

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Atropine Sulfate Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atropine Sulfate 0.06% w/v

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, Colourless Solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Surgery: Atropine may be given as a pre-anaesthetic medication to inhibit excessive salivary and bronchial secretions and to diminish the risk of vagal inhibition of the heart. The use of atropine as an antisialagogue is rarely necessary since the introduction of halothane and similar anaesthetics in place of ether anaesthesia. Atropine may be administered concurrently with anticholinesterase agents (e.g. neostigmine, physostigmine) to block the adverse muscarinic effects when they are used after surgery to terminate curarisation.

Cardiopulmonary Resuscitation: It may be used in the management of patients with acute myocardial infarction and sinus bradycardia who have associated hypotension and increased ventricular irritability.

Anticholinesterase Poisoning: It is also used concomitantly with a cholinesterase reactivator (e.g. pralidoxime) to reverse muscarinic effects associated with toxic exposure to anticholinesterase compounds (e.g. organophosphate pesticides).

Atropine may be used in conjunction with morphine or other agents for the relief of biliary or renal colic.

4.2 Dose and method of administration

Atropine Sulfate Injection may be administered by subcutaneous (SC), intramuscular (IM) or direct intravenous (IV) injection. Atropine Sulfate Injection contains no antimicrobial agent. It should be used only once and any residue discarded. Atropine Sulfate Injection should not be added to any IV infusion solution.

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Surgery

Adults:

300-600 mcg of Atropine Sulfate Injection IM or SC, approximately 1 hour before anaesthesia, usually in conjunction with a narcotic. Alternatively, 300-600 mcg Atropine Sulfate Injection may be given IV immediately prior to induction of anaesthesia.

To reverse the effects of non-depolarising muscle relaxants, 600 mcg - 1.2 mg Atropine Sulfate Injection may be given to adults as a slow IV injection in conjunction with the anticholinesterase agent (e.g. neostigmine methylsulphate) of choice.

Paediatrics:

Suitable premedication doses to be given subcutaneously 30-60 minutes prior to surgery in children are suggested below:

Infants weighing less than 3 kg: 100 mcg

Children weighing 7 to 9 kg: 200 mcg

Children weighing 12 to 16 kg: 300 mcg

Children weighing 20 to 27 kg: 400 mcg

Children weighing 32 kg: 500 mcg

Children weighing 41 kg: 600 mcg

To reverse the effects of non-depolarising muscle relaxants, Atropine 0.02 mg/kg for each 0.04 mg/kg of neostigmine methylsulphate may be given to children as a slow IV injection.

Cardiopulmonary Resuscitation

Adults:

Atropine Sulfate Injection 0.5-1 mg IV may be repeated every 5 minutes until the desired effect on heart rate or asystole is achieved. IV doses of less than 0.5 mg should usually not be used in adults, since paradoxical slowing of the heart rate may occur. The total dose should not exceed 2 mg.

Paediatrics:

The usual paediatric dose is 0.02 mg/kg with a minimum of 0.1 mg (maximum single dose 0.5 mg) intravenously, which may be repeated at 5 minute intervals until the desired heart rate is achieved.

The total dose should not exceed 1 mg in children and 2 mg in adolescents.

When cardiac arrest has occurred, external cardiac massage or other method of resuscitation is required to distribute the medicine after intravenous injection.

Treatment of Anticholinesterase Poisoning

Adults:

An initial dose of 1-2 mg for mild poisoning, and up to 6 mg for severe poisoning; this is given IV preferably, or IM. Atropine Sulfate Injection can be given as often as every 5 minutes until secretions are minimal and ventilation is adequate. Treatment should be repeated if muscarinic symptoms reappear. In moderate to severely poisoned adults, atropine is given for at least two days. In severe

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cases atropine therapy should be withdrawn gradually to avoid abrupt recurrence of symptoms (e.g. pulmonary oedema). Pralidoxime enhances the effect of Atropine.

Paediatrics:

0.05 mg/kg intramuscularly or intravenously repeated at 10 to 30 minute intervals until muscarinic signs and symptoms subside. This is to be repeated if these reappear.

As an antispasmodic in the symptomatic relief of biliary or renal colic, 600 mcg IM up to three times a day may be given.

