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Chloroquine phosphate tablets/suspension - Lariago

DESCRIPTION

Chloroquine is a 4-aminoquinoline compound. It is an antimalarial and amebicidal drug. Chemically, it is 7-chloro-4-[[4- (diethylamino) - 1 - methylbutyl]amino] quinoline phosphate (1:2)

COMPOSITION

Lariago

Each film coated tab contains:
Chloroquine Phosphate IP 250mg

Lariago-DS

Each film coated tab contains:
Chloroquine Phosphate IP 500mg

Lariago Suspension

Each 5ml contains:
Chloroquine Phosphate IP eqv. Chloroquine 50 mg base

Lariago Injection - 2ml/5ml

Each ml contains chloroquine phosphate IP 64.5mg
(equivalent to 40mg of chloroquine base)

Lariago 30ml

Each ml contains chloroquine phosphate IP 64.5mg
equivalent to chloroquine 40mg

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Chloroquine has been found to be active against the asexual erythrocytic forms of all species of malaria parasites; *P. vivax*, *P. ovale*, *P. malariae* and susceptible strains of *P. falciparum*. It is a rapid acting blood schizontocide with some gametocytocidal activity against *P. ovale*, *P. vivax*, *P. malariae* and immature gametocytes of *P. falciparum*.

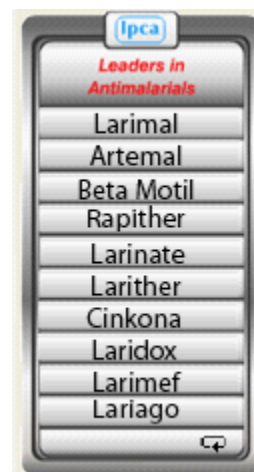
The mechanism of plasmodicidal action of chloroquine is not completely certain. Its effect is believed to result, at least in part, from its interaction with DNA. It acts mainly on the large ring form and mature trophozoite stages of the parasite.

Chloroquine also is taken up into the acidic food vacuoles of the parasite in the erythrocyte. It increases the pH of the acid vesicles, interfering with vesicle functions and possibly inhibiting phospholipid metabolism. In suppressive treatment, chloroquine inhibits the erythrocytic stage of development of plasmodia. In acute attacks of malaria, chloroquine interrupts erythrocytic schizogony of the parasite. Its ability to concentrate in parasitized erythrocytes may account for its selective toxicity against the erythrocytic stages of plasmodial infection.

In vitro studies with trophozoites of *Entamoeba histolytica* have demonstrated that chloroquine also possesses amebicidal activity comparable to that of emetine.

PHARMACOKINETICS

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration and peak plasma concentrations of the drug are generally attained within 1-2 hours. Chloroquine



is widely distributed into body tissues such as the eyes, heart, kidneys, liver and lungs, where retention is prolonged. Concentrations are two to five times higher in erythrocytes than in plasma. Very low concentrations are found in intestinal wall. Chloroquine crosses the placenta and is distributed into breast milk.

Approximately 55% of the drug in the plasma is bound to plasma proteins. It is metabolised in the liver to active de-ethylated metabolites. Principal metabolite is desethylchloroquine. The plasma half life of chloroquine in healthy individuals is generally reported to be 72-120 hours.

Chloroquine is eliminated by renal route. 42 to 47% of chloroquine is excreted unchanged in the urine; 7 to 12% desethylchloroquine is excreted in urine. Chloroquine is excreted very slowly and may persist in urine for months or years after medication is discontinued. Urine acidification increases renal excretion by 20 to 90%.

Hemodialysis increases the clearance of chloroquine; however, due to chloroquine's large volume of distribution, hemodialysis may not remove appreciable amounts in an overdose.

INDICATIONS

Treatment of acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*.

Chemoprophylaxis in non-immune individuals at risk.

Chloroquine does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exoerythrocytic forms of the parasite.

The drug is also indicated for the treatment of extraintestinal amebiasis.

CONTRAINDICATIONS

Hypersensitivity to 4-aminoquinoline compounds or to any of its derivatives.

Retinal or visual field changes attributable to the drug or any other etiology.

History of epilepsy.

Psoriasis

WARNINGS

In recent years it has been found that certain strains of *P. falciparum* have become resistant to 4-aminoquinoline compounds (including chloroquine and hydroxychloroquine). Treatment with quinine or other specific forms of therapy is therefore advised for patients infected with a resistant strains of parasites.

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy. Retinopathy has been reported to be dose related.

