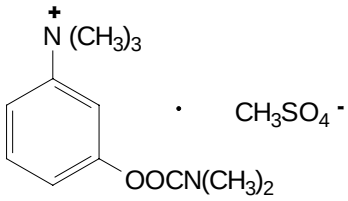
Neostigmine Injection BP
PRODUCT INFORMATION

NAME OF DRUG

The active ingredient in Neostigmine Injection BP is neostigmine methylsulfate.
The chemical name for neostigmine methylsulafate is (3-dimethyl-carbamoxyloxy) trimethylanilinium methyl sulfate. The CAS number for neostigmine methylsulfate is 51-60-5. The Australian Approved Name is neostigmine methylsulfate. Empirical formula $C_{13}H_{22}N_2O_6S$, MW: 334.4.

The chemical structure of neostigmine methylsulfate is:



DESCRIPTION

Neostigmine Injection BP is a clear, colourless sterile solution of neostigmine methylsulfate with sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate and water for injections at pH 4.5 to 6.5.

The presentations of Neostigmine Injection BP solution contain no antimicrobial agents. They are intended for single use only and any solution remaining from an opened container should be discarded.

PHARMACOLOGY

Neostigmine is a anticholinesterase agent which inhibits reversibly the hydrolyosis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase. As a result acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated. Neostigmine is therefore capable of producing a generalised cholinergic response, including miosis, increased tonus of intestinal and skeletal musculature, constriction of bronchi and ureters, bradycardia and stimulation of salivary and sweat glands.

In addition neostigmine is used mainly for its direct cholinomimetic effect on skeletal muscle and to a lesser extent to increase the activity of smooth muscle.

Because of its quaternary ammonium structure, in moderate doses, neostigmine does not cross the blood-brain barrier to produce CNS effects. Extremely high doses, however produce CNS stimulation followed by CNS depression.

Pharmacokinetics

Following IV administration the elimination half-life ranges from 47 to 60 minutes and after IM administration 50 to 91 minutes. Approximately 80% of a single IM dose of neostigmine is excreted in the urine in 24 hours, about 50% as unchanged drug and the remainder as metabolites. The major site of uptake is in the liver. It is metabolised partly by the hydrolysis of the ester linkage and partly by microsomal enzymes in the liver.

INDICATIONS

Neostigmine is indicated for:
- Reversal of the effects of non-depolarising neuromuscular blocking agents (e.g. tubocurarine, pancuronium etc).
- Prophylaxis and treatment of post-operative intestinal atony and urinary retention.
- Treatment of myasthenia gravis during acute exacerbations, when the condition is severe or in neonates.

CONTRAINDICATIONS

Mechanical obstruction of intestinal or urinary tract.
Known hypersensitivity to neostigmine.
Peritonitis.

PRECAUTIONS

**Neostigmine should be used with extreme caution in patients who have undergone recent intestinal or bladder surgery and in patients with bronchial asthma.*

Use with caution in patients with, cardiac disease **and cardiovascular disorders including arrhythmias, bradycardia, recent myocardial infarction or coronary occlusion, and hypotension as well as in patients with* epilepsy, **vagotonia*, parkinsonism, peptic ulceration, **renal impairment*, Addison's disease or hyperthyroidism.

With large doses, simultaneous parenteral administration of atropine sulfate may be advisable. Atropine sulfate should always be available along with other anti-shock medications (adrenaline) in case of hypersensitivity to neostigmine.

Neostigmine may prolong the depolarising neuromuscular blocking action of depolarising muscle relaxants such as suxamethonium and prolonged apnoea may result (see DRUG INTERACTIONS).

Neostigmine should not be given whilst anaesthesia with cyclopropane and halothane continues but may be used after withdrawal of these agents.

As the severity of myasthenia gravis can fluctuate considerably, care is required to avoid cholinergic crisis due to overdosage with neostigmine (see OVERDOSE).

Use in pregnancy Category B2

The maternal need for neostigmine may be absolute in the context of myasthenia gravis. Cholinergic effects in the neonate are rare.

