ATROPINE INJECTION BP (Atropine sulfate monohydrate)

1. NAME OF THE MEDICINE

Atropine sulfate monohydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atropine Injection BP is a sterile, isotonic, preservative free solution containing 600 microgram of atropine sulfate monohydrate in 1 mL or 1.2 mg of atropine sulfate monohydrate in 1 mL.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Preanaesthetic medication to reduce salivary secretions and bronchial secretions
- to prevent cholinergic cardiac effects such as cardiac arrhythmias, hypotension and bradycardia
- management of patients with acute myocardial infarction and sinus bradycardia who have associated hypotension and increased ventricular irritability
- concurrent administration with anticholinesterase agents (e.g. neostigmine, physostigmine) to block the adverse muscarinic effects of these agents following surgery to terminate curarisation
- for poisoning by organophosphate pesticides, atropine may be used concomitantly with a cholinesterase reactivator such as pralidoxime to reverse muscarinic effects.

4.2 Dose and Method of Administration

Atropine Injection may be given by subcutaneous (SC), intramuscular (IM) or direct intravenous (IV) injection.

Atropine Injection should not be added to any IV infusion solutions for administration. Atropine Injection contains no microbial agent. It should be used only once and any residue discarded.

Cardiopulmonary resuscitation

The usual adult dose is 0.4 - 1 mg IV, which may be repeated at 5 minute intervals until the desired heart rate is achieved. The total dose should not exceed 2 mg.

The usual paediatric dose is 0.02 mg/kg (maximum single dose 0.5 mg) IV, which may be repeated at 5 minute intervals until the desired heart rate is achieved. The total dose should not exceed 1 mg.

Premedication

300 - 600 micrograms Atropine Injection may be given IM or SC 30 to 60 minutes prior to induction of anaesthesia, usually in conjunction with a narcotic. Alternatively 300 - 600 micrograms IV may be given immediately before induction of anaesthesia.

Suitable premedication doses to be given SC 30 to 60 minutes prior to surgery in infants and children are:

- infants < 3 kg: 100 micrograms
- 7 to 9 kg: 200 micrograms
- 12 to 16 kg: 300 micrograms
- 20 to 27 kg: 400 micrograms
- 32 kg: 500 micrograms
- 41 kg: 600 micrograms.

Reversal of competitive neuromuscular block

May be given by slow IV injection in conjunction with an anticholinesterase agent (e.g. neostigmine, physostigmine). Six hundred micrograms (600 micrograms) - 1.2 mg atropine for each 0.5 - 2.5 mg neostigmine methylsulfate in adults and 0.02 mg/kg atropine for each 0.04 mg/kg neostigmine methylsulfate in children.

Organophosphate poisoning

1 - 2 mg atropine may be given IV. Additional 2 mg doses may be administered IM or IV every 5 to 60 minutes until muscarinic signs and symptoms subside; and repeated if these reappear. For severe cases 2 - 6 mg may be administered IV, with subsequent additional doses of 2 - 6 mg being administered IM or IV every 5 to 60 minutes until muscarinic signs and symptoms subside.

Doses up to 50 mg may be required within the first 24 hours. With severe cases atropine therapy should be withdrawn gradually to avoid sudden recurrence of symptoms (e.g. pulmonary oedema). A cholinesterase reactivator (e.g. pralidoxime) is administered concomitantly.

The dose for children is 0.05 mg/kg IM or IV, repeated at 10 to 30 minute intervals until muscarinic signs and symptoms subside. This is to be repeated if these reappear.

4.3 Contraindications

- Known hypersensitivity to atropine or other anticholinergic agents

- severe ulcerative colitis
- toxic megacolon complicating ulcerative colitis
- gastrointestinal obstruction, e.g. pyloroduodenal stenosis, achalasia, cardiospasm, paralytic ileus, intestinal atony
- closed-angle glaucoma
- obstructive uropathy, e.g. bladder neck obstruction caused by prostatic hypertrophy
- myasthenia gravis
- tachycardia secondary to cardiac insufficiency or thyrotoxicosis
- acute haemorrhage with unstable cardiovascular status
- febrile patients or patients exposed to elevated ambient temperature, due to the risk of provoking hyperpyrexia and heat prostration
- prostatic enlargement
- pregnancy induced hypertension.

4.4 Special Warnings and Precautions for Use

Atropine should be used with caution in all patients and especially those over 40 years old as they may be more susceptible to its adverse effects.

Atropine should be used with caution in patients with hyperthyroidism, hepatic or renal disease, hypertension, severe heart disease, ulcerative colitis, ileus, chronic pulmonary disease, or autonomic neuropathy, prostatic hypertrophy, oesophageal reflux or hiatus hernia.

Cardiovascular status

Atropine should be used with caution in conditions characterised by tachycardia, such as cardiac insufficiency or failure (see Section 4.3 Contraindications), acute myocardial infarction or ischaemia and in cardiac surgery where it may further accelerate the heart rate. Tachycardia may result from vagal inhibition and induce angina pectoris in patients with coronary heart disease. 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.

Mental confusion

Atropine may cause mental confusion, especially in elderly or brain damaged patients.

