PRESCRIBING INFORMATION

[Pr]Atropine Sulfate Injection

Solution for Injection

0.5 mg / 5 mL, 1 mg / 5 mL, 3 mg / 10 mL Pre-Filled Syringes

House Standard

intravenous, intramuscular, subcutaneous
Anticholinergic

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PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS LEAFLET BEFORE PRESCRIBING THIS DRUG

ACTION AND CLINICAL PHARMACOLOGY

Atropine Sulfate Injection is commonly classified as an anticholinergic or antiparasympathetic (parasympatholytic) drug. More precisely, however, it is termed an antimuscarinic agent since it antagonizes the muscarine-like actions of acetylcholine and other choline esters.

Atropine inhibits the muscarinic actions of acetylcholine 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 antagonized by atropine are the peripheral structures that are stimulated or inhibited by muscarine (i.e., exocrine glands and smooth and cardiac muscle). Responses to postganglionic cholinergic nerve stimulation 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 heart, intestine and bronchial muscle than scopolamine, but its action on the iris, ciliary body and certain secretory glands is weaker than that of scopolamine. Unlike the latter, atropine, in clinical doses, does not depress the central nervous system but may stimulate the medulla and higher cerebral centers. 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 drug also prevents or abolishes bradycardia or asystole produced by injection of choline esters, anticholinesterase agents or other parasympathomimetic drugs, and cardiac arrest produced by stimulation of the vagus. Atropine also may lessen the degree of partial heart block when vagal activity is an etiologic factor. In some patients with complete heart block, the idioventricular rate may be accelerated by atropine; in others, the rate is stabilized. Occasionally, a large dose may cause atrioventricular (A-V) block and nodal rhythm.

Atropine, in clinical 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 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.

The effects of atropine on heart rate (maximum heart rate) and saliva flow (minimum flow) after intravenous administration (rapid, constant infusion over 3 min.) are delayed by 7 to 8 minutes after drug administration and both effects are non-linearly related to the amount of drug in the peripheral compartment. Changes in plasma atropine levels following intramuscular administration (0.5 to 4 mg doses) and heart rate closely overlapped, but the time course of the changes in atropine levels and behavioral impairment indicates that pharmacokinetics is not the primary rate-limiting mechanism for the central nervous system effect of atropine.

Atropine disappears rapidly from the blood following injection and is distributed throughout the body. Much of the drug is destroyed by enzymatic hydrolysis, particularly in the liver; from 13% to 50% is excreted unchanged in the urine. Traces are found in various secretions, including milk. Atropine readily crosses the placental barrier and enters the fetal circulation.

The major metabolites of atropine are noratropine, atropine-n-oxide, tropine, and tropic acid. The metabolism of atropine is inhibited by organophosphate pesticides. The elimination half-life of atropine is more than doubled in children under two years and the elderly (>65 years old) compared to other age groups. There is no gender effect on the pharmacokinetics and pharmacodynamics (heart rate changes) of atropine.

INDICATIONS AND CLINICAL USE

Atropine Sulfate Injection is indicated:

- As an antisialagogue for pre-anesthetic medication to prevent or reduce secretions of the respiratory tract;
- To restore cardiac rate and arterial pressure during anesthesia when vagal stimulation, produced by intra-abdominal surgical traction, causes a sudden decrease in pulse rate and cardiac action;
- To lessen the degree of atrioventricular (A-V) heart block when increased vagal tone is a major factor in the conduction defect, as in some cases due to digitalis;
- To overcome severe bradycardia and syncope due to a hyperactive carotid sinus reflex;
- As an antidote (with external cardiac massage) for cardiovascular collapse from the injudicious use of a choline ester (cholinergic) drug;
- In the treatment of anticholinesterase poisoning from organophosphorus insecticides;
- As an antidote for the “rapid” type of mushroom poisoning due to the presence of the alkaloid, muscarine, in certain species of fungus such as Amanita muscaria.

CONTRAINDICATIONS

Atropine Sulfate Injection is generally contraindicated in patients with glaucoma, gastrointestinal obstruction, pyloric stenosis, or prostatic hypertrophy, except in doses ordinarily used for pre-anesthetic medication.

Atropine Sulfate Injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container.

WARNINGS

Atropine Sulfate Injection is a highly potent drug and due care is essential to avoid overdosage, especially with intravenous administration. Children are more susceptible than adults to the toxic effects of anticholinergic agents (agitation, confusion, drowsiness).

