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Association Between Long-term Quinine Exposure and All-Cause Mortality

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This cohort study uses UK primary care database data to explore the association between long-term quinine exposure and all-cause mortality.

Quinine has been used since the 1930s to treat idiopathic muscular cramps. However, in 2006, because of efficacy and safety issues, the US Food and Drug Administration cautioned about this off-label use of quinine, citing “665 reports of adverse events with serious outcomes…including 93 deaths.” Despite

daily. This study explored the association between long-term quinine exposure and all-cause mortality.

Methods

This study used data recorded in The Health Improvement Network (THIN), a UK primary care database containing anonymized data on more than 12 million individuals representative of the UK population. The protocol for THIN to obtain and provide anonymous patient data was approved by a national ethics committee in 2002; need for informed consent was waived. Adults who received incident quinine salt (sulfate, bisulfate, dihydrochloride) prescriptions for idiopathic muscular cramps or restless leg syndrome for at least 1 year from January 1990 to December 2014 (last follow-up December 2015) at a mean dosage of 100 mg/d or more were considered to be exposed. This definition was chosen because the period of risk is unknown and most patients stopped quinine within weeks of death. The start date (ie, start of at-risk period) was defined as the first day of the first prescription of quinine. Individuals with muscular cramps or restless leg syndrome, never exposed to quinine or its derivatives, and with at least 1-year follow-up after a randomly selected start date were eligible to be included in the unexposed sample. Three unexposed individuals were selected for every exposed individual. The samples were stratified by sex and age. Group characteristics were compared using the χ^2 test or the Wilcoxon rank-sum test. The primary outcome (all-cause mortality) was compared between the exposed and the unexposed populations using Cox proportional hazards models adjusted for sociodemographic data, underlying conditions, and concomitant prescriptions. Post hoc subgroup analyses were conducted by age and amount of exposure (averaged over the exposure period). The proportional hazards assumption for Cox models was checked graphically using the Schoenfeld residuals. Analyses were done using Stata (StataCorp), version 14.0. A 2-sided *P* value less than .05 denoted statistical significance.

Results

The study population included 175 195 individuals (median age, 70 years [interquartile range, 61-78]; women, 57.8%; median follow-up, 5.7 years [interquartile range, 3.1-8.9]) (Table 1). Exposed persons received a median 203 mg/d (interquartile range, 163-252) of quinine. There were 11 598 deaths (4.2 per 100 person-years) among the 44 699 exposed individuals vs 26 753 (3.2 per 100 person-years) among the 130 496 unexposed individuals (adjusted hazard ratio [HR], 1.24 [95% CI, 1.21-1.27]). The increase in the risk of death was more pronounced in those younger than 50 years (adjusted HR, 3.06 [95% CI, 2.51-3.73]), whatever the indication for prescription (Table 2). A dose-effect was found for exposure of 200 to 299 mg/d (adjusted HR, 1.25 [95% CI, 1.20-1.30]), 300 to 399 mg/d (adjusted HR, 1.83 [95% CI, 1.72-1.94]), and 400 mg/d or more (adjusted HR, 2.24 [95% CI, 1.95-2.58]) compared with less than 200 mg/d (*P* value for trend, <.001).

Discussion

In this study, long-term quinine exposure was associated with increased mortality. Individuals in this study received more than 100 mg/d of quinine, equivalent to a daily consumption of more than 1 L of bitter lemon or tonic waters.

Quinidine, an isomer of quinine, increases by 3-fold the risk of death (mainly sudden cardiac arrests) compared with placebo or no treatment. Short-term quinine exposure may lead to life-threatening adverse events, such as thrombocytopenia, hypoglycemia, or cardiac arrhythmia. In a study, the incidence rate ratio of death in individuals with heart failure initiating quinine for leg cramps was 1.19 (95% CI, 1.14-1.24) compared with unexposed patients. However, mortality of long-term users has not been studied.

explain the lower increased risk in the elderly. Because death certificates were not accessible, the mortality causes are unknown.

The benefits of quinine in reducing cramps should be balanced against the risks.

Notes

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References

1. US Food and Drug Administration, Dept of Health and Human Services . *Drug products containing quinine; enforcement action dates*. https://www.fda.gov/OHRMS/DOCKETS/98fr/06-9713.htm. Accessed March 22, 2017.

2. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care*. 2011;19(4):251-255. [PubMed: 22828580]

3. Feas X, Brasic JR, Fente CA, Cepada A. La quinina y sus posibles implicaciones toxicológicas: análysis de aguas tónicas en España [in Spanish]. *Rev Esp Nutr Comunitaria*. 2009;15:97-102.

4. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation*. 1990;82(4):1106-1116. [PubMed: 2144796]

5. Katzberg HD, Khan AH, So YT. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the therapeutics and technology assessment subcommittee of the American academy of neurology. *Neurology*. 2010;74(8):691-696. [PubMed: 20177124]

6. Gjesing A, Gislason GH, Christensen SB, et al. . Use of quinine and mortality-risk in patients with heart failure—a Danish nationwide observational study. *Pharmacoepidemiol Drug Saf*. 2015;24(3):310-318. [PubMed: 25656791]

Figures and Tables

Table 1.

Characteristics of Individuals in the United Kingdom Exposed vs Unexposed to Quinine

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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

[a]Start date was defined as the first day of the first prescription of quinine.
[b]Including Steinert disease, nemaline body disease, and Becker muscular dystrophy.
[c]Can induce idiopathic muscular cramps

Table 2.

All-Cause Deaths in the Individuals Exposed And Unexposed to Quinine

	No. of Deaths/Total Exposed Individuals (%)	No. of Deaths/Total Unexposed Individuals (%)	Crude Hazard Ratio (95% CI)[a]	Adjusted Hazard Ratio (95% CI)[a,b]
Overall population	11 598/44 699 (26.0)	26 753/130 496 (20.5)	1.32 (1.29-1.35)	1.24 (1.21-1.27)
Age, y				
≤50	258/3361 (7.7)	198/10 374 (1.9)	4.16 (3.46-5.01)	3.06 (2.51-3.73)
51-70	3069/18 935 (16.2)	5957/56 280 (10.6)	1.60 (1.53-1.67)	1.37 (1.31-1.43)
>70	8271/22 403 (36.9)	20 598/63 842 (32.3)	1.20 (1.17-1.23)	1.16 (1.13-1.19)
Individuals with muscular cramps	11 138/42 865 (26.0)	25 810/125 424 (20.6)	1.32 (1.29-1.35)	1.24 (1.21-1.27)
Age, y				
≤50	248/3156 (7.9)	188/9759 (1.9)	4.23 (3.50-5.12)	3.06 (2.50-3.76)
51-70	2952/18 186 (16.2)	5750/54 109 (10.6)	1.60 (1.53-1.67)	1.36 (1.30-1.42)
>70	7938/21 523 (36.9)	19 872/61 556 (32.3)	1.20 (1.17-1.23)	1.16 (1.13-1.19)
Individuals with restless leg syndrome	460/1834 (25.1)	943/5072 (18.6)	1.35 (1.21-1.51)	1.22 (1.09-1.36)
Age, y				
≤50	10/205 (4.9)	10/615 (1.6)	2.95 (1.22-7.08)	2.82 (1.17-6.81)[c]
51-70	117/749 (15.6)	207/2171 (9.5)	1.64 (1.31-2.06)	1.54 (1.22-1.95)
>70	333/880 (37.8)	726/2286 (31.8)	1.19 (1.05-1.36)	1.11 (1.02-1.21)

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[a]All hazard ratios were statistically significant (all *P* values <.001, except for adjusted hazard ratios regarding individuals older than 70 years with restless leg syndrome [*P* = .02]).

[b]All adjusted models were adjusted on age and sex. All the following variables were further considered to be included in the Cox multivariable models: body mass index (<18, 18-24.9, 25-29.9, ≥30; calculated as weight in kilograms divided by height in meters squared), Townsend deprivation score, smoking status, history of cancer, hematological malignancy, diabetes, hypertension, coronary artery disease, congestive heart failure, peripheral ischemic vascular disease, cardiac conduction disorders, cardiac dysrhythmias, amyotrophic lateral sclerosis, multiple sclerosis, or muscular dystrophies, number of prescriptions of diuretics, β-blockers, calcium channel blockers (including diltiazem), oral glucocorticoids, and oral nonsteroidal anti-inflammatory drugs. Some first-order interaction terms (eg, interactions between group and sex, coronary artery disease and congestive heart failure, coronary artery disease and peripheral ischemic vascular disease) were also considered to be included in the models. Variables to be retained in the models were selected using manual stepwise procedures with backward selection. The final models were selected as those that provided the lowest Akaike information criterion and Bayesian information criterion.

[c]Adjusted on age and sex only.