Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people

Malcolm Man-Son-Hing, George Wells

Abstract

***Objective*—To assess quantitatively the efficacy of quinine (as quinine sulphate) compared with placebo in the treatment of nocturnal leg cramps.**

***Design*—A meta-analysis of six randomised, double blind, crossover trials.**

***Setting*—Randomised trials that were available as of April 1994.**

***Subjects*—A total of 107 general ambulatory patients who suffered from regular nocturnal leg cramps from six clinical trials.**

***Results*—Data from individual patients were used to calculate point estimates and 95% confidence intervals for each of the outcome measures reported by these studies. Treatment with quinine resulted in a significant reduction in the number of cramps for a four week period compared with placebo (8·83 fewer cramps; 95% confidence interval 4·16 to 13·49). Treatment with quinine reduced the number of nights with cramps by 27·4% (24·0% to 30·8%) compared with placebo. Treatment did not produce a significant change in the severity or duration of individual nocturnal leg cramps. Side effects were uncommon.**

***Conclusions*—The results indicate that quinine can prevent nocturnal leg cramps in general ambulatory populations. Given the possible serious side effects of treatment with quinine, the benefits and risks in patients taking this drug should be closely monitored.**

Introduction

Nocturnal leg cramps are painful involuntary muscle cramps that occur when the patient is recumbent. They are an extremely common complaint in elderly people. In one survey over 70% of elderly people had leg cramps at night at one time or another.[1] Many treatments, both non-pharmacological and pharmacological, have been attempted for this condition. Non-pharmacological treatments included walking, stretching, and massage.[2] Pharmacological treatments that have been reported include calcium channel blockers,[3] vitamin E,[4] and quinine (as quinine sulphate).

Quinine has been suggested as the most effective pharmacological treatment available.[5] The first report of beneficial effects of quinine was in 1940.[6] In fact, most of the trials investigating drug treatment for nocturnal leg cramps in elderly people have studied the efficacy of quinine. Interestingly, the results of these studies have been mixed despite similar patient populations. Moreover, there have been increasing numbers of reports of side effects including pancytopenia,[7] cinchonism,[8] and visual toxicity.[9] We therefore undertook a meta-analysis of the efficacy of quinine for the treatment of nocturnal leg cramps in ambulatory people.

Methods

IDENTIFICATION OF RELEVANT CLINICAL STUDIES

To identify all published studies we carried out a computerised literature search by using MEDLINE (January 1966 to April 1994) and EMBASE (January 1975 to April 1994) databases. The key words quinine, muscle cramps, and legs were used to locate relevant articles. We then searched *Current Contents* from January to April 1994 for further trials. We also reviewed the references of all relevant articles found by our search, studied relevant textbooks, and spoke to authorities about any published and unpublished work that they might be aware of.

Before this search we decided to include in the meta-analysis only those studies that met the following criteria: randomisation of patients; double blind, placebo controlled, crossover design; and a general ambulatory population (that is, non-dialysis patients). A crossover design was part of the inclusion criteria for two related reasons: firstly, by removing differences between subjects it allows analytical techniques that increase the statistical power of the analysis; and, secondly, before we started this study the only relevant randomised trials we were aware of had a crossover design.

With access only to photocopies of the methods section of each article, potentially eligible trials were assessed by four independent people blinded to the study for fulfilment of the above inclusion criteria. For the clinical trials that met all inclusion criteria but did not include data on individual patients in their published reports we contacted the respective authors in an attempt to obtain these data.

DATA EXTRACTION

We obtained from each study the following information: number of patients, sex, age range, criteria for eligibility, setting, dose of quinine, length of treatment period, presence of a washout period, presence of side effects, and outcome measures used. Data extraction was performed by two independent assessors. Any points of disagreement were settled by collaborative review.

META-ANALYSIS

By using the data on individual patients for each study we calculated a point estimate and 95% confidence interval for the efficacy of quinine (as quinine sulphate) compared with placebo by using paired differences for the following outcomes: reduction in number of nocturnal leg cramps for a four week period; severity of nocturnal leg cramps; duration of nocturnal leg cramps; and cramp index (duration × severity of leg cramps).