PRECAUTIONS

Atropine Sulfate Injection should be used with caution in all individuals over 40 years of age. Conventional systemic doses may precipitate acute glaucoma in susceptible patients, convert partial organic pyloric stenosis into complete obstruction, and lead to complete urinary retention in patients with prostatic hypertrophy or cause inspissation of bronchial secretions and formation of dangerous viscid plugs in patients with chronic lung disease.

Atropine should be used only with extreme caution in febrile children, or in high ambient temperatures, because of the danger of hyperpyrexia. Atropine should be used cautiously in all patients with fever.

Atropine should be used with caution in conditions characterized by tachycardia such as thyrotoxicosis, cardiac insufficiency, and in cardiac surgery where it may further accelerate the heart rate.

Doses of atropine up to 1 mg are mildly stimulant to the central nervous system (CNS). Atropine may cause mental confusion, especially in the elderly. Higher doses may induce mental disturbances and depression of the CNS (see OVERDOSAGE). Children and elderly people are particularly susceptible.

The effects of atropine may be enhanced by the concomitant administration of other drugs with anticholinergic properties such as tricyclic antidepressant, MAOIs, phenothiazines, amantadine, some antihistamines, butyrophenones, and disopyramide. Reduced gastrointestinal motility caused by atropine may affect the absorption of other drugs such as mexiletine and ketoconazole. Atropine induced dry mouth may prevent dissolution of sublingual preparations such as the nitrates, reducing their effectiveness.

Pregnant Women

Animal reproduction studies have not been conducted with atropine. It also is not known whether atropine can cause fetal harm when given to a pregnant woman or can affect reproduction capacity. Intravenous administration of atropine during pregnancy may cause tachycardia in fetus. However, data from a limited number of pregnancies have not shown adverse events on the pregnancy, the fetus, or the newborn.

Atropine should be given to a pregnant woman only if clearly needed.

Nursing Women

Trace amounts of atropine is excreted in breast milk and may cause antimuscarinic effects in the infant. Lactation may be inhibited.

Geriatrics

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Most of the side effects of atropine are directly related to its antimuscarinic action and are dose related. Dryness of the mouth, blurred vision, photophobia, and tachycardia commonly occur with chronic administration of therapeutic doses. Anhidrosis also may occur and produce heat intolerance or impair temperature regulation in persons living in a hot environment. Constipation and difficulty in micturition may occur in elderly patients.

Occasional hypersensitivity reactions and anaphylaxis have been observed, especially skin rashes, which in some instances progressed to exfoliation. Less common adverse events include bradycardia following low-dose atropine (as low dose may be parasympathomimetic), palpitations, arrhythmias, paradoxical heart block, hypertension, increased myocardial ischemia; ataxia, confusion, agitation, somnolence, seizures and psychosis; vomiting, impaired GI motility and ileus; urinary retention; increased intraocular pressure and cycloplegia. Elderly patients are more prone to hallucinations, delirium, agitation and confusion.

Adverse effects following single or repeated injections of atropine are most often the result of excessive dosage. These include palpitation, dilated pupils, difficulty in swallowing, hot dry skin, thirst, dizziness, restlessness, tremor, fatigue, and ataxia.

Toxic doses lead to marked palpitation, restlessness and excitement, hallucinations, delirium, and coma. Depression and circulatory collapse occur only with severe intoxication. In such cases, blood pressure declines and death due to respiratory failure may ensue, following paralysis and coma.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms of overdosage include flushing and dryness of the skin, dilated pupils, dry mouth, tachycardia, hypertension, rapid respiration, hyperpyrexia, nausea, vomiting. Symptoms of CNS stimulation may include restlessness, confusion, hallucinations, paranoid and psychotic reactions, incoordination, delirium, and occasionally convulsions. In severe overdose, CNS depression may occur with coma, circulatory and respiratory failure, and death.

In the event of toxic overdosage (see ADVERSE REACTIONS), a short-acting barbiturate or diazepam may be given, as needed, to control marked excitement and convulsions. Large doses for sedation should be avoided because central depressant action may coincide with the depression occurring late in atropine poisoning. Central stimulants are not recommended.

Physostigmine, given as an atropine antidote by slow intravenous injection of 1 mg to 4 mg (0.5 mg to 1 mg in children), rapidly abolishes delirium and coma caused by large doses of atropine. Since physostigmine is rapidly destroyed, the patient may again lapse into coma after one to two hours and repeated doses may be required. Artificial respiration with oxygen may be necessary. Ice bags and alcohol sponges help to reduce fever, especially in children.

