Frida von Arenstorff Vilstrup
04-05-2023

Treatment with Quinine and the risk of exacerbations and mortality in patients with chronic obstructive pulmonary disease

Supervisors

Jens-Ulrik Stæhr Jensen, Ph.d., klinisk professor, forskningsansvarlig overlæge Lungemedicinsk sektion, Medicinsk afdeling, Herlev-Gentofte Hospital

Pradeesh Sivapalan, Ph.d., Post doc Lungemedicinsk sektion, Medicinsk afdeling, Herlev-Gentofte Hospital

Background

Idiopathic muscle cramps are a common and distressing phenomenon - especially in elderly people. It often occurs in the legs as the so-called “restless leg syndrome”, which can be quite invalidating if for example it occurs at night and interrupts the sleep. Quinine is commonly used in treatment of these nocturnal leg cramps [1], although the documentation of its effect on this condition is sparse.

Originally, this drug was used in malaria treatment, but in the 1940s its beneficial effects in the treatment of cramps were indicated in a series of studies, and since Quinine has been used for this purpose [1]. It helps by decreasing the excitability of the motor end plate, which leads to a reduced response to nerve stimulation. Furthermore, the drug increases the muscle refractory period and thereby reduces its response to repetitive stimulation [2].

A randomized controlled trial by Jansen et al from 1997 found that the use of Quinine compared to placebo significantly reduced the number of muscle cramps (65% of participants reported at least 50% reduction in number of cramps). This study found that Quinine only resulted in mild side-effects [3]. Similarly, observational before-after studies and small randomized controlled trials have suggested a moderate but significant effect of quinine on muscle cramps [4]. A subcommittee of the American Academy of Neurology correspondingly found quinine derivatives to be effective in reducing the frequency of muscle cramps in a review from 2010 [5]. However, they also found that the extent of benefits is small, while the drugs are associated with serious side effects, and they thus recommend against the use of Quinine as treatment for muscle cramps.

In malaria treatment the dosage of Quinine is usually 600 mg four times a day, while the dosage for treatment of muscle cramps is usually 200-300 mg, which obviously minimizes the dose-related adverse effects of the drug [1]. However, there is indication to believe that the drug - even in smaller doses - is not without side effects.

In 2006, the US Food and Drug Administration warned against the use of quinine to treat muscle cramps because of efficacy and safety issues [6]. In 2018, the Danish Medicines Agency changed the status on drugs containing minimum 100 mg Quinine from over the counter to by prescription. This change was based on the European Medicines Agency’s recommendations, which

state that Quinine entails an increased mortality risk in patients with heart failure [7].

The correlation between the use of Quinine and mortality has been investigated in previous scientific studies. A cohort study (N:175,195) by Fardet et al from 2017 found a significantly increased mortality risk in persons exposed to Quinine compared to persons not exposed to the drug (Hazard Ratio (HR) 1.24, 95% Confidence Interval (CI) 1.21-1.27) [8]. Similar results were found in an observational study (N:135,529) by Gjesing et al from 2015, in which a slightly increased mortality risk with the use of Quinine alone was found (incidence rate ratio (IRR) 1.04, 95% CI 1.01-1.07). However, the highest mortality risk in this study was found with Quinine-use combined with beta-blockers (IRR 1.15, 95% CI 1.09-1.21) [9].

The first-mentioned study included all patients with a prescription of Quinine for minimum 12 months. Meanwhile, the study by Gjesin et al focused only on patients with heart failure because they often experience leg cramps and therefore the drug is frequently prescribed to these patients [9].

Aim

The goal of this study is to clarify whether there is a connection between the use of Quinine and the number and severity of exacerbations of COPD. Furthermore, the goal is to investigate the effect of Quinine-use on the mortality related to COPD-exacerbations.

Hypothesis

The use of Quinine enhances the risk of exacerbations and mortality among patients with severe or very severe COPD*.

*defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) group C/D and/or FEV1<30% [10].

Method

Study design: National observational cohort study.

Study population: Danish patients with COPD registered in Dansk Register for Kronisk Obstruktiv Lungesygdom (DrKOL). DrKOL is a nationwide database, which contains information on the quality of treatment of patients with COPD in Denmark.

The Danish Health Authority administers the Register of Pharmaceutical Sales (Lægemiddelstatistikregistret, LSR) and the National Patient Register (landspatientregistret, LPR). LSR contains information on all prescriptions made in Denmark, which among other things includes dosage and date of issuance of the prescription. LPR contains information on all hospital admissions and outpatient visits in Denmark.

