SPECIAL ARTICLE

Assessment: Symptomatic treatment for muscle cramps (an evidence-based review)

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

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ABSTRACT

Background: A Food and Drug Administration advisory in 2006 warned against the off-label use of quinine sulfate and its derivatives in the treatment of muscle cramps. Physicians are faced with a difficult scenario in choosing a treatment regimen for patients with muscle cramps. This American Academy of Neurology assessment systematically reviews the available evidence on the symptomatic treatment of muscle cramps.

Methods: A total of 563 potential articles were reviewed, of which 24 met the inclusion criteria of prospective trials evaluating the efficacy of a particular treatment on muscle cramps as a primary or secondary outcome.

Results: There are Class I studies showing the efficacy of quinine derivatives for treatment of muscle cramps. However, the benefit is modest and there are adverse effects from published prospective trials as well as case reports. There is one Class II study each to support the use of Naftidrofuryl, vitamin B complex, lidocaine, and diltiazem in the treatment of muscle cramps.

Recommendations: Although likely effective (Level A), quinine derivatives should be avoided for routine use in the management of muscle cramps because of the potential of toxicity, but in select patients they can be considered for an individual therapeutic trial once potential side effects are taken into account. Vitamin B complex, Naftidrofuryl, and calcium channel blockers such as diltiazem are possibly effective and may be considered in the management of muscle cramps (Level C). Further studies are needed to identify agents that are effective and safe for the treatment of muscle cramps. *Neurology*® 2010;74:691–696

GLOSSARY

ALS = amyotrophic lateral sclerosis; **CI** = confidence interval; **FDA** = Food and Drug Administration.

Muscle cramps are involuntary, generally painful contractions of a muscle or muscle group. Some patients are bothered by very frequent and severe muscle cramps that may be disabling. A cross-sectional prevalence study of 365 outpatients aged 65 or older in the United Kingdom reports that 50% of outpatients report frequent cramps.[1] Another review of 515 elderly veterans reports a similar prevalence of 56%, with half having cramps occurring at least once per week.[2] When the motor system is stressed, either by a neuromuscular disease or by a physiologic stress such as dehydration or excessive exercise, cramps become more frequent. Muscle cramps are caused by ectopic discharges from nerves or nerve terminals[3]; therefore, a variety of neuropathic conditions such as amyotrophic lateral sclerosis (ALS), peripheral neuropathies, and cramp-fasciculation syndrome are commonly associated with cramps.[4] In addition to neurologic conditions, multiple medical conditions such as hypomagnesemia, hypocalcemia, hypothyroidism, and renal or liver dysfunction may be the cause of cramps. Cramps are also frequent during the last trimester of pregnancy and in athletes such as marathon runners.[5,6] When no underlying cause of recurrent muscle cramps can be identified, they are referred to as idiopathic muscle cramps, which can be variable in presentation from patient to patient but are usually most prominent in the lower leg and foot muscles and more evident at night.

Since early reports in the 1930s and 1940s,[7] quinine and its derivatives have been the mainstay of

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Appendices e-1 through e-4 and table e-1 are available on the *Neurology*® Web site at www.neurology.org.

Approved by the Therapeutics and Technology Assessment Subcommittee on April 28, 2009; by the Practice Committee on July 1, 2009; and by the AAN Board of Directors on November 9, 2009.

Disclosure: Author disclosures are provided at the end of the article.

therapy for idiopathic muscle cramps. However, a United States Food and Drug Administration (FDA) Federal Register statement released on December 15, 2006, ordered unapproved quinine drugs to be removed from the market and cautioned consumers about their "off-label" use, citing "665 reports of adverse events with serious outcomes associated with quinine use, including 93 deaths" since 1969.[8] Quinine sulfate, in particular Qualaquin®, is the only FDA-approved drug for the treatment of plasmodium falciparum malaria. Use of the drug for any other indication, including muscle cramps, is unapproved. In addition to quinine, a number of other agents have been studied in the treatment of muscle cramps, including antiepileptics, calcium channel blockers, and various vitamins, supplements, and minerals. This assessment addresses the available evidence on the efficacy as well as possible adverse effects of symptomatic treatment of idiopathic muscle cramps.

