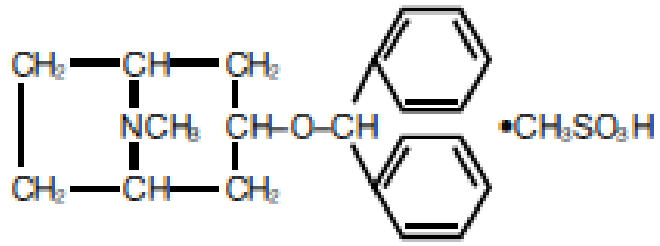
COGENTIN® Injection
(benztropine mesylate)

NAME OF THE MEDICINE

Benztropine mesylate is a synthetic compound resulting from the combination of the active portions of atropine and diphenhydramine.

Chemical structure:



CAS number: 132-17-2

DESCRIPTION

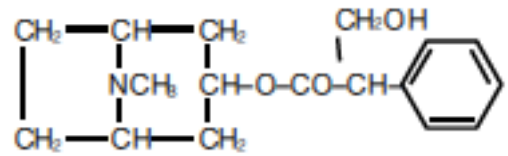
COGENTIN Injection contains benztropine mesylate as the active ingredient. Benztropine mesylate is a crystalline white powder and is very soluble in water.

COGENTIN Injection is available in 2 mL ampoules. Each millilitre of COGENTIN Injection contains:

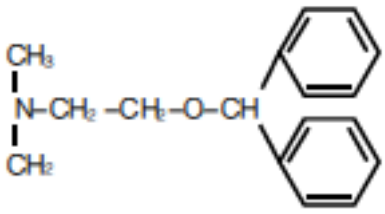
- Benztropine mesylate 1.0 mg
- Sodium chloride 9.0 mg
- Water for injection q.s 1 .0 mL

PHARMACOLOGY

If the formula for benztropine mesylate is compared with that of atropine:



and that of diphenhydramine:



it can be seen that benztropine contains the tropine portion of the atropine molecule and the benzohydryl portion of diphenhydramine.

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Benztropine possesses both anticholinergic and antihistaminic effects, although only the former have been established as therapeutically significant in the management of parkinsonism.

In laboratory animals the antihistaminic activity and duration of action approach those of pyrilamine maleate.

In the isolated guinea pig ileum, the anticholinergic activity of this drug is about equal to that of atropine; however, when administered orally to unanaesthetised cats, benztropine is only about half as active as atropine.

INDICATIONS

COGENTIN is recommended for all forms of parkinsonism - including arteriosclerotic, post-encephalitic, idiopathic, as well as drug-induced extrapyramidal disorders (except tardive dyskinesia). It can be effective at any stage of the disease, even when a patient has become bedridden. COGENTIN often is helpful in patients who have become unresponsive to other agents. COGENTIN is a powerful anticholinergic agent which is mainly effective in relieving tremor and rigidity. Therapy is directed toward control of disturbing symptoms to permit the patient maximum integration of function with minimum discomfort.

In non-drug-induced parkinsonism, partial control of symptoms is usually achieved.

CONTRAINDICATIONS

Because of the atropine-like side effects, COGENTIN is contraindicated in children under three years of age, and should be used with caution in older children.

COGENTIN is contraindicated in patients who are hypersensitive to any component of this product.

PRECAUTIONS

Benztropine mesylate may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Since benztropine mesylate has cumulative action, continued supervision is advisable. Patients with a tendency to tachycardia and patients with prostatic hypertrophy, should be closely observed during treatment.

In large doses, the drug may cause complaints of weakness and inability to move particular muscle groups. For example, if the neck has been rigid and suddenly relaxes, it may feel weak, causing some concern. In this event, dosage adjustment may be required.

