

PACKAGE LEAFLET
for medical use of medicinal product

ATROPINE-DARNITSA

Qualitative and quantitative composition:

Active substance: atropine sulfate;

1 ml of solution contains atropine sulfate 1 mg;

Excipients: hydrochloric acid, water for injections.

Pharmaceutical form

Solution for injection.

Basic physicochemical properties: clear colourless liquid.

Pharmacotherapeutic group

Alimentary tract and metabolism. Drugs for functional gastrointestinal disorders. Belladonna alkaloids, tertiary amines. Atropine. ATC code A03B A01.

Pharmacological properties

Pharmacodynamic properties

Atropine is an alkaloid contained by plants belonging to the Solanaceae family; it is a blocker of M-cholinoreceptors binding equally to M₁-, M₂-, and M₃-subtypes of muscarine receptors. It has influence on both central and peripheral M-cholinoreceptors. Atropine exercises its influence also on H-cholinoreceptors, this influence being, however, weaker. The drug inhibits stimulating acetylcholine action decreasing the secretion of salivary, gastric, bronchial, lacrimal, and sudoriferous glands. The drug decreases the tonicity of visceral muscles (bronchi, gastrointestinal tract, bile ducts and gallbladder, urethra, bladder); causing tachycardia and improving AV-conductivity. The gastrointestinal tract motility is decreased by atropine, no atropine influence is seen concerning bile secretion and pancreas. The drug leads to mydriasis preventing the outflow of intraocular fluid and causes the accommodation paralysis. Moderate therapeutic doses of atropine demonstrate the influence on the central nervous system and cause delayed, but long sedative effect and stimulate breathing.

Pharmacokinetic properties

Atropine sulfate is quickly absorbed into the blood flow from the site of its injection. It is quickly distributed in the organism penetrating through blood-brain and placental barriers as well as into mother's milk. Following intravenous atropine injection, the maximal effect is seen in 2-4 minutes. Atropine bioavailability reaches 25 %. 50 % of drug is metabolized in the liver due to enzymatic hydrolysis, final products becoming tropin and troponic acid. The atropine level bound to blood plasma proteins reaches 18 %. Significant atropine concentrations are found in the central nervous system in 0.5-1 hr post injection. The drug semi-excretion period is 2 hr. The drug is excreted by kidneys partly without any changes (50 %), the rest atropine quantity being discharged as products of hydrolysis and conjugation.

Clinical particulars

Therapeutic indications

Atropine is used as a symptomatic drug in cases of gastric and duodenal ulcers, pylorospasm, acute pancreatitis, cholelithiasis, spasms of intestine and urinary tracts, bronchial asthma, bradycardia being a result of increased vagus nerve tonus, as a remedy decreasing the secretion of salivary, gastric, bronchial, and sometimes of sudoriferous glands, for realization of roentgen investigation of digestive tract (atropine decreases its tonus and motional activity).

The drug is indicated for use before narcosis and during surgical procedures as remedy preventing broncho- and laryngospasms, decreasing the gland secretion, reflective reactions, and adverse effects due to vagus nerve excitability. It is also used as a specific antidote in cases of

intoxications due to cholinomimetic compounds and anti-cholinesterase reagents (including also phosphororganic ones).

Contraindications

Increased sensitivity to drug components. Cardiovascular diseases when increased rate of heartbeats is not desirable: ciliary arrhythmia, tachycardia, chronic heart failure, ischemic heart disease, mitral stenosis, severe arterial hypertension. Acute bleeding. Thyrotoxicosis. Hyperthermic syndrome. Pathologies of gastrointestinal tract accompanied by obstruction (achalasia of esophagus, pyloric stenosis, intestinal atony and toxic megacolon). Glaucoma. Liver and kidney failure. *Myasthenia gravis*. Urine retention or predilection for such this pathology (for example, due to prostate or urethral disease). Brain injury.

Interaction with other medicinal products and other forms of interaction

If atropine sulfate is used together with *monoaminoxidase inhibitors* cardiac arrhythmias appear; if it is given together with *quinidine novocainamide* the summing up of cholinolytic effects takes place

Atropine intake together with *Convallaria* preparations and with tannin causes physicochemical interactions leading to reciprocal weakening of these remedies actions.

Atropine sulfate decreases the duration and intensity of *narcotic remedies* action, weakens analgetic *opiates* effect.