Debilitated patient

Caution is required in administering atropine to debilitated patients, especially with chronic

pulmonary disease, since reduced bronchial secretions may cause inspissation and bronchial plug formation.

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.

Glaucoma

Systemic administration of conventional doses of atropine may precipitate acute glaucoma in susceptible individuals.

Use in the elderly

Atropine should be used with caution in geriatric patients since they may be more susceptible to its adverse effects. 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 geriatric patients, especially those who already have memory problems, with the continued use of anticholinergics since these drugs block the actions of acetylcholine, which is responsible for many functions of the brain, including memory functions.

Paediatric use

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

Effects on laboratory tests

No data available

4.5 Interactions with Other Medicines and Other Forms of Interactions

Atropine may cause increased anticholinergic activity when administered concomitantly with other anticholinergic drugs such as phenothiazines, antispasmodics, antiparkinsonian drugs, antiarrhythmics with anticholinergic activity e.g. disopyramide and quinidine, some antihistamines, tricyclic antidepressants or butyrophenones.

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

Atropine antagonises the actions of a number of compounds, including: synthetic choline esters e.g. bethanechol and carbachol, anticholinesterase drugs e.g. physostigmine, neostigmine and

pyridostigmine, and cholinomimetic alkaloids e.g. pilocarpine.

Ketoconazole

Anticholinergics may increase gastrointestinal pH, possibly resulting in a marked reduction in ketoconazole absorption during concurrent use with anticholinergics; patients should be advised to take these medications at least 2 hours after ketoconazole.

Cisapride and metoclopramide

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

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.

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

Effects on fertility

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

Use in pregnancy – Pregnancy Category A

Atropine has been used in 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 having been observed. However, proven safety of atropine in pregnancy has not been established. As with all drugs caution is essential in the use of atropine in pregnant women. Atropine crosses the placental barrier and may cause tachycardia in the foetus.

Use in lactation

Atropine inhibits lactation. It is reported to distribute into breast milk in small quantities. Since some infants can be sensitive to atropine, and atropine may cause antimuscarinic effects in the infant, use of atropine during breastfeeding is not recommended.

4.7 Effects on Ability to Drive and Use Machines

Since antimuscarinics may cause drowsiness or blurred vision, patients should be warned not

to engage in activities requiring mental alertness and/or visual acuity (e.g. driving a car or operating machinery).

4.8 Adverse Effects (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.

More common reactions

Cardiovascular

Tachycardia and palpitations. Atropine blocks vagal impulses with consequent increase in heart rate with possible atrial arrhythmias, atrioventricular dissociation, multiple ventricular ectopics and angina.

Central nervous system

Xerostomia, thirst, dryness of the mouth. These are due to the reduction of salivary, bronchial and sweat secretions and are dose related.

Gastrointestinal

Constipation due to the inhibition of parasympathetic control of the GI tract.

Genitourinary

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

Ocular

Dilatation of the pupils (mydriasis) with loss of accommodation (cycloplegia), blurred vision, photophobia can occur with increasing doses of atropine.

Dermatological

Flushing, dryness of the skin.

Less common reactions

Cardiovascular

The development of angina in patients with known cardiac problems has been reported.

Central nervous system

Tremor, headache, nervousness, drowsiness, weakness, insomnia, fatigue, ataxia, hyperpyrexia, dizziness, confusion and/or excitement.

Anhidrosis also may occur and can produce heat intolerance in patients living in a hot environment.

Gastrointestinal

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

Dermatological

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

Ocular

Increased ocular tension.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

There is considerable patient variability in the susceptibility to atropine. Atropine overdosage is characterised by both peripheral and central symptoms. Toxic doses cause dilated pupils, difficulty in swallowing, hot dry skin, vasodilation, urinary retention, tachycardia, rapid respiration, hyperpyrexia, and central nervous system stimulation marked by restlessness, confusion, excitement, paranoid psychotic reactions, delirium, hallucinations and occasionally seizures or convulsions. A rash may appear on the face or upper trunk. In severe toxicity, CNS stimulation may give way to CNS depression, coma, circulatory and respiratory failure and death. 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.

Treatment

Symptomatic and supportive therapy should be provided. Close monitoring, including ECG monitoring is recommended. Fluid therapy and other standard treatments for shock should be administered. Hyperthermia should be treated with cold packs, mechanical cooling devices or sponging with tepid water. Maintenance of adequate airway is essential, with respiratory assistance if necessary. Urinary catheterisation may be required if the patient is comatose. If photophobia occurs, the patient may be kept in a dark room.

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.

Relative contraindications to the use of physostigmine include asthma, gangrene, cardiovascular disease and mechanical obstruction of the gastrointestinal or genitourinary tract. In such patients physostigmine should only be used where a life threatening emergency occurs.

Diazepam may be administered to control excitement, delirium or other symptoms of acute psychosis. Phenothiazines should be avoided since these may exacerbate antimuscarinic effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: Anticholinergic agent.

