Association between chronic quinine exposure and all-cause mortality

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Background

Quinine has been used since the 1930s to treat idiopathic muscular cramps. However, in 2006, because of efficacy and safety issues, the U.S. Food and Drug Administration cautioned about this off-label use of quinine, citing "665 reports of adverse events with serious outcomes (…), including 93 deaths".[1] Despite warnings, quinine is still prescribed to individuals with idiopathic muscular cramps. Further, many drinks such as bitter lemon or tonic waters contain quinine, and hence, many are exposed to quinine 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.[2] Adults who received incident quinine sulfate/bisulfate/dihydrochloride prescriptions for idiopathic muscular cramps or restless leg syndrome for at least one year from January 1990 to December 2014 (last follow-up December 2015) at a mean dosage ≥100 mg/day were considered to be *exposed*. The 'start date' (i.e., 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 one 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 in term of sex and age. Groups' characteristics were compared using the Chi^2 test or the Wilcoxon rank-sum test. The primary outcome (i.e., all-cause mortality) was compared between the exposed and the unexposed populations using Cox proportional hazards models adjusted on socio-demographic data, underlying conditions and concomitant prescriptions. Post-hoc subgroup analyses were conducted according to age and

to amount of exposure. The proportional hazards assumption for Cox models was checked graphically using the Schoenfeld residuals. All analyses were done using Stata 14.0. A two-sided p-value ≤0.05 denoted statistical significance. The scheme for THIN to obtain and provide anonymous patient data was approved by a national ethic Committee in 2002. The need for informed consent was waived.

Results

The study population was made of 175,195 individuals (median age (IQR): 70 (61-78) years, women: 57.8%, median follow-up: 5.7 (3.1-8.9) years) (Table 1). There were 11,598 deaths (4.2 per 100 person-years) among the 44,699 exposed individuals versus 26,753 (3.2 per 100 person-years) among the 130,496 unexposed individuals (adjusted HR: 1.24 (95%CI, 1.21-1.27)). The increase in the risk of death was more pronounced in those under 50 years of age (adjusted HR: 3.06 (2.51-3.73)), whatever the indication for prescription (Table 2). A dose-effect was found (adjusted HRs: 1.25 (1.20-1.30), 1.83 (1.72-1.94), and 2.24 (1.95-2.58), respectively for exposure 200-299, 300-399 and ≥400 mg/day by comparison to <200 mg/day, p-value for trend <0.001).

Discussion

Quinine compared to placebo is effective in reducing both cramps number and intensity.[3] Individuals included in this study received on average more than 100 mg/day of quinine, equivalent to a daily consumption of one liter of bitter lemon or tonic waters. [4]

Short term quinine exposure may lead to life threatening adverse events such as thrombocytopenia, hypoglycemia, or cardiac arrhythmia.[3] In a recent study, the incidence rate ratio of death in individuals with heart failure initiating quinine for leg cramps was 1.19 (1.14-

1.24) when compared to unexposed patients.[5] Mortality of long-term users was not compared to mortality of short-term users.[5]

The findings have limitations. Cramps may be due to underlying conditions or unmeasured confounders that predispose patients to higher mortality rather than exposure to quinine per se. No data was available regarding quinine beverages consumption. A competing risk may explain the lower increase of risk in the elderly but as death certificates were not accessible the mortality causes are unknown.

Quinidine, an isomer of quinine increases by three-fold the risk of deaths by comparison to placebo or no treatment.[6] These deaths are mainly explained by sudden cardiac arrests.[6]

Acknowledgment

Laurence Fardet had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Fardet, Dr Nazareth and Dr Petersen have nothing to disclose. There are no financial or material supports for this work.

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Table 1: Characteristics of the study population

	Exposed (n=44,699)	**Unexposed** (n=130,496)	**p-value**
Age, median [IQR], years	71 (61-78)	70 (61-78)	<0.001
Female, n (%)	25,818 (57.8)	75,379 (57.8)	0.98
'Start date', median [IQR]	Jul 2006 (Feb 2003-Sept 2009)	Jul 2006 (Apr 2003-Oct 2009)	<0.001
Duration of follow-up after 'start date', median [IQR], years	5.5 (3.0-8.7)	5.7 (3.1-8.9)	<0.001
Time between end of exposure and end of follow-up, , median [IQR], days	25 (0-310)	-	-
Quinine dosage, median [IQR], mg/day	203 (163-252)	-	-
Underlying diseases, n (%)			0.04
Idiopathic muscular cramps	42,865 (95.9)	125,424 (96.1)	
Restless leg syndrome	1,834 (4.1)	5,072 (3.9)	
Smoking status, n (%)			<0.001
Non-smokers	18,597 (41.6)	64,707 (49.6)	
Ex-smokers	16,622 (37.2)	41,636 (31.9)	
Smokers	7,814 (17.5)	20,214 (15.5)	
Missing	1,666 (3.7)	3,939 (3.0)	
BMI, median [IQR], kg/m^2	27.6 (24.2-31.6)	26.9 (24.0-30.4)	<0.001
Past history of, n (%)			
Cancer	5,976 (13.4)	16,984 (13.0)	0.06
Hematological malignancy	593 (1.3)	1,069 (0.8)	<0.001
Hypertension	19,748 (44.2)	53,046 (40.7)	<0.001
Diabetes	8,522 (19.1)	15,645 (12.0)	<0.001
Coronary artery disease	9,199 (20.6)	21,424 (16.4)	<0.001
Congestive heart failure	2,610 (5.8)	5,696 (4.4)	<0.001
Peripheral ischemic vascular disease	2,351 (5.3)	5,766 (4.4)	<0.001
Cardiac conduction disorder	239 (0.5)	958 (0.7)	0.60
Cardiac dysrythmia	3,309 (7.4)	11,242 (8.6)	<0.001
Amyotrophic lateral sclerosis	64 (0.1)	18 (0.01)	<0.001
Multiple sclerosis	207 (0.5)	753 (0.6)	0.005
Muscular dystrophy[a]	13 (0.03)	17 (0.01)	0.03
Number of prescriptions of, n (%)			
Diuretics [b]	0 (0-27)	0 (0-25)	<0.001
Beta blockers [b]	0 (0-18)	0 (0-18)	<0.001

