

Quinine

Quinine is the chief alkaloid of cinchona, the powdered bark of the South American cinchona tree. Cinchona contains a mixture of more than 20 structurally related alkaloids, with the most important being quinine and quinidine. Both compounds are classed as quinolones and are still obtained from natural sources.

Use

The labeled indication for quinine (Qualaquin®) as set by the FDA is to treat uncomplicated malaria caused by the parasite *Plasmodium falciparum*. Lexi-Drugs states a very similar indication which is, the treatment of uncomplicated chloroquine-resistant *P.falciparum* malaria, in conjunction with other antimalarial agents. Although quinine has been the mainstay for treatment of this type of malaria, other antimalarials are beginning to replace its use because of increasing resistance of *P.falciparum* to quinine, as well as the drug's toxicity.

In severe malarial illness a loading dose of IV quinine can be imperative. Then oral medication can be given to maintain blood levels. For multi-drug resistant strains, sulfonamide or a tetracycline are given concurrently to enhance the efficacy of quinine.

An unlabeled use of quinine that Lexi-Drugs states is in the treatment of *Babesia microti* infection (a deer-tick transmitted infection) in conjunction with clindamycin.

A common unlabeled use of quinine that is not approved and strongly discouraged by the FDA is in the treatment or prevention of leg cramps, including nocturnal and dialysis-associated leg cramps. Quinine's use in the treatment of leg cramps is very controversial. The FDA warns of serious side effects or even death that can occur when the drug is used for this purpose.

Pharmacokinetics

Absorption: Quinine is readily absorbed when given orally or intramuscularly. The oral bioavailability is 76-88% in healthy adults and absorption mainly occurs from the upper small intestine. Quinine's exposure is higher in patients with malaria than in healthy subjects. In the FDA prescribing information it states that after a single oral dose of quinine sulfate, the mean T_{max} was longer, and the mean AUC and C_{max} were higher in patients with uncomplicated *P.falciparum* malaria than in healthy subjects. Most pharmacokinetic parameters are unaffected when the drug is administered with food.

Distribution: After an oral dose, plasma levels reach a maximum in 3 to 8 hours depending on the severity of the infection. The apparent volume of distribution in healthy individuals is 1.5 L/kg and the Vd of those with a malarial infection ranges from 2.5-7.1 L/kg depending on the severity of the infection. Quinine is moderately protein-bound in the blood in healthy subjects, ranging from 69 to 92%. But during a malarial infection, levels of α_1 -acid glycoprotein increase which corresponds to a lower Vd, with levels of plasma protein bound drug ranging from 78-95%. Intra-erythrocytic levels of quinine are approximately 30-50% of the plasma concentration. Quinine poorly enters the CSF but does enter the breast milk.

Metabolism: Quinine is extensively metabolized by the hepatic CYP3A4 enzymes. Only about 20% of an administered dose is excreted unaltered in the urine. There is no accumulation of the drug in the body on continued administration. However, if a patient has renal failure, a metabolite of quinine can accumulate and cause toxicity.

Elimination/Excretion: As mentioned above quinine is mostly eliminated via hepatic metabolism but 20% is excreted unchanged in the urine. Quinine is reabsorbed if the urine is alkaline so renal excretion is twice as rapid when the urine is acidic. The half-life of quinine can increase from 9.7 to 12.5 hours depending on the severity of the infection and the plasma clearance of the drug also ranges depending on the health of the patient. The mean clearance values are 0.08-0.47 L/h/kg, with clearance decreasing with an increase in infection severity.

Mechanism of Action

The precise mechanism of the anti-malarial activity of quinine sulfate is not completely understood. It is believed to depress oxygen uptake and carbohydrate metabolism and intercalate into DNA, which disrupts the parasite's replication and transcription. It acts primarily on erythrocytic forms and has little effect on hepatic forms of malarial parasites.

The textbook, *Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 11e*, accessed through AccessPharmacy describes the mechanism by which quinine acts on skeletal muscle. It is thought to increase the tension response to a single maximal stimulus delivered to muscle directly or through nerves, but it also increases the refractory period of muscle so that the response to tetanic stimulation is diminished. The excitability of the motor end-plate region decreases so that responses to repetitive nerve stimulation and to acetylcholine are reduced. Thus, quinine can antagonize the actions of physostigmine on skeletal muscle and may produce alarming respiratory distress and dysphagia in patients with myasthenia gravis.

Quinine reduces the magnitude or severity of muscle cramps but does not reduce the frequency with which cramps occur.

Side Effects

Quinine has a wide variety of side effects. The most commonly published side effect is cinchonism. Symptoms of mild cinchonism include:

- Headache
- Vasodilation (flushing)
- Sweating
- Nausea
- Tinnitus
- Hearing impairment
- Vertigo or dizziness
- Blurred vision

More severe symptoms of cinchonism include:

- Vomiting
- Diarrhea
- Abdominal pain
- Deafness
- Blindness

Most symptoms of cinchonism are reversible and resolve with discontinuation of quinine, but severe symptoms can persist for months. The visual and auditory effects are probably the result of direct neurotoxicity, although secondary vascular changes may have a role.

More serious side effects of quinine include hypoglycemia, which is more common in pregnancy and hematologic abnormalities. Hypoglycemia and hyperinsulinemia occur due to quinine's powerful stimulatory effect on pancreatic beta cells. Hematological abnormalities include hemolytic uremic syndrome- thrombotic thrombocytopenia purpura, disseminated intravascular coagulation and bleeding diathesis.

Quinine rarely causes cardiovascular complications unless therapeutic plasma concentrations are exceeded. Complications include hypotension and even fatal cardiac dysrhythmias.

Contraindications

- Hypersensitivity to quinine or to mefloquine or quinidine (cross-sensitivity reported)
- Appears to be fairly safe in pregnancy, but caution must be used to monitor the elevated risk of hypoglycemia
- Heart rhythm problems (QT prolongation) or an abnormal ECG
- G6PD deficiency (an enzyme which removes oxidative substances which can build up while taking anti-malarials)
- Optic neuritis
- Myasthenia gravis
- History of potential hypersensitivity reactions associated with prior quinine use

Drug-Drug Interactions

- Absorption of quinine from the gastrointestinal tract can be delayed by antacids containing aluminum
- Quinine can delay the absorption of elevate plasma levels of digoxin and related cardiac glycosides as well as warfarin and its related anticoagulants
- Quinine will enhance the effect of neuromuscular blocking agents and oppose the action of acetylcholinesterase inhibitors

Works Cited

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