Antiepileptic properties of Quinine: A systematic review

Clifford Mwita,[1,2] Leah Mwai[1,2] and Charles Newton[1,3,4]

[1]Centre for Geographic Medicine Research (Coast), Kenya Medical Research Institute (KEMRI)/ Wellcome Trust Research Programme, [2]Joanna Briggs Institute Affiliate Center in Kenya, [3]Neurosciences Unit, Institute of Child Health, University College London, United Kingdom, [4]Departement of Psychiatry, University of Oxford, Oxford, United Kingdom

KEY WORDS

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Corresponding Author:

Clifford C. Mwita, MD
Tel : +254-41–522535
E-mail : cliffmwita@gmail.com

ABSTRACT

Background: Quinine has anti-epileptic properties in animals. However, in humans this has not been systematically investigated. **Purpose:** To examine the available research evidence on the effects of quinine on seizures in adults or children. **Methods**: We searched online databases for published and unpublished studies in any language from January 1966 to March 2011. We considered randomized controlled trials (RCTs) evaluating the use of quinine in comparison to other drugs in humans with malaria or other conditions, and that reported the prevalence of seizures. Random effects meta-analysis was used to pool effect estimates in order to determine the effect of quinine on the prevalence of seizures. **Results**: We identified six randomized controlled trials on severe malaria. Quinine was compared to the artemisinin derivatives in all trials. A total of 8,244 patients were included. In the meta-analysis, there was no significant effect of quinine on the prevalence of seizures when compared to the artemisinin derivatives (Odds ratio (OR) =0.90, 95% Confidence Interval (95%CI) =0.63-1.30). There was significant heterogeneity (I^2=66%, Chi-square=17.44, p=0.008). Subgroup analysis showed that quinine significantly reduced seizures when compared to artemether (OR = 0.66, 95%CI = 0.49−0.88) but when compared to artesunate, prevalence of seizures increased significantly (OR = 1.24, 95%CI = 1.05−1.47). **Conclusion**: There is no sufficient evidence to conclude that quinine has any antiepileptic properties in humans.

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Introduction

Quinine was originally used by Peruvians to treat fever.[1] It has been in use for more than three centuries to treat severe malaria before the introduction of the artemsinins in malaria endemic areas. It has antipyretic, analgesic and anti-inflammatory properties and has been used to treat arthritis, systemic lupus erythematosus (SLE) and nocturnal leg cramps.[2–4] Quinine causes cinchonism, which manifests as tinnitus, impaired hearing, blurred vision, headache, confusion, vertigo, dizziness and dysphoria.[5,6] These neurological symptoms suggest that it has direct interaction with the nervous system.

Research in animal models suggests that quinine may have antiepileptic properties.[7–11] In rodent models, it reduces seizure duration[10] and the expression of seizure discharges but does not influence basic electrocortical activity.[9] Studies on Wistar rats suggest that this may be a dose-dependent effect.[8] This antiepileptic property of quinine is thought to be mediated through blockade of connexin 36, a gap junction channel expressed in mammalian neurons, since quinine is thought to bind an intracellular receptor involved in mediating this action.[12] However, the structure of the receptor and how it mediates this action is still unknown.

In humans, quinine is the mainstay of therapy for falciparum malaria in both South East Asia and Africa.[13] In children and adults, seizures are a feature of cerebral malaria, the most severe neurological complication of falciparum malaria.[14] On admission, up to 80% of children and 20% of adults with falciparum malaria present with seizures with an increased risk for death and neuro-cognitive impairment.[15–18] Subtle seizure manifestations may go unnoticed with prolongation of seizures and this increases the risk for neurological deficits.[19]

The antiepileptic properties of quinine have not been systematically investigated in humans, even in the context of falciparum malaria treatment. If it has antiepileptic properties in humans, quinine may reduce the neurological damage associated with acute seizures in severe malaria, since seizures are associated with neurological sequelae in this condition and influence the choice of antimalarial drugs in treating severe falciparum malaria.