One way analysis of variance was used to test for homogeneity. Again with data on individual patients relevant studies were combined to produce a best estimate (95% confidence interval) for each of the

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above outcome measures. For the outcome measure of number of nights with cramps, analysis was performed by χ^2 tests to compare rates as data on individual patients were not available.

Results

SYSTEMATIC OVERVIEW

Eleven potentially eligible clinical trials were identified through the computer literature search. Despite exhaustive searching for other published and unpublished relevant trials none could be found.

There was complete agreement among the four independent assessors on which trials met all inclusion criteria. Five trials did not meet these criteria and were excluded (table I).[10-14] The six remaining trials were included in the meta-analysis.[15-20] Three of these trials did not publish data on individual patients. We were successful in obtaining outcome data but not demographic data for individuals from the authors for two of these studies.

TABLE I—*Trials excluded because all criteria for inclusion not met*

	Criteria for eligibility				
Reference	Randomised patients	Double blinded	Crossover	Drug *vs* placebo	General ambulatory patients
Kaji *et al*[4]	✓	✓	✓	✓	—
Lim *et al*[11]	—	✓	—	✓	✓
Baltodano *et al*[10]	—	—	✓	—	✓
Gorlich *et al*[12]	✓	✓	—	✓	✓
Roca *et al*[13]	✓	✓	—	—	—

Adherence to the data extraction process resulted in complete agreement between the two assessors. Table II summarises the six trials included in the meta-analysis and relevant information about each.

META-ANALYSIS

Absolute change in number of nocturnal leg cramps for a four week period (fig 1)

Five of the six eligible studies reported the absolute change in the number of cramps while the subjects were taking quinine compared with placebo as an outcome measure. Because each study had treatment periods with varying lengths of time, studies that did not have treatment periods of four weeks were standardised to the number of cramps experienced in a four week period. The standardisation method used was to increase proportionately the number of cramps experienced by each individual patient in a study with treatment periods less than four weeks. For example, if a study had a two week treatment period the number of cramps experienced in each treatment period was doubled to simulate a four week treatment period. The longest treatment period of any relevant study was four weeks.

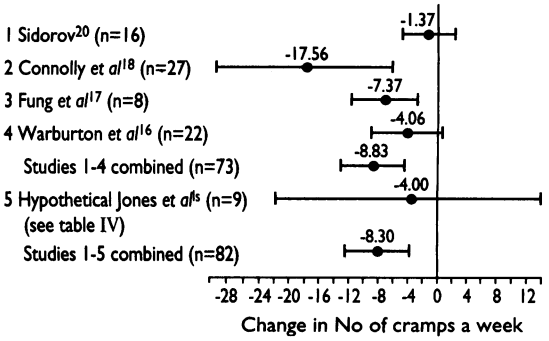

FIG 1—*Absolute change in number of cramps in patients taking quinine compared with placebo (four week period)*

These data show that there are two individual trials in which a significant reduction in the number of cramps was obtained in patients taking quinine sulphate compared with those taking placebo and two that did not. Combination of the results of these four trials showed that the use of quinine resulted in a significant reduction of 8·83 (95% confidence interval 4·16 to 13·49) nocturnal leg cramps in a four week period.

Data on individual patients from one study were not available.[15] As a form of sensitivity analysis we used the published information provided by this clinical trial to derive a hypothetical set of results for individual patients (tables III and IV). These results were derived such that the maximum standard deviation possible for the given parameters of the data was created. We then combined this "worst case scenario" with the four other studies. The result was similar (8·30 (3·85 to 12·75) fewer nocturnal leg cramps in four weeks with quinine) to those obtained without the addition of the derived data.