DESCRIPTION OF THE ANALYTIC PROCESS

The main search strategy was a comprehensive search of MEDLINE and EMBASE from 1950 to May 31, 2008, using the search term "muscle cramp" limited to keywords "therapy," "drug therapy," and "prevention and control," which yielded 558 results in 4 languages (including French, German, Spanish, and English). Additional articles were identified by cross-referencing bibliographies from meta-analyses, review articles, and case reports identified in the initial search, which yielded 5 additional articles. "Muscle cramp" was defined as a sustained, generally painful, involuntary contraction of a muscle or muscle group. "Cramps" alone was not used as a search term due to excessive articles on gynecologic and gastrointestinal cramps.

The abstracts and titles from the 563 articles identified were reviewed, and a study was included if it was a prospective clinical trial with effect on muscle cramps as a primary or secondary outcome. Exclusion criteria were 1) review articles, 2) meta-analyses, 3) case reports or case series that did not involve a treatment, 4) phenomena not consistent with muscle cramps, such as muscle spasms, dystonia, or muscle pains, 5) pregnancy-induced cramps, 6) medical conditions such as hemodialysis and cirrhosis, and 7) cramps due to extreme physiologic stress such as excessive exercise, heat, or dehydration. Cramps secondary to medical conditions were excluded from this analysis because the mechanisms underlying the formation of cramps and often the treatment directed to correct them are distinct from the routine treatment of muscle cramps, and most treatment trials assessing idiopathic cramps also excluded these conditions. Muscle cramps due to myopathies were also excluded due to the distinct underlying mechanisms. Articles excluded after initial review of the 563 titles and abstracts included 13 articles on hemodialysis, 6 articles on cirrhosis, 4 articles on physiologically induced cramps, 11 articles on pregnancy, 39 review articles, and 10 case reports without treatments (total 63 articles). Upon further review, 450 articles were excluded as they were letters or types of publications other than clinical trials or did not deal with muscle cramps or therapy. A total of 50 potential studies were identified for full review. Full review of the articles led to further exclusion of 26 articles that were review articles, letters, or repeat publications of the same clinical trials. The remaining 24 articles were chosen for inclusion in the final review, including one article dealing with nonpharmacologic therapy, 5 open-label pharmacologic trials, and 18 randomized pharmacologic trials.

The final 24 articles involving symptomatic treatment of cramps were distributed to all 3 panel members for critical analysis and classification. Each member of the panel made an independent determination of class of evidence and a final meeting was called to discuss the articles and resolve differences. Data regarding cohort size, completion rate, inclusion and exclusion criteria, treatment and dosage, design of the study, length of study, primary and secondary outcomes, efficacy, and effect size were extracted from each article and tabulated (table e-1 on the *Neurology*® Web site at www.neurology.org). Each article was classified according to the American Academy of Neurology therapeutic classification of evidence scheme (appendix e-3) and recommendations were based on the level of evidence (appendix e-4).

ANALYSIS OF EVIDENCE

Question 1: Are there effective nonpharmacologic treatments for muscle cramps? Many nonpharmacologic therapies are employed by patients prior to prescription treatment, but there is little evidence to support the use of any of them. Hydration, particularly for exercise-associated cramping, is frequently used by patients; however, there are no formal studies supporting its use. An open-label (Class IV) study from 1979 suggested that stretching affected muscles 3 times a day could reduce cramping.[9] A randomized Class II study of 191 patients compared patients who stretched their calves 3 times a day to patients instructed in a sham exercise that involved moving the legs without stretching and found no benefit of stretching on the frequency of cramps or number of cramp-free nights.[10] This trial was limited because it had acknowledged difficulties maintaining good patient blinding, and the control

patients were given sham exercises that could theoretically provide some benefit.

Conclusion. Data are insufficient to draw any conclusion on the efficacy of calf stretching in reducing the frequency of muscle cramps.

Recommendation. None (Level U).

Question 2: Is quinine effective in the treatment of muscle cramps? Thirteen studies were found involving quinine or quinine derivatives: 2 Class I studies showing efficacy,[11,12] 4 Class II studies (2 showing efficacy and 2 showing lack of efficacy),[13-16] 5 Class III studies (2 showing efficacy and 3 showing lack of efficacy),[17-21] and 1 Class IV study showing efficacy.[22] Only the Class I and II studies are discussed below.

