

Data Sheet

Quinine Dihydrochloride Injection 60 mg/ml

Presentation

Quinine Dihydrochloride Injection 60 mg/ml is a clear, straw-coloured solution in 10 ml glass ampoules. The product contains no preservatives, has been sterilised by autoclaving and must be diluted for infusion.

Uses

Actions

Quinine is a rapidly acting blood schizontocide. The exact mechanism of action of quinine in malaria is uncertain, but its actions appear to interfere with the function of plasmodial DNA. It inhibits protein synthesis by preventing strand separation and therefore DNA replication and transcription to RNA. No lethal effect is exerted on sporozoites or pre-erythrocytic tissue forms. It is gametocytocidal for *P. vivax* and *P. malariae* and is active against the asexual erythrocytic forms of *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*.

CNS:

Quinine has slight analgesic and antipyretic activity. It has indifferent action on fevers except malarial fever.

Cardiovascular:

The central actions of quinine and its isomer quinidine on cardiac muscle are qualitatively similar. However normal therapeutic doses have small effect on normal cardiovascular systems. Toxic doses may cause myocardial depression and vasodilatation.

Smooth muscle:

Quinine has a slight oxytocic action on the gravid uterus. The spleen may contract by action on the musculature of its capsule, thus producing a lymphocytosis.

Skeletal muscle

Quinine has a dual action on skeletal muscle. It acts directly on muscle fibres, increasing the tension response and refractory period. It can have a curare-like effect on skeletal muscle.

Pharmacokinetics

This is significantly altered by malarial infection, the major effect being reduction in both its apparent volumes of distribution and its clearance. Quinine is metabolised in the liver and rapidly excreted mainly in the urine. Excretion is increased in acid urine and decreased in alkaline urine. Plasma protein binding is about 70 % in healthy subjects and rises to about 90 % or more in patients with malaria. The elimination half life in healthy patients is 11 hours but may be prolonged in patients with malaria. This suggests that during malaria there is impaired hepatic metabolism of quinine.

Indications

Quinine dihydrochloride is indicated for the acute treatment of malaria. It may also be used in the treatment of Babesiosis in conjunction with clindamycin.

Dosage and administration

Whenever possible, patients should be transferred to oral therapy as soon as possible. For intramuscular use, refer Warnings and Precautions

Intravenous Infusion:

Adults

The following doses may be used as a guideline. Quinine Dihydrochloride Injection must be diluted in 500 ml sodium chloride infusion 0.9 % or glucose infusion 5 % (usually 600 mg in 500 ml) and infused slowly over 4 hours.

A loading dose of 20 mg/kg up to a maximum of 1400 mg is given slowly by infusion over 4 hours. Commence the maintenance doses 8 - 12 hours after the loading dose. A loading dose is not required if anti-malarials have been given during the previous 24 hours.

A maintenance dose of 10 mg/kg up to a maximum of 700 mg over 4 hours is given slowly by infusion. Repeat every 8 - 12 hours if necessary. If parenteral therapy is required for longer than 48 hours, the maximum dose of quinine should be reduced by one-third to one-half to 5 mg/kg to avoid accumulation and drug level monitoring is important. (Refer precautions.)

Alternatively, in intensive care units only, an initial loading dose of 7 mg/kg may be given over 30 minutes followed immediately by the first of the maintenance doses.

Paediatric

Intravenous - 10 mg/kg diluted and infused slowly at a rate not exceeding 0.5 mg/minute, preferably with ECG monitoring.

Contraindications

Quinine dihydrochloride injection is contraindicated in the following:

- Hypersensitivity to quinine or quinidine
- Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency
- History of Blackwater Fever
- Patients with tinnitus or optic neuritis
- The presence of haemolysis or concurrent anticoagulant therapy

Warnings and precautions

Check for hypersensitivity to quinine or quinidine before administration. It is important that when given intravenously it should be given by slow infusion and the patient observed closely for signs of cardiotoxicity. All patients receiving quinine should receive cardiac monitoring. Pulse and blood pressure should be closely monitored and the rate of infusion attenuated if dysrhythmias occur, and blood glucose concentrations should be monitored. Therapy should be changed to oral administration as soon as possible.

Intramuscular use not recommended

If intravenous administration is not possible, quinine dihydrochloride has been given intramuscularly. This can be an irritant, cause pain, focal necrosis and abscess formation. Fatal tetanus has developed in some patients and there have been concerns regarding its safety and efficacy. The intramuscular route should only be used as a last resort.

Haemolysis

Quinine dihydrochloride should be stopped immediately and supportive measures instituted if signs of haemolysis appear. Haemolysis with a potential for haemolytic anaemia has been reported when given to patients with G-6-PD deficiency.

Prothrombin formation

Quinine dihydrochloride is capable of causing hypoprothrombinaemia and may enhance the effect of anticoagulants.

Atrial fibrillation

Patients with this condition should be digitalised before receiving quinine as it may otherwise cause an increase in the ventricular rate.

Hypersensitivity

Reactions include cutaneous flushing, pruritis, rash, fever, facial oedema, GI distress, dyspnoea, tinnitus and vision impairment. The most frequently reported hypersensitivity reaction is extreme flushing of the skin with intense pruritis. If evidence of hypersensitivity occurs, quinine therapy should be discontinued.

Liver Disease

The half-life of quinine is prolonged in moderate chronic liver disease.