TABLE III—*Information used in meta-analysis from double blind comparison of quinine sulphate and placebo carried out in 1983 by Jones and Castleden*[15]

Detail	Quinine	Placebo
Average No of cramps over two weeks	3·6	5·6
Range	0-20	1-15
Distribution	Four patients had no cramps	—
Total No of cramps over two weeks	3·6×9 patients =32·4	5·6×9 patients =50·4

TABLE II—*Relevant characteristics of trials included in meta-analysis*

										Outcome measures			
Reference (year)	No of patients	Sex: Men	Sex: Women	Mean age (range) years	Eligibility	Setting	Dose (mg) of quinine	Length of treatment period	Washout period	No of cramps/ unit time	Severity of cramps	Duration of cramps	No of nights with cramps
Jones *et al* (1983)[15]	9	?	?	? (elderly)	>Two cramps a week	General practice	300 At bedtime	Two weeks	✓	✓	✓	✓	—
Warburton *et al* (1987)[16]	22	6	16	78 (SD 8)	>Two cramps a week	General practice	300 At bedtime	Three weeks	—	✓	*	*	—
Fung *et al* (1989)[17]	8	1	7	63 (47-81)	>Two cramps a week	Internal medicine clinic	200 At bedtime	Four weeks	✓	✓	✓	✓	—
Connolly *et al* (1992)[18]	27	27	0	59 (38-73)	>Six cramps on survey	General medicine clinic	200 supper 300 At bedtime	Four weeks	✓	✓	✓	—	✓
Dunn (1993)[19]	25	? (about equal)	? (about equal)	67 (51-82)	Received regular quinine	General practice	300/day	30 Days	—	—	—	—	✓
Sidorov (1993)[20]	16	2	14	58·5 (29-85)	>Two cramps a week	Internal medicine clinic	200 At bedtime	Two weeks	✓	✓	✓	✓	—

*Severity and duration of cramps combined into measure called cramp index.

TABLE IV—*Data for individual patients derived from information given in study of Jones and Castleden.*[15] *Values are numbers of cramps*

Patient	Quinine	Placebo	Difference over two weeks (quinine-placebo)	Standardisation to four week treatment period (quinine-placebo)
1	20	1	19	38
2	9·4	1	8·4	16·8
3	1	1	0	0
4	1	1	0	0
5	1	1	0	0
6	0	1	−1	−2
7	0	14·4	−14·4	−28·8
8	0	15	−15	−30
9	0	15	−15	−30
Total	32·4	50·4		
Mean			−2·0	−4·0

*See also table III.

Change in severity of individual nocturnal leg cramps (fig 2)

Five studies used the severity of nocturnal leg cramps as an outcome measure. One study, however, combined the reporting of severity and duration into one measure called the "cramp index" and thus individual severity scores were not available.[16] Also, as stated before, individual results from one study could not be obtained.[15] Therefore, three studies were available to assess the efficacy of quinine to reduce the severity of individual cramps.

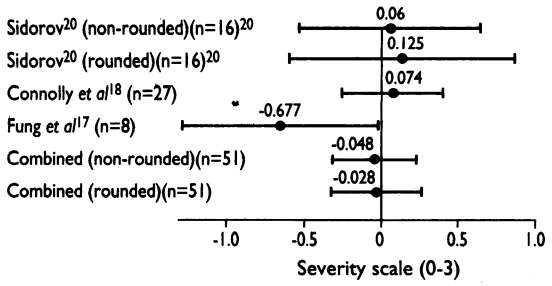

FIG 2—*Change in severity of cramps in patients taking quinine compared with placebo*

Methods of determining severity of cramp differed between studies. One study used a 10 cm visual analogue scale, and the other two used a 3 point scale (1—mild, 2—moderate, 3—severe). To allow us to combine data on severity from each of these three studies we used two standardisation methods to convert the 10 cm visual analogue data to a 3 point scale: non-rounded—mean cramp severity for individual patients was divided by 3·33 and the point estimate (95% confidence interval) calculated; and rounded—the mean cramp severity for each patient was converted to numerical values corresponding to mild, moderate, or severe (that is, mean visual analogue scores from 0 to 3·3 were assigned a value of 1, 3·4 to 6·6 assigned 2, and 6·7 to 10 assigned 3).

There was no significant change (−0·048 units (−0·314 to 0·218) on a 3 point visual analogue scale) in the mean severity of individual leg cramps with quinine compared with placebo. The difference in the results was negligible when we used either the non-rounded or rounded method of standardisation. Sensitivity analysis including hypothetical data from Jones and Castleden[15] had no significant effect on this result.

