Clinical Medicine

Placebo-Controlled Trial of Quinine Therapy for Nocturnal Leg Cramps

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A prospective, double-blind, placebo-controlled crossover study of the use of quinine for nocturnal leg cramps was carried out in 8 elderly volunteer patients. The patients were randomly assigned to receive either placebo or 200 mg of quinine sulfate by mouth at bedtime. After 4 weeks of treatment and after a one-week washout period, the group taking quinine switched to placebo and vice versa for another 4 weeks. The differences in the number, duration, and severity of cramps and the side effects were compared. All of the patients had fewer cramps and decreased severity and duration of attacks while receiving quinine. Mild side effects developed in only 2 patients, and these subsided without treatment or discontinuing the medication. We conclude that quinine was effective in relieving nocturnal leg cramps in a selected group of elderly patients.

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Nocturnal leg cramps are a common clinical problem seen most frequently in the elderly. Although there have been many hypotheses to explain the cause of these night cramps, the pathophysiology is still poorly understood. Currently many therapeutic approaches are offered. Some patients may benefit from measures such as raising the foot of the bed or dorsiflexing the feet.[1-3] The most commonly prescribed medication is quinine sulfate. Some clinicians think that it is effective and prescribe it on an empiric basis, even though there is no scientific consensus concerning its efficacy or mechanism of action.

Quinine therapy was reported in early studies from the 1930s and 1940s to be effective in relieving nocturnal leg cramps.[4-6] Unfortunately, these studies were based on uncontrolled data and suffered from inadequacies in their designs. More recent controlled studies have shown contradictory results. Jones and Castleden reported in 1983 that the use of quinine was superior to that of placebo in patients with night cramps,[7] but in 1987 Warburton and co-workers claimed that using quinine was no better than giving a placebo.[8] In view of this controversy, we studied quinine therapy in a prospective, double-blind, placebo-controlled crossover study in patients with nocturnal leg cramps and herein report the results.

Subjects and Methods

We screened patients with nocturnal leg cramps who came to our internal medicine clinic from June to December of 1987 and recruited 15 volunteer outpatients to participate in the study. All of the patients had at least a one-year history of night cramps that were not relieved by traditional approaches. Each patient reported an average of at least two cramps per week. Patients were included only if they did not have any identifiable cause of muscle cramps such as neuromuscular diseases, an electrolyte imbalance, atherosclerotic peripheral vascular disease, or the concomitant use of nifedipine or terbutaline sulfate—all of which have been reported to induce leg cramps. Exclusion criteria were as follows: a known or suspected hypersensitivity to quinine or glucose-6-phosphate dehydrogenase deficiency, a history of optic neuritis and tinnitus, impaired liver or kidney function, or a concurrent use of muscle relaxants, narcotics, nonsteroidal anti-inflammatory agents or other analgesics that may influence the results of the study. Before the beginning of the study, all subjects received a physical examination and selected screening laboratory studies—complete blood count, urinalysis, and serum electrolyte determinations. Each subject gave an informed written consent.

The design of the study included a four-week treatment period followed by a one-week washout time and crossover to a second four-week treatment period. The study was done on an outpatient basis, and patients were randomly assigned in a double-blind manner to begin receiving either quinine sulfate (Quine 200, Reid-Rowell Company, Marietta, Georgia) or a placebo. Each subject was asked to take either 200 mg of quinine or placebo by mouth at bedtime every night for the first four weeks and then was switched over to the other regimen for the second four weeks. Patients were interviewed every week during the study to assess the number of cramps, the severity and duration of each attack, and any side effects experienced. They were asked to keep a diary of these events. Patient compliance was also addressed during each interview and was further assessed by counting the number of pills left at the end of the study.

The results in each trial period were assessed and compared in three categories: the total number of cramps, the cumulative duration of attacks in minutes, and the cumulative scores of the severity of the attacks, with three different intensity scores—1 signifying mild, 2 moderate, and 3 se-

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TABLE 1.—*Number, Duration, and Severity of Leg Cramps With Quinine Sulfate Therapy Versus Placebo*

Patient No.	Age, yr	Sex	No. of Cramps		Cumulative Duration of Cramps, min		Cumulative Scores of Severity*	
			Quinine	Placebo	Quinine	Placebo	Quinine	Placebo
1 . .	47	♀	3	6	3	6	3	9
2 . .	56	♀	0	8	0	12	0	12
3 . .	56	♀	2	6	2	6	4	11
4 . .	67	♀	1	5	1	14	1	9
5 . .	71	♀	0	12	0	70	0	25
6 . .	68	♂	2	14	12	64	4	25
7 . .	81	♀	2	13	11	255	6	45
8 . .	61	♀	3	8	13	47	5	17
Wilcoxon's signed rank test			$P<.01$		$P<.01$		$P<.01$	

*The severity of attacks was scored as follows: 1=mild, 2=moderate, 3=severe.

vere. The results of each period were then compared and analyzed by Wilcoxon's signed rank test.

Results

Of the original 15 patients recruited for the study, 6 withdrew before the beginning of the trial. Another patient had a history of esophagitis and dropped out after two days—while receiving quinine—because of nausea. One man and seven women with a mean age of 63 years—range, 47 to 81 years—completed the study. Compliance was good in all patients.