Class I studies. A randomized trial in 1997 assessed the efficacy of hydroquinine hydrobromide dihydrate 300 mg at night in 112 patients.[11] The trial showed a greater reduction in median number of cramps in treated patients compared to placebo (5 fewer cramps, 95% confidence interval [CI] 2–8 cramps) and a reduction of cramp days in treated patients compared to placebo (1 fewer cramp day, 95% CI 0–3 cramp days) during the 3-week study period. The mean number of cramps was reduced by 37%. Another Class I study (n = 109) using 400 mg of quinine showed a modest though significant reduction in the median number of cramps between the run-in and treatment phases (8 cramps, 95% CI 7–10 cramps vs 6 cramps, 95% CI 3–7 cramps).[12] The median number of cramps was reduced by 25%. One criticism of this trial was the restrictive inclusion criteria, which excluded patients above age 70 (who are often the patients with difficult-to-treat muscle cramps).

Class II studies. All 4 Class II studies involved small cohorts (20–43 patients) and none addressed sample size and power calculation.[13-16] Two showed efficacy but were limited by inadequate description of baseline characteristics of the treatment and placebo groups,[13,14] which does not allow for a fair comparison between the groups and does not control for the potential of inadequate randomization. A trial published in 1994 showed a significant decrease in the mean number of cramps in the group treated with hydroquinine hydrobromide 300 mg in the treatment phase compared to the run-in phase (16.1 cramps, SD 14.7 cramps), whereas the placebo group did not (5 cramps, SD 16.3 cramps).[13] A second Class II study found a significant reduction in the mean number of cramps from 44 in the run-in phase to 19.2 ± 5.3 in the treatment group (500 mg quinine sulfate at night) and from 44 to 36.6 ± 6.6 in the placebo group ($p = 0.0046$). There were also beneficial effects on the number of nights with cramps and sleep disturbance.[14]

Two other Class II studies were limited by poor patient compliance and low completion rates of 52% and 70%.[15,16] Neither showed a significant effect of quinine sulfate (200–300 mg qhs quinine sulfate) on frequency or intensity of muscle cramps.

Adverse effects of quinine and its derivatives. Common and serious side effects reported in the literature as case reports or series as well as all side effects identified in the 13 studies are listed in the table. A total of 10 minor and 11 serious side effects were identified; the most consistently reported minor side effects were cinchonism (headache and tinnitus) and bitter taste. The most common serious side effects reported were hematologic abnormalities such as hemolytic uremic syndrome–thrombotic thrombocytopenia purpura, disseminated intravascular coagulation, and bleeding diathesis. There were no reports of cinchonism leading to deafness. The frequency of any serious side effect from the studies published in this review was 2% to 4%. We did not find any reports of fatalities from quinine sulfate in any of the studies reviewed in this article. A recent FDA statement reports 93 fatalities and 663 serious adverse events related to quinine; however, no details regarding these events are available for general review.[8] Although inclusion of all references for case reports is outside the scope of this article, an article that overviews the majority of common and serious side effects of quinine is referenced here.[23]

Conclusion. On the basis of data from 2 Class I studies, quinine derivatives are effective in reducing the frequency of muscle cramps, although the magnitude of benefit is small. Moreover, these agents are associated with serious though uncommon side effects.

Recommendation. Although likely effective (Level A), the use of quinine derivatives for treatment of muscle cramps should be avoided for routine treatment of cramps. These agents should only be considered when cramps are very disabling, no other agents relieve symptoms, and there is careful monitoring of side effects. They should only be used after informing the patient of the potentially serious side effects.

Question 3: Are there any other pharmacologic treatments effective for the treatment of muscle cramps? ***Class I studies.*** A double-blind randomized controlled trial of 3,600 mg per day of gabapentin in 204 patients with ALS evaluated muscle cramps (among other symptoms such as fasciculations, stiffness, sleeping, and emotionality) using a severity score from 0 to 10 and found no difference between treatment and placebo with respect to any symptom score.[24]

Class II studies. A Class II study of 28 patients in 1998 showed that vitamin B complex (including 30 mg per day of vitamin B6) induced remission of muscle cramps in 86% of treated patients who were not known to be vitamin deficient compared to pla-

Table Reported side effects in case reports and prospective trials using quinine sulfate or derivatives