4.3 Contraindications

- Known hypersensitivity to atropine or other anticholinergic agents
- Patients with obstructive disease of the gastrointestinal tract (e.g. pyloroduodenal stenosis, achalasia), cardiospasm, paralytic ileus or intestinal atony (especially in geriatric or debilitated patients)
- Reflux oesophagitis
- Severe ulcerative colitis or megacolon complicating ulcerative colitis
- Prostatic enlargement
- Atropine should not be given to patients with closed angle glaucoma
- Unstable cardiovascular status in acute haemorrhage
- Tachycardia secondary to cardiac insufficiency or thyrotoxicosis
- Toxaemia of pregnancy
- Obstructive uropathy (e.g. bladder neck obstruction caused by prostatic hypertrophy)
- Myasthenia gravis (unless used to treat the adverse effects of an anticholinesterase agent)

Due to risk of provoking hyperpyrexia due to reduced sweating, Atropine should not be given to febrile patients, or when the ambient temperature is high.

4.4 Special warnings and precautions for use

Atropine should be used with caution in all patients, and especially in patients over 40 years old as they may be more susceptible to adverse effects. Atropine should be administered with extreme care in patients with any severe heart disease, hypertension, mild or moderate ulcerative colitis, ileus, chronic pulmonary disease, hyperthyroidism, autonomic neuropathy, hepatic or renal disease or prostatic hypertrophy, oesophageal reflux or hiatus hernia, gastric ulcer, diarrhoea or gastrointestinal infection.

Elderly patients may react with excitement, agitation, drowsiness or confusion to even small doses of atropine. Changes in dosage should be gradual.

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Children

Atropine should be used with caution in infants and small children as they may be more susceptible to its adverse effects. It should be used with caution in children with Down's syndrome, spastic paralysis or brain damage as they may be hypersensitive to the effects of atropine.

Debilitated and Elderly Patients

Atropine should be used with caution in debilitated patients. These patients, especially those with chronic pulmonary disease, may be susceptible to the formation of bronchial mucous plugs due to decreased bronchial secretions.

Atropine should be used with caution in elderly patients since they may be more susceptible to its adverse effects. Atropine may cause mental confusion, especially in elderly or brain damaged patients.

Elderly patients may react with excitement, agitation, drowsiness or confusion to even small doses of atropine. Changes in dosage should be gradual.

Memory may become severely impaired in elderly patients, especially those who already have memory problems, with the continued use of anticholinergics since these medicines block the actions of acetylcholine, which is responsible for many functions of the brain, including memory functions.

Glaucoma

Conventional parenteral doses of atropine may precipitate acute glaucoma in susceptible individuals.

Myasthenia Gravis

Atropine should be used with extreme caution in patients with myasthenia gravis and should generally only be given to reduce adverse muscarinic effects of an anticholinesterase (see section 4.3).

Cardiovascular Status

In conditions characterised by tachycardia, such as cardiac insufficiency or failure, extreme caution must be exercised (see section 4.3). Care is also required in cardiac surgery, in patients with acute myocardial infarction or ischaemia as atropine may worsen the symptoms, and in patients with hypertension.

Patients with known cardiac problems have developed angina following administration of atropine. Atropine has been associated with the development of arrhythmias in adult and paediatric patients.

Accelerated heart rate and intraventricular conduction delays have been associated with the development of ventricular fibrillation.

Gastrointestinal

Since atropine decreases gastrointestinal motility, it should be used with caution in patients with gastric ulcer, oesophageal reflux, known or suspected gastrointestinal infections, e.g. *Clostridium difficile* associated diarrhoea and colitis (antibiotic associated pseudomembranous colitis), incomplete intestinal obstruction or ulcerative colitis. Atropine should also be used with caution in patients with diarrhoea, since diarrhoea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy.

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Down's syndrome and albinism

Persons with Down's syndrome appear to have an increased susceptibility to some of the actions of atropine, whereas those with albinism may have a reduced susceptibility.

