

# Quinine sulphate

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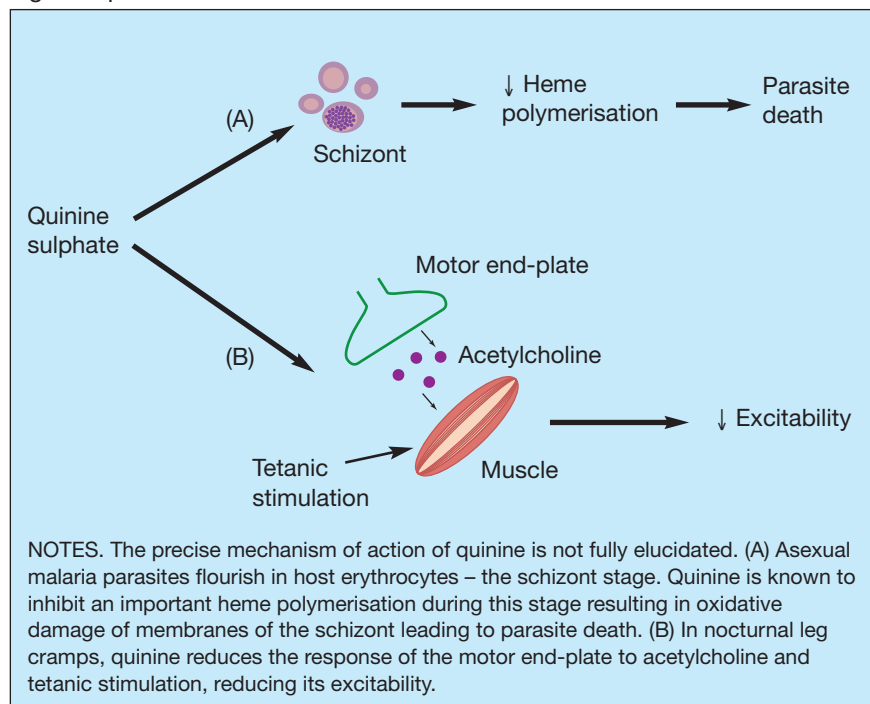
## Introduction

Quinine sulphate (quinine) was originally developed as an anti-malarial but has been used in the United Kingdom for many years as a treatment for nocturnal leg cramps. Muscle cramps are a common symptom, affecting patients with and without diabetes. A study of over 65-year-olds reported that 50% of outpatients complained of frequent nocturnal muscle cramps. Muscle cramps are defined as involuntary, generally painful contractions of a muscle or muscle group and can be frequent, severe and disabling. They are caused by ectopic discharges from nerves and – although thought to be exacerbated by metabolic disorders, neuropathic conditions, pregnancy, hypomagnesaemia, hypocalcaemia, hypothyroidism, renal and liver dysfunction – are most commonly caused by metabolic disorders. A number of drugs commonly used in diabetes such as lipid lowering agents, diuretics, beta-blockers and insulin are also thought to increase risk of cramps.

Patients with diabetic neuropathy can experience muscle cramps, along with other symptoms of pain and altered sensation. Symptoms of neuropathy in patients with diabetes are a therapeutic challenge and treatment often involves multiple therapies.

When, as is usually the case, the aetiology of nocturnal muscle cramps is unknown, treatment is symptomatic. Many non-pharmacological treatments including stretching, massage and walking have been tried with little evidence of benefit. Pharmacological treatments with calcium-channel blockers or vitamin E have been used but quinine has historically been the treatment of choice in the UK.

**Figure 1.** Proposed mechanism of action of quinine sulphate for malaria and leg cramps



## Pharmacology

Figure 1 outlines the proposed mechanism of action of quinine for malaria and leg cramps, although the precise mechanism has not been fully elucidated. It is a cinchona alkaloid, a 4-methanolquinoline anti-malarial with activity against malarial parasites. In the treatment of malaria it works in the schizont stage inhibiting an important heme polymerisation stage resulting in oxidative damage and parasite death. In nocturnal leg cramps, quinine reduces the response of the motor end-plate to acetylcholine and tetanic stimulation, reducing its excitability.

Quinine is 95% metabolised in the liver and has a half-life of around 10 hours.

Given in usual therapeutic doses quinine may give rise to a cluster of

symptoms known as cinchonism, characterised in its mild form by tinnitus, impaired hearing, headache, nausea, and disturbed vision, with, in its more severe manifestations, vomiting, abdominal pain, diarrhoea, and vertigo. Hypersensitivity reactions such as angio-oedema, flushing and dyspnoea can also occur.