The safety of neostigmine in pregnancy has not been established with respect to possible adverse effects on fetal development. Anticholinesterase agents may cause uterine irritability and induce premature labour when given IV to pregnant women near term. Therefore neostigmine should not be used in pregnant women or those likely to become pregnant unless the expected benefits outweigh any potential risk.

Use in lactation

Evidence indicates that only negligible amounts of neostigmine enter the breast milk; nevertheless, the possibility of adverse effects on the breast-feeding infant should be considered.

Interactions with other drugs

Corticosteroids
Corticosteroids may decrease the anticholinesterase effects of neostigmine. Conversely anticholinesterase effects may increase after stopping corticosteroids.

Depolarising Muscle Relaxants
Neostigmine may prolong the Phase I block of depolarising muscle relaxants such as suxamethonium. Prolonged respiratory depression with extended periods of apnoea may occur.

Atropine
Atropine reverses the muscarinic effects of neostigmine. This interaction is used to counteract the muscarinic symptoms of neostigmine toxicity, however masking the signs of overdosage can lead to inadvertent induction of cholinergic crisis with the use of atropine.

Aminoglycosides, **Local/General Anaesthetics, Antiarrythmic Agents*
Anticholinesterase agents can be effective in reversing neuromuscular block induced by aminoglycoside antibiotics. Aminoglycoside antibiotics, local and some general anaesthetics, antiarrhythmic agents and other drugs that interfere with neuromuscular transmission should be used cautiously, if at all, in patients with myasthenia gravis. The dose of neostigmine may need to be increased accordingly.

**Quinine, chloroquinine, hydroxychloroquine, beta-blockers and lithium may reduce the effectiveness of treatment with neostigmine.*

ADVERSE REACTIONS

Adverse reactions generally associated with neostigmine overdosage are:

Cardiovascular: Cardiac arrhythmias (especially bradycardia), hypotension, **syncope* , cardiac arrest.

Central Nervous System: Headache, **dizziness*, convulsions, **loss of consciousness,* coma, **drowsiness*, restlessness, **ataxia*, slurred speech, agitation and fear.

Gastrointestinal: Nausea, vomiting, diarrhoea, abdominal cramps, **flatulence*, increased peristalsis and involuntary defaecation.

Genitourinary: Involuntary urination or desire to urinate.

Musculoskeletal: Muscle cramps, fasciculation, general weakness and paralysis.

Respiratory: Increased **oral, pharyngeal and* bronchial secretions, **dyspnoea*, bronchospasm, respiratory depression, **respiratory arrest*, tight chest and wheezing.

Allergic: allergic reactions including anaphylaxis.

Skin: rash and urticaria

Other: Increased sweating and salivation, miosis, vision changes, nystagmus and lacrimation.

DOSAGE AND ADMINISTRATION

Neostigmine Injection BP can be given as an intramuscular (IM), intravenous (IV) or subcutaneous (SC) injection. The following doses are approximately equivalent in effect: 0.5 mg IV = 1.0 - 1.5 mg IM or SC.

When Neostigmine Injection BP is given, a syringe of atropine sulfate should be available to counteract severe cholinergic reactions, if they occur. Do not mix atropine with other drugs in the same syringe as compatibility data are not available.

Neostigmine Injection BP in ampoules contains no antimicrobial agent. It should be used once and any residue discarded.

Antagonist to Nondepolarising Neuromuscular Blockade:

Usually, reversal of neuromuscular blockade with Neostigmine Injection BP should not be attempted until spontaneous recovery from paralysis is evident. It is recommended that the patient be well ventilated and patent airway maintained until complete recovery of normal respiration is affirmed.

Adults: A single dose of neostigmine 0.5 to 2.5 mg (0.05 - 0.07 mg/kg) to be administered simultaneously (in separate syringes) with atropine sulfate 0.6 - 1.2 mg (0.02 to 0.03 mg/kg) by slow IV injection over 1 minute is generally adequate for complete reversal of nondepolarising muscle relaxants within 5 to 15 minutes. The maximum recommended dose of neostigmine in adults is 5 mg.