We conducted a systematic review of available literature to examine the evidence on the antiepileptic properties of quinine in humans. The outcome of interest was seizure prevalence.

Methods

This review examines the effect of quinine on seizures in adults or children who present with seizures or who develop seizures in the course of treatment.

Search strategy

The search strategy aimed to find both published and unpublished randomized controlled studies from 1966–2011 and that compared quinine to other drugs for malaria or non-malaria conditions. The review question was broken down into search terms as recommended by the National Health Service Centre for Reviews and Dissemination.[20]

A three-step search strategy was then used. An initial limited search of PubMed and CINAHL was 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 was then undertaken across all included databases. Third, the reference list of all identified reports and articles were searched for additional studies.

The following databases were searched systematically: PubMed, CINAHL, EMBASE, Cochrane Library (CENTRAL), and Web of Knowledge. The search for unpublished studies included: BVS Virtual Library, Proquest and Mednar.

The search strategy we used for Pubmed was:

((((((((((((((((((((malaria[MeSH Terms])) OR (falciparum malaria[MeSH Terms])) OR (cerebral malaria[MeSH Terms])) OR (malaria[Title/Abstract])) OR (severe malaria[Title/Abstract])) OR (falciparum malaria[Title/Abstract])) OR (cerebral malaria[Title/Abstract])) OR (lupus vasculitis, central nervous system[MeSH Terms])) OR (systemic lupus erythematosus[Title/Abstract])) OR (SLE[Title/Abstract])) OR (arthritis[MeSH Terms])) OR (arthritis[Title/Abstract])) OR (muscle cramps[MeSH Terms])) OR (nocturnal leg cramps[Title/Abstract])) OR (arrhythmias, cardiac[MeSH Terms])) OR (arrhythmia[Title/Abstract])) OR (ventricular arrhythmia[Title/Abstract]))) AND ((((quinine[MeSH Terms])) OR (cinchona alkaloids[MeSH Terms])) OR (quinine[Title/Abstract]))) AND ((((((((((((randomized controlled trial[MeSH Terms])) OR (clinical trial[MeSH Terms])) OR (randomized controlled trial[Publication Type])) OR (controlled clinical trial[Publication Type])) OR (clinical trial[Publication Type])) OR (multicenter study[Publication Type])) OR (randomized controlled trial[Title/Abstract])) OR (controlled clinical trial[Title/Abstract])) OR (clinical trial[Title/Abstract])) OR (multicenter study[Title/Abstract])) OR (comparison[Title/Abstract])) OR (trial[Title/Abstract]))

Inclusion and exclusion criteria

We included papers reporting randomized controlled trials of either adults or children or both that evaluated quinine in comparison to other drugs and that included seizure prevalence as an outcome measure. We excluded observational studies.

Assessment of methodological quality

The Joann Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) Critical appraisal tool[21] was used to assess methodological quality (risk of bias). This was assessed independently by two authors (CM and LM). Disagreements were resolved through discussion with the third author (CN).

Data collection

Data was extracted by one author (CM) using the standardised JBI data extraction tool[21] and transferred to a spreadsheet. CN and LM re-extracted data from a sample of included trials each. Any disagreements were resolved through discussion.

From each included trial, the following information was collected: author, year of study, study site, participants (age group, total number, number randomized to each trial arm), entry criteria, exclusion criteria, intervention (type, dose, route of administration, frequency) and outcome (total number having the event, number having the event in each trial arm).

Data synthesis

Statistical pooling of extracted results was done using Review Manager Software version 5.[22]

Meta-analysis was performed using a random effects model. Seizure prevalence was defined as the proportion of patients having seizures after commencement of treatment. This was compared in both arms (quinine and non-quinine) using Mantel-Haenszel odds ratio (OR) with 95% confidence interval (95%CI). Heterogeneity was tested using the chi-square test.

