THE NORTHERN HOSPITAL

QUININE

Cinchona Trees

Flowering Cinchona Trees, Columbia

Nineteenth century collection of Cinchona Tree bark, Manchester Herbarium Museum

QUININE

Introduction

Quinine was the first effective treatment for malaria.

Remarkably it still remains an effective agent today, where its prime indication is as a second line option for the treatment malaria including the potentially life-threatening *P. falciparum* malaria.

Both oral and IV preparations are available.

Quinine has potential for significant toxicity, including cardiac conduction disturbances, hypersensitivity reactions and drug accumulation.

Cardiac monitoring is necessary for patients receiving **IV** therapy.

Acute intentional overdose of quinine can be lethal

See also separate document:

- **Quinine overdose (cinchonism) (in Toxicology folder).**

Expert advice should always be sought when prescribing quinine, especially in cases of IV therapy.

History

The first effective antimalarial agent

Quinine from the bark of the cinchona trees was utilized by South America tribes people for many centuries.

Portuguese and Spanish conquistadors took the bark back to Europe in the Seventeenth century to provide the old world with the first effective cure for malaria.

It was first used to treat malaria in Rome in 1631.

Gin and Tonic

Quinine is also used as a **flavouring agent** for tonic water and bitter lemon.

In the days of the British Raj, British colonials found the bitter taste of their antimalarial quinine tonic hard to stomach.

Instead they would mix this tonic with gin to increase palatability, which was the origin of the now famous "**gin and tonic**" cocktail.

Chemical synthesis

Cinchona trees remain the best economically practical source of quinine.

The first synthetic organic dye, mauveine, was discovered by William Henry Perkin in 1856 while he was attempting to synthesize quinine.

With the vastly increased demand for antimalarial agents during the Second World War, chemical synthesis of quinine was finally achieved by the American chemists R.B. Woodward and W.E. Doering in 1944.

Quinine and nocturnal leg cramps

In the past quinine was extensively used to treat *nocturnal leg cramps* in the elderly, however due to its toxicity and the non-serious nature of nocturnal leg cramps the FDA (US Food and Drug Administration) banned the marketing of over the counter quinine as a treatment for nocturnal leg cramps in 1994.

Chemistry

Quinine is an **isomer** of the historical antiarrhythmic agent **quinidine**

Preparations

Tablets:

Two oral preparations are available:

- Quinine sulfate: 300 mg tablets.
- Quinine **bi**sulfate: 300 mg tablets.

Quinine sulfate 600 mg is approximately equivalent to quinine bisulfate 900 mg.

Ampoules:

- Quinine dihydrochloride:

Mechanism of Action

The precise mechanism of action of quinine with regard to its antimalarial activity is not known:

Possible mechanisms include: [2]

- Quinine may inhibit plasmodial haem polymerase causing haem to accumulate (which is toxic to plasmodium membranes)

- Interference with plasmodium DNA or RNA synthesis
- Increases intravacuolar pH.

Pharmacodynamics

The clinical effects of quinine include

1. **Antimalarial action**
    - **This is quinine's current therapeutic use.**
2. Mild antipyretic
3. Mild anti-inflammatory activity.
4. Cardiac effects:
    - Quinine acts in a similar qualitative manner on cardiac muscle as does its **isomer quinidine**, the antiarrhythmic drug.
    - However, therapeutic doses of quinine have little or no effect on the normal cardiovascular system in humans.
5. Anaesthetic action:
    - Quinine has a slight local anaesthetic activity.

      The anaesthesia may last for many hours or days.
6. Mild smooth muscle stimulation:
    - Quinine has a mild oxytocic effect on the uterus.
    - Quinine may also cause the smooth muscle in the spleen to contract producing lymphocytosis, sometimes observed after therapeutic doses of the drug.

Pharmacokinetics

Absorption:

- Quinine can be given orally or IV

  Oral absorption is good.

  Plasma concentrations after single oral doses are approximately the same as after comparable intravenous doses.

Peak plasma concentrations occur within 1 -3 hours after a single **oral** dose

Distribution

- Vd is 1.2-2.7 L / kg.
- Quinine sulfate is around 70% bound to plasma proteins.
- Quinine can cross the human placenta.
- Quinine is excreted into human breast milk

Metabolism and excretion:

- Metabolism occurs predominantly largely in the liver.

  The inactive metabolites are excreted mainly in the urine.
- Less than 5% is excreted unaltered in the urine.
- After cessation of quinine therapy, the plasma level falls rapidly, and only a negligible concentration is present after 24 hours.

  No accumulation in body tissues occurs with continued administration.

Indications

Quinine is a second line option for the treatment malaria including the potentially life-threatening *P. falciparum* malaria.

Mortality from severe *P. falciparum* malaria is lower with IV artesunate (an artemisinin derivative) than it is with IV quinine. However, emerging **artemisinin resistance** has been described in some areas of Asia

Although the impact of artemisinin resistance on the efficacy of IV artesunate in severe malaria is not yet known, combination therapy with IV artesunate plus IV quinine may be required and **expert advice should always be sought.**

Note that, as for all antimicrobial agents, the prevalence of microorganism resistance may vary geographically and over time for selected species and so local information on resistance is also important, particularly when treating severe infections.