4.5 Interaction with other medicines and other forms of interaction

POTENTIATING EFFECTS

Antimuscarinic Effects

The effect of atropine may be enhanced by concomitant administration of other medicines with antimuscarinic properties, such as:

- amantadine
- some antihistamines, including cyproheptadine, promethazine
- butyrophenones e.g. haloperidol
- phenothiazines e.g. chlorpromazine, fluphenazine, perphenazine, prochlorperazine, promazine, thioridazine, trifluoperazine
- tricyclic antidepressants e.g. amitriptyline, desipramine, doxepin, imipramine, nortriptyline
- belladonna
- procainamide
- antispasmodics
- antiparkinsonian medicines
- antiarrhythmics with anticholinergic activity (e.g. disopyramide, quinidine)

Patients should be advised to report occurrence of gastrointestinal problems promptly since paralytic ileus may occur with concurrent therapy.

MAOIs

Inhibition of medicine metabolising enzymes by MAOIs may possibly enhance the effects of atropine.

Opioid (narcotic) analgesics

Concurrent use with anticholinergics may result in increased risk of severe constipation, which may lead to paralytic ileus and/or urinary retention.

Urinary Alkalisers

Urinary excretion of atropine may be delayed by alkalization of the urine, thus potentiating its effects.

ABSORPTION

The absorption of other medicines may be affected by the reduction in gastric motility caused by atropine.

Ketoconazole

Anticholinergics may increase gastrointestinal pH, possibly resulting in a marked reduction in ketoconazole absorption during concurrent use. If concomitant therapy is necessary, atropine should be given at least two hours after oral ketoconazole.

ANTAGONIST INTERACTIONS

Atropine antagonises the actions of a number of compounds, including:

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- synthetic choline esters e.g. bethanecol, carbachol
- anticholinesterase medicines e.g. physostigmine, neostigmine, pyridostigmine
- cholinomimetic alkaloids e.g. pilocarpine
- parasympathomimetics (each may counteract the effect of the other)

Cisapride and metoclopramide

Concurrent use with anticholinergics may antagonise the effects of cisapride and metoclopramide on gastrointestinal motility.

Haloperidol

Antipsychotic effectiveness of haloperidol may be decreased in schizophrenic patients.

Cholinesterase inhibitors

In view of the pharmacodynamic effects of atropine, atropine may interfere with the activity of cholinesterase inhibitors such as rivastigmine, donepezil.

4.6 Fertility, pregnancy and lactation

USE IN PREGNANCY

Category A

Although atropine has been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the foetus being observed, the safety of atropine in pregnancy has not been positively established. As with all other medicines, caution must be exercised in the use of atropine in pregnant women and women of child-bearing age.

Atropine crosses the placental barrier and may cause tachycardia in the foetus.

USE IN LACTATION

Small amounts of atropine have been found in human breast milk, therefore Atropine should only be administered to breast-feeding mothers if absolutely necessary. Atropine may cause antimuscarinic effects in the infant. Atropine may inhibit lactation.

Studies have not been done in either animals or humans to evaluate the potential to impair fertility.

4.7 Effects on ability to drive and use machines

Systemic administration of antimuscarinics may cause drowsiness, blurred vision, dizziness and other effects that may impair a patient's ability to perform tasks requiring mental alertness and/or visual acuity (such as driving or operating machinery).

4.8 Undesirable effects

Most side effects are directly related to the antimuscarinic actions of atropine. Adverse effects following single or repeated doses are most often the result of excessive dosage.

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Cardiovascular:

Transient bradycardia followed by tachycardia with palpitations and arrhythmia. Atropine blocks vagal impulses with consequent increase in heart rate with possible atrial arrhythmias, atrioventricular dissociation, multiple ventricular ectopics and angina.

The development of angina in patients with known cardiac problems has been reported. Hypertensive crises and atrioventricular block have also been reported.

Central Nervous System:

Dryness of the mouth with difficulty in swallowing or talking, thirst. These are due to the reduction of salivary, bronchial and sweat secretions and are dose related. Active and passive functions of the Eustachian tube may be affected.

Tremor, fatigue, drowsiness, ataxia, mental confusion and/or excitement, dizziness, loss of taste, headache, nervousness, weakness, nausea, vomiting, insomnia, psychotic reactions, sedation and seizures. Anhidrosis also may occur and produce heat intolerance in patients living in a hot environment. The inhibition of sweat secretions may also result in hyperthermia.

Gastrointestinal:

Constipation; due to inhibition of parasympathetic control of the gastrointestinal tract. Paralytic ileus.

Nausea, vomiting, retrosternal pain due to increased gastric reflux, bloated feeling.