The protocol that guided this review is available, on request, from the review protocols section of the Joanna Briggs Institute website; http://www.joannabriggs.edu.au

Results

Study selection

Figure 1 depicts the study selection process. A total of 2,074 titles were considered. On reviewing titles and abstracts, 1,978 titles were excluded. Of the 96 studies that remained, 90 studies were later excluded because they did not report prevalence of seizures. Of these, 18 were on nocturnal leg cramps, 70 were on malaria and one each on arrhythmia and arthritis. The remaining six studies all met the inclusion criteria and were critically appraised using the JBI-MAStARI assessment tool and subsequently included in the review. No studies were excluded after critical appraisal.

Characteristics of included studies

All included studies were randomised controlled trials (RCT) on severe malaria published in English and conducted in South East Asia[23–26] or sub-Saharan Africa,[27,28] comparing quinine to artemisinin derivatives. Three RCTs recruited only children,[24,27–28] two recruited only adults[23-25] and one included both children and adults.[26] Mortality was the main outcome in all included studies and it was assessed by intention to treat analysis. None of these studies reported the type of seizures that were evaluated or the method of ascertainment of seizures i.e. electroencephalography or clinical observation.

In two RCTs, quinine was compared to artemether. In the first,[23] a total of 560 adults of age range 15–79 years with severe malaria were randomized to receive either quinine or artemether. In this study patients given artemether had

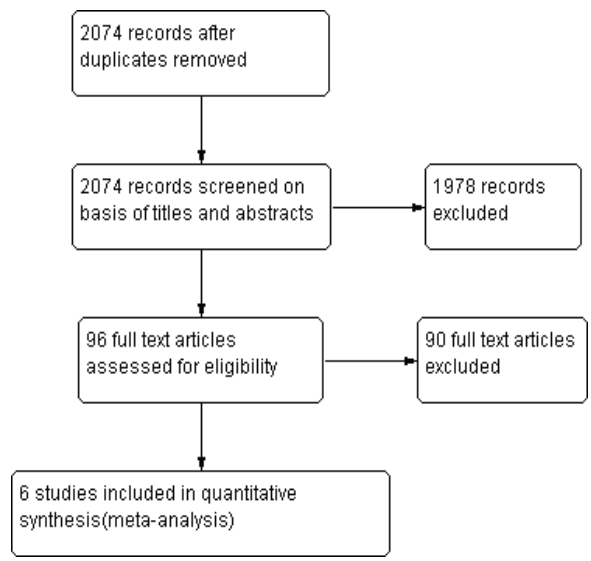

Fig. 1: Flow diagram of study selection

a higher risk for convulsions compared to those given quinine although this was not statistically significant (Relative risk (RR) 1.3 95%CI 0.8–2.1). The second RCT[27] involved children (n=576) with cerebral malaria. Mean age in the quinine group was 46 months and 48 months in the artemether group respectively. Significantly less children in the quinine group developed seizures than those in the artemether group (38.5% Vs 28.1%, p=0.01).

Three studies compared quinine to artesunate. In one study,[25] 113 adults of age range 15–66 years (median 25 years) were randomised with no difference between the two groups on prevalence of seizures (6 patients had convulsions in the artesunate group compared to 5 patients in the quinine group (p=1.0)). In another study,[26] both children and adults (n=1461) were recruited. Mean age was 27.9 years in both groups. Artesunate did not significantly reduce prevalence of seizures (OR 0.70 95%CI 0.44–1.12). The third study[28] was a large pragmatic trial involving only children (n=5425) from sub-Saharan Africa. Median age (Inter-quartile range) was 2.8 years (1.6–4.2) in the artesunate group and 2.9 years (1.7–4.3) in the quinine group. Prevalence of seizures after 6 hours of admission was 10.1% in the quinine group and 8.3% in the artesunate group (p=0.0199). One RCT[24] (n=109) had three arms involving quinine, artemisinin suppositories and artesunate. Median age was 5, 7 and 6 years respectively. 11% of the children in the artemisinin group developed convulsions, 8% in the artesunate group and 3% in the quinine group. Table 1 presents a summary of the characteristics of included studies.