Simultaneous atropine uses with *diphenhydramine* or *pipolphen* promotes the atropine effect. Simultaneous atropine administration with nitrates, *haloperidol*, *corticosteroids of systemic use* increases the probability of intraocular pressure increase; *sertraline* used together with atropine promotes depressive effect of these compounds; *spironolactone* and *minoxidal* effect becomes weaker in the presence of atropine; simultaneous administration of atropine and penicillins promotes the effect of both preparations; *nizatidine* given simultaneously with atropine demonstrates its increased effect; the *ketaconazole* absorption is increased in the presence of atropine; ascorbic acid and *attapulgit* weaken the atropine effect; atropine decreases *pilocarpine* effect in cases of glaucoma treatment and antihypertensive effect of *oxprenolon*. Secretion decrease due to atropine may be weakened in the presence of *oktadine*, the last being able to weaken the effect of M-cholinomimetics and anti-cholinesterase remedies. The simultaneous atropine use with *sulfonamides* increases the risk of kidney injury; the use of *potassium-containing drugs* together with atropine enables the ulcer formation in the intestine; non-steroid anti-inflammatory compounds given simultaneously with atropine increase the risk of gastric ulcer formation and bleeding.

The effect of atropine sulfate may be enhanced by increasing the risk of atropine side effects (urinary retention, constipation, dry mouth) with the simultaneous use of other drugs with antimuscarinic effect: *M-cholinoblockers*, *drugs intended for parkinsonism treatment (amantadine)*, *spasmolytics*, *several drugs of antihistamine action*, *mechitazine*, *drugs of butyrophenon group*, *phenothiazines*, *dispyramides*, *quinidine* and *tricyclic antidepressants*, *non-selective inhibitors of monoamine re-intake by neurons*.

Depression of peristalsis due to atropine may change the absorption of other remedies.

Special warnings and precautions for use

Atropine should be used with special caution in cases of prostate hypertrophy without urinary tract obstruction, Down disease, infantile cerebral paralysis, with pyloric stenosis, reflux esophagitis (because atropine can delay gastric emptying, reduce gastric motility and relax the esophageal sphincter), paraesophageal hernia accompanied by reflux esophagitis, with intestinal atony in the elderly, non-specific ulcerative colitis, megacolon, xerostomia, for patients of elderly age or debilitated ones, patients with chronic lung diseases without reversible obstruction proceeding with non-abundant production of sputum expectorated with difficulty, especially in young infants and debilitated patients as well as in cases of vegetative (autonomic) neuropathy, patients with heart failure, arrhythmia, hyperthyroidism, fever or when the ambient temperature is high.

Atropine should not be used in patients with myasthenia gravis unless it is used in combination with an anticholinesterase.

Use atropine with caution in patients with a high degree of atrioventricular block (second degree Mobitz type II or third degree).

Patients with tachyarrhythmia, congestive heart failure, coronary heart disease should use atropine with caution, as it is possible to block the vagal inhibition of the driver of the rhythm of the sinoatrial node.

Fertility, pregnancy and lactation

The drug is contraindicated during the pregnancy period.

The atropine use during the breast feeding is contraindicated because of its possible toxic effect for infants.

Effects on ability to drive and use machines

Because of possible development of such adverse effects as dizziness, drowsiness, hallucinations, vision and accommodation disturbances etc., transport driving or working with other mechanisms should be avoided in periods of the drug use.

Posology and method of administration

The atropine sulfate may be introduced as intradermal, intramuscular, and intravenous drug. Using initial narcosis to decrease the risk of heart rate inhibition and salivary and bronchial gland inhibition due to vagus activity, atropine is introduced in 30-60 min before anesthesia intradermally or intramuscularly (0.3-0.6 mg); if the drug is given in combination with morphine (morphine sulfate, 10 mg) the injection should be made in 1 hr before anesthesia. In cases of anti-cholinesterase drug intoxication, the atropine sulfate is administered intramuscularly (2 mg) in 20-30-minute intervals until the development of skin reddening and dryness, pupil dilation, development of tachycardia and breath normalization. In cases of severe and moderate intoxications the drug may be introduced during two days (until the signs of excessive atropine level appear).

Depending on children age, the maximal single doses are the following:

- up to 6 months – 0.02 mg;
- from 6 months up 1 year – 0.05 mg;
- from a year up to 2 years – 0.2 mg;
- from 3 up to 4 years – 0.25 mg;
- from 5 up to 6 years – 0.3 mg;
- from 7 up to 9 years – 0.4 mg;
- from 10 up to 14 years – 0.5 mg.

The maximal intradermal doses for adults are the following: single dose – 1 mg and day dose – 3 mg.

The drug should be given with caution to patients of elderly age.

Children

Infants below 3 months are especially atropine susceptible.

The drug should be prescribed in doses indicated in the chapter «Mode of administration and doses».

Overdose

Symptoms: increased expression of adverse reactions, redness, rash and dry skin, dry mucous membranes, dry mouth, dry tongue with burning, dilated pupils and photosensitivity, increased intraocular pressure, difficulty swallowing, rapid breathing, tachycardia, nausea, vomiting, increasing/decreased arterial blood pressure, excitement, tremor, spasms, sleeplessness, headache, dizziness, somnolence, irritability, hyperthermia, difficulty and delay in urination, intestinal atony, impaired heat transfer, decreased sweating.

