PRESCRIBING INFORMATION

[Pr] ATROPINE SULFATE INJECTION USP

Anticholinergic (spasmolytic agent)

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[Pr]Atropine Sulfate Injection USP

THERAPEUTIC CLASSIFICATION

Anticholinergic (Spasmolytic Agent)

ACTION AND CLINICAL PHARMACOLOGY

Atropine is commonly classified as an anticholinergic or 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 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 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 CNS 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 probably the result of bronchial dilatation. Accordingly, atropine is an unreliable respiratory stimulant and large or repeated doses may depress respiration.

Adequate doses of atropine abolish various type 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 (AV) 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.

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.

INDICATIONS AND CLINICAL USE

Atropine Sulfate Injection USP is used principally for its spasmolytic effect on smooth muscle and for its action in diminishing secretions (in anesthesia to control excessive salivation and bronchial secretions).

The drug is also used for its spasmolytic effect on the eye to produce dilatation and cycloplegia.

Atropine Sulfate Injection USP is also utilized for its CNS effects in the treatment of Parkinsonism.

Atropine Sulfate Injection USP is also used as an antidote to pilocarpine, physostigmine, isoflurophate, certain species of amanita, and in cases of anticholinesterase insecticide poisoning.

CONTRAINDICATIONS

Atropine should not be given to patients with glaucoma or paralytic ileus. It should not be administered to patients with symptoms of prostatism.

PRECAUTIONS

Use with caution in patients with prostatic hypertrophy, coronary insufficiency, or cardiac failure. Parenteral atropine administration is not advised in asthmatic patients since an excessive drying effect upon mucous plugs in the bronchi may occur. Tachycardia may result from vagal inhibition and induce angina pectoris in patients with coronary heart disease. With respect to the central nervous system, doses of 0.5 to 1 mg of atropine are mildly stimulating. After larger doses, there may be mental disturbances; still larger doses are depressing. Death from atropine poisoning, though rare, is usually due to paralysis of the medullary centres.

Use with caution in patients above 40, to avoid the risk of glaucoma.

Tolerance to belladonna alkaloids occurs in man to a limited extent. This is noticed particularly in

patients with Parkinsonism. Habituation and addiction do not occur, although vomiting, malaise, sweating and salivation have been recorded in patients with Parkinsonism, upon sudden withdrawal of the large doses required for therapeutic benefit.

Atropine is a highly potent drug and due care is essential to avoid overdosage, especially with IV administration.

ADVERSE REACTIONS

Most of the side effects of atropine are directly related to its antimuscarinic action. 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 hot environment. Constipation and difficulty in micturition may occur in elderly patients. Occasional hypersensitivity reactions have been observed, especially skin rashes which in some instances progressed to exfoliation.

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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

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

In the event of toxic overdosage, 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. Physostigmine, given as an atropine antidote by slow IV (not exceeding 1 mg/min.) injection of 1 to 4 mg, rapidly abolishes delirium and coma caused by large doses of atropine. Since physostigmine is rapidly destroyed, the patient may again lapse into coma after 1 to 2 hours, and repeated doses may be required.

PHARMACEUTICAL INFORMATION

Drug substance

Chemical Name:	dl-hyoscyamine, endo-(±)-α-(Hydroxymethyl)benzene-acetic acid 8-methyl-8-azabicyclo [3.2.1] oct-3-yl ester
Molecular Formula:	$C_{34}H_{48}N_2O_{10}S$
Molecular Weight:	694.82
Description:	White powder, very bitter, soluble in water, in glycerol, slightly soluble in chloroform and insoluble in ether.

DOSAGE AND ADMINISTRATION

Atropine Sulfate Injection USP may be given subcutaneously, intramuscularly, or intravenously.

Adults: 400 to 600 mcg every four to six hours.

Children:	1 year:	120 mcg
	2 to 4 years:	180 mcg
	Greater than 4 years:	the dose may be increased by 20 mcg for each year of age to a maximum of 300 mcg.

N.B.: The complete atropinizing dose in man is usually believed to be in the order of 2 mg intravenously.

COMPOSITION, STORAGE AND STABILITY

Atropine Sulfate Injection USP 0.4 mg/mL
Ampoules: Each mL contains: atropine sulfate•H_2O 0.4 mg, sodium chloride for isotonicity, sulfuric acid to adjust pH and water for injection. Store between 15 and 30°C.

Vials (multidose): Each mL contains: atropine sulfate•H_2O 0.4 mg, chlorobutanol 0.5% (as preservative), ethanol 0.39%, sodium chloride for tonicity, sulfuric acid to adjust pH and water for injection. Store between 15 and 30°C. Protect from light. Discard 28 days after initial use.

Atropine Sulfate Injection USP 0.6 mg/mL
Ampoules: Each mL contains: atropine sulfate•H_2O 0.6 mg, sodium chloride 8.5 mg, sulfuric acid to adjust pH and water for injection. Store between 15 and 30 °C.

PACKAGING

Atropine Sulfate Injection USP 0.4 mg/mL is available in 1 mL ampoules, boxes of 10 and 10 mL multidose vials, boxes of 10.

Atropine Sulfate Injection USP 0.6 mg/mL is available in 1 mL ampoules, boxes of 10.