Contra-indications/precautions

These include:

1. Allergy to quinine or quinidine

    - Quinidine cross reactivity can occur but it uncommon.

2. Patients with risk factors for prolonged QT interval:

    - Quinine may prolong the QT interval and increase the risk of arrhythmia; correct risk factors and use with caution.

3. Patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.

4. Pregnancy (relative - see below).

5. **Excessive** quantities of quinine containing beverages while taking quinine tablets may increase the risk of adverse reactions and toxicity.

6. Quinine may worsen the following pre-existing conditions:

    - Optic neuritis

    - Tinnitus

    - Myasthenia gravis.

Pregnancy

Quinine is classified as a **class D drug** with respect to pregnancy.

Class D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Although the Australian Therapeutic Goods Administration (TGA) lists quinine as category D in pregnancy, quinine has in fact been used extensively in pregnant women to treat life-threatening *P. falciparum* malaria based on risk versus benefit assessments. Specialist advice should be sought. [1]

From the limited information available, maternal use of quinine at the recommended doses has not been associated with an increased risk of major congenital malformations or adverse pregnancy outcomes.

However, optic nerve damage and auditory defects have occurred when quinine has been used at toxic doses as an abortifacient.

Therefore, consider an alternative medicine during pregnancy if possible.

If quinine is the medicine of choice, it should not be withheld during pregnancy and dose adjustments are not required.

As adverse effects such as hypoglycaemia, hypotension and haemolytic anaemia may be observed, follow-up and monitoring of both maternal and fetal wellbeing is recommended.

Consultation with an Infectious Diseases Specialist or Clinical Microbiologist for further advice is also recommended.

Breast feeding

Small amounts of quinine are excreted into breast milk, but these amounts are unlikely to pose harm to the breastfed infant .

Quinine is considered safe to use during breastfeeding.

However, consider an alternative medicine when treating women who are breastfeeding infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as there is a risk of haemolysis in these infants.

Adverse Effects

1. GIT upset:

    - With oral use GIT upset can occur
    - Quinine is also very bitter to taste.

2. **Cinchonism:**

    - Hypersensitivity or drug accumulation may lead to a toxic syndrome known as **cinchonism**, with cardiac, and retinal toxicity and tinnitus.

      See separate document on quinine overdose (cinchonism) (in Toxicology folder).

3. Cardiac:

    - Quinine like its closely related isomer quinidine, is a Class 1a antiarrhythmic agent and as such is a blocker of fast sodium channels resulting in prolongation of both the QRS and QT intervals on the 12 lead ECG.

      Quinine may cause therefore cause conduction disturbances, hypotension and arrhythmias (similar effects to the toxic effects of quinidine).

4 Dermatological:

- Urticaria type reactions may be seen.

5. Hypoglycaemia:

   - **IV** quinine stimulates insulin secretion and can lead to hypoglycaemia

6. Haematological effects:

   Principally:

   - Thrombocytopenia
   - Haemolytic uraemic syndrome with acute renal failure

7. Glucose-6-phosphate dehydrogenase deficiency:

   - Haemolytic anaemia, in patients with glucose-6-phosphate dehydrogenase deficiency.

Dosing

Uncomplicated malaria:

For uncomplicated malaria, for the following can be used: [1]

- Quinine sulfate 600 mg (adult less than 50 kg: 450 mg) orally, 8 hourly for 7 days

  Child: 10 mg/kg up to 600 mg

Plus

- Either oral doxycycline or clindamycin.

See latest Antibiotic Therapeutic Guidelines for full prescribing details and other options.

Severe/ life-threatening malaria:

Expert advice should always be sought when prescribing IV quinine.

In general terms:

For severe /threatening malaria, **IV** quinine can be used as a second line alternative to **IV artesunate.** [1]

- Quinine dihydrochloride (adult and child) **20 mg / kg IV** over **4 hours** as a loading dose (to a maximum of **1.4 grams**). [2]

  The infusion should preferably be given in **glucose 5%** to reduce hypoglycaemia, although sodium chloride 0.9% may be used.

Followed by:

- **10 mg / kg IV over 4 hours** (starting **4 hours after the loading dose is completed**), **8 hourly** until oral therapy is tolerated.

The IV **loading dose of quinine** is not required if the patient has received:

- 3 or more doses of quinine or quinidine in the last 48 hours
- Mefloquine prophylaxis in the last 24 hours
- A treatment dose of mefloquine in the last 3 days.

For patients receiving **IV** quinine, measure blood pressure and blood glucose concentration frequently (because quinine stimulates insulin secretion and can cause hypoglycaemia).

Cardiac monitoring is also necessary.

If treatment with IV quinine continues for longer than 48 hours, dose adjustment may be necessary, especially in patients with renal impairment.

References

1. eTG - July 2017

    - Antibiotic Therapeutic Guidelines, 15th ed 2014.

2. Quinine in Australian Medicines Handbook, Accessed April 2015.

3. Quinine in MIMs, Website, 1 April 2011

4. Quinine in RWH Pregnancy & Breastfeeding Guidelines, 17 January 2017

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