When prolonged therapy with any antimalarial compound is contemplated, initial (base line) and periodic ophthalmologic examinations (including visual acuity, expert slit-lamp, fundoscopic, and visual field tests) should be performed.

If there is any indication (past or present) of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress even after cessation of therapy.

All patients on long-term therapy with this drug should be questioned and examined periodically, including testing knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug.

A number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 g or 1 g chloroquine phosphate in one 3-year-old child). Patients should be strongly warned to keep this drug out of the reach of children because they are especially sensitive to the 4-aminoquinoline compounds.

Use of chloroquine in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated. The drug should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the potential risks.

PRECAUTIONS

Risk benefit should be considered when the following medical problems exist:

1. Chloroquine may cause blood dyscrasias, including agranulocytosis, aplastic anemia, neutropenia, or thrombocytopenia. Discontinuance of the drug should be considered, if any severe blood severe blood disorder appears which is not attributable to the disease under treatment. Complete blood cell counts should be made periodically if patients are given prolonged therapy.

2. Chloroquine may cause hemolytic anemia in G6PD deficient patients, although this is unlikely when chloroquine is given in therapeutic doses. The drug should be administered with caution to patients having G6PD deficiency.

3 . Because chloroquine may concentrate in the liver, the drug should be used with caution in patients with hepatic function impairment, alcoholism and in patients receiving other hepatotoxic drugs.

4 . Chloroquine may cause corneal opacities, keratopathy or retinopathy. Although chloroquine may have a temporary effect on visual accommodation during short term treatment, irreversible retinal damage may occur with prolonged treatment. Therefore, patients should be advised to discontinue the medication and seek immediate medical advice if they notice any deterioration in their vision, which persists for more than 48 hours.

5 . Caution is advised in cases of porphyria, renal disease, severe gastrointestinal and neurological disorders and in patients with myasthenia gravis.

6 . Chloroquine has a temporary effect on visual accommodation and patients should be warned that they should not drive or operate machinery if they are affected.

Usage in pregnancy and lactation

There are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women. Usage of chloroquine during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the potential risk to the fetus.

However, chloroquine has been used for treatment of malaria in pregnant women without evidence of adverse effects on the fetus and the WHO and most clinicians state that the benefits of chloroquine therapy in pregnant women suffering from malaria outweigh the potential risks of the drug to the fetus.

Small amounts of chloroquine and desethylchloroquine are distributed into breast milk. Because of the potential for serious adverse effects from chloroquine in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the woman.

Usage in paediatrics

Children are especially sensitive to the 4-aminoquinoline compounds. Fatalities following accidental ingestion of relatively small doses and sudden deaths from parenteral chloroquine have been recorded. Do not exceed a single dose of 5mg base/Kg of chloroquine HCl in infants or children.

Patients should be strongly warned to keep this drug out of the reach of children because they are especially sensitive to the 4-aminoquinoline compounds.

A number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 g or 1 g chloroquine phosphate in one 3-year-old child).

Fatalities have been reported following the ingestion of as little as 300mg chloroquine base in a 12-month old child.

Children are extremely susceptible to overdosage of parenteral chloroquine. Severe reactions and sudden death have been reported following parenteral administration of chloroquine in children. If chloroquine hydrochloride injection is given intravenously in pediatric patients, it should be diluted and administered very slowly by intravenous infusion. Oral therapy is preferred and should be initiated as soon as possible.

Usage in geriatrics

Appropriate studies on the relationship of age to the effects of chloroquine have not been performed in the geriatric population. However, no geriatrics specific problems have been documented to date. Providing renal function is normal, no special precautions are required.

Drug interactions

Caution is advised in patients receiving anticoagulant therapy.

Concomitant administration of chloroquine at recommended dosages for malaria suppression or chemoprophylaxis during preexposure prophylaxis of rabies with intradermally administered rabies vaccine (human diploid-cell rabies vaccine, HDCV) may interfere with the antibody response to the vaccine and result in decreased mean serum titers of rabies antibody. It is recommended that HDCV be administered IM, not intradermally in patients who are receiving chloroquine for malaria prophylaxis.

In vitro and in vivo data show that antacids or kaolin reduce the systemic availability of oral chloroquine. It has been suggested that the administration of chloroquine and antacid preparations or kaolin should be separated by about 4h.

Chloroquine antagonizes the effect of neostigmine and pyridostigmine. Cimetidine inhibits the metabolism of chloroquine, resulting in increased plasma concentration.

In healthy subjects, ampicillin bioavailability was significantly reduced by co-administration of chloroquine.

Administration of ampicillin at least 2 hours after chloroquine is recommended.