Mental confusion and excitement may occur with large doses, or in susceptible patients. Visual hallucinations have been reported occasionally. Furthermore, in the treatment of extrapyramidal symptoms due to central nervous system drugs, such as phenothiazines and reserpine, in patients with mental disorders, occasionally there may be intensification of mental disorders. In such cases antiparkinsonian drugs can precipitate a toxic psychosis.

Patients with mental disorders should be kept under careful observation, especially at the beginning of treatment or if dosage is increased.

Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy when these drugs have been discontinued. Antiparkinsonian agents usually do not alleviate their symptoms of tardive dyskinesia, and in some instances may aggravate or unmask such symptoms. COGENTIN is not recommended in tardive dyskinesia.

Since benztropine mesylate contains structural features of atropine, it may produce anhydrosis. For this reason, it should be given with caution during hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, the alcoholic, those who have central nervous system disease and those who do manual labour in a hot environment.

Anhydrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhydrosis, the possibility of hyperthermia should be considered. Dosage should be decreased at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired. Severe anhydrosis and fatal hyperthermia have occurred.

The physician should be aware of the possible occurrence of glaucoma. Although the drug does not appear to have any adverse effect on simple glaucoma, COGENTIN probably should not be used in narrow-angle glaucoma.

Use in Pregnancy (Category B2)

It is not known whether COGENTIN can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. COGENTIN should be given to a pregnant woman only if clearly needed.

Use in lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COGENTIN is administered to a nursing mother.

Paediatric Use

See CONTRAINDICATIONS.

INTERACTIONS WITH OTHER MEDICINES

When COGENTIN is given concomitantly with phenothiazines, haloperidol or other drugs with anticholinergic or antidopaminergic activity, patients should be advised to report fever, heat intolerance and gastrointestinal complaints promptly. Paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

ADVERSE EFFECTS

Adverse reactions, most of which are anticholinergic or antihistaminic in nature are listed below by body system in order of decreasing severity:

Cardiovascular

Tachycardia

Digestive

Constipation, dry mouth, nausea, vomiting

If dry mouth is so severe that there is difficulty in swallowing or speaking, or loss of appetite and weight occur, reduce dosage, or discontinue the drug temporarily.

Slight reduction in dosage may control nausea and still give sufficient relief of symptoms. Vomiting may be controlled by temporary discontinuation, followed by resumption at a lower dosage.

Nervous System

Toxic psychosis, including confusion, disorientation, memory impairment, visual hallucinations, exacerbation of pre-existing psychotic symptoms, nervousness, depression, listlessness, numbness of fingers.

Special Senses

Blurred vision, dilated pupils

Urogenital

Urinary retention, dysuria

Metabolic/Immune and Skin

Occasionally, an allergic reaction e.g. skin rash, develops. If this cannot be controlled by dosage reduction, the medication should be discontinued.

Other

Heatstroke, hyperthermia, fever

DOSAGE AND ADMINISTRATION

COGENTIN is available as an injection for intravenous and intramuscular use. Each millilitre of the injection contains:

- Benztropine mesylate 1.0 mg
- Sodium chloride 9.0 mg
- Water for injection q.s 1 .0 mL

Because COGENTIN is cumulative in action, therapy should be initiated with a small dose which then can be increased gradually at five- or six-day intervals. Increases in dosage should be made in increments of 0.5 mg, to a maximum of 6mg.

The injection is especially useful for psychotic patients with acute dystonic reactions or other reactions that make oral medication difficult or impossible.

There is no significant difference in the onset of effect following intravenous or intramuscular injection. Improvement is noticeable within a few minutes after injection.

In emergency situations, when the patient's condition is alarming, administration of 1 to 2mL of COGENTIN Injection will provide quick relief. If the signs of parkinsonism begin to return, the dose can be repeated.

Some patients experience greatest relief when taking the entire dose at bedtime; others react more favourably to divided doses, two to four times a day.

The long duration of action of COGENTIN makes it particularly suitable for administration at bedtime when the effects may persist throughout the night. Consequently, COGENTIN enables the patient to turn in bed more easily and to rise in the morning.

