

Quinine Sulfate Tablets and Quinine Dihydrochloride Injection
QINARSOL

COMPOSITION

QINARSOL-300 Tablets

Each tablet contains:

Quinine Sulfate 300 mg

QINARSOL Injection 1 ml

Each ml contains:

Quinine Dihydrochloride 300 mg/ml

QINARSOL Injection 2 ml

Each ml contains:

Quinine Dihydrochloride 300 mg/ml

DOSAGE FORM/S

Oral tablet and solution for intravenous (I.V.)/intramuscular (I.M.) administration

DESCRIPTION

Quinine, an alkaloid obtained from the bark of the cinchona tree, and which is also the levorotatory isomer of quinidine, is an antimalarial agent. Its chemical formula is 6'-methoxycinchonan-9-ol and its molecular formula is $C_{20}H_{24}N_2O_2 \cdot H_2O$

PHARMACOLOGY

Pharmacodynamics

Quinine is a blood schizonticidal agent and is active against the asexual erythrocytic forms of *Plasmodium (P.) falciparum*, *P. malariae*, *P. ovale* and *P. vivax*. The drug is not active against sporozoites or pre-erythrocytic or exoerythrocytic forms of plasmodia. Quinine is also gametocytocidal for *P. malariae* and *P. vivax*, but has no direct activity against the gametocytes of *P. falciparum*

The precise mechanism of the antimalarial activity of quinine is not completely understood. It is thought that pH elevation in the intracellular organelles of the parasites by quinine plays a role in the mechanism. The drug appears to interfere with the function of plasmodial DNA.

Because quinine is active only against the asexual erythrocytic forms of plasmodia, the drug cannot prevent delayed primary attacks or relapse of *P. ovale* or *P. vivax* malaria and cannot provide a radical cure in malaria caused by these species since they have exoerythrocytic stages. Therefore, primaquine phosphate may be indicated in conjunction with quinine if the drug is used for the treatment of *P. vivax* malaria.

Pharmacokinetics

Absorption

Quinine is readily absorbed orally, mainly from the upper small intestine. Bioavailability is approximately 80% in healthy subjects. Absorption is almost complete, even in patients with marked diarrhea. Quinine is ~70–85% protein-bound.

Distribution

Quinine is widely distributed into body tissues. Small amounts of the drug are distributed into bile and saliva.

Metabolism and Elimination

The cinchona alkaloids are primarily metabolized in the liver and 5% is excreted unaltered in the urine. There is no accumulation in the body upon continued administration.

The plasma elimination half-life of quinine reportedly averages 8–21 hours in adults with malaria and 7–12 hours in healthy or convalescing adults. In children, 1 to 12 years of age, the plasma elimination half-life of quinine reportedly averages 11–12 hours in those with malaria and 6 hours in those convalescing from the disease.

Quinine is extensively metabolized, mainly in the liver (>80%). The metabolites are excreted in the urine, mainly as hydroxy derivatives; small amounts also appear in the feces, gastric juice, bile and saliva. Renal excretion of quinine is twice as rapid when the urine is acidic as when it is alkaline; greater tubular re-absorption of the alkaloidal base occurs in an alkaline medium.

The pharmacokinetics of quinine is affected by malarial infection, with the volume of distribution and systemic clearance decreasing. Also, protein binding increases to >90% in patients with cerebral malaria, in pregnant patients and in children.

INDICATIONS

Quinine is indicated for the treatment of chloroquine-resistant falciparum malaria, either alone, with pyrimethamine and a sulfonamide, or with a tetracycline. It is also considered alternative therapy for chloroquine-sensitive strains of *P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax*.

DOSAGE AND ADMINISTRATION

Quinine can be given by the oral, I.V. or I.M. routes.

Quinine should be given orally for the treatment of uncomplicated multidrug-resistant falciparum malaria and to complete the treatment of patients with severe or complicated malaria who have been initially treated parenterally. If part or all of a dose is vomited within 1 hour, the same amount must be re-administered immediately. It is administered parenterally to patients with severe or complicated malaria who cannot take drugs by mouth because of coma, convulsions or vomiting.

Areas where parasites are sensitive to quinine: Quinine, 8 mg of base per kg three times daily for 7 days.

Areas where parasites are sensitive to both sulfa drug-pyrimethamine and quinine, and where adherence may be a problem: Quinine, 8 mg of base per kg three times daily for 3 days plus Sulfadoxine 1500 mg or Sulfalene 1500 mg plus pyrimethamine 75 mg given on the first day of quinine treatment.

Areas with marked decrease in susceptibility of *P. falciparum* to quinine: Quinine 8 mg of base per kg three times daily for 7 days plus doxycycline 100 mg of salt daily for 7 days (not in children below 8 years of age and not during pregnancy); a pharmacologically superior regimen would include a loading dose of 200 mg of doxycycline followed by 100 mg daily for 6 days. Or tetracycline 250 mg four times daily for 7 days (not in children below 8 years of age and not in pregnancy). Or clindamycin 300 mg four times daily for 5 days (not contraindicated in children and pregnancy).