Concurrent use with mefloquine may increase the risk of seizures.

There is an increased risk of inducing ventricular arrhythmias if chloroquine is given together with halofantrine or other arrhythmogenic drugs such as amiodarone.

ADVERSE EFFECTS

Ocular reactions : Irreversible retinal damage in patients receiving long-term or high-dosage 4-aminoquinoline therapy; visual disturbances (blurring of vision and difficulty of focusing or accommodation); nyctalopia; scotomatous vision with field defects of paracentral, pericentral ring types, and typically temporal scotomas, e.g., difficulty in reading with words tending to disappear, seeing half an object, misty vision, and fog before the eyes.

Ophthalmological examination should always be carried out before and regularly (3-6 monthly intervals) during treatment. Retinal damage is particularly likely to occur if treatment has been given for longer than one year or if the total dosage has exceeded 1.6g/Kg bodyweight. Although these precautions are more applicable when chloroquine is used as disease modifying antirheumatic agent in rheumatoid arthritis, these precautions also apply to patients receiving chloroquine continuously at weekly intervals as a prophylactic against malarial attack for more than three years.

Neuromuscular reactions : Convulsive seizures

Auditory reactions : Nerve type deafness; tinnitus, reduced hearing in patients with preexisting auditory damage.

Gastrointestinal system : Anorexia, nausea, vomiting, diarrhea, abdominal cramps.

Dermatologic reactions : Pleomorphic skin eruptions, skin and mucosal pigmentary changes; lichen planus-like eruptions, pruritus and hair loss

CNS reactions : Mild and transient headache, psychic stimulation, fatigue, nervousness, anxiety, apathy, irritability, agitation, aggressiveness, confusion, personality changes, depression.

Cardiovascular reactions : Rarely, hypotension, electrocardiographic change, cardiomyopathy

Otic effects : Rarely ototoxicity, tinnitus, reduced hearing, nerve deafness after prolonged therapy

Hematologic effects : Neutropenia, agranulocytosis, aplastic anemia and thrombocytopenia.

Others : Allergic and anaphylactic reactions, peripheral neuritis, neuromyopathy, changes in liver function including hepatitis and abnormal liver function tests occurs rarely.

DOSAGE AND ADMINISTRATION

Children and adults for whom the use of chloroquine is indicated, should receive a full treatment dose of 25 mg of chloroquine base per kg given over 3 days. The pharmacokinetically superior regimen consists of 10 mg of base per kg followed by 5 mg/kg 6-8 h later and 5 mg/kg on each of the following 2 days.

A more practical regimen used in many areas consists of 10 mg/kg on the first and second days and 5 mg/kg on the third. Both these regimens provide a total dose of 25 mg/kg (e.g. 1 500 mg of base for a 60-kg adult).

There is no evidence to suggest that increasing the dosage will increase the clinical cure rate in such situations and repeated administration of such high doses may produce adverse reactions. GI upsets may be avoided by administering the dose after a meal.

Recommended chemoprophylaxis

5 mg of base per kg weekly in a single dose, or 10 mg of base per kg weekly, divided into 6 daily doses.

Extraintestinal Amebiasis

Adults, 1 g (600 mg base) daily for two days, followed by 500 mg (300 mg base) daily for at least two to three weeks. Treatment is usually combined with an effective intestinal amebicide.

OVERDOSAGE

Symptoms : Toxic doses of chloroquine can be fatal. As little as 1 g may be fatal in children. Toxic symptoms can occur within minutes. These consist of headache, drowsiness, visual disturbances, nausea and vomiting, cardiovascular collapse, shock and convulsions followed by sudden and early respiratory and cardiac arrest. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

Treatment : Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital) or gastric lavage until the stomach is completely

emptied.

Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultra short-acting barbiturate may be tried but, if due to anoxia, it should be corrected by oxygen administration and artificial respiration. Monitor ECG. In shock with hypotension, a potent vasopressor should be administered. Replace fluids and electrolytes as needed. Cardiac compressing or pacing may be indicated to sustain the circulation. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, may also be necessary. Peritoneal dialysis and exchange transfusions have also been suggested to reduce the level of the drug in the blood.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least six hours. Fluids may be forced, and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine to help promote urinary excretion in cases of both overdosage or sensitivity.

Storage

Store in cool dry dark place.

Presentation

Lariago Tablets - 25 x 10's

Lariago DS Tablets - 20 x 5's

Lariago Suspension - Bottle of 60ml

Lariago Injection - 25 x 5ml , 100 x 2ml , 30 x 30ml

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