Antiepileptic properties of quinine: A systematic review

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Review objective
The review objective is to synthesize the best available research evidence on the effects of quinine on seizures in adults or children who present with seizures or who develop seizures in the course of treatment.

Review question
Does quinine have antiepileptic properties?

Background
Quinine was originally used by Peruvians to treat fever. ¹ It was found to have specific antimalarial properties and has been in use for more than three centuries to treat severe malaria before the introduction of the artemisinins to malaria endemic areas. Quinine has antipyretic, analgesic and anti-inflammatory properties and has been used to treat arthritis, systemic lupus erythematosus (SLE) and nocturnal leg cramps.²⁻⁴ It is a stereoisomer of quinidine and although it has been used to treat ventricular arrhythmias⁵, its toxicity has limited its widespread use for this indication. Quinine causes cinchonism, which manifests as tinnitus, impaired hearing (particularly high-frequency hearing loss), blurred vision, headache, confusion, vertigo, dizziness and dysphoria.⁶⁻⁷ These neurological symptoms suggest that it has direct interaction with the nervous system.

Research in animal models suggests that quinine may have antiepileptic properties⁸⁻¹². Thus, Nassiri¹¹ found that quinine reduced seizure latency and duration and Gajda¹⁰ showed that it reduced expression of seizure discharges but did not influence basic electrocortical activity. Both Bikson⁸ and Bostanci⁹ found that quinine reduced epileptic activity but Bostanci further suggests that this may be a dose-dependent effect. This action is thought to be mediated through blockade of connexin 36, a gap junction channel.
expressed in mammalian neurons\textsuperscript{13}. Gap junction coupling provides a second pathway, besides chemical synapses, contributing to seizure generation and propagation\textsuperscript{10,11}. Quinine is thought to bind an intracellular receptor involved in mediating this action\textsuperscript{13}, which is postulated to prevent seizure spread in abnormally synchronous neurons. However, the structure of the receptor and how it mediates this action is still unknown.

Other drugs used in the treatment of severe malaria, such as the artemisinins appear to have neuro-pathological effects mostly in the medulla and pons of animals\textsuperscript{14-18}. This is known to be a dose dependent effect\textsuperscript{15} and furthermore, the neurotoxic effect is observed more in oil based derivatives, such as artether\textsuperscript{16}. In vitro, artemisinin neurotoxicity does not manifest immediately upon exposure to the drugs however, the effect is inevitable\textsuperscript{19,20}. Mefloquine has also been found to be neurotoxic in rats by causing degeneration of nuclei in the brainstem of these animals but the effect of both these drugs on seizures in animal models has not been fully investigated\textsuperscript{21}.

In humans, the antiepileptic properties of quinine have not been systematically investigated. However, some of its derivatives have been known to cause seizures. Thus, chloroquine has been observed to cause seizures and is thought to reduce concentrations of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) by inhibiting the enzyme glutamate dehydrogenase\textsuperscript{22-24} while mefloquine has been reported to cause convulsions even in patients without risk for seizures\textsuperscript{24-27}. However, the exact mechanism for this effect remains unclear. The artemisinins are known to cause hearing loss, ataxia and tremors\textsuperscript{20} but not seizures.

Quinine is the mainstay of therapy in both South East Asia and Africa\textsuperscript{28} for falciparum malaria which affects the nervous system and is associated with acute seizures\textsuperscript{29}. In children and adults, seizures are a feature of cerebral malaria, the most severe neurological complication of malaria\textsuperscript{30}. On admission, more than 80% of children present with a history of seizures and in these more than 60% will have a recurrent episode\textsuperscript{31} with an increased risk for death and neurocognitive impairment\textsuperscript{32-34}. More than half of these seizures are partial motor, 23% are subtle manifesting as hypoventilation, nystagmus, salivation and eye deviation and status epilepticus is common\textsuperscript{35}. These subtle manifestations may go unnoticed with prolongation of seizures and this increases risk for neurological deficits\textsuperscript{36}. In adults, only 20% present with seizures of which generalized tonic-clonic type is most common with status epilepticus being rare.\textsuperscript{37,38}

If quinine has antiepileptic properties, it may reduce the neurological sequelae associated with acute seizures in severe malaria. These sequelae may be responsible for impairments in many children in malaria endemic areas and they have a huge socio-economic burden\textsuperscript{39}. Given the high cost of the artemisinin derivatives and the availability of quinine, this information may help in the choice of antimalarial drugs in resource poor settings.