Methodological quality of included studies

Assignment to treatment was random in four RCTs[23,26..28] with poor reporting of randomisation procedures in the remaining two studies.[24,25] Only one RCT was reported as being

Table 1: Characteristics of included studies

Author(year)	Study site	Participants	Entry criteria	Quinine	Other drug	No. of Participants; Proportion with seizures (A vs. B)
Hien (1996) [23]	Vietnam	Adults with severe malaria	Asexual forms of *P.falciparum* on blood slide age>14yrs	IM quinine 20mg/kg then 10mg/kg q8hrs	IM artemether 4mg/kg then 2mg/kg every 8hrs	560; 27/276 Vs 36/284
Van Hensbroek (1996)[27]	Gambia	Children with cerebral malaria	Children age 1–9yrs BCS<2 asexual forms of *P.falciparum* on thick blood film	IM quinine 20mg/kg initial dose then 10mg/kg q12hrs for 5d then oral quinine+SP	IM artemether 3.2mg/kg initial dose then 1.6mg/kg daily for 4d then oral quinine+Sulphadoxine-Pyrimethamine	576; 80/288 Vs 110/288
Phuong (1997)[a][24]	Vietnam	Children with severe malaria	Age <15yrs asexual forms of *P. falciparum* on blood film one of: coma, severe anaemia, hyperparasitemia, jaundice, hypolgycemia, spontaneous bleeding, shock, convulsions, renal impairment	IV quinine 20mg/kg loading dose over 4hrs then 10mg/kg every 8hrs to complete 7d of treatment. single dose SP on day 7	artemisinin suppositories 40mg/kg initially then 20mg/kg at 4,24,48 and 72hrs then mefloquine 15mg/kg at 96 hrs	109; 1/35 Vs 4/37
Phuong (1997)[b][24]	Vietnam	Children with severe malaria	Age <15yrs asexual forms of *P.falciparum* on blood film one of: coma, severe anemia, hyperparasitemia, jaundice, hypolgycemia, spontaneous bleeding, shock, convulsions, renal impairment	IV quinine 20mg/kg loading dose over 4hrs then 10mg/kg every 8hrs to complete 7d of treatment. single dose SP on day 7	IM artesunate 3mg/kg loading dose then 2mg/kg at 12,24,48, and 72h then oral mefloquine 15mg/kg at 96h	------- 1/35 Vs 3/37
Newton (2003)[25]	Thailand	Adults with severe malaria	Age >15yrs slide-confirmed, single-species falciparum parasitemia >0.1%	IV quinine 20mg/kg over 4h then 10mg/kg over 2h 3 times daily. when able to take orally, oral quinine 10mg/kg q8h with tetracylcine or doxycylcine	IV artesunate 2.4mg on entry, then 1.2mg/kg 12h later then 1.2mg/kg/day. when able to take orally, oral artesunate 12mg/kg with either tetracycline or doxycycline for total of 7d	113; 5/54 Vs 6/59

Dondorp (2005)[26]	Multicentre (Bangladesh, Burma, India, Indonesia)	Children and adults with severe malaria	Age >2yrs positive blood antigen stick test severe malaria according to admitting physician	IV quinine 20m/kg loading dose over 4hrs then 10mg/kg over 2-8hrs three times a day till able to take oraly then 10mg/kg every 8hrs for a total of 7 days	IV artesunate 2.4mg/kg on admission then at 12h,24h and once daily thereafter till able to take orally then 2mg/kg/day for a total of 7days	1461; 43/731 Vs 31/730
Dondorp (2010)[28]	Multicentre (Mozambique, Gambia, Ghana, Kenya, Tanzania, Nigeria,Uganda, Rwanda, DRC)	Children with severe malaria	Age younger <15yrs positive rapid diagnostic test severe malaria according to admitting physician's opinion fully informed consent	IV / IM quinine 20mg/kg loading dose over 4h then 10mg/kg over 2-8hrs three times daily till able to take orally then oral artemether lumefantrine in a full standard dose	IV / IM artesunate 2.4mg/kg on admission, at 12h, at 24h then once daily until able to take orally then oral artemether-lumefantrine in a full standard dose	5425; 273/2713 Vs 224/2712

