

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-146**

**Final Printed Labeling**

Store at 25°C (77°F); excursions permitted to 15° to 30°C  
(59° to 86°F).

**ATROPINE SULFATE**

**Injection, USP**

**0.1 mg/mL (Adult)**

**APPROVED**

**0.05 mg/mL (Pediatric)**

**Ansyr® Plastic Syringe**

**JUL - 9 2001**

**DESCRIPTION**

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

Each milliliter (mL) contains atropine sulfate, monohydrate 0.1 mg (adult strength) or 0.05 mg (pediatric strength), and sodium

58- **6380** -R1-Rev. February, 2001

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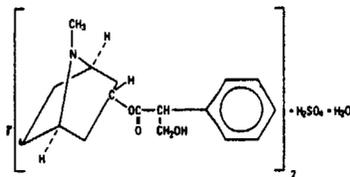
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

chloride, 9 mg. May contain sodium hydroxide and/or sulfuric acid for pH adjustment 0.308 mOsmol/mL (calc.). pH 4.2 (3.0 to 6.5).

The solution contains no bacteriostat, antimicrobial agent or added buffer (except for pH adjustment) and is intended for use only as a single-dose injection. When smaller doses are required the unused portion should be discarded.

Atropine Sulfate Injection is a parenteral anticholinergic agent and muscarinic antagonist.

Atropine Sulfate, USP is chemically designated 1 $\alpha$ , 5 $\alpha$ -H-Tropan-3- $\alpha$ -ol ( $\pm$ )-tropate (ester), sulfate (2:1) (salt) monohydrate, (C<sub>17</sub>H<sub>23</sub>NO<sub>3</sub>)<sub>2</sub> • H<sub>2</sub>SO<sub>4</sub> • H<sub>2</sub>O, colorless crystals or white crystalline powder very soluble in water. It has the following structural formula:



Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and l-hyocyamine, whose activity is due almost entirely to the levo isomer of the drug.

Sodium Chloride, USP is chemically designated NaCl, a white crystalline powder freely soluble in water.

The syringe is molded from a specially formulated polypropylene. Water permeates from inside the container at an extremely slow rate which will have an insignificant effect on solution concentration over the expected shelf life. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the syringe material.

#### CLINICAL PHARMACOLOGY

Atropine is commonly classified as an anticholinergic or antiparasymphathetic (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 Sulfate Injection, USP 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. The major metabolites of atropine are noratropine, atropin-n-oxide, tropine, and tropic acid. The metabolism of atropine is inhibited by organophosphate pesticides (e.g., diazon). Atropine readily crosses the placental barrier and enters the fetal circulation, but is not found in amniotic fluid. Exercise, both prior to and immediately following intramuscular administration of atropine, significantly increases the absorption of atropine due to increased perfusion in the muscle and significantly decreases the clearance of atropine. The pharmacokinetics of atropine is nonlinear after intravenous administration of 0.5 to 4 mg. Atropine binds poorly (about 44%) to plasma protein, mainly to alpha-1 acid glycoprotein; age has no

effect on the serum protein binding of atropine. Atropine binding to  $\alpha$ -1 acid glycoprotein was concentration-dependent (2-20  $\mu$ g/mL) and nonlinear *in vitro* and *in vivo*. 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 (2-64 years old). There is no gender effect on the pharmacokinetics and pharmacodynamics (heart rate changes) of atropine.

The effects of intravenous atropine on heart rate (maximum heart rate) and saliva flow (minimum flow) after I.V. 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 are 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.

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 ( $\text{Na}^+$ ) and chloride ( $\text{Cl}^-$ ) ions.

**INDICATIONS AND USAGE**

Atropine Sulfate Injection, USP, is indicated when excessive (or sometimes normal) muscarinic effects are judged to be life threatening or are producing symptoms severe enough to call for temporary, reversible muscarinic blockade. Examples, not an exhaustive list, of such possible uses are: (1) as an antisialagogue when reduction of secretions of the respiratory tract are thought to be needed; its routine use as a preanesthetic agent is discouraged, (2) to blunt the increased vagal tone (decreased pulse and blood pressure) produced by intra-abdominal traction or ocular muscle traction, its routine use to prevent such events is discouraged, (3) to temporarily increase heart rate or decrease AV-block until definitive intervention can take place, when bradycardias or AV-block are judged to be hemodynamically significant and thought to be due to excess vagal tone, (4) as an antidote for inadvertent overdose of cholinergic drugs or for cholinesterase poisoning such as from organophosphorus insecticides, (5) 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*, and (6) to alleviate the muscarinic side effects of

anticholinesterase drugs used for reversal of neuromuscular blockade.