We plan to conduct a systematic review of the literature in order to synthesize the best available evidence on the antiepileptic properties of quinine. We will consider studies in which quinine was compared to other drugs for any one of its known indications i.e. malaria, SLE, nocturnal leg cramps, arthritis and ventricular arrhythmias and that examine the effect of quinine on seizures. The outcome of interest will be seizure prevalence, defined as the proportion of patients with seizures after administration of drug.

This systematic review therefore intends to summarize the effectiveness of quinine on seizures in humans. A search of the major databases including Pubmed, CINAHL, Cochrane database of systematic
reviews and the JBI database of systematic reviews has shown that there are no published or in progress systematic reviews on this topic.

**Inclusion criteria**

**Types of participants**
This review will consider studies that include adults or children or both with malaria (uncomplicated or severe) as defined by the WHO, systemic lupus erythematosus as defined by the American college of rheumatology criteria, arthritis, nocturnal leg cramps or ventricular arrhythmia who presented with seizures or who developed seizures in the course of treatment. There will be no age limitation.

**Types of intervention**
We will consider studies that evaluate quinine in comparison to other drugs used for malaria, arthritis, nocturnal leg cramps, arrhythmia and systemic lupus erythematosus.

**Types of outcomes**
The primary outcome of interest for this review is the proportion of subjects who have seizures after the administration of quinine, compared with those who were not given quinine.

**Types of studies**
This review will consider clinical human studies, randomized controlled trials; in the absence of RCTs other clinical research designs, such as non-randomized controlled trials and before and after studies, will be considered for inclusion to enable the identification of current best evidence regarding the potential antiepileptic effects of quinine.

**Search strategy**
The search strategy aims to find both published and unpublished studies from 1966-2010 that are in English. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. The databases to be searched include:

a) PubMed  
b) CINAHL  
c) EMBASE  
d) Cochrane CENTRAL  
e) Web of Knowledge.

The search for unpublished studies will include:

a) BVS Virtual Library  
b) Mednar  
c) Proquest

*Initial keywords to be used will be:*
Malaria, nocturnal leg cramps, arthritis, systemic lupus erythematosus, arrhythmia  
Quinine, cinchona alkaloids
Randomized controlled trial, controlled clinical trial, clinical trial, comparison, trial

Assessment of methodological quality
Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers (CM and LM) will be resolved through discussion, or with a third reviewer (CN).

Data collection
Quantitative data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis
Quantitative papers will, where possible be pooled in statistical meta-analysis using the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). All results will be subject to double data entry. For each included trial, the proportion of patients with seizures in each trial arm will be compared. A Mantel-Haenszel odds ratio with 95% confidence intervals will then be calculated with statistical pooling of results. Heterogeneity will be assessed using the standard Chi-square. Where statistical pooling is not possible the findings will be presented in narrative form.

Conflicts of interest
There are no conflicts of interest.
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Appendix I - Appraisal instruments

MAStARI Appraisal instrument

**Assessment for: Name of Assessment**

**Type:** Primary  
**User:** Default  
**Design:** Randomised Control Tables / Psuedo-randomised Trial

| Criteria                                                                 | Yes | No | Unclear |
|-------------------------------------------------------------------------|-----|----|---------|
| 1) Was the assignment to treatment groups truly random?                 |     |    |         |
| 2) Were participants blinded to treatment allocation?                   |     |    |         |
| 3) Was allocation to treatment groups concealed from the allocator?     |     |    |         |
| 4) Were the outcomes of people who withdrew described and included in the analysis? |     |    |         |
| 5) Were those assessing outcomes blind to the treatment allocation?     |     |    |         |
| 6) Were the control and treatment groups comparable at entry?           |     |    |         |
| 7) Were groups treated identically other than for the named interventions? |     |    |         |
| 8) Were outcomes measured in the same way for all groups?               |     |    |         |
| 9) Were outcomes measured in a reliable way?                           |     |    |         |
| 10) Was appropriate statistical analysis used?                          |     |    |         |

**Include:** Yes  
**Reason:** 

[Update] [Cancel]
## Appendix II - Data extraction instruments

**MASTARI data extraction instrument**

| Extraction Details | Extraction Name | Randomised Control Tables / Pseudo-randomised Trial | Study Information |
|--------------------|-----------------|----------------------------------------------------|-------------------|
| Method             |                 |                                                    |                   |
| Setting            |                 |                                                    |                   |
| Participants       |                 |                                                    |                   |
| # Participants     | Group A:        | Group B:                                           |                   |
| Interventions      | Interventions A:|                                                    |                   |
|                    | Interventions B:|                                                    |                   |
| Authors            |                 |                                                    |                   |
| Conclusion         |                 |                                                    |                   |
| Reviewers          |                 |                                                    |                   |
| Comments           |                 |                                                    |                   |
| Complete           | No              | Yes                                                | Save Details      |