Symptoms of CNS stimulation include anxiety, confusion / loss of consciousness, hallucinations, paranoid and psychotic reactions, incoordination, delirium, tremor, and recurrent seizures.

With severe overdose may cause drowsiness, stupor, inhibition of the activity of the respiratory and vascular centers, CNS depression, coma, circulatory and respiratory disorders, possibly fatal.

Treatment: administration of the antidote - proserine (1 ml of 0.05% solution under the skin) or physostigmine (0.5-1 ml of 0.1% solution under the skin). Ensuring airway patency, gastric lavage, parenteral administration of cholinomimetics and anticholinesterase drugs. At a hyperthermia ice on a head, an inguinal site, damp wipes and antipyretics are shown; with psychomotor arousal - aminazine intramuscularly (2 ml of 2.5% solution); for convulsions - barbiturates (5-10 ml of 2.5% sodium thiopental solution); with mydriasis - topically in the form of eye drops phosphacol, physostigmine, pilocarpine; with tachycardia - inderal; with urinary retention - catheterization; with severe intoxication - forced diuresis, blood alkalization. If a glaucoma attack develops, 1% pilocarpine solution should be instilled into the conjunctival sac in 2 drops every hour and 1 ml of 0.05% proserine solution should be injected subcutaneously 3-4 times a day. Diazepam can be administered to control agitation and seizures, but the risk of CNS depression should be considered.

Intravenous administration of glucose with ascorbic acid is shown. Antiarrhythmic drugs are not recommended in case of arrhythmia.

Undesirable effects

The nature of the adverse effects observed with atropine may be mainly due to their pharmacological action on muscarinic and, in the case of high doses, nicotinic receptors. Side effects are dose-dependent and usually reversible upon discontinuation of therapy. The most common side effects that occur at relatively small doses are visual disturbances, decreased bronchial secretion, dry mouth, constipation, reflux, hot flashes, difficulty urinating, and dry skin. The development of transient bradycardia with subsequent tachycardia, palpitations and arrhythmia is possible.

All adverse reactions are listed by system organ class and frequency: very common ($\geq 1/10$), common ($\geq 1/100 - <1/10$), uncommon ($\geq 1/1000 - <1/100$), isolated ($\geq 1 / 10000 - <1/1000$), rare ($<1/10000$), frequency unknown (cannot be estimated from the available data).

Eye disorders: very common - dilation of the pupils, photophobia, paralysis of accommodation, increased intraocular pressure, visual disturbances.

Respiratory, thoracic and mediastinal disorders: very common - decreased secretory activity and bronchial tone, which leads to the formation of viscous sputum, which is difficult to cough.

Gastrointestinal disorders: very common - dry mouth (dysphagia, difficulty communicating, thirst), taste disturbances, decreased intestinal motility to atony, constipation, reflux, decreased tone of the biliary tract and gallbladder, suppression of gastric secretion nausea, vomiting, bloating.

Renal and urinary disorders: frequent - difficulty and delayed urination.

Nervous system disorders: frequent - nervousness, dizziness, incoordination, impaired consciousness and / or hallucinations (especially at higher doses), hyperthermia; infrequent - mental disorders; isolated - convulsions, drowsiness; frequency unknown - headache, anxiety, ataxia, dysarthria, insomnia.

Heart disorders: frequent - tachycardia, arrhythmia, transient exacerbation of bradycardia; rare - extrasystole, atrial arrhythmia, ventricular fibrillation, myocardial ischemia, hypertensive crisis.

Vessels disorders: frequent - a feeling of hot flashes, redness of the face.

Immune system disorders: isolated - hypersensitivity reactions; rare - anaphylactic reactions, anaphylactic shock.

Skin and subcutaneous tissue disorders: very common - skin rashes, dry skin, urticaria, exfoliative dermatitis.

General disorders and administration site conditions: very common - decreased sweating; infrequent - changes in the injection site.

Special population groups.

Atropine may cause agitation, incoordination, impaired consciousness and / or hallucinations, especially in the elderly. Similar epidemiological studies have reported a decrease in cognitive performance in elderly patients receiving antimuscarinic drugs.

Patients with Down syndrome may be more sensitive to antimuscarinic effects.

Reported suspected adverse reactions.

Reporting suspected adverse reactions after registration of a medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective drug. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

Shelf life

3 years.

Special precautions for storage

Store in the original package at temperature not above 25°C. Do not freeze.

Keep out of reach of children.

Incompatibilities

The drug should not be stored together with other remedies. Only the solvent recommended for atropine should be used.

Nature and contents of container

1 ml in an ampoule; 5 ampoules in a blister, 2 blisters in a pack.

Category of release

Prescription only medicine.

Manufacturer

PrJSC "Pharmaceutical firm "Darnitsa".

The manufacturer's location and address of the place of business

13, Boryspilska Street, Kyiv, 02093, Ukraine.

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26.06.2020