Side effects	Risk	Exposure	Class (reference)
Serious			
HUS-TTP with DIC, HUS-TTP with acral necrosis, pancytopenia, thrombocytopenia, bleeding diathesis	SER	Typical dosage (300 mg PO qhs)	IV
	1/49 (2%)	300 mg hydroquinine/day	I (11)
	1/23 (4%)	200 mg quinine sulfate qhs	II (16)
Hypoglycemia	SER	Typical dosage (300 mg PO qhs)	IV
Vision loss (retinal toxicity)	SER	Typical dosage (300 mg PO qhs)	IV
Hepatotoxicity	SER	Typical dosage (300 mg PO qhs)	IV
Cardiac arrhythmias	SER	Typical dosage (300 mg PO qhs)	IV
	1/49 (2%)	300 mg hydroquinine/day	I (11)
Acute pulmonary edema	SER	Typical dosage (300 mg PO qhs)	IV
Acute hypersensitivity reaction	SER	Typical dosage (300 mg PO qhs)	IV
	1/30 (3%)	500 mg/day, mention rest of rxns not doc	II (14)
Psychosis	SER	Typical dosage (300 mg PO qhs)	IV
Abortion	SER	Typical dosage (300 mg PO qhs)	IV
Esophagitis	SER	Typical dosage (300 mg PO qhs)	IV
Minor			
Photosensitivity reactions, blurry vision	SER	Typical dosage (300 mg PO qhs)	IV
	1/8 (12.5%)	200 mg quinine sulfate qhs	II (17)
Cinchonism	SER	Typical dosage (300 mg PO qhs)	IV
	1/8 (12.5%)	200 mg quinine sulfate qhs	II (17)
	1/49 (2%)	300 mg hydroquinine/day	I (11)
	1/47 (2%)	400 mg quinine sulfate/day	I (12)
Hyperpigmentation, lichen planus	SER	Typical dosage (300 mg PO qhs)	IV
Bitter taste, dry mouth	10/49 (20%)	300 mg hydroquinine/day	I (11)
	3/20 (15%)	Hydroxyquinine hydrobromide 300 mg qhs	II (13)
Gastrointestinal related, nausea and vomiting	10/49 (20%)	300 mg hydroquinine/day	I (11)
	1/20 (5%)	Hydroxyquinine hydrobromide 300 mg qhs	II (13)
Headache	5/49 (10%)	300 mg hydroquinine/day	I (11)
Dizziness	3/49 (6%)	300 mg hydroquinine/day	I (11)
	1/23 (4%)	200 mg quinine sulfate qhs	II (16)
Tremor	2/49 (4%)	300 mg hydroquinine/day	I (11)
Itching	2/49 (4%)	300 mg hydroquinine/day	I (11)
Tingling	1/20 (5%)	Hydroxyquinine hydrobromide 300 mg qhs	II (13)

Abbreviations: DIC = disseminated intravascular coagulation; HUS-TTP = hemolytic uremic syndrome–thrombotic thrombocytopenia purpura; SER = single event reported, no statistics available.

cebo, but the completion rate and compliance were not detailed in the study.[25] The use of severity as an outcome measure is also questionable, as almost all other trials use the frequency of cramps as the major outcome measure. A small Class II study using Naftidrofuryl 300 mg BID in 14 patients showed efficacy in the reduction of cramps, but dropouts were not adequately accounted for.[26] Naftidrofuryl oxalate is a drug that may enhance utilization of oxygen and glucose in peripheral vascular disease and protection of brain parenchyma during anoxia; it is not available for use in the United States. A trial (n = 27) evaluated the efficacy of vitamin E 800 U qhs vs placebo and found no effect on the mean number of cramps, number of nights with cramps, or sleep disturbance.[14] A Class II study using magnesium citrate (900 mg) with a sample size of 58 calculated to detect 25% reduction in cramp frequency at a power of 80% could not conclude that there was a significant improvement in the number of cramps in patients on treatment ($p = 0.07$),[27] and further had a high dropout rate (64%). Another Class II study evaluating the efficacy of magnesium sulfate (dose 300 mg of Mg) with a sample size of 42 calculated to detect 25% reduction in cramp frequency at a power of 90% found that treatment was not superior to placebo for number of cramps, severity, duration, or sleep disturbance.[28] A Class II, double-blind, crossover study of 13 patients studied the effects of 30 mg of diltiazem hydrochloride on the number and intensity of cramps in patients experiencing 2 or more cramps per week. The trial showed a reduction (−5.84 to −0.16 cramps per 2-week treatment phase, $p = 0.04$) in the number of cramps over time in patients treated with diltiazem compared to placebo, with no effect on the intensity of cramps.[29]