**CONTRAINDICATIONS**

Atropine generally is contraindicated in patients with glaucoma, pyloric stenosis or prostatic hypertrophy, except in doses ordinarily used for preanesthetic medication.

**WARNINGS**

Atropine is a highly potent drug and due care is essential to avoid overdosage, especially with intravenous administration. Pediatric populations are more susceptible than adults to the toxic effects of anticholinergic agents.

Atropine I.V. decreased the rate of mexiletine absorption without altering the relative oral bioavailability; this delay in mexiletine absorption was reversed by the combination of atropine and intravenous metoclopramide during pretreatment for anesthesia. Atropine is not removed by dialysis.

**PRECAUTIONS**

Do not administer unless solution is clear and seal is intact. Discard unused portion.

Atropine Sulfate Injection, USP 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, 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.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Studies have not been performed to evaluate the carcinogenic or mutagenic potential of atropine or its potential to adversely affect fertility.

**Pregnancy Category C.** 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. Atropine should be given to a pregnant woman only if clearly needed.

**Pediatric Use**

Safety and effectiveness in pediatric populations have not been established.

**Geriatric Use**

An evaluation of current literature revealed no clinical experience identifying differences in response between elderly and younger

patients. 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. 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 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.

#### **OVERDOSAGE**

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 to 4 mg (0.5 to 1 mg in pediatric populations), 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 pediatric populations.

The fatal adult dose of atropine is not known; 200 mg doses have been used and doses as high as 1000 mg have been given.

In pediatric populations, 10 mg or less may be fatal. With a dose 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).

#### **DOSAGE AND ADMINISTRATION**

Atropine Sulfate Injection, USP in the Ansyr Syringe is intended for intravenous use, but may be administered subcutaneously or intramuscularly. Its use usually requires titration, using heart rate, PR interval, blood pressure and/or patient's symptoms as a guide for having reached an appropriate dose.

#### **Adults**

*Initial* single doses in adults vary from around 0.5 mg to 1 mg (5-10 mL of the 0.1 mg/mL solution for antisialagogue and other anticholinergic effects, to 2 to 3 mg (20-30 mL) of the 0.1 mg/mL solution) as an antidote for organophosphorous or muscarinic mushroom poisoning. When used as an antidote, the 2 to 3 mg dose should be repeated no less often than every 20 to 30 minutes until the signs of poisoning are sufficiently lessened or signs of atropine poisoning (see ADVERSE REACTIONS and OVERDOSAGE) occur.

When the recurrent use of atropine is essential in patients with coronary artery disease, the total dose should be restricted to 2 to 3 mg (maximum 0.03 to 0.04 mg/kg) to avoid the detrimental

effects of atropine-induced tachycardia on myocardial oxygen demand. For patients with bradysystolic cardiac arrest, a 1 mg dose of atropine is administered intravenously and is repeated every 3-5 minutes if asystole persists. Three milligrams (0.04 mg/kg) given I.V. is a fully vagolytic dose in most patients. The administration of this dose of atropine should be reserved for patients with bradysystolic cardiac arrest. Administration of less than 0.5 mg can produce a paradoxical bradycardia because of the central or peripheral parasympathomimetic effects of low doses in adults.

Endotracheal administration of atropine can be used in patients without I.V. access. The recommended adult dose of atropine for endotracheal administration is 1 to 2 mg diluted to a total not to exceed 10 mL of sterile water or normal saline.

Titration intervals of one or two hours are recommended in circumstances that are not life-threatening.

**Pediatrics**

Dosing information in pediatric populations has not been well studied. Usage history of initial dose has been in the range of 0.01 to 0.03 mg/kg body weight.

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration (see PRECAUTIONS).

**HOW SUPPLIED**

Atropine Sulfate Injection, USP is supplied in single-dose containers as follows:

List No.	Container	Size	Conc.	Total Content (Atropine)
9629	Ansyr® Plastic Syringe	5 mL	0.1 mg/mL (Adult)	0.5 mg
1630	Ansyr® Plastic Syringe	10 mL	0.1 mg/mL (Adult)	1 mg
9630	Ansyr® Plastic Syringe	5 mL	0.05 mg/mL (Pediatric)	0.25 mg