Change in number of nights with cramps (fig 3)

Two trials measured the number of nights with cramps. Because Dunn used a 30 day treatment period in his trial[19] his results were standardised to a four week treatment period by using the same method described earlier. Each trial individually showed a significant reduction in the number of nights with leg cramps, and the combination of the two trials showed similar results (−27·5% (−30·6% to −24·4%) change in the number of nights with cramps).

Change in duration of individual nocturnal leg cramps

Duration of individual nocturnal leg cramps was an outcome measured in four studies. Again, individual data were not available from Warburton *et al* as severity and duration were combined into one index[16] and data from Jones and Castleden were not available.[15]

Sidorov[20] and Fung[17] found a −4·2 minute (−22·8 to 14·5) and −54·0 minute (−121·3 to 13·3) change in duration of an individual leg cramp, respectively, with quinine compared with placebo. The results of combining these data show no significant change (−20·8 minutes (−43·7 to 2·1) in duration of individual leg cramps with quinine versus placebo. Sensitivity analysis including hypothetical data for Jones and Castleden[15] did not significantly change this result.

Change in Cramp Index

Warburton *et al* combined the results of cramp severity and duration into a single result they called the cramp index.[16] The cramp index was based on the product of the total duration of leg cramps for each period and the mean severity of the cramps. Three other studies measured both severity and duration. Cramp index scores for each study were derived from these data. To allow combination of data on cramp severity from individual studies the same methods as described above were used to calculate respective cramp indices.

Results from individual studies showed a change in the cramp index as follows: Sidorov −2·87 units (−13·86 to 8·07)[20]; Fung *et al* −37·87 units (−68·80 to −6·95)[17]; and Warburton *et al* 26·84 units (−0·95 to 54·64).[16] Combination of the data for the individual patients from these three trials showed no significant change (5·25 units (−10·43 to 20·93)) in the cramp index with quinine or placebo. Inclusion of hypothetical data for Jones and Castleden[15] did not significantly change this result.

Side effects of treatment with quinine

Pooling of the descriptive data on side effects reported by the six studies (n=107) showed that only one person in any of the studies experienced serious side effects. This person experienced nausea, myalgia, leucopenia, and thrombocytopenia that resolved three days after discontinuation of quinine. Only a small minority of patients reported any side effects at all while taking quinine.

Discussion

There is current uncertainty about whether prescribing quinine for patients who complain of frequent nocturnal leg cramps is beneficial. Treatment with quinine is not without risk as there have been several reports of serious adverse effects. Many studies have tested the efficacy of quinine sulphate for this condition since 1976. Overall, the results of these studies have not been definitive. We conducted this meta-analysis to attempt to clarify whether quinine is more efficacious than placebo in providing relief for sufferers of nocturnal leg cramps.

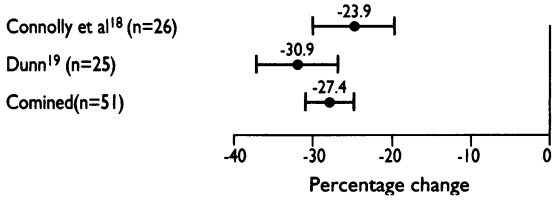

FIG 3—*Percentage change in number of nights with cramps in patients taking quinine compared with placebo*

Pooling of data from the six eligible trials, all of which had strong methodological designs, indicated that quinine does reduce the number of nocturnal leg cramps suffered by patients and also reduces the number of nights on which they actually have cramps. Quinine did not seem to reduce the severity or duration of a cramp once it had occurred, though the confidence intervals were wide. Serious side effects of treatment with quinine were uncommon in these trials, though treatment periods were not long enough to exclude long term complications. The inability to obtain data on individual patients from one of the eligible studies did not have any significant effect on our results. We therefore believe that treatment with quinine is efficacious in the prevention of nocturnal leg cramps in general ambulatory populations.