Number of Cramps

Table 1 shows the results of the trial of quinine therapy and the placebo trial. There was a significant reduction in the number of cramps in all patients when they were taking quinine ($P<.01$). In two patients there were absolutely no cramps in the entire four-week period while they were on quinine therapy.

Although all patients claimed to have an average of at least two cramps per week before the trial, three patients had fewer than eight cramps during the four weeks when they were receiving a placebo. Even if the results in these three patients were excluded, however, the difference between the quinine and placebo trial is still statistically significant ($P<.01$).

Duration of Cramps

The duration of each attack (in minutes) was added together in each period and is compared in Table 1. Again, there was a significant reduction in the total duration of cramps in all patients when they were taking quinine ($P<.01$).

Severity of Cramps

Each attack of cramps was assessed by a scale using three intensity scores. The cumulative total of the scores in each period was compared, and the scores are shown in Table 1. Again, there was a significant reduction in the severity of cramps in all patients when they were receiving quinine ($P<.01$).

Side Effects

Only two patients experienced some mild side effects. Patient 3 had tinnitus for two days in the second week when she was on quinine therapy. Patient 5 had blurred vision for one day in the third week when she was receiving quinine. In both patients, the symptoms subsided spontaneously without stopping the medication. In general, quinine was well tolerated by our patients.

Discussion

Nocturnal leg cramps are common in the elderly population. One manufacturer of quinine has claimed that "one out of seven people over the age of 45 years occasionally suffers from night cramps."[9] Many hypotheses are offered to explain the pathophysiology of nocturnal leg cramps: venostasis due to varicose veins,[1] accumulation of metabolites in the lower extremities,[2] and muscle hypoxia.[7] There are no data to support these hypotheses, however. Some medications have been reported to provoke night cramps. For example, Zelman reported in 1978 that terbutaline could induce night cramps that could be reversed by drug withdrawal.[10] In 1982 Keidar and colleagues reported a similar finding with nifedipine therapy.[11]

Quinine has long been used as an effective antimalarial agent. It also has analgesic and muscle relaxant properties. Over the past few decades, it has become increasingly more common for clinicians to use this agent in the treatment of nocturnal leg muscle cramps.[12] Although many clinicians think that quinine is effective in relieving leg cramps, there are no conclusive data to support its use. Early studies in the 1930s and 1940s such as those of Gootnick, Harvey, and Moss and Hermann claimed that quinine therapy was effective.[4-6] Unfortunately, early studies were based on uncontrolled data and suffered from inadequacies of design.

In 1976 Kaji and associates studied the effect of quinine use in nine patients with leg cramps who were on maintenance hemodialysis therapy. They found that the use of quinine was more effective than placebo in this specific patient population in reducing the frequency of cramps, but quinine apparently did not alter the severity of the cramps. Recently reported studies, however, have been contradictory. Jones and Castleden in a double-blind crossover study in nine patients found that quinine was superior to placebo in relieving night cramps.[7] Warburton and co-workers found that there was no statistically significant difference between quinine and placebo use in the 22 patients they studied.[8] In 1986 Lim, reporting on 25 inpatients, noted that quinine therapy was ineffective in reducing leg cramps.[14]

In view of these contradictory data, we attempted to investigate the effectiveness of quinine therapy. Quinine sulfate is available in many doses. To minimize side effects and possible drug interactions, we chose to give 200 mg of quinine instead of the higher doses that are commonly used. Serum quinine concentrations were not measured in our patients because a therapeutic serum level is not known, and a reliable method was not available locally.

We analyzed our results by determining the number, duration, and severity of cramps. Our results showed that there was a statistically significant reduction in all three of these categories when patients were taking quinine as compared with placebo. Side effects of the quinine use were also minimal. Of all the patients who participated in the study, only two experienced some side effects that subsided without the need of treatment or discontinuing the study.

Our results are consistent with the reports of Jones and Castleden.[7] Warburton and associates found quinine therapy to be ineffective in relieving leg cramps. The differences in

our results compared with those of Warburton and colleagues may be related to differences in patient populations; the definition of leg cramps and the basis of excluding patients from the studies were not comparable. Another possibility may be a longer period of treatment in our study (four weeks of taking quinine) versus a shorter period (three weeks) in their study. Third, most of our patients appeared to have a milder problem (the range of cramps was 2 to 4 cramps per week) than the patients in their study (as many as 15 cramps per week). Finally, despite the fact that overall improvement was not statistically significant in their study, Warburton and co-workers reported that "in the group as a whole, fewer cramps were reported in the early morning on quinine than on placebo."[8] The negative results in the study of Lim[14] are difficult to interpret because of problems in the study design and the reporting of the data.

The exact mechanism of action of quinine is poorly understood. It may act by decreasing the excitability of the motor end-plate region so that the responses to repetitive nerve stimulation and to acetylcholine are reduced. Quinine also increases the refractory period of muscle contraction so that the response to tetanic stimulation is diminished.[15,16]

The use of quinine has some risks.[12,15,16] Commonly reported side effects include nausea, vomiting, and diarrhea. Cinchonism has also been reported to occur from single overdoses or the repeated use of as little as 300 mg of quinine sulfate per day.

In summary, we conclude that quinine use is effective in a selected group of older patients in relieving nocturnal leg cramps. Although the number of subjects in this study was small, the results were statistically significant. Because most of the patients were women, the results may not be applicable to the population at large.

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