The fatal adult dose of atropine is not known. In children, 10 mg or possibly less may be fatal, and with doses as low as 0.5 mg, undesirable minimal symptoms or responses of overdosage may occur. These increase in severity and extent with larger doses of the drug (excitement, hallucinations, delirium, and coma with a dose of 10 mg or more).

Atropine is not removed by dialysis.

DOSAGE AND ADMINISTRATION

Atropine Sulfate Injection may be administered intravenously, intramuscularly, or subcutaneously.

The intravenous administration is the preferred route for life-threatening indications.

Average adult dose: 0.5 mg. Range: 0.4 mg to 0.6 mg.

As an antisialagogue, it is usually injected intramuscularly prior to induction of anesthesia. This produces only minimal blocking of vagal activity. In children, the dosage ranges from 0.1 mg in the newborn to 0.6 mg in a child aged 12 years, injected subcutaneously 30 minutes before surgery.

During surgery, the drug is given intravenously when reduction in pulse rate and cessation of cardiac action are due to increased vagal activity; however, if the anesthetic is cyclopropane, doses less than 0.4 mg should be used and should be given slowly to avoid the possible production of ventricular arrhythmia. Usual doses are used to reduce severe bradycardia and syncope associated with hyperactive carotid sinus reflex.

For bradyarrhythmias, the usual intravenous adult dosage ranges from 0.4 mg to 1 mg every one to two hours as needed; larger doses up to a maximum of 2 mg may be required. In children, intravenous dosage ranges from 0.01 mg to 0.03 mg per kg of body weight.

Atropine is also a specific antidote for cardiovascular collapse resulting from injudicious administration of choline ester. When cardiac arrest has occurred, external cardiac massage or other method of resuscitation is required to distribute the drug after intravenous injection.

In anticholinesterase poisoning from exposure to insecticides, large doses of at least 2 mg to 3 mg should be administered parenterally and repeated until signs of atropine intoxication appear. In the “rapid” type of mushroom poisoning, atropine should be given in doses sufficient to control parasympathomimetic signs before coma and cardiovascular collapse supervene.

DOSAGE FORM, COMPOSITION, AND PACKAGING

Dosage Form

Atropine Sulfate Injection is a sterile, nonpyrogenic solution of atropine sulfate in water for injection with sodium chloride sufficient to render the solution isotonic. It is administered parenterally by intravenous, intramuscular, or subcutaneous injection.

Atropine Sulfate Injection is supplied in a single-dose pre-filled syringe as follows:

Container	Size	Concentration	Total Content (Atropine)
Pre-filled syringe	5 mL	0.1 mg / mL	0.5 mg
Pre-filled syringe	5 mL	0.2 mg / mL	1 mg
Pre-filled syringe	10 mL	0.3 mg / mL	3 mg

Note: *Medication and fluid path are sterile and nonpyrogenic if caps are undisturbed and the package intact.*

Parenteral drug products should be inspected visually for clarity, particulate matter, precipitation, discolouration, and leakage prior to administration, whenever solution and container permit. Do not use unless the solution is clear and container or seal intact. Discard if it contains a precipitate. The solution contains no bacteriostat, antimicrobial agent, nor added buffer (except for pH adjustment).

Composition

0.5 mg / 5 mL Strength (0.1 mg / mL): Each millilitre (mL) contains atropine sulfate 0.1 mg, and sodium chloride 9 mg (for tonicity) in water for injection, pH adjusted with hydrochloric acid.

1 mg / 5 mL Strength (0.2 mg / mL): Each millilitre (mL) contains atropine sulfate 0.2 mg, and sodium chloride 9 mg (for tonicity) in water for injection, pH adjusted with hydrochloric acid.

3 mg / 10 mL Strength (0.3 mg / mL): Each millilitre (mL) contains atropine sulfate 0.3 mg, and sodium chloride 9 mg (for tonicity) in water for injection, pH adjusted with hydrochloric acid.

Sodium chloride added to render the solution isotonic for injection of the active ingredient is present in amounts insufficient to affect serum electrolyte balance of sodium (Na^+) and chloride (Cl^-) ions.

Packaging

Atropine Sulfate Injection is supplied in sterile, polypropylene pre-filled syringes, packaged in sterile blister packs. Each carton contains 10 pre-filled syringes.

SINGLE USE PRE-FILLED SYRINGE.

When smaller doses are required, discard the unused portion.

Latex free stopper. Preservative free.

STORAGE AND STABILITY

Store syringe in blister pack in original package between 15 °C– 30 °C. Avoid excessive heat. Protect from freezing.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html for information on how to report online, by mail, or by fax
- Calling toll-free 1.866.234.2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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