Calcium channel blockers	0 (0-17)	0 (0-15)	<0.001
Including diltiazem [c]	0 (0-2)	0 (0-1)	<0.001
B complex vitamin [c]	0 (0-0)	0 (0-0)	<0.001
Statins [b]	0 (0-16)	0 (0-13)	<0.001
Oral glucocorticoids [b]	0 (0-2)	0 (0-1)	<0.001
Non steroidal anti-inflammatory drugs	0 (0-15)	0 (0-9)	<0.001

Continuous variables are reported as medians and interquartile ranges except for medication prescriptions which are reported as medians and 5%-95% ranges

[a] including Steinert's disease, nemaline body disease, Becker muscular dystrophy

[b] can induce idiopathic muscular cramps

[c] recommended for idiopathic muscular cramp treatment

Table 2: All-cause deaths in the exposed and unexposed populations

	Exposed N (%)	**Unexposed N (%)**	**Crude Hazard Ratios (95% CI)**	**Adjusted Hazard Ratios (95% CI)**
Overall population				
All individuals				
n	44,699	130,496		
Deaths, n (%)	11,598 (26.0)	26,753 (20.5)	1.32 (1.29-1.35)	1.24 (1.21-1.27)
Individuals aged ≤ 50 y				
n	3,361	10,374		
Deaths, n (%)	258 (7.7)	198 (1.9)	4.16 (3.46-5.01)	3.06 (2.51-3.73)
Individual aged 51-70 y				
n	18,935	56,280		
Deaths, n (%)	3,069 (16.2)	5,957 (10.6)	1.60 (1.53-1.67)	1.37 (1.31-1.43)
Individuals aged > 70 y				
n	22,403	63,842		
Deaths, n (%)	8,271 (36.9)	20,598 (32.3)	1.20 (1.17-1.23)	1.16 (1.13-1.19)
Individuals with muscular cramps				
All individuals				
n	42,865	125,424		
Deaths, n (%)	11,138 (26.0)	25,810 (20.6)	1.32 (1.29-1.35)	1.24 (1.21-1.27)
Individuals aged ≤ 50 y				
n	3,156	9,759		
Deaths, n (%)	248 (7.9)	188 (1.9)	4.23 (3.50-5.12)	3.06 (2.50-3.76)
Individuals aged 51-70 y				
n	18,186	54,109		
Deaths, n (%)	2,952 (16.2)	5,750 (10.6)	1.60 (1.53-1.67)	1.36 (1.30-1.42)
Individuals aged > 70 y				
n	21,523	61,556		
Deaths, n (%)	7,938 (36.9)	19,872 (32.3)	1.20 (1.17-1.23)	1.16 (1.13-1.19)
Individuals with restless leg syndrome				

All individuals				
n	1,834	5,072		
Deaths, n (%)	460 (25.1)	943 (18.6)	1.35 (1.21-1.51)	1.22 (1.09-1.36)
Individuals aged ≤ 50 y				
n	205	615		
Deaths, n (%)	10 (4.9)	10 (1.6)	2.95 (1.22-7.08)	2.82 (1.17-6.81)[a]
Individuals aged 51-70 y				
n	749	2,171		
Deaths, n (%)	117 (15.6)	207 (9.5)	1.64 (1.31-2.06)	1.54 (1.22-1.95)
Individuals aged > 70 y				
n	880	2,286		
Deaths, n (%)	333 (37.8)	726 (31.8)	1.19 (1.05-1.36)	1.11 (1.02-1.21)

All adjusted models were adjusted on age and sex. All the following variables were further considered to be included in the Cox multivariable models: BMI (<18, 18-24.9, 25-29.9, ≥ 30 kg/m^2), Townsend deprivation score (categorical), smoking status (non smoker, ex-smoker, smoker, missing), history of cancer (yes/no), hematological malignancy (yes/no), diabetes (yes/no), hypertension (yes/no), coronary artery disease (yes/no), congestive heart failure (yes/no), peripheral ischemic vascular disease (yes/no), cardiac conduction disorders (yes/no), cardiac dysrythmias (yes/no), amyotrophic lateral sclerosis (yes/no), multiple sclerosis (yes/no), or muscular dystrophies (yes/no), number of prescriptions of diuretics, beta blockers, calcium channel blockers (including diltiazem), oral glucocorticoids, and oral non-steroidal anti-inflammatory drugs (continuous or categorical depending of the log likelihood ratio test results). Some first-order interaction terms (e.g., 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 kept in the models were selected using manually stepwise procedures with backward selection. The final models were selected as those that provided the lowest Akaike information criterion and Bayesian information criterion.

All HRs were statistically significant (all p-values <0.001except for adjusted HR regarding those >70 year-old with restless leg syndrome p-value=0.02).

[a] Adjusted on age and sex only