Use of quinine is associated with increased mortality in chronic heart failure – a nationwide register-based cohort study

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We have no relevant disclosures to report!

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Background

- Leg cramps are common in patients with heart failure due to impaired peripheral blood flow, and side effects from medications, including electrolyte derangements.

- The anti-malaria drug quinine is often prescribed off-label to these patients, but the safety of this practice is unknown.
Background

FDA NEWS RELEASE
FOR IMMEDIATE RELEASE
P06-195
December 11, 2006

FDA Advances Effort Against Marketed Unapproved Drugs
FDA Orders Unapproved Quinine Drugs from the Market and GPs

The Food and Drug Administration (FDA) today ordered firms to stop marketing unapproved drugs, concerns, including deaths, associated with quinine products. There are multiple unapproved by the FDA.

As part of its action, FDA is also cautioning consumers about off-label use of quinine to treat leg cramps and similar conditions. Because malaria is life-threatening, the FDA believes it should not be used to prevent or treat leg cramps.

The action posted in a Federal Register notice is part of FDA’s continued efforts to protect the public health.

"Providing the American public with safe and effective medical products is our co-
presence of unapproved drugs on the U.S. market is in stark contrast to our current effectiveness, quality, and labeling. As part of our drug safety efforts, we are committed to ensuring the public health.

One quinine drug product, Mutual Pharmaceutical Company, Inc.’s Qualaquin, is FDA

unapproved quinine drug products are marketed without labeling cautioning against extensive warnings regarding serious adverse events associated with use of quinine products. Quinine is a drug with a narrow margin between an effective dose and a toxic dose. The dosing for the unapproved drugs has not been reviewed and approved by the FDA."

The text is from the FDA news release on December 11, 2006, discussing the removal of unapproved quinine drugs from the market due to safety concerns.
Background

FDA NEWS RELEASE
FOR IMMEDIATE RELEASE
P06-195
December 11, 2006

Using Malaria Medication for Leg Cramps is Risky

People who use the drug Qualaquin to treat or prevent nighttime leg cramps may be at risk for serious and life-threatening reactions, according to the Food and Drug Administration (FDA).

Qualaquin (quinine sulfate) is FDA-approved only to treat a certain type of malaria (uncomplicated malaria) caused by the parasite Plasmodium falciparum. This infection, which is rare in the United States, is found mainly in travelers who have been to countries where malaria occurs.

However, most of Qualaquin’s use in the U.S. is for the treatment or prevention of nighttime leg cramps—a use not approved by FDA.

FDA has received reports of side effects, including bleeding, blood in your urine or stool, bleeding gums, or the appearance of unusual purple, brown, or red spots on your skin.

The action

Providing the presence of effective

One quinine unapproved extensive used. Qualaquin the product
Potential adverse effects

- Conduction disorders
- QT-prolongation
- Bone marrow suppression
Aims

• To investigate the proportion of heart failure patients treated with quinine in Denmark and the outcomes associated with use of quinine.
Methods

• Nationwide administrative registers
  – The Danish prescription register
  – National patient register
  – Population register

• Linked at an individual level

• Risks analysed by multivariable Poisson regression models.
Methods

- All patients discharged from first-time hospitalization for heart failure between 1997-2010 and alive 30 days after discharge (study start).
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- Prescription claims on quinine and loop diuretics updated continuously.

- Loop diuretic dosages used as a proxy for heart failure severity.
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- Followed for the risk of death, maximally until December, 31, 2010.

- Prescription claims on quinine and loop diuretics updated continuously.

- Loop diuretic dosages used as a proxy for heart failure severity.

- Analyses also adjusted for sex, comorbidities, concomitant pharmacotherapy at study start, and for calendar year of hospitalization.
Population

- 136,427 patients included.
- 47% women.
- Mean age 74 (± standard deviation 13) years.
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- 47% women.
- Mean age 74 (± standard deviation 13) years.
- Median time of follow 2.8 years (IQR 1.0-5.6 years).
- 88,878 (65%) died.
Results

- 14,306 patients (11%) used quinine at some point throughout the study period.
- Quinine users were older and used higher loop diuretic dosages than non-users.
- Adjusted RR 1.03 (1.00-1.06)
<table>
<thead>
<tr>
<th></th>
<th>IHD (50,793)</th>
<th>No IHD (85,634)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>No beta</td>
</tr>
<tr>
<td>Numbers</td>
<td>30,281 (60%)</td>
<td>20,512 (40%)</td>
</tr>
<tr>
<td>Exposed to quinine</td>
<td>3016 (10%)</td>
<td>2941 (14%)</td>
</tr>
<tr>
<td>Quinine</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Events</td>
<td>16292</td>
<td>1007</td>
</tr>
</tbody>
</table>

**Ischemic heart disease**

- **Betablockers**
  - Quinine: 20 (100 PY)
  - No quinine: 10 (100 PY)

- **No betablockers**
  - Quinine: 30 (100 PY)
  - No quinine: 20 (100 PY)

**No ischemic heart disease**

- **Betablockers**
  - Quinine: 5 (100 PY)
  - No quinine: 5 (100 PY)

- **No betablockers**
  - Quinine: 6 (100 PY)
  - No quinine: 5 (100 PY)
Limitations

• Register-based
• Residual confounding
• Lacked a variety of important variables:
  – LVEF
  – Measurements of renal function
  – NYHA class
Conclusions

- Use of quinine was associated with increased mortality in chronic heart failure, especially among those with ischemic heart disease.

- The adverse effect was much potentiated by concomitant use of beta blockers and the combination should be avoided.
Conclusions

- Clinicians should attempt to find a way of treating leg-cramps other than to prescribe quinine.

Contact: ca@heart.dk
### Baseline table

<table>
<thead>
<tr>
<th></th>
<th>Quinine</th>
<th>No quinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>78 (10)</td>
<td>74 (14)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>39%</td>
<td>54%</td>
</tr>
<tr>
<td>Mean Charlson score</td>
<td>2.0 (1.9)</td>
<td>1.3 (1.6)</td>
</tr>
<tr>
<td>COPD</td>
<td>30%</td>
<td>18%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21%</td>
<td>15%</td>
</tr>
<tr>
<td>Cardiac dysrythmias</td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Loop class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21%</td>
<td>30%</td>
</tr>
<tr>
<td>1</td>
<td>39%</td>
<td>42%</td>
</tr>
<tr>
<td>2</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>3</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>21%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Time-dependent exposure

• Ischemic heart disease and no betablockers
  – 0-14 days of exposure RR 0.96 (0.72-1.29)
  – >14 days of exposure RR 1.08 (1.03-1.14)

• Ischemic heart disease and betablockers
  – 0-14 days of exposure RR 1.37 (1.02-1.84)
  – >14 days of exposure RR 1.15 (1.08-1.23)
Extra slides

• Absorption: Oral: Readily absorbed mainly from the upper small intestine
• Protein binding: 70% to 95%
• Metabolism: Primarily in the liver
• Half-life: 8-14 hours
Mechanism of action

- affects calcium distribution within muscle fibers and decreases the excitability of the motor end-plate region