POSSIBLE ERRORS IN METHODS

As with all meta-analyses, publication bias is a possible source of error in this study. As the medical community has genuine uncertainty about the efficacy of quinine sulphate in the treatment of nocturnal leg cramps, however, all well designed clinical trials investigating quinine for this condition are likely to be published, regardless of their final results.

Another source of possible error is the method of standardisation used to allow combination of the data from different studies. Standardisation was necessary as different studies used different lengths of treatment periods. We chose to standardise all studies to a four week treatment period as two of the studies used this length of treatment period and it was the longest treatment period length in any study measuring the number of cramps for individual patients. Interestingly, the two studies with four week treatment periods showed treatment with quinine significantly reduced the number of cramps compared with treatment with placebo. Studies with shorter periods of treatment were not able to show such significant benefit. In fact, the longer the treatment period the greater the point estimate of benefit for quinine sulphate. Considering this result, treatment periods of less than four weeks may be insufficient to show benefit of treatment. We therefore believe that our method of standardising the data takes a conservative approach in estimating the probable efficacy of quinine.

The inability of quinine to affect the severity or duration of individual cramps suggests that this drug must be taken on a regular as opposed to an as needed basis.

The test for homogeneity with respect to reduction in the number of nocturnal leg cramps with data from the four studies in which information on individual patients was available was significant, indicating that the absolute reduction was not constant across these four studies. Inspection of the absolute reductions with their confidence intervals indicated that the study by Connolly *et al*[18] is responsible for the heterogeneity. When we reviewed the data on individual patients from this study we found four extreme sets of results (range −83 to −62 fewer cramps with quinine compared with placebo). These were the four sets of results that showed the greatest efficacy of quinine. As a form of sensitivity analysis we removed these four sets of results from our analysis, which would have the effect of reducing the estimate of efficacy of the meta-analysis results. The absolute reduction in cramps still remained significant, and the test for homogeneity became non-significant (P=0·41). To further our sensitivity analysis, when we then excluded the data from Connolly *et al*[18] altogether and repeated the analysis we found that the absolute reduction remained significant, and the three remaining studies satisfied the assumption of homogeneity. Considering that the study of Connolly *et al* also showed the greatest absolute reduction in leg cramps for quinine compared with placebo,[18] we chose to combine the data of all four studies in which data for individual patients were available.

Key messages

- Nocturnal leg cramps are a common complaint, occurring in more than 70% of elderly people at one time or another
- The results of this meta-analysis show that quinine sulphate is more effective than placebo in reducing the number of cramps experienced by patients
- This analysis also suggests that dosing is cumulative, therefore a trial of at least four weeks of quinine may be necessary to show a beneficial effect
- Quinine should be taken on a regular as opposed to as needed basis as it could not be shown definitively to reduce the severity or duration of an individual cramp

The study of Connolly *et al* was also the only one that used only male subjects. We were unable to find any reference to suggest or confirm that nocturnal leg cramps are different from a physiological or epidemiological perspective in men and women. All other trials included in this meta-analysis included more women. Unfortunately, data on the sex of individual patients were unavailable.

There was one study which met all inclusion criteria except that of crossover design.[18] In this study subjects were randomised to one of three arms: quinine alone, quinine and aminophylline, or placebo. The results showed that treatment with quinine alone produced a significant reduction in the number of nocturnal leg cramps compared with treatment with placebo. To further our sensitivity analysis we modified the protocol of the meta-analysis to allow inclusion of this trial. By analysing the data for individual patients while they received quinine compared with placebo for the first treatment period of each crossover study, we continued to find a significant reduction in nocturnal leg cramps in patients receiving quinine (12·85 fewer cramps in a four week period; 95% confidence interval 4·26 to 21·44). Thus, modifying the protocol of this meta-analysis to allow inclusion of the study of Gorlich *et al*[18] would slightly change the point estimate of efficacy for quinine sulphate but not the significance of its results.

Gorlich *et al*[18] and another German study[21] studied the combination of quinine and aminophylline. Both of these studies showed significant benefit for this combination.