[a,b] **The study by Phuong *et al* had three arms and was split into two (Phuong (1) and Phuong (2)) to enable comparison of quinine to the other drugs.**

Table 2: Methodological quality of included studies

Author (Year)	Randomization	Allocation Concealment	Blinding of participants and outcome assessors	Intention to treat analysis
Hien (1996)[23]	Adequate	Adequate	Adequate	Adequate
Van Hensbroek (1996)[27]	Adequate	Inadequate	Unclear	Adequate
Phuong (1997)[24]	Unclear	Unclear	Unclear	Unclear
Newton (2003)[25]	Unclear	Unclear	Inadequate	Adequate
Dondorp (2005)[26]	Adequate	Adequate	Unclear	Adequate
Dondorp (2010)[28]	Adequate	Adequate	Unclear	Adequate

double blind.[23] The other five were open label trials. Table 2 presents a summary of methodological quality of included studies. Overall, the studies were of good methodological quality.

Effect of quinine on seizures

Because all of the six included studies involved quinine in comparison to the artemisinin derivatives for severe malaria, we performed a meta-analysis in order to derive a pooled effect estimate of quinine on prevalence of seizures in comparison to these drugs. The RCT by Phuong *et al*.[24] had three arms and it was therefore split into two (Phuong(1) and Phuong(2)) so as to compare quinine to the other two drugs (artemisinin suppositories and artesunate) separately.

Overall, the trials randomised a total of 8,244 patients. In the pooled analysis quinine appeared to indicate reduction in incidence of seizure as compared to artemether. (OR=0.90, 95% CI=0.63–1.30). However it was similar to that of artesunate (I^2=66%, Chi-squared=17.44, p=0.008). Figure 2 shows a forest plot of included studies with individual study odds ratio as well as a pooled analysis of their results.

We performed a subgroup analysis in order to investigate the heterogeneity further. Studies in which quinine was compared to artemether[23,27] or artesunate[25–26,28] were pooled separately as were studies that compared adults or children. Subgroup analysis based on drug type reduced the previously observed heterogeneity (I^2=0%, Chi-squared=0.32, p=0.57 for quinine vs. artemether; I^2=0%, Chi-squared=2.56, p=0.46 for quinine vs. artesunate). Analysis based on age yielded higher heterogeneity (I^2=79%, Chi-squared=14.33, p=0.003).

When compared to artemether, quinine significantly reduced the prevalence of seizures (OR=0.66, 95%CI=0.49–0.88). A total of 1116 patients were randomised in this comparison. However, when quinine was compared to artesunate the effect was reversed and prevalence of seizures was significantly increased in the quinine group (OR=1.24, 95%CI=1.05–1.47) with a total of 7071 patients being randomised. Figures 3 and 4 show forest plots of studies comparing quinine to artemether and to artesunate with individual study odds ratio and pooled analysis.

Discussion

To the best of our knowledge, this is the first systematic examination on the antiepileptic properties of quinine in humans. We identified six randomized trials, all on patients with severe malaria. Each of the trials compared quinine to an artemisinin derivative and we therefore pooled the studies in a meta-analysis. We found that compared to the artemisinin derivatives,

