Quinine for nocturnal leg cramps: a meta-analysis including unpublished data
Man-Son-Hing M, Wells G, Lau A

Authors' objectives
To assess whether the inclusion of data from unpublished studies alters findings on the efficacy and side-effects of quinine when used in the treatment of nocturnal leg cramps.

Searching
To update the searches conducted for an earlier systematic review (see Other Publications of Related Interest), MEDLINE and EMBASE were searched from April 1994 to July 1997 (using the same search terms), and Current Contents from January to July 1997. Drug regulatory authorities in the USA, UK and Germany, as well as pharmaceutical companies, were contacted.

Study selection

Study designs of evaluations included in the review
The review included individual patient data (IPD) from double-blind placebo-controlled crossover and parallel trials.

Specific interventions included in the review
Studies of quinine compared with placebo were eligible for inclusion. The included studies used doses ranging from 200 to 500 mg taken at supper and/or bedtime. Treatment was between 1 and 4 weeks in duration.

Participants included in the review
Studies of ambulatory patients experiencing regular nocturnal leg cramps were eligible for inclusion. The participants in the included studies had more than two cramps per week. The mean age of the participants ranged from 44 to 78 years. Apart from one study of males only, the included studies were of males and females.

Outcomes assessed in the review
The reduction in the number of nocturnal leg cramps over 4 weeks, the severity and duration of cramps, and side-effects were assessed.

How were decisions on the relevance of primary studies made?
The authors did not state how they established the relevance of individual studies.

Assessment of study quality
The authors did not report any data checking procedures. The authors did not state who was involved in the decision on including and excluding studies, but a table of excluded trials was presented.

Data extraction
Two investigators independently extracted the data. Due to the lack of 4-week outcome data for most of the studies, the number of cramps experienced for shorter time periods was increased proportionately to standardise across studies the number of cramps experienced in a 4-week period. Cramp severity measured by a 10-cm visual analogue scale was converted into a 3-point scale (1 = mild, 2 = moderate, 3 = severe). The relative risk reduction (RRR) was based on the difference in the number of cramps in the placebo and quinine groups, divided by the number of cramps in the placebo group. A point estimate and 95% confidence interval (CI) were calculated for individual studies.

Methods of synthesis
How were the studies combined?
The studies were combined to achieve an overall estimate and 95% CI using a one-way analysis of variance.
Results on the number of cramps were expressed as absolute change in number of cramps and the proportional benefits. Side-effects were listed. McNemar's test was used to test statistical significance.

How were differences between studies investigated?
The studies were grouped based on whether they were published or unpublished. A one-way ANOVA was used to investigate heterogeneity and a sensitivity analysis was conducted. Regression analyses were used to investigate the relationship between individual study effects and length of treatment and sample size.

Results of the review
IPD from 8 studies (n=659) were included: 7 crossover trials and one parallel design. Four studies were published and four unpublished.

Number of cramps over 4 weeks: based on the 7 crossover trials, there were 3.6 fewer cramps (95% CI: 2.15, 5.05) with quinine compared with placebo. Data from the published trials provided a greater estimate of benefit (8.83 fewer cramps, 95% CI: 4.16, 13.49) than unpublished trials (2.45 fewer cramps, 95% CI: 1.03, 3.87, P=0.0008). Combining IPD from the parallel trial with data from the first treatment period of the crossover studies showed 2.87 fewer cramps (95% CI: 0.20, 5.54) with quinine compared with placebo. The RRR was 21% (95% CI: 12, 30). Based on a regression analysis, the benefits of quinine over placebo increased with longer treatment duration (P=0.01).

There was evidence of heterogeneity for absolute reduction in cramps (P=0.001). When the study with the largest dose of quinine and male only participants was excluded from the analysis, the test for heterogeneity was no longer significant. Based on these 6 studies there were 2.62 fewer cramps (95% CI: 1.32, 3.91).

Severity of cramps: based on a 3-point scale, quinine reduced the severity of leg cramps (0.13 units, 95% CI: 0.05, 0.21).

Quinine was associated with an increased incidence of side-effects, particularly tinnitus (20 patients with quinine and 7 with placebo), and greater withdrawal in comparison with placebo. Data on the duration of cramps were not available from the unpublished studies, therefore an analysis of this outcome was not conducted.

Authors' conclusions
Quinine is efficacious in the prevention of nocturnal leg cramps, though its benefits may not be as large as those reported when pooling published data only. Short-term use is associated with side-effects, particularly tinnitus.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. Some appropriate sources were searched for published and unpublished data, though it was unclear whether language restrictions were applied. Processes for checking the validity of the data were not reported. Key characteristics of the studies were reported, though more information on the participants and washout period would have been helpful. The data were analysed using appropriate techniques for meta-analysis of IPD. Heterogeneity was assessed and some sensitivity analyses were conducted. The authors' conclusions about quinine seem appropriate given the evidence presented, though it was not possible to fully assess the thoroughness of this review of IPD.

Implications of the review for practice and research
Practice: The authors stated that, owing to the side-effect profile of quinine, non-pharmacologic therapy such as passive muscle stretching is the best first-line treatment, though the use of quinine is warranted if this therapy is ineffective. Prescribing physicians should closely monitor the risks and benefits in individual patients.

Research: The authors stated that large randomised controlled trials of longer duration, preferably of at least 4 weeks, are required. Meta-analyses should seek high-quality unpublished data from drug regulatory agencies and pharmaceutical companies to minimise the effects of publication bias.
Bibliographic details

PubMedID
9754515

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Humans; Leg; Muscle Cramp /drug therapy; Muscle Relaxants, Central /therapeutic use; Quinine /therapeutic use; Randomized Controlled Trials as Topic; Risk Assessment; Treatment Outcome

AccessionNumber
11998001581

Date bibliographic record published
30/04/2006

Date abstract record published
30/04/2006

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.