Children: The suggested dose in children is 0.05 mg/kg and atropine sulfate 0.02 mg/kg by slow IV injection over 1 minute. Maximum recommended dose of neostigmine in children is 2.5 mg.

The two drugs are often given simultaneously in separate syringes, but in patients with bradycardia, the pulse rate should be increased to about 80 beats/minute with atropine before administering neostigmine.

The speed of recovery from neuromuscular blockade is primarily determined by the intensity of the block at the time of antagonism. It is also influenced by other factors including the presence of drugs (e.g. anaesthetic drugs, antibiotics and antiarrhythmic drugs) and physiological changes (e.g. electrolyte and acid-base imbalance, renal impairment). These factors may prevent successful reversal with Neostigmine Injection BP or lead to re-curarisation after apparently successful reversal. It is imperative that the patients should **not** be left unattended until these possibilities have been excluded.

Myasthenia Gravis:
Adults: 1 mg to 2.5 mg given as an IM or SC injection at intervals throughout the day when greater strength may be needed, (e.g. mornings and before meals) giving a total daily dose of 5 to 20 mg. Duration of action of a single dose is 2 to 4 hours.

Neonates: 0.05 - 0.25 mg as an IM injection every 2 - 4 hours, half an hour before feeding. Treatment is not usually required beyond 8 weeks of age. Because the condition is usually self-limiting the daily dosage should gradually be reduced until the drug can be withdrawn.

Older Children: 0.2 to 0.5 mg by injection as required. Dosage should be adjusted according to response.

When large doses of neostigmine are given to myasthenic patients, atropine sulfate may be required to counteract the muscarinic side effects.

Intestinal Atony:
Prophylaxis: 0.25 mg as an IM or SC injection before or immediately after the operation, repeated every 4 to 6 hours, for 2 to 3 days.

Treatment: 0.5 mg as an IM or SC injection repeated at intervals of 4 to 6 hours.

Urinary Retention:
Prophylaxis: 0.25 mg as an IM or SC injection as for intestinal atony.

Treatment: 0.5 mg as an IM or SC injection and apply heat to lower abdomen. After patient has voided continue 0.5 mg SC or IM every 3 hours for at least 5 injections. If there has been no urinary response within one hour of the first dose, the patient should be catheterised.

OVERDOSAGE

Overdosage with neostigmine can cause cholinergic crisis, which is characterised by increasing muscle weakness. Myasthenic crisis is due to an increase in severity of the disease and may be difficult to distinguish from cholinergic crisis on a symptomatic basis. Cholinergic crisis can lead to respiratory paralysis, which may result in death, while myasthenic crisis is extreme muscle weakness. The differentiation between the two crises is extremely important as treatment is different for each. The two types of crises can be differentiated by the use of edrophonium and clinical judgement.

Symptoms

Signs of overdosage due to muscarinic effects may include abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, increased bronchial secretion, salivation, diaphoresis and miosis. Nicotinic effects consist of muscular cramps, fasciculations and general weakness. Bradycardia and hypotension may also occur.

Treatment

The treatment of cholinergic crisis requires the discontinuation of all cholinergic medication. The immediate use of atropine is also recommended, muscarinic effects are controlled with IV atropine sulfate (1 to 2 mg) followed by IM atropine sulfate every 2 to 4 hours. Assistance of ventilation may be required if respiration is severely depressed.

PRESENTATION

Polyamp DuoFit® ampoules:	0.5 mg/mL, 1 mL in packs of 10
	2.5 mg/mL, 1 mL in packs of 50

STORAGE

Neostigmine Injection in Polyamp DuoFit® ampoules should be stored below 25°C.

Neostigmine Injection should be protected from light.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road, North Ryde
NSW 2113 Australia

Polyamp DuoFit is a trade mark of the AstraZeneca group of companies

Date of TGA approval letter 12 September 1996
Date of Safety Related Changes 18 June 2003**Please note change in Product Information*