It can produce cardiovascular toxicity similar to that seen with quinidine. Toxic effects include conduction disturbances, arrhythmias, anginal symptoms, and hypotension leading to cardiac arrest and circulatory failure. Cardiotoxicity after overdosage with quinine is well recognised, but prolongation of the QT interval has been noted with therapeutic doses. Additionally, overdose of quinine can result in reversible or irreversible visual disturbance.

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## Quinine sulphate

It is also recognised that quinine can induce hypoglycaemia. This is most commonly seen when quinine is used intravenously in the treatment of malaria, but there have been several case reports published of quinine-induced hypoglycaemia in patients on treatment for nocturnal leg cramps. This is clearly an issue for patients with diabetes on oral hypoglycaemic agents or insulin as quinine can potentiate the hypoglycaemic effects of these drugs by stimulating endogenous insulin release.

There are also important drug interactions which may affect patients with diabetes and cardiovascular complications, including the inhibition of the renal excretion of digoxin and the potentiation of the anticoagulant effect of warfarin.

### Trials of safety and efficacy

There has been uncertainty regarding the efficacy of quinine as a treatment for nocturnal leg cramps for some time. Several studies have attempted to clarify this, but these have generally been small and the results are non-conclusive.

A systematic review in 1995, including eight randomised, double-blinded, placebo-controlled trials and 659 ambulatory patients who regularly suffered leg cramps, meta-analysed individual patient data and found that quinine significantly reduced the frequency of nocturnal leg cramps compared with placebo over a four-week period. The actual reduction for quinine vs placebo was 8.83 cramps per month (CI 4.16–13.49 cramps/month) and relative reduction 0.21. The severity and duration of cramps when they did occur were not affected. Serious side effects were uncommon in the trials reviewed, but it was felt the treatment periods were not long enough to exclude long-term complications. It was concluded that quinine is more effective than placebo in reducing nocturnal leg cramps in ambulatory patients but that, because of the risk of serious side effects, a therapeutic trial with close monitoring of the benefits and side effects should be carried out for at least four weeks when being considered as a treatment option.<sup>1</sup>

A further review including unpublished data showed that, although quinine was efficacious in the treatment of leg cramps, the actual benefit was smaller than in the published data. The reduction in the number of cramps was 3.6 per month (CI 2.15–5.05 cramps/month), thus highlighting a publication bias for the use of quinine for this indication.<sup>2</sup>

Alternative, non-pharmacological treatments of leg cramps have also been studied. A total of 191 patients prescribed quinine for nocturnal leg cramps were randomised to one of four groups based to two 'advice factors': undertake stretching exercise and stop quinine. After six weeks all patients were told they could resume taking quinine. After 12 weeks, there was no difference in the reported number of leg cramps, symptom burden or severity of cramps. It was concluded that calf-stretching is not effective in reducing leg cramps. Evidence for the efficacy of massage is also lacking but, because of the lack of side effects, it is recommended that non-pharmacological treatments are first line.<sup>3</sup>

There are no randomised controlled trials assessing the optimal dose or length of treatment for quinine, and there are no trials specifically looking at the safety and efficacy of quinine in patients with diabetes.

### Discussion

Quinine has traditionally been used for the treatment of nocturnal leg cramps, in the absence of effective alternative therapies. However, concerns about its efficacy and potential side effects have led to a Food and Drug Administration (FDA) ruling in America that quinine should no longer be used in the treatment of nocturnal leg cramps. A review of reports submitted to the FDA's Adverse Event Reporting System, from 2005–2008, found 38 cases of serious adverse events associated with quinine. The majority of patients (25) took quinine to prevent or treat leg cramps. A similar ban has been imposed in Australia.

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### Key points

- Quinine sulphate reduces the frequency of nocturnal leg cramps but the severity and duration of cramps are not affected
- There are serious side effects associated with quinine; hypoglycaemia and cardiovascular effects are particularly of note and relevant for patients with diabetes
- The MRHA has issued advice that quinine should not be used routinely in the management of nocturnal leg cramps

Regulatory Agency (MRHA) in the UK stated that quinine should not be used as a routine treatment for nocturnal leg cramps. Quinine should only be considered when cramps cause regular disruption of sleep and when cramps are very painful or frequent. Treatable causes of cramps should be excluded and non-pharmacological measures tried before quinine is considered. When quinine is commenced, it is recommended that patients be monitored closely for adverse events in the early stages of treatment and that treatment should be stopped after four weeks if there is no benefit. When quinine is effective, treatment should be interrupted approximately every three months to reassess the benefit.<sup>4</sup>

### Acknowledgement

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### Conflict of interest statement

There are no conflicts of interest.

### References

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