Therapy with other agents in parkinsonism should not be terminated abruptly when COGENTIN is started, but reduced or discontinued gradually. Many patients obtain the greatest relief with a combination of COGENTIN and other drugs.

COGENTIN may be used concomitantly with SINEMET® (carbidopa/ levodopa, MSD), or with levodopa in which case periodic dosage adjustment may be required in order to maintain optimum response.

<u>Arteriosclerotic, Idiopathic and Postencephalitic Parkinsonism</u>

The usual daily dose of COGENTIN is 1 to 2 mg, with a range of 0.5 to 6 mg parenterally.

Dosage must be individualised. In determining the dosage, the age and weight of the patient and the type of parkinsonism must be taken into consideration. Older patients, thin patients

and patients with arteriosclerotic parkinsonism generally cannot tolerate large doses. However, most patients with postencephalitic parkinsonism require and, indeed, tolerate fairly large doses. Patients with a poor mental outlook are usually poor candidates for therapy.

In arteriosclerosis and idiopathic parkinsonism, therapy may be initiated with a single daily dose of 0.5 mg to 1 mg at bedtime. This dosage will be adequate in some patients, whereas 4 mg to 6 mg a day may be required by others.

In postencephalitic parkinsonism, therapy may be initiated in most patients with 2 mg a day in one or more doses. In highly sensitive individuals, therapy may be initiated with 0.5 mg at bedtime and increased as necessary.

Drug-Induced Parkinsonism

When treating extrapyramidal disorders due to central nervous system drugs such as phenothiazines or reserpine, a dosage of 1 to 4 mg once or twice a day is recommended.

Dosage should be varied to suit the needs of the patient. After one or two weeks of administration, COGENTIN should be withdrawn to determine the continued need for medication.

If parkinsonism recurs therapy with COGENTIN can be reinstituted.

Usually the injection of 1 to 2 mL of COGENTIN quickly relieves acute dystonic reactions.

OVERDOSAGE

Symptoms:

May be any of those seen in atropine poisoning or antihistamine overdosage: CNS depression, preceded or followed by stimulation; confusion; nervousness; listlessness; intensification of mental symptoms or toxic psychosis in patients with mental illness being treated with phenothiazine derivatives or reserpine; hallucinations (especially visual); dizziness; muscle weakness; ataxia; dry mouth; mydriasis; blurred vision; palpitations; tachycardia; nausea; vomiting; dysuria; numbness of fingers; dysphagia; allergic reactions, e.g. skin rash; headache; hot, dry, flushed skin, delirium; coma; shock; convulsions; respiratory arrest; anhydrosis; hyperthermia; glaucoma; constipation.

The oral LD_{50} in the mouse is 94 mg/kg. The intravenous LD_{50} in the mouse is 24 mg/kg.

Treatment:

Physostigmine salicylate, 1 to 2 mg s.c. or i.v., will reverse symptoms of anticholinergic intoxication. A second injection may be given after two hours if required. Otherwise treatment is symptomatic and supportive. Maintain respiration. A short-acting barbiturate may be used for CNS excitement, but with caution to avoid subsequent depression; supportive care for depression (avoid convulsant stimulants such as picrotoxin, pentylenetetrazole or bemegride); artificial respiration for severe respiratory depression; a local miotic for mydriasis and cycloplegia; ice bags or other cold applications and alcohol sponges for hyperpyrexia, a vasopressor and fluids for circulatory collapse. Darken room for photophobia.

PRESENTATION AND STORAGE CONDITIONS

COGENTIN injection, 1 mg/mL, clear, colourless solution. Supplied 5 x 2 mg ampoules.

Protect from light. Protect product from freezing. Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

A.Menarini Australia Pty Ltd
Level 8, 67 Albert Ave,
Chatswood NSW 2067

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 July 1991

DATE OF MOST RECENT AMENDMENT

13 June 2013