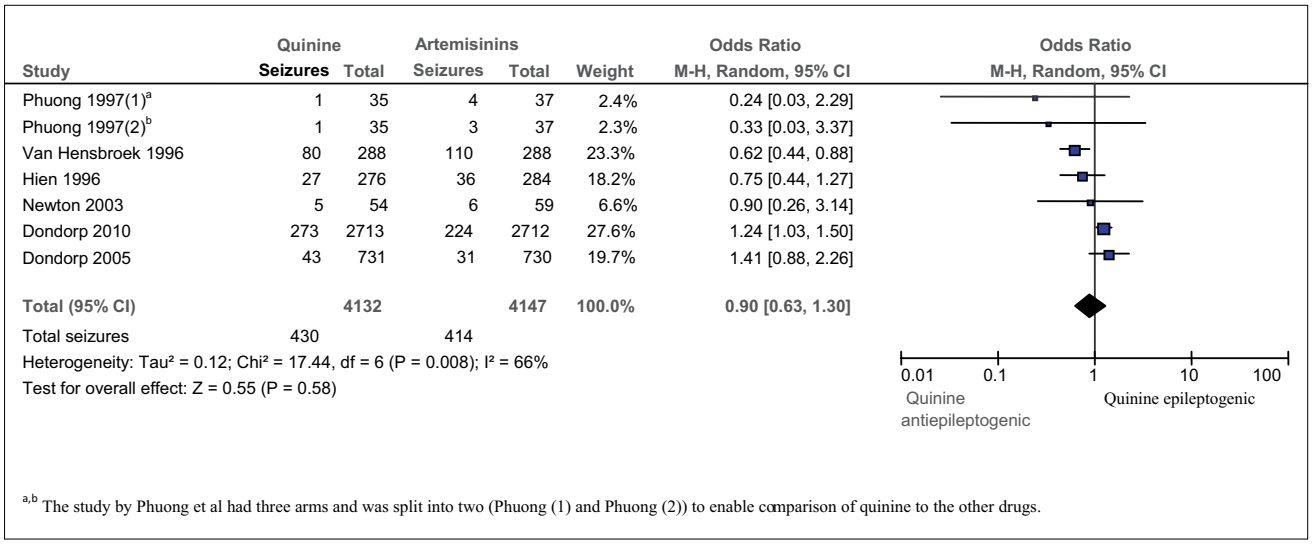

Fig. 2: Forest plot and Meta-analysis of all included studies.

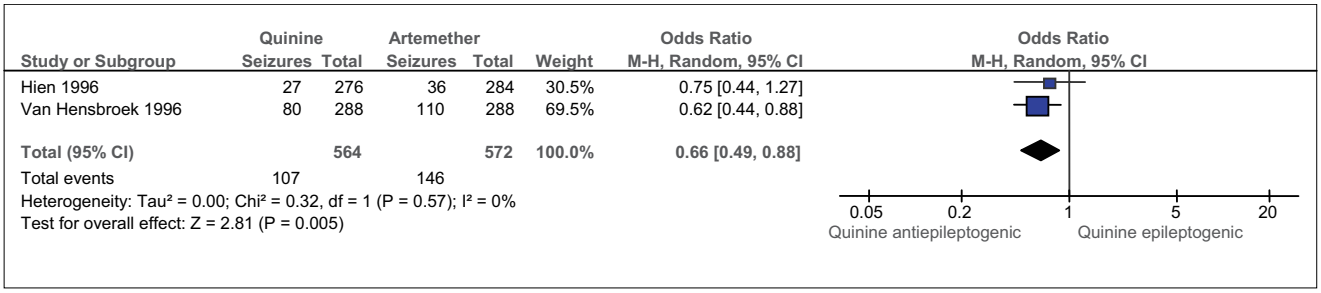

Fig. 3: Forest plot and Meta-analysis of studies comparing quinine to artemether.