Genitourinary

Urinary difficulty and retention due to inhibition of parasympathetic control of the bladder.

Ocular:

Visual changes, including blurred vision. Dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia can occur with increasing doses of atropine. Increased ocular tension.

Dermatological:

Flushing and dryness of the skin. Hypersensitivity reactions may manifest as conjunctivitis or skin rash which, in some instances, progresses to exfoliation and various dermal manifestations.

Other

More common: Redness or other signs of irritation at the injection site.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

SYMPTOMS

Acute overdosage of atropine produces both peripheral and central signs and symptoms characterised by dilated pupils, difficulty swallowing, hot dry skin, vasodilation and urinary retention. A rash may appear on the face or upper trunk. Tachycardia and hypertension with arrhythmias, anxiety, delirium, hallucinations, hyperactivity convulsions, marked dryness of the mouth, photophobia, raised body temperature, leucocytosis, nausea, vomiting and restlessness also occur. In severe overdosage, CNS

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depression, circulatory collapse and hypotension may be followed by coma, skeletal muscle paralysis and death from respiratory and circulatory failure.

In addition to tachycardia, cardiac manifestations may include ECG abnormalities (e.g. ventricular arrhythmias, extrasystoles resulting from enhanced re-entrant excitation secondary to reduced conduction velocity). Widening of the QRS complex, prolongation of the QT interval and ST segment depression may also be seen.

There is considerable variation in susceptibility to atropine; recovery has occurred even after 1 g, whereas deaths have been reported from doses of 100 mg or less for adults and 10 mg in children.

TREATMENT

Symptomatic treatment should be instigated to ensure an adequate airway is maintained, fluids are replaced and body temperature is lowered using cold packs and tepid sponging. Artificial respiration with oxygen may be necessary and urinary catheterisation may be required. Hypoxia and acidosis should be corrected and sodium bicarbonate may be given even if acidosis is not present. If photophobia occurs, the patient may be kept in a dark room.

Diazepam may be given to control marked excitement and convulsions however the risk of central depression occurring late in the course of atropine poisoning contraindicates large doses of sedative; phenothiazines should not be given since they may exacerbate antimuscarinic effects.

Antiarrhythmics are not recommended if arrhythmias develop.

The use of physostigmine as an antidote for atropine poisoning is controversial due to the potential for physostigmine to produce severe adverse effects, e.g. seizures, asystole. The use of physostigmine should be reserved for treatment of patients with extreme delirium or agitation, patients with repetitive seizures, patients with severe sinus tachycardia or supraventricular tachycardia or unresponsive extreme hyperthermia in patients who fail to respond to alternative therapy.

Physostigmine should not be used to treat cardiac conduction defects or ventricular tachyarrhythmias. IV propranolol may be useful for treatment of supraventricular tachyarrhythmias unresponsive to physostigmine or where physostigmine is contraindicated. Physostigmine should be used with caution in the presence of asthma, gangrene, cardiovascular disease or mechanical obstruction of the gastrointestinal or genitourinary tract. Physostigmine should be used in these circumstances **only if a life-threatening emergency occurs**.

Dialysis is not effective in atropine overdose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atropine (dl-hyoscyamine) is often classified as an anticholinergic medicine but is more accurately described as an antimuscarinic agent since it inhibits the muscarinic actions of acetylcholine, possessing both central and peripheral activity.

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Atropine has activity both on structures innervated by postganglionic cholinergic nerves, and on smooth muscles which respond to endogenous acetylcholine but are not so innervated. As with other antimuscarinic agents, the major action of atropine is a competitive or surmountable antagonism which can be overcome by increasing the concentration of acetylcholine at receptor sites of the effector organ (e.g. by using anticholinesterase agents which inhibit the enzymatic destruction of acetylcholine). The receptors antagonised by atropine in therapeutic doses are primarily the peripheral structures that are stimulated or inhibited by muscarine (i.e. exocrine glands and smooth and cardiac muscle). Responses to postganglionic cholinergic nerve solution also may be inhibited by

Atropine but this occurs less readily than with responses to injected (exogenous) choline esters. Atropine-induced parasympathetic inhibition may be preceded by a transient phase of stimulation, especially on the heart where small doses first slow the rate before characteristic tachycardia develops due to paralysis of vagal control. Atropine exerts a more potent and prolonged effect on the heart, intestine and bronchial muscle than hyoscine, but its action on the iris, ciliary body and certain secretory glands is weaker than that of hyoscine. Unlike the latter, atropine in therapeutic doses does not depress the central nervous system but may stimulate the medulla and higher cerebral centres.