Intravenous administration: An initial dose of 16.4 mg (equivalent to 20 mg of dihydrochloride)/kg is infused over 4 hours followed by 8.2 mg (equivalent to 10 mg of dihydrochloride)/kg every 8 hours in adults and every 12 hours in children. The initial dose should be halved if the patient has received quinine, quinidine or mefloquine during the previous 12–24 hours. The maintenance dose should be reduced threefold in patients with impaired renal function.

Where facilities for I.V. infusion do not exist, quinine I.M. can be administered in the same dosage. The required dose should be divided equally between two sites, one in each anterior thigh. Whenever parenteral quinine is used, oral treatment should be resumed as soon as the patient is able to take it, and continued for the completion of the course.

CONTRAINDICATIONS

Quinine is contraindicated in patients with hypersensitivity to quinine, in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, optic neuritis, tinnitus, a history of black water fever and thrombocytopenic purpura (associated with previous quinine ingestion), and during pregnancy.

Because thrombocytopenic purpura may occur during therapy with quinine in highly sensitive patients, a history of this adverse hematologic effect with previous administration of quinine is also a contraindication for the use of the drug.

WARNINGS AND PRECAUTIONS

Cinchonism

Repeated doses or overdose of quinine may precipitate cinchonism. The mildest symptoms include tinnitus, headache and nausea, and slightly disturbed vision, all of which usually subside rapidly upon discontinuation of the drug. When quinine is continued, or after large single doses, symptoms also involve the gastrointestinal (GI) tract, the nervous and cardiovascular systems and the skin.

Patients should be warned to discontinue the drug and contact a physician if tinnitus, hearing loss, rash or visual disturbance occurs during quinine therapy.

Tinnitus and Impaired Hearing

These may occur at plasma quinine concentrations >10 mcg/ml, a level not normally attained with quinine 260 to 520 mg/day. In a hypersensitive patient, as little as 300 mg may produce tinnitus.

Hemolysis (with the potential for hemolytic anemia)

This has been associated with G-6-PD deficiency in patients taking quinine. Stop therapy immediately if hemolysis appears.

Cardiac Disease

Use with caution in patients with cardiac arrhythmias; quinine has quinidine-like activity. In patients with atrial fibrillation, quinine use requires the same precautions as those for quinidine. May cause cardiotoxicity. Rapid I.V. administration of quinine dihydrochloride has resulted in severe hypotension, arrhythmias and acute circulatory failure.

Hypersensitivity Reactions

Discontinue quinine if there is any evidence of hypersensitivity. Cutaneous flushing, pruritus, skin rashes, fever, gastric distress, dyspnea, ringing in the ears and visual impairment may occur, particularly with only small doses of quinine. Extreme flushing of the skin accompanied by intense, generalized pruritus is most common. Hemoglobinuria and asthma are idiosyncratic.

Others

Quinine should be avoided in patients with myasthenia gravis as it may aggravate their condition.

It is important that when quinine I.V. is given, it should be given by slow infusion and the patient observed closely for signs of cardiotoxicity.

Blood glucose concentrations should also be monitored. Both the disease itself and the administration of quinine may promote insulin secretion and induce hypoglycemia.

Drug Interactions

Antacids: Aluminum-containing antacids may delay or decrease the absorption of concurrent quinine. Cimetidine may reduce quinine's oral clearance and increase its elimination half-life.

Mefloquine: Quinine and mefloquine are both quinoline methanols and have similar cardiac adverse effects; consequently, there has been concern about the potentially additive toxicity from the combination. Do not use mefloquine concurrently with quinine. If these agents are to be used in the initial treatment of severe malaria, delay mefloquine administration by >12 hours after the last dose of quinine. Electrocardiogram (ECG) abnormalities or cardiac arrest may occur. The risk of convulsions may also be increased with co-administration.

Rifamycins: These potent inducers of hepatic microsomal enzymes increase the hepatic clearance of quinine. Enzyme induction can persist for several days following discontinuation of the rifamycins.

Urinary alkalinizers: If administered concurrently with quinine, these may increase quinine blood levels and can be potentially toxic.

Warfarin: Quinine may depress the hepatic enzyme system that synthesizes the vitamin K-dependent clotting factors and, thus, may enhance the action of warfarin and other oral anticoagulants.

Digoxin: Digoxin serum concentrations may be increased by concurrent quinine. Monitor digoxin levels periodically.

Neuromuscular blocking agents: Quinine may potentiate the effects of neuromuscular blocking agents, particularly pancuronium, succinylcholine and tubocurarine, which may result in respiratory difficulties.

Antihistamines: Increases in plasma concentrations of astemizole and its desmethyl metabolite occurred in patients receiving astemizole concomitantly with food products containing quinine (e.g., tonic water). But, such increases were small and were not associated with clinically or statistically significant prolongation of the QT interval when consumption was limited to approximately 1 liter of tonic water a day (about 80 mg of quinine sulfate).

Although interactions between terfenadine and quinine have not been reported to date, concerns have existed that terfenadine may interact with quinine in a similar fashion to astemizole since both antihistamines undergo metabolism via hepatic microsomal enzymes and have been reported to produce similar cardiac effects.

