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

1. Katz MH. Arch Int Med. 2011.
2. Heidelbaugh JJ et al. Am J Gastroenterol. 2009

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.

Observational Studies' Results Table

Study	Fracture	Odds Ratio	Duration of PPI Tx	Dose-Response Relationship?
Vestergaard *et al.* 2006	All Hip Spine	1.18 1.45 1.60	<1 year since last use	No
Yang *et al.* 2006	Hip Hip	1.44 2.65	>1 year >1 year with high dose	Yes
	Hip Hip	1.22 1.59	1 year 4 years	
Targownik *et al.* 2008	All Hip Hip	1.92 1.62 4.55	≥7 years 5+ years 7+ years	N/A
Corley *et al. 2010*	Hip Hip	1.30 1.41	>2 years >2 years with high dose	Yes
Gray *et al. 2010*	All Hip Spine Wrist	aHR = 1.25 aHR = 1.00 aHR = 1.47 aHR = 1.26	Mean 7.8 years	N/A
Yu *et al. 2008*	Hip (F) Hip (M) Nonspine (F) Nonspine (M)	aRH = 1.16 aRH = 0.62 aRH = 1.34 aRH = 1.21	Female: mean 7.6 years, Male: mean 5.6 years	N/A

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

† FDA Drug Safety Communication. May 25, 2010.

Thank you!

Back Up Slides

New Safety Language

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

Corley, D.A., Kubo, A., Zhao, W., Quesenberry, C., Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients, *Gastroenterology* (2009), doi:10.1053/j.gastro.2010.03.055.

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