CYPRODIN

Tablet & Syrup

Composition

Cyprodin Syrup
Each 5 ml contains Cyproheptadine HCl (as anhydrous) 2 mg.

Cyprodin Tablets
Each tablet contains Cyproheptadine HCl (as anhydrous) 4 mg.

Action

Cyproheptadine hydrochloride is a serotonin and histamine antagonist with anticholinergic and sedative effects. Antiserotonin and antihistamine drugs appear to compete with serotonin and histamine, respectively, for receptor sites.

Animal studies have shown Cyproheptadine hydrochloride to be an effective serotonin and histamine antagonist, comparable, in general, to the most active known substances.

Cyproheptadine hydrochloride antagonizes the following effects of serotonin in laboratory animals:

- bronchoconstrictor (guinea pig)
- vasodepressor (dog)
- spasmogenic (isolated rat uterus)
- oedema (rat)
- Lethal (*Haemophilus pertussis*-treated mouse).

In all these effects, Cyproheptadine hydrochloride approaches, equals or surpasses the activity of specific serotonin antagonists, such as 1-benzyl-2-methyl-5-methoxy-tryptamine (BAS) and 1-benzyl-2-methyl-5-hydroxy-tryptamine (BMS). In contrast, specific antihistamines, even the most potent, show little or no serotonin antagonism. Thus, Cyproheptadine hydrochloride must be considered a serotonin antagonist as well as a histamine antagonist.

Cyproheptadine hydrochloride antagonizes or blocks the following effects of histamine in laboratory animals:

- bronchoconstrictor (guinea pig)
- vasodepressor (dog)
- spasmogenic (isolated guinea pig ileum)
- anaphylactic shock, active and passive (guinea pig, mouse)
- increased gastric secretion (Heidenhain pouch dog)

That Cyproheptadine hydrochloride protects both guinea pigs and mice against anaphylactic shock is unusual. In guinea pigs, the pulmonary aspects of anaphylactic shock are attributable to the release of endogenous histamine and can be controlled by substances with specific antihistaminic activity. In mice, however, where histamine release seems to be less important and serotonin release may be involved, specific antihistamines are of little value in protecting against anaphylaxis. Thus, the protective effect of Cyproheptadine hydrochloride in mice may be an antiserotonin effect.

The inhibitory effect of Cyproheptadine hydrochloride in histamine-induced gastric secretion is also unusual because specific antihistamines do not influence this effect of histamine.

Because of its marked activity as an antagonist of serotonin and histamine in laboratory animals, Cyproheptadine hydrochloride was evaluated in man in situations where standard antihistamines are not effective.

In one evaluation, skin reactions were induced in test subjects by the intradermal injection of histamine, serotonin, and histamine-releasing substances, such as Compound 48-80. The wheals and flares resulting from the injections were observed, as well as the degree of blueness of the wheals

produced by intravenous injection of a protein dye, Coomassie Blue. Coomassie Blue was used as an indicator of capillary leakage of plasma proteins because of its propensity for plasma binding and its safety for use in man. Cyproheptadine hydrochloride and two standard antihistamines were administered orally in moderate therapeutic doses. Only Cyproheptadine hydrochloride led to a suppression of the whealing responses and the capillary damage demonstrated by the bluing reaction.

Acute and chronic toxicity studies in various laboratory animals indicate that Cyproheptadine hydrochloride has an adequate margin of safety. In doses far greater than those in the therapeutic range, ataxia, sedation and tachycardia can be produced, but other objective signs of toxicity are not evident.

The oral LD50 of Cyproheptadine is 123 mg/kg, and 295 mg/kg in the mouse and rat, respectively.

There was no evidence of histomorphologic changes in the various organs when doses approximating subacute lethal doses were administered to dogs, monkeys, rabbits, and mice. Twelve months of oral toxicity studies in dogs did not reveal functional or anatomical changes. In chronic toxicity studies in rats, only at dosages of 10 to 12 mg/kg/day, far in excess (approximately 200 times) of those required for pharmacodynamic effects was reversible vacuolization of the beta cells of the pancreatic islets noted. This was not observed in the other four species of animals used in the toxicity studies. After six months of continuous drug administration there was no evidence of derangement of carbohydrate metabolism in man, as measured by serial blood sugar determinations and glucose tolerance tests.

Cyproheptadine hydrochloride has central nervous system effects in laboratory animals, including anticonvulsant and antitremor activity and behavioral effects. It has weak peripheral anticholinergic activity and moderate local anaesthetic action. It exerts highly effective protection against burn shock in mice. Most of these properties are evident only with doses much larger than those used in therapy. In the rat, for instance, behavioral effects are produced only by doses 50 to 100 times greater than those required to produce antiserotonin activity.

Indications

- Perennial and seasonal allergic rhinitis.
- Vasomotor rhinitis
- Allergic conjunctivitis due to inhalant allergens and foods.
- Mild, uncomplicated allergic skin manifestations of urticaria and angioedema.
- Amelioration of allergic reactions to blood or plasma.
- Cold urticaria
- Dermatographism
- As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

Contraindications

Newborn or Premature Infants

This drug should not be used in newborn or premature infants.