Cinchona alkaloids: Cinchona alkaloids, including quinine, reportedly may depress the hepatic synthesis of vitamin-K dependent coagulation factors and the resulting hypoprothrombinemic effect may enhance the caution of warfarin and other oral anticoagulants.

There is an increased risk of inducing ventricular arrhythmias if quinine is given together with halofantrine or other arrhythmogenic drugs such as amiodarone, cisapride and the antipsychotic, pimozide.

Hypoglycemic drugs: As quinine stimulates the release of insulin from islet cells, diabetic control may be compromised.

Renal Impairment

The maintenance dose should be reduced threefold in patients with impaired renal function.

Hepatic Impairment

Quinine is extensively metabolized, mainly in the liver (>80%); hence, hepatic dysfunction can reduce quinine clearance.

Pregnancy

If the drug is administered during pregnancy or if the woman becomes pregnant while receiving the drug, she should be informed of the potential hazard to the fetus. Quinine can cause fetal harm when administered to pregnant women. Stillbirths, in which there was no obvious cause for the fetal deaths, have been reported in mothers receiving quinine. Quinine has caused congenital malformations in humans when used in large doses (up to 30 g) for attempted abortion. Deafness related to auditory nerve hypoplasia was reported in about half of these cases; limb anomalies, visceral defects, and visual changes have also been reported.

Quinine should not be withheld during pregnancy, despite its alleged abortifacient properties at a high dosage, since it safeguards the life of the mother.

Attention should be given to the considerable risk of hypoglycemia in pregnant women with severe malaria.

Lactation

Because quinine is distributed into human milk, the drug should be used with caution in nursing mothers.

Pediatrics

Antimalarial studies performed to date have shown that children have a decreased elimination half-life and volume of distribution; however, pediatrics-specific problems that would limit the usefulness of quinine in children have not been documented.

Geriatric Use

Quinine is negatively inotropic and may exacerbate heart failure. The drug also has important adverse drug interactions, which are more likely in the elderly, who often take several drugs concurrently. Neither of these considerations should interfere with the use of quinine for severe malaria.

UNDESIRABLE EFFECTS

Cardiovascular: Anginal symptoms, conduction disturbances, ventricular tachycardia, severe hypotension, arrhythmias and acute circulatory failure.

Central nervous system (CNS): Tinnitus, deafness, vertigo, headache, fever, apprehension, restlessness, confusion, syncope, excitement, delirium, hypothermia, convulsions, dizziness.

GI: Nausea, vomiting, epigastric pain, hepatitis, GI disturbance.

Hematologic: Acute hemolysis, hemolytic anemia, thrombocytopenic purpura, agranulocytosis, hypoprothrombinemia.

Hypersensitivity: Cutaneous rashes (urticarial, papular, scarlatinal), pruritus, flushing, sweating, facial edema, asthmatic symptoms.

Ophthalmic: Visual disturbances (including disturbed color vision and perception), photophobia, blurred vision with scotomata, night blindness, amblyopia, diplopia, diminished visual fields, mydriasis, and optic atrophy.

Miscellaneous: Cinchonism, vasculitis, hypoglycemia, lichenoid photosensitivity, granulomatous hepatitis, hepatocellular cholestatic hepatotoxicity, and renal failure associated with coagulopathy and quinine-dependent antibodies.

I.M. injections of quinine can be an irritant and have caused pain, focal necrosis and abscess formation; tetanus has developed in some patients.

OVERDOSAGE

Symptoms

The more common signs and symptoms are tinnitus, dizziness, skin rash and GI disturbance (intestinal cramping). With higher doses, cardiovascular and CNS effects may occur, including headache, fever, vomiting, apprehension, confusion, and convulsions.

Fatalities with quinine have occurred from single oral doses of 2 to 8 g; a single fatality reported with a dose of 1.5 g may reflect an idiosyncratic effect. Several cases of blindness following large overdoses of quinine, with partial recovery of vision in each instance, have been reported.

Treatment

Employ gastric lavage or induce emesis. Support blood pressure and maintain renal function; provide mechanical ventilation if needed. Use sedatives, oxygen and other supportive measures as necessary. Maintain fluid and electrolyte balance with I.V. fluids.

Urinary acidification will promote the renal excretion of quinine; however, in the presence of hemoglobinuria, acidification of the urine may augment renal blockade. Quinine is readily dialyzable by hemodialysis or hemoperfusion.

Angioedema or asthma may require epinephrine, corticosteroids or antihistamines. In the acute phase of toxic amaurosis caused by quinine, I.V. vasodilators may have a salutary effect. A stellate block also has been used effectively for quinine-associated blindness. Residual visual impairment occasionally yields to vasodilators.

STORAGE AND HANDLING INSTRUCTIONS

Protect from light

PACKAGING INFORMATION

QINARSOL-300 Tablets

Strip pack of 10 tablets

QINARSOL Injection 1 ml

Pack of 10 ampoules

QINARSOL Injection 2 ml

Pack of 10 ampoules

Last updated: September 2010