תעשיות פרמצבטיות בע"מ

ספטמבר , 2012

רופא/ה, רוקח/ת נכבד/ה
חברת טבע מודיעה שמשרד הבריאות אישר את העלון לרופא החדש של התכשיר:

Atropine Sulfate 20 mg/10 ml אטרופין סולפט 20 מ"ג/10 מ"ל
(Atropine sulfate 20 mg /10 ml ampoule)

עלון חדש לרופא

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

Relaxation of spastic situations of the gastro-intestinal tract such as pylorospasm, relaxation of biliary and genitourinary tracts, reduction of salivation and bronchial secretion.
Atropine is used to combat CNS and peripheral toxic effects and to suppress vagally-mediated bradyarrhythmias.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות http://www.health.gov.il, וניתן לקבלו מודפס ע"י פניה לחברת טבע.

טבע תעשיות פרמצבטיות בע"מ.
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Physician's Package Insert

עלון לרופא

ATROPINE SULPHATE 20 mg/10 ml

SOLUTION FOR INJECTION

אטרופין סולפאט 20 מ"ג / 10 מ"ל

תמיסה להזרקה לתוך הוריד או לתוך השריר

Composition
Each ampoule of 10 ml contains:
Active Ingredient
Atropine sulfate 20 mg
Other Ingredients
Sodium chloride, sulphuric acid (q.s.), water for injection.

Action
Atropine is a parasympatholytic drug which causes relaxation of smooth muscle and inhibition of secretory glands.

Indications
Relaxation of spastic situations of the gastro-intestinal tract such as pylorospasm, relaxation of biliary and genitourinary tracts, reduction of salivation and bronchial secretion.
Atropine is used to combat CNS and peripheral toxic effects and to suppress vagally-mediated bradyarrhythmias.

Contraindications
Known hypersensitivity to atropine and other anticholinergic drugs.
Ocular: Closed angle glaucoma, adhesions (synechiae) between the iris and lens.
Cardiovascular: Tachycardia secondary to cardiac insufficiency or thyrotoxicosis, unstable cardiovascular status in acute hemorrhage, myocardial ischemia.
Gastrointestinal: Obstructive disease (e.g. achalasia, pyloroduodenal stenosis or pyloric obstruction, cardiospasm); paralytic ileus, intestinal atony of the elderly or debilitated, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, hepatic disease; reflux esophagitis.
Genitourinary: Obstructive uropathy (e.g., bladder neck obstruction due to prostatic hypertrophy), renal disease. Prostatic enlargment.
Musculoskeletal: Myasthenia gravis (unless used to treat the adverse effects of an anticholinesterase agent).
Atropine is contraindicated in asthma patients. 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. Toxemia of pregnancy.

Warnings
Heat prostration can occur with anticholinergic drug use (fever and heat stroke due to decreased sweating) in the presence of a high environmental temperature (see Contraindications).
Anticholinergic psychosis has been reported in sensitive individuals given anticholinergic drugs. CNS signs and symptoms include: confusion, disorientation, short-term memory loss, hallucinations, dysarthria, ataxia, coma, euphoria, decreased anxiety, fatigue, insomnia, agitation, mannerisms and inappropriate affect. These CNS signs and symptoms usually resolve 12-24 hours after drug discontinuation.
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, esophageal 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.

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 drugs 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 Contraindications).

Cardiovascular Status
In conditions characterised by tachycardia, such as cardiac insufficiency or failure, extreme caution must be exercised. 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 pediatric 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, esophageal reflux, known or suspected gastrointestinal infections, e.g., Clostridium difficile associated diarrhea and colitis (antibiotic associated pseudomembranous colitis), incomplete intestinal obstruction or ulcerative colitis. Atropine should also be used with caution in patients with diarrhea , since diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy.

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.

Use in Pregnancy
Safety of use in pregnancy has not been established.
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 fetus being observed, the safety of atropine in pregnancy has not been positively established. As with all other drugs, 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 fetus.

Use in Lactation
Atropine may be excreted in milk causing infant toxicity and may reduce milk production. Documentation is lacking or conflicting. Generally, this drug should not be used in nursing mothers.

Use in Pediatrics
Safety and efficacy are not been established.

Adverse Reactions
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.

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 GI 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 conjuncitivitis 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.

Precautions
(See also Warnings)
Atropine should be used with caution in the presence of the following:
Ocular: Light irides. If there is mydriasis and photophobia, dark glasses should be worn. Caution should be exercised in the elderly because of increased incidence of glaucoma.
Gastrointestinal : Early evidence of ileus as in peritonitis, ulcerative colitis (large doses may suppress intestinal motility and precipitate or aggravate toxic megacolon), hiatal hernia associated with reflux esophagitis (anticholinergics may aggravate this condition).
Genitourinary : Renal disease, prostatic hypertrophy. Patients with prostatism can have dysuria and may require catheterization.
Cardiovascular: Coronary artery disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension.
Pulmonary: Debilitated patients with chronic lung disease, reduction in bronchial secretions can lead to inspissation and formation of bronchial plugs. Caution should be exercised in patients with allergies.
Miscellaneous: Hepatic disease, autonomic

neuropathy, hyperthyroidism. The risk of hyperpyrexia is increased in patients with fever. In elderly patients, confusional states are more common.
Special Risk Patients: Caution should be exercised in infants, small children, blondes, persons with Down's syndrome, brain damage, or spastic paralysis.
Hazardous Tasks: Drowsiness, dizziness, or blurred vision may be produced. Caution should therefore be exercised when driving or performing other tasks requiring alertness.
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 0.5-1 mg of atropine are mildly stimulating. After larger doses, there may be mental disturbances; still larger doses may cause depression. Tolerance may occur to a limited extent, particularly in patients with parkinsonism. Patients should be cautioned not to exceed the prescribed dose, to decrease the dose if dry mouth occurs and to discontinue use if rapid pulse, blurred vision or dizziness occur.

Drug Interactions

POTENTIATING EFFECTS

Antimuscarinic Effects
The effect of atropine may be enhanced by concomitant administration of other drugs 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 drugs
- 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 drug metabolizing 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 Alkalizers
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 antagonizes the actions of a number of compounds, including:
- synthetic choline esters e.g. bethanecol, carbachol
- anticholinesterase drugs 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 antagonize 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, it may interfere with the activity of cholinesterase inhibitors such as rivastigmine, donepezil.

Effect on the ability to drive or operate machinery
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).

Dosage and Administration
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Recommended dosage is 0.4-0.6 mg by I.M. or I.V. injection. The complete atropinizing dose in man is believed to be in the order of 2 mg I.V.

Overdosage
Manifestations
Acute overdosage of atropine produces both peripheral and central signs and symptoms characterized by dilated pupils, difficultly 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 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 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 catheterization 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 of 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 phystostigmine 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.

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, sulfadiazine sodium, sulfafurazole diethanolamine, tetracycline hydrochloride, thiopentone sodium, vitamin B complex and ascorbic acid, warfarin sodium. This list is not exhaustive.

Presentation
Available in institutional dispensaries only.

Product Registration Number: 021 02 27809 21

Storage
Store below 25°C.

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