Nursing Mothers

Because of the higher risk of antihistamines for infants generally and for newborns and premature in particular, antihistamine therapy is contraindicated in nursing mothers.

Other Conditions

- Hypersensitivity to Cyproheptadine and other drugs of similar chemical structure
- Monoamine oxidase inhibitor therapy.
- Angle-closure glaucoma.
- Stenosing peptic ulcer.
- Symptomatic prostatic hypertrophy.
- Bladder neck obstruction.

- Pyloroduodenal obstruction.
- Elderly, debilitated patients.

Warnings

Children

Over Dosage of antihistamines, particularly in infants and children, may produce hallucinations, central nervous system depression, convulsions, and death.

Antihistamines may diminish mental alertness; conversely, particularly, in the young child, they may occasionally produce excitation.

CNS Depressants

Antihistamines may have additive effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, tranquilizers, anti-anxiety agents.

Activities Requiring Mental Alertness

Patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a car or operating machinery.

Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

Adverse Reactions

Adverse Reactions that have been reported with the use of antihistamines are as follows:

Central Nervous System

Sedation and sleepiness (often transient), dizziness, disturbed coordination, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, paresthesias, neuritis, convulsions, euphoria, hallucinations, hysteria, faintness.

Integumentary

Allergic manifestation of rash and edema, excessive perspiration, urticaria, photosensitivity.

Special Senses

Acute labyrinthitis, blurred vision, diplopia, vertigo, tinnitus.

Cardiovascular

Hypotension, palpitation, tachycardia, extrasystoles, anaphylactic shock.

Hematologic

Hemolytic anemia, leukopenia, agranulocytosis, thrombocytopenia.

Digestive System

Dryness of mouth, epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation, jaundice.

Genitourinary

Urinary frequency, difficult urination, urinary retention, early menses.

Respiratory

Dryness of nose and throat, thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Miscellaneous

Fatigue, chills, headache.

Precautions

General

Cyproheptadine has an atropine-like action and, therefore, should be used with caution in patients with:

- History of bronchial asthma
- Increased intraocular pressure
- Hyperthyroidism
- Cardiovascular disease
- Hypertension

Information for Patients
Antihistamines may diminish mental alertness; conversely, particularly, in the young child, they may occasionally produce excitation

Patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a car or operating machinery.

Pregnancy
Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Cyprodin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use
Safety and effectiveness in children below the age of two have not been established.

Drug Interactions
MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines.

Antihistamines may have additive effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, tranquilizers and anti-anxiety agents.

Dosage and Administration
Dosage should be individualized according to the needs and the response of the patient.

Although intended primarily for administration to children, the syrup is also useful for administration to adults who cannot swallow tablets.

Children
The total daily dosage for children may be calculated on the basis of body weight or body area using approximately 0.25 mg/kg/day or 8 mg per square meter of body surface (8 mg/M2). In small children for whom the calculation of dosage based upon body size is most important, it may be necessary to use Cyprodin syrup to permit accurate dosage.

Age 2 to 6 years
The usual dose is 2 mg (1/2 tablet or 1 teaspoon) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 12 mg a day.

Age 7 to 14 years
The usual dose is 4 mg (1 tablet or 2 teaspoons) two or three times a day, adjusted as necessary to the size and response of the patient. The dose is not to exceed 16 mg a day.

Adults

The total daily dose for adults should not exceed 0.5 mg/kg/day.

The therapeutic range is 4 to 20 mg a day, with the majority of patients requiring 12 to 16 mg a day. An occasional patient may require as much as 32 mg a day for adequate relief. It is suggested that dosage be initiated with 4 mg (1 tablet or 2 teaspoons) three times a day and adjusted according to the size and response of the patient.

Over Dosage

Manifestations

Antihistamine over dosage reactions may vary from central nervous system depression to stimulation especially in children. In addition, atropine-like signs and symptoms (dry mouth; fixed, dilated pupils; flushing, etc.) as well as gastrointestinal symptoms may occur.

Treatment

If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac.
If the patient is unable to vomit, perform gastric lavage followed by activated charcoal. Isotonic or 1/2 isotonic saline is the lavage of choice. Precautions against aspiration must be taken especially in infants and children.

When life threatening CNS signs and symptoms are present, intravenous physostigmine salicylate may be considered. Dosage and frequency of administration are dependent on age, clinical response, and recurrence after response.

Saline cathartics, as milk of magnesia, by osmosis draw water into the bowel and, therefore, are valuable for their action in rapid dilution of bowel content.

Stimulants should not be used.
Vasopressors may be used to treat hypotension.
The oral LD_{50} of Cyproheptadine is 123 mg/kg, and 295 mg/ kg in the mouse and rat, respectively.

Presentation

Cyprodin Syrup

Bottle of 100 ml.

Cyprodin Tablets

Box of 20 tablets