Diabetes

Quinine has the potential to cause refractory hypoglycaemia, especially when used in combination with sulphonylureas.

Pregnancy and Lactation

In pregnancy, the risks associated with the use of quinine should be balanced against the risks posed by the malarial infection. In cases of life threatening malaria, the risk of quinine use may be considered acceptable. In high doses, quinine causes foetal injuries in the form of deafness, development disturbances and malformations of the extremities and cranium. It has the ability to cause uterine contractions and constitutes a risk of abortion. Listed as Category D drug in 4th edition of *Prescribing medicines in pregnancy*.

Quinine is excreted in breast milk in small concentrations and caution should be exercised during breastfeeding.

Driving and Using Machinery

Quinine is likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

Adverse effects

Cinchonism

When quinine is given repeatedly, a group of symptoms known as cinchonism occurs. Cinchonism symptoms include tinnitus, impaired hearing, headache, nausea, disturbed vision, vomiting, abdominal pain, diarrhoea and vertigo.

Haematological effects

Haematological effects include acute haemolysis, thrombocytopenic purpura (which may be fatal), agranulocytosis and hypoprothrombinaemia.

CNS effects

CNS effects include visual disturbances, blurred vision with scotomata, photophobia, diplopia, mydriasis, constricted visual fields, night-blindness and disturbed colour perception. In severe cases optic atrophy may result in blindness. Tinnitus, vertigo, deafness, headache, confusion and syncope.

Dermatological effects

Dermatological effects include rashes, urticaria, pruritis, flushing of the skin, facial oedema and photosensitivity.

Asthma

Treatment may precipitate asthma.

Cardiac effects

Disturbances in cardiac rhythm on conduction, widening of the QRS complex, hypotension, ventricular tachycardia, angio-oedema, and angina symptoms in sensitive patients. Severe or even fatal cardiotoxicity can result from rapid IV administration if quinine.

Gastrointestinal effects

Gastrointestinal effects include nausea, vomiting and epigastric pain.

Myasthenia effects

Treatment may aggravate myasthenia gravis.

Other effects

Other adverse effects may include hepatotoxicity, anuria, uraemia haemoglobinuria (rare) and aggravation of hypoglycaemia

Interactions

Urinary alkalinisers such as acetazolamide, and sodium bicarbonate increase blood quinine levels by decreasing renal clearance of quinine.

Urinary acidifiers such as ammonium chloride and some other drugs that decrease the pH of urine, increase the excretion of quinine, resulting in lower blood levels.

Cimetidine may reduce clearance of quinine if taken concurrently.

Digoxin serum levels and effects may increase if taken concurrently with quinine. Serum digoxin concentrations should be monitored and dosage adjustments made when necessary.

Hypoprothrombinaemic effects may be increased when quinine is used with warfarin, coumarin or indanedione derivatives.

Anti-malarials such as pyrimethamine may displace quinine from protein binding sites resulting in excessive free quinine levels and possible toxicity.

The following neuromuscular agents are known or thought to interact with quinine causing respiratory difficulties: pancuronium bromide, atracurium besylate, suxamethonium chloride, mivacurium chloride, pipecuronium bromide, rapacuronium bromide, alcuronium chloride, cisatracurium besylate, doxacurium chloride, gallamine triethiodide, metocurine iodide, decamethonium bromide or biiodatum, rocuronium bromide, vecuronium chloride and tubocurarine chloride.

Agents that enhance neuromuscular blocking drugs must be monitored if used concurrently with quinine. These drugs include:

- antiarrhythmics (lignocaine, procainamide, quinidine, nifedipine and verapamil),
- anticholinesterases (neostigmine and edrophonium),
- diuretics (frusemide and mannitol)
- antibacterials (some antibacterials in high concentrations may produce a muscle paralysis, which may be additive to or synergistic with that produced by neuromuscular blockers. This may be enhanced in patients with intracellular potassium deficiency or low plasma calcium concentration following large doses or renal impairment. The agents most commonly implicated are aminoglycosides, lincosamides, polymixins, vancomycin and rarely, tetracyclines. These should be used with care with quinine or monitored very closely.
- Ganglion blockers, including trimetaphan.
- General anaesthetics (Dose dependent enhancement by inhalation anaesthetics especially with competitive blockers. The greatest potentiation is from isoflurane, enflurane, desflurane and sevoflurane followed by halothane and cyclopropane.)
- Magnesium salts if given parenterally.
- Sympathomimetics (IV salbutamol has been reported to enhance the blockade obtained with pancuronium and vecuronium.
- Others, including antimyasthenics, haemolytics, neurotoxic medication, mefloquine, lithium and quinidine.

The use of quinine in combination with mefloquine is not recommended due to an increased risk of cardiac arrhythmias.

Quinine and chloroquine may be antagonistic when used together in falciparum malaria.

Overdosage

Contact the Poisons Information Centre, Dunedin School of Medicine, University of Otago, P O Box 90134, Dunedin 9054. Telephone 0800 764 766 (24 hours, 7 days).

Pharmaceutical precautions

Store between 15 - 30 °C. Protect from light. Use immediately after opening and discard unused portion

Medicine Classification

Prescription Medicine.

Package quantities

Product is packed in 10 ml ampoules containing 600 mg quinine dihydrochloride (60 mg/ml) sold individually.

Name and Address

Biomed Limited
52 Carrington Road
Point Chevalier
Auckland

Date of preparation

25 March 2009