Although mild vagal excitation occurs, the increased respiratory rate and (sometimes) increased depth of respiration produced by atropine are more probably the result of bronchiolar dilatation.

Accordingly, atropine is an unreliable respiratory stimulant and large or repeated doses may depress respiration.

Adequate doses of atropine abolish various types of reflex vagal cardiac slowing or asystole. The medicine also prevents or abolishes bradycardia or asystole produced by injection of choline esters, anticholinesterase agents or other parasympathetic medicines, and cardiac arrest produced by stimulation of the vagus.

Atropine injection in therapeutic doses counteracts the peripheral dilatation and abrupt decrease in blood pressure produced by choline esters. However, when given by itself, atropine does not exert a striking or uniform effect on blood vessels or blood pressure. Systemic doses slightly raise systolic and lower diastolic pressures and can produce significant postural hypotension. Such doses also slightly increase cardiac output and decrease central venous pressure. Occasionally, therapeutic doses dilate the cutaneous blood vessels, particularly in the "blush" area (atropine flush), and may cause atropine "fever" due to suppression of sweat gland activity in infants and small children.

5.2 Pharmacokinetic properties

Absorption

Atropine is well absorbed following IM administration. Peak plasma levels are observed within 30 minutes of injection, accompanied by an increase in heart rate which reaches a maximum at 15 to 50 minutes. The duration of effect on the heart rate is reported to be up to 5 hours. The effect on salivation is delayed, with a peak effect occurring approximately 100 minutes after the injection and persisting for up to 4 hours.

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Distribution

Following intravenous administration serum levels of atropine drop rapidly within the first ten minutes and then decrease more gradually. One hour after either IM or IV injection atropine levels are very similar.

Atropine is well distributed throughout the body, crossing both the blood-brain and placental barriers, and distributing into the milk in small quantities. It has a large apparent volume of distribution (2-4 L/kg).

Atropine shows a high inter-individual variability in serum protein binding, ranging from 22.5% ± 20.6% (children); 14% ± 9.1% (age 16 to 58); 22.2% ± 16.7% (age 65 to 75).

Metabolism and Excretion

Atropine is metabolised by the liver and excreted mainly in the urine. About 30 to 50% of a dose is excreted in urine unchanged, the rest as metabolites. Atropine has a plasma half-life of approximately 4 hours in adults, with a longer half-life of approximately 6.5 hours in children.

5.3 Preclinical safety data

Studies have not been undertaken in either animals or humans to evaluate the carcinogenic or mutagenic potential of atropine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Water for Injections

The pH may be adjusted using Sodium Hydroxide or Sulfuric Acid.

6.2 Incompatibilities

INCOMPATIBILITIES

Atropine has been reported to be incompatible with alkaline solutions and solutions containing the following: adrenaline hydrochloride, amylobarbitone sodium, ampicillin sodium, chloramphenicol sodium succinate, chlortetracycline hydrochloride, cimetidine, heparin sodium, hydroxybenzoate preservatives, metaraminol bitartrate, methicillin sodium, methohexitone sodium, nitrofurantoin sodium, novobiocin sodium, oxacillin sodium, pentobarbitone sodium, sodium bicarbonate, sulphadiazine sodium, sulphafurazole diethanolamine, tetracycline hydrochloride, thiopentone sodium, vitamin B complex and ascorbic acid, warfarin sodium. This list is not exhaustive.

6.3 Shelf life

36 months.

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6.4 Special precautions for storage

Do not store above 25°C.

Keep the ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

1ml (Type 1) clear glass ampoules.

Fusion sealed.

Packed into carton of 10 ampoules.

6.6 Special precautions for disposal and other handling

Use contents once opened.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Max Health Ltd, P O Box 65 231, Mairangi Bay, Auckland 0754

Ph:(09) 815 2664.

9 DATE OF FIRST APPROVAL

10 August 2017

10 DATE OF REVISION OF THE TEXT

28 July 2017

SUMMARY TABLE OF CHANGES

New registration – N/A