In conclusion, our results show that quinine sulphate is efficacious in the treatment of nocturnal leg cramps on ambulatory patients. As quinine may have considerable side effects, however, patients starting it for nocturnal leg cramps should undergo a therapeutic trial with close monitoring of its benefits and risks. These data suggest that patients should receive quinine on a regular basis and for a period of at least four weeks before conclusions about its efficacy are made. Given the possible risks and benefits of quinine an n of 1 trial may be indicated for individual patients.

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Weight in infancy and prevalence of coronary heart disease in adult life

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Abstract

***Objective*—To determine whether low birth weight and low weight at 1 year are followed by an increased prevalence of coronary heart disease in adult life.**

***Design*—A follow up study of men born during 1920-30 whose birth weights and weights at 1 year were recorded.**

***Setting*—Hertfordshire, England.**

***Subjects*—290 men born and still living in East Hertfordshire.**

***Main outcome measure*—The prevalence of coronary heart disease, defined by the Rose/WHO chest pain questionnaire, standard electrocardiographic criteria, or history of coronary artery angioplasty or graft surgery.**

***Results*—42 (14%) men had coronary heart disease. Their mean birth weight, 7·9 lb (3600 g), was the same as that of the other men. Their mean weight at 1 year, 21·8 lb (9·9 kg), was 1 lb (454 g) lower (95% confidence interval 0·1 to 1·8, P=0·02). Percentages of men with coronary heart disease fell from 27% in those who weighed 18 lb (8·2 kg) or less at 1 year to 9% in those who weighed more than 26 lb (11·8 kg) (P value for trend=0·03). This trend occurred in both smokers and non-smokers and within each social class.**

***Conclusion*—These findings add to the evidence that coronary heart disease is "programmed" during early growth.**

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Introduction

Recent findings suggest that the pathogenesis of coronary heart disease begins in fetal life and infancy. Among 10 141 men born during 1911-30 in Hertfordshire, England, whose birth weights and weights at 1 year had been recorded, men with the lowest birth weights and weights at 1 year had the highest death rates from coronary heart disease.[1 2] The association with weight at 1 year was stronger than that with birth weight, though both were significant. Reduced growth in utero and during infancy has also been shown to be associated with an increased risk of hypertension and non-insulin dependent diabetes and higher concentrations of low density lipoprotein cholesterol and fibrinogen in adult life.[3-6] These findings have led to the hypothesis that coronary heart disease originates from early programming whereby undernutrition during sensitive periods in early life permanently changes the body's structure and physiology.[7 8]

The Hertfordshire study was based on diagnosis of coronary heart disease on death certificates.[2] We now present data on disease in living subjects. using validated methods we have measured the prevalence of symptomatic and asymptomatic coronary heart disease in a sample of 290 men born and still living in East Hertfordshire.

Methods

In Hertfordshire from 1911 onwards each birth was notified by the attending midwife, and a health visitor saw the child periodically throughout infancy. The child's birth weight and weight at 1 year of age were recorded.[1] We used these records to trace 5654 men who were born as singletons in the six districts of East Hertfordshire between 1911 and 1930 and who had both birth weight and weight at 1 year recorded to determine mortality from cardiovascular disease.[1] Of the total, 1186 men had died, 434 of them from coronary heart disease.[1] We subsequently approached the 1157 men who were born in East Hertfordshire between 1920 and 1930 and still lived there.[3] Of these, 845 men agreed to be interviewed at home. Their current occupation or their occupation before retirement and their father's occupation at the time of their birth were used to determine socioeconomic class currently and at birth.[9] Their blood pressure was measured.[3] After the interview men were asked if they would be willing to attend a local clinic to have blood samples taken, and 468 men agreed. Serum concentrations of lipids and concentrations of plasma clotting factors, glucose, and insulin were measured, and the results have been reported.[3 4 6]

For the study reported here, we reapproached the 370 men who had complete measurements on all blood samples. Of the 370, seven had died and 11 had moved away. Of the remaining 352, 290 (82%) took part. The men were visited at home by a nurse who asked for details of current smoking habits. After the interview the subjects were asked to come to a local clinic where the Rose/WHO chest pain questionnaire[10] was administered and standard 12 lead electrocardiography carried out according to the 1982 Minnesota protocol.[11] Height was measured with a portable stadiometer and