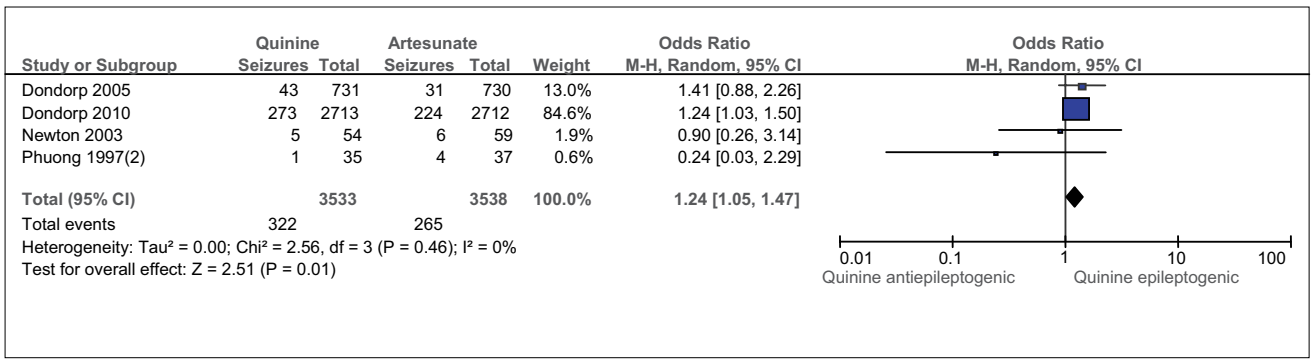

Fig. 4: Forest plot and Meta-analysis of studies comparing quinine to artesunate.

quinine does not significantly reduce the proportion of patients with seizures (OR=0.90 95%CI 0.63–1.30). The comparison showed significant heterogeneity (Chi-square=17.44, p=0.008) which on further investigation was due to the different drugs used in the included studies.

Two pooled studies in which a total of 1116 patients were randomised to receive either quinine or artemether showed that quinine had a statistically significant effect on seizures (odds ratio of 0.66). By contrast, four pooled studies that compared quinine to artesunate in which a total of 7071 patients were randomised showed an opposite effect (OR=1.24, 95%CI=1.05–1.47). Explanation of this discrepancy needs to take into consideration two confounding factors. First the artemisinins are known to be neurotoxic and so may increase seizures in both the artemether and artesunate groups and

reduced prevalence in the quinine group. Secondly, quinine clears parasites slower than the arteminisins.[29] Although our results suggest that there may be a difference between the anti-epileptic properties of artemether and artesunate, a recent randomised trial[30] comparing artemether to artesunate for severe malaria in Vietnamese adults showed no significant difference in seizure prevalence between the two groups. No similar studies have been reported from children.

In all of the included trials quinine was administered either intravenously or intramuscularly at a loading dose of 20 mg/kg and was later stepped down to 10 mg/kg. An oral formulation was then prescribed as soon as the patient was able to take medication orally. However, none of the studies monitored blood levels of quinine and it is possible that the doses of quinine used for malaria were insufficient to achieve the optimal blood levels required to control seizures. Higher doses of quinine may demonstrate its antiepileptic properties as observed in animals, but at the expense of increased toxicity.

We broadened our search as wide as possible in order to capture studies in which quinine was compared to drugs other than the artemisinins and in conditions other than malaria that may also present with seizures. However, the majority of identified studies did not report on the outcome of interest (prevalence of seizures) and therefore were excluded from the review. It is possible that data on this outcome were collected during the conduction of these studies but were not reported. This makes the review prone to publication bias. For those studies that reported on prevalence of seizures none reported how the seizures were detected or the type of seizures that were evaluated. Thus, it is difficult to determine whether or not quinine is effective for a specific type of seizure.

We were unable to assess seizure incidence in the review because it was not reported as an outcome in any of the included studies. Further, none of the studies reported on variables that may help in the calculation of incidence of seizures as an outcome. While quinine may not reduce the proportion of patients with seizures it may have an effect on the occurrence and possibly the duration of seizure episodes in humans. These attributes may be of clinical benefit.

As a limitation, the risk of bias attributed to some of the included studies could not be fully identified due to poor reporting of study design.

Conclusion

No clinical evidence to suggest an antiepileptic property of quinine would be found. At best it was shown to have lesser potential for causing seizure as probable side effect when compared to artemether.

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