Mechanism of action

Atropine is often classified as an anticholinergic drug but is more accurately described as an antimuscarinic agent since it competitively inhibits the muscarinic actions of acetylcholine and has both peripheral and central actions. It reduces secretions especially salivary and bronchial secretions, and also reduces perspiration. It has little effect on intestinal, biliary or pancreatic secretions since these secretions are principally controlled by hormonal rather than vagal mechanisms.

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 may also 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. Atropine has an antispasmodic action on smooth muscle and diminishes gastric and intestinal motility.

Atropine has central nervous system (CNS) activity. Average doses (400 microgram - 1 mg) produce stimulation of the medulla and higher cerebral centres, causing mild vagal excitation. The increased respiratory rate and, sometimes, increased depth of respiration produced by atropine are more probably the result of bronchiolar dilation. 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 parasympathetic drugs, and cardiac arrest produced

by stimulation of the vagus. Larger doses cause prominent central excitation, blocking the vagus nerve resulting in restlessness, irritability, disorientation, hallucinations or delirium.

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.

Clinical trials

No data available

5.2 Pharmacokinetic properties

Absorption

Atropine is well absorbed following intramuscular administration and peak plasma concentrations are reached within 30 minutes 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 five hours. Inhibition of salivation occurs within 30 minutes, peaks within 1 - 2 hours and persists for 4 hours following intramuscular administration. Increased heart rate occurs within 5 - 40 minutes and peaks within 20 minutes to 1 hour after intramuscular administration. With intravenous administration increased heart rate effect peaks within 2 - 4 minutes. Low doses of the drug cause a paradoxical decrease in heart rate. Following intravenous infusion, serum levels of atropine drop rapidly within the first ten minutes and then decrease more gradually. One hour after either intramuscular or intravenous injection, atropine levels are very similar.

Distribution

Atropine is well distributed throughout the body. It crosses the blood-brain barrier and also the placental barrier and is distributed into milk in small quantities. It has a large apparent volume of distribution (2 to 4 L/kg) and shows a high interindividual variability in serum protein binding.

Metabolism

Atropine is metabolised in the liver to several metabolites and excreted mainly in the urine. Approximately 30 - 50% of a dose is excreted in the urine unchanged. Small amounts of atropine may also be eliminated in expired air as carbon dioxide and in faeces.

Excretion

Atropine has a plasma half life of 2 - 3 hours. Following intramuscular administration elimination appears biphasic with an initial phase of about 2 hours and a half life in the terminal phase of 12.5 hours or longer. In children, the plasma half life is approximately 6.5 hours.

5.3 Preclinical Safety Data

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride

Water for injections

6.2 Incompatibilities

Atropine Injection has been shown to be incompatible with solutions containing adrenaline hydrochloride, amylobarbitone sodium, pentobarbitone sodium, promazine hydrochloride, ampicillin sodium, chloramphenicol sodium succinate, chlortetracycline hydrochloride, heparin sodium, metaraminol tartrate, methicillin sodium, nitrofurantoin, novobiocin, oxacillin sodium, sodium bicarbonate, sulfadiazine sodium, sulfafurazole diethanolamine, tetracycline hydrochloride, thiopentone sodium, vitamin B complex with ascorbic acid and warfarin sodium. This list is not exhaustive.

6.3 Shelf life

Refer to outer carton of expiration date.

6.4 Special Precautions for Storage

Store below 25°C. Single use only. Discard unused portion.

6.5 Nature and Contents of Container

Atropine Injection BP 600 mcg in 1 mL (sterile) Steriluer® ampoules, 50's & 10's (available in Australia only).

Atropine Injection BP 1.2 mg in 1 mL (sterile) Steriluer® ampoules, 50's.

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

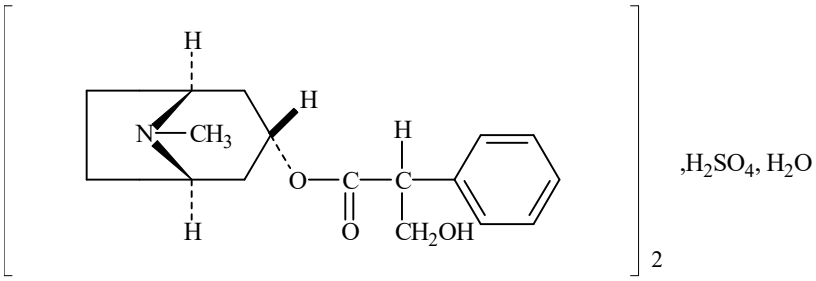
Any unused medicine or waste material should be disposed of in accordance with local

requirements.

6.7 Physicochemical Properties

Atropine sulfate monohydrate is bis (1*R*,3*r*,5*S*)-3-[(*RS*)-(3-hydroxy-2-phenylpropionyl)oxy]-8-methyl-8-azabicyclo[3.2.1]octane sulfate. It appears as colourless crystals or a white, crystalline powder. It is very soluble in water, freely soluble in alcohol and practically insoluble in ether.

Chemical structure



Molecular Formula: $(C_{17}H_{23}NO_3)_2, H_2SO_4, H_2O$

Molecular Weight: 695

CAS number

5908-99-6

7. PRODUCT OWNER

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