Open-label studies. Thirty patients treated with gabapentin for 9 months showed a decrease in frequency of cramps in an open-label, unblinded study.[30] Eight elderly patients refractory to quinine for treatment of cramps showed response to verapamil in a small open-label study.[31] A small study (n = 24) of lidocaine injected directly into the calf was shown to be as effective as quinine in reducing cramps, but there are practical limitations of this mode of administration.[32] A recent open-label study on the use of levetiracetam in 20 patients with motor neuron disease showed a reduction in the frequency and severity of muscle cramps over placebo in the 9 months of treatment compared to the 3-month run-in period.[33]

It is worthwhile to note that although agents such as baclofen, carbamazepine, and oxcarbazepine are frequently used in clinical practice for the management and treatment of muscle cramps, there are no clinical trials in the literature evaluating their efficacy for this indication. A few case reports and reviews commenting on the efficacy of some of these agents in the treatment of particular neuropathic conditions

(such as cramp-fasciculation syndrome) have been published.[34,35]

Also of note, variable amounts of quinine derivatives are present in consumer products such as tonic water. Although there are a few case reports reporting their efficacy in treatment of muscle cramps, there are insufficient data to allow a specific comment on their use.[36]

Adverse events. No serious side effects occurred in trials evaluating gabapentin, vitamin B complex, diltiazem, and magnesium for treatment of muscle cramps. Minor side effects such as lightheadedness, nausea, and abdominal discomfort occurred infrequently and with equal frequency in controls and treatment groups in trials of vitamin B[25] and magnesium.[27,28] Diarrhea was equally common (10%) in magnesium- and placebo-treated patients in one trial[27] and slightly more frequent in magnesium-treated patients (30% vs 17%, $p = 0.1$) in another trial.[28] Minor side effects that occurred more frequently with gabapentin treatment included lightheadedness, drowsiness, falls, and limb swelling[24] and with Naftidrofuryl treatment included mild gastrointestinal discomfort.[26] A small trial of diltiazem did not report any side effects in treated or placebo patients.[29]

Conclusion. On the basis of single Class II studies, Naftidrofuryl, vitamin B complex, and diltiazem are possibly effective in the treatment of muscle cramps. Naftidrofuryl is currently not available in the United States. Data regarding the use of magnesium preparations (2 Class II studies) and gabapentin (1 study in ALS) show that these agents are probably not effective in the treatment of muscle cramps.

Recommendation. Naftidrofuryl, diltiazem, and vitamin B complex may be considered for the treatment of muscle cramps (Level C).

RECOMMENDATIONS FOR FUTURE RESEARCH

Given the lack of evidence for any convincing treatments for muscle cramps, further research is indicated. Further investigations into the efficacy and adverse effects of medications such as baclofen, carbamazepine, oxcarbazepine, levetiracetam, lidocaine, vitamin B complex, Naftidrofuryl, gabapentin, magnesium, and calcium channel blockers are warranted. Future studies should also include an assessment of the impact of cramps on the quality of life and nonpharmacologic interventions in the treatment of muscle cramps.

DISCLOSURE

Dr. Katzberg has received funding for travel from the Muscular Dystrophy Association. Dr. Khan reports no disclosures. Dr. So receives royalties from the publication of *Occupational & Environmental Medicine* (Appleton & Lange, 2007) and articles published in *UpToDate* (2007); receives research support from Pfizer Inc, NeurogesX, Inc., and the NIH (NIEHS R01 [Co-I], NIEHS R01 [Co-I], and NINDS R01 [Site PI]); estimates 10% of his clinical effort is spent on EMG; and holds equity in Satoris, Inc.

DISCLAIMER

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Received July 23, 2009. Accepted in final form November 9, 2009.

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Endorsed by the American Association of Neuromuscular & Electrodiagnostic Medicine.

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Neurology 2010;74;691-696
DOI 10.1212/WNL.0b013e3181d0ccca