Use of Proton Pump Inhibitors and Risk of Bone Fractures in Adults

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Overview

• Background
• Results of Observational Studies
• Additional Questions to Answer
• Conclusion and FDA Actions
Background - Proton Pump Inhibitors (PPIs)

• First PPI approved in 1989
• PPIs work by reducing acid production in the stomach.
• PPIs available by prescription treat conditions such as gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and inflammation of the esophagus.
• PPIs are available over-the-counter (OTC) for the treatment of frequent heartburn.
Background - Safety Signal

• Medical literature has reported an overuse of PPIs whereby PPIs are prescribed off-label and/or for longer periods of time than initially labeled.¹, ²

• Several publications in the late 2000’s reported an association of PPI use with an increased risk of bone fractures.

• FDA evaluated the new safety information to determine if necessary to require a safety labeling change

Observational Studies

Case-control studies

- Populations:
  Danish nationwide registry; UK/GPRD; PHRDR Manitoba, Canada; Kaiser Permanente Northern California
- Selection: Cases with incident fracture, matched controls
- Duration: PPI exposure ranged from 1 to 12 years

Prospective cohort studies

- Populations:
  WHI OS/ WHI CT, MrOS/SOF
- Selection: PPI users and non-users with no prior hip fracture
- Duration: mean follow-up time 5 ½ to 8 years
- Outcome:
  - Fracture assessment
  - Bone mineral density measurements by DEXA
Varied Study Results

• Majority of studies reporting an increase in fractures with proton pump inhibitor use.
• One study did not find a relationship between proton pump inhibitor use and fractures. This study limited the study population to those without major risk factors for fracture. (Kaye et al. 2008)
• No consistent association between chronic PPI use and bone mineral density.
• Dose information not always available.
<table>
<thead>
<tr>
<th>Study</th>
<th>Fracture</th>
<th>Odds Ratio</th>
<th>Duration of PPI Tx</th>
<th>Dose-Response Relationship?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestergaard et al. 2006</td>
<td>All</td>
<td>1.18</td>
<td>&lt;1 year since last use</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>1.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spine</td>
<td>1.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al. 2006</td>
<td>Hip</td>
<td>1.44</td>
<td>&gt;1 year</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>2.65</td>
<td>&gt;1 year with high dose</td>
<td></td>
</tr>
<tr>
<td>Targownik et al. 2008</td>
<td>All</td>
<td>1.92</td>
<td>≥7 years</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>1.62</td>
<td>5+ years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>4.55</td>
<td>7+ years</td>
<td></td>
</tr>
<tr>
<td>Corley et al. 2010</td>
<td>Hip</td>
<td>1.30</td>
<td>&gt;2 years</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Hip</td>
<td>1.41</td>
<td>&gt;2 years with high dose</td>
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<tr>
<td>Gray et al. 2010</td>
<td>All</td>
<td>aHR = 1.25</td>
<td>Mean 7.8 years</td>
<td>N/A</td>
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<tr>
<td></td>
<td>Hip</td>
<td>aHR = 1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spine</td>
<td>aHR = 1.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wrist</td>
<td>aHR = 1.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu et al. 2008</td>
<td>Hip (F)</td>
<td>aRH = 1.16</td>
<td>Female: mean 7.6 years</td>
<td>N/A</td>
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<tr>
<td></td>
<td>Hip (M)</td>
<td>aRH = 0.62</td>
<td>Male: mean 5.6 years</td>
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</tr>
<tr>
<td></td>
<td>Nonspine (F)</td>
<td>aRH = 1.34</td>
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<td></td>
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<tr>
<td></td>
<td>Nonspine (M)</td>
<td>aRH = 1.21</td>
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</tbody>
</table>
What We Learned

- Increased risk of hip, wrist, and spine fractures amongst PPI users.
- Greatest increased risk involved people who had been taking prescription PPIs for at least 1 year or who had been taking high doses of prescription PPIs.
- Time to emergence of fractures varied; an increase being observed after 1 year to 5-7 years of PPI use.
- Association demonstrated in studies where the population had at least one major risk factor for fracture.
- Majority of the studies evaluated individuals 50 years of age or older. The increased risk of fracture was primarily observed in this age group.
Limitations of Data

• Observational Studies
  – Claims data from administrative databases
    • Not consistent with actual use
    • Missing information
  – Self-report questionnaires
    • Dose not always captured
  – Cannot assess causality

• Publications
  – No access to raw data
Additional Questions to Answer

• Which more significantly contributes to risk, PPI dose, duration of use, or both?
• Is there a particular PPI dose associated with fracture risk?
• What is the variable level of risk by drug metabolism level (CYP2C19 poor and intermediate vs. extensive metabolizers)?
• What is the mechanism that contributes to increased fracture risk?
• What is the impact of PPIs on bone in pediatric patients?
**Conclusions and FDA Actions**

- FDAAA safety labeling change enacted [under Section 505(o)(4) of the FDCA] due to possible increased risk of fractures of the hip, wrist, and spine with multiple daily dose and long term PPI use†

- Need further investigation regarding causality and the magnitude of this risk
  - A postmarketing clinical trial evaluating bone turnover markers in the presence of PPIs
  - DGIEP continues to assess risk via other CDER collaborations
  - Keep abreast of new scientific data

Thank you!
Back Up Slides
WARNINGS AND PRECAUTIONS:
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines. [see Dosage and Administration (2) and Adverse Reactions (6)]
References


Katz MH. Opportunities to decrease inappropriate uses of proton pump inhibitors: comment on "proton pump inhibitor use and the antifracture efficacy of alendronate". *Arch Intern Med*. 2011 Jun 13;171(11):1004-5.