A user of Quinine is defined as a person with a prescription of Quinine (minimum 100 mg) for 12 months (based on Anatomical Therapeutic Chemical (ATC) code: M09AA).

Study period: Patients are included at first outpatient visit in the period January 1st, 2010 - December 31st, 2018. The follow-up period is twelve months after inclusion in the study.

Inclusion criteria:

- Patient in the DrKOL-population with outpatient visit
- Age $\geq$ 40 years

Exclusion criteria:

- Cancer diagnosed within the last five years before inclusion date except from basocellular carcinoma (International Classification of Disease (ICD)-10 koder: C00-C97 ex. C44 and D00-D09 ex. D04)

Primary endpoints: Hospitalization-requiring exacerbation of COPD or death within twelve months.

Secondary endpoints: Moderate exacerbations of COPD, defined as:

> The patient is not hospitalized but issued a prescription of oral corticosteroids (ATC: H02AB06) and/or respiratory antibiotics (Amoxicillin, Bioclavid with cluvalanic acid, Penicillin, Moxifloxacin, Azithromycin, Flurithromycon, Roxithromycin Clarithromycin, Doxycyklin and Ciprofloxacin (ATC: J01CA04, J01CR02, J01CE01 + J01CE02, J01MA14, J01FA14, J01FA06, J01FA09, J01AA02 + A01AB22 and J01MA02)) within twelve months.

The paper follows guidelines from STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology).

Statistical Analyses

Statistical analyses will be performed in SAS version 9.4 through The Danish Health Authority. Categorical variables are presented as frequencies and proportions, while continual variables are presented as median values and interquartile intervals (IQRs) for data. A p-value of <0.05 is accepted as statistically significant.

Comparisons will be performed by t-tests if they are normally distributed. If they are not, non-parametric tests such as Wilcoxon or Mann-Whitney, will be used. Survival analyses will be made with Cox proportional hazards model.
The analyses will be adjusted for GOLD-class (1-4), age group, gender (male/female), BMI-group, smoking status (group I: active smoker, group II: previous smoker or non-smoker), number of COPD-exacerbations one year before baseline (0, 1, $\geq$2), inclusion year (2010, $\geq$2011), and

Charlson Comorbidity Index ten years before inclusion date (0-2 points = mildly ill, 3-4 points = moderately ill, ≥5 points = severely ill [11,12]).

Model control will be performed and chosen interactions will be tested.

Sensitivity analyses:

A propensity score matched cohort will be created, which is matched on a number of known predictors of the investigated outcome; GOLD-class (1-4), age group, gender (male/female), BMI-group, smoking status (group I: active smoker, group II: previous smoker or non-smoker), number of COPD-exacerbations one year before baseline (0, 1, ≥2), inclusion year (2010, ≥2011), and Charlson Comorbidity Index ten years before inclusion date (0-2 points = mildly ill, 3-4 points = moderately ill, ≥5 points = severely ill [11,12]).

Missing data:

In the Cox-analysis, patients with missing data in one or more of the variables adjusted for will *not* be excluded from the population. Instead, the missing variable will be searched for in the next outpatient-visit and in cases where this is not found, multiple imputation will be performed.

Afterwards outcome tables with 12-month mortality among patients with imputed data compared to patients with complete data sets and therefore no imputations will be performed. If this shows a significant difference between the two groups, a supplementary Complete Case Analysis will be performed, in which patients with missing data will be excluded.

Timeline

Analyses will be performed in May, June, and July. First draft of the paper is ready in August, and it will be submitted in October 2023.

Approval

There will be applied for approval from the Danish Data Protection Agency. In Denmark retrospective use of register data does not require ethical approval or patient consent.

References

1. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005044.pub2/full

2. Goodman and Gilman's: The Pharmacological Basis of Therapeutics, https://accessmedicine.mhmedical.com/content.aspx?bookid=1613&sectionid=102124003

3. https://core.ac.uk/reader/16113722?utm_source=linkout

4. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005044.pub2/full

5. https://n.neurology.org/content/74/8/691.long

6. https://www.fda.gov/media/75097/download

7. https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-prac-meeting-10-13-may-2016_en.pdf

8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5815033/

9. https://pubmed.ncbi.nlm.nih.gov/25656791/

10. https://goldcopd.org/wp-content/uploads/2018/02/WMS-GOLD-2018-Feb-Final-to-print-v2.pdf

11. *Charlson.-1987.-Comorbidity*. (n.d.).

12. Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J.-C., Saunders, L. D., Beck, C. A., Feasby, T. E., & Ghali, W. A. (2005). *Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data*.