Long Term Proton Pump Inhibitor Use and Effect on Risk of Fractures

Allison Conforto, PA-S and Hannah Messer PA-S
James Madison University, Harrisonburg ,VA

INTRODUCTION

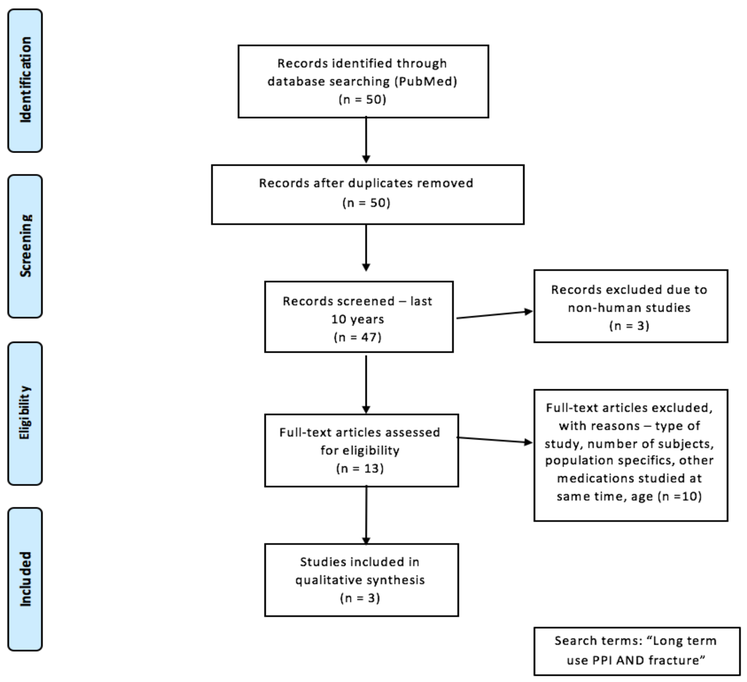
Since their introduction in the late 1980s, proton pump inhibitors (PPIs) have become one of the most widely used class of drugs, and one of the most commonly prescribed medications in clinical practice. PPIs treat a variety of acid related disorders including: peptic ulcer disease (PUD), *H. pylori*, NSAID-related ulcers, Zollinger-Ellison Syndrome, and gastroesophageal reflux disease (GERD).

All PPIs share a common structure, and accumulate selectively in the highly acidic space within the parietal cell. The drugs interact with the surface of the H-K-ATPase proton pump, inhibiting this enzyme, and resulting in specific and long-lasting decrease in gastric acid secretion. PPIs are one of the most potent gastric acid secretion inhibitors on the market today. Long-term effects include hypochlorhydria, hypergastrinemia, and gastric atrophy. Hypochlorhydria is believed to be associated with an increased risk of infection and malabsorption of vitamins such as vitamin B12. It is believed that gastric acid secretion might help facilitate the absorption of calcium, so the use of acid suppressants like proton pump inhibitors have been linked to decreased calcium absorption and decreased bone density. Another mechanism that has been looked at was long term acid suppression leading to both primary and secondary hyperparathyroidism, which in turn leads to increased bone resorption and decreased bone strength.

CLINICAL QUESTION

Among individuals 50 years and older, does the long-term use of proton pump inhibitor therapy increase the incidence of fractures as compared to similar populations who do not use long-term PPIs?

METHODS



RESULTS

Study 1: Use of proton pump inhibitors and risk of osteoporosis related fractures. *Targownik et al.*

Study Type: This study was a retrospective, matched cohort
Sample Size: 63,008 individuals
Length of Study: 8 years were included in the study (1996-2004)
Objective: To examine the relation between duration of exposure to proton pump inhibitors and osteoporosis-related fractures.
Conclusion: The study found that the use of PPIs increases the risk of hip fracture after 5 or more years of continuous exposure, and the risk of any osteoporotic fracture was increased after the 7 years of continuous exposure to PPIs.
Critique: ***Strengths:*** Researchers included patients from a very large time period (1996-2004) so they were able to pinpoint which year of continuous PPI use they started seeing an association with increased fractures. Another strength of the study was that they used 3 matched controls for every case they included in the study. ***Limitations:*** They were not able to obtain information about the use of over-the-counter medications such as calcium and vitamin D supplements. They were unable to determine whether increased fracture risk from PPIs were related to reduced bone density or increased risk for falls.

Study 2: Long-term proton pump inhibitory therapy and falls and fracture in elderly women: A prospective cohort study. *Lewis et al.*

Study Type: Prospective cohort study, replicating a longitudinal population-based prospective cohort study
Sample Size: *Study #1*: 1,025 individuals; *Replication study:* 686 individuals
Length of Study: *Study #1:* 5 years; *Replication study:* 9 months
Objective: To examine the association in elderly postmenopausal women between PPI use greater than or equal to one year ("long-term use") and fracture risk factors, including bone structure, falls, and balance-related functioning.
Conclusion: *Study #1*: There was an association between long-term PPI use and increased fall risk and hospitalizations related to fractures; *Replication study*: There was an association between long-term PPI use and increased risk of falling (self-reported). No associations were found between long-term PPI use and bone structure, but users with long-term PPI exposure were more likely to have low vitamin B12 levels than those who did not have the long-term PPI exposure.
Critique: ***Strengths:*** Use of comprehensive prospective information collected regularly over a 5-year period. Important information was used, including duration, dose, frequency, and type of PPI exposure. The use of hospital records eliminated patient recall bias or error in self-reporting. ***Limitations***: Observational studies only identify association (not causation). Findings of the study can only be applied to similar populations of postmenopausal women with mean age of 80.

Study 3:Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture. *Yang et al.*

Study Type: Nested case-control study
Sample Size: 148,942 individuals
Length of Study: 16 years were included in the study (1987-2003)
Objective: To determine the association between PPI therapy and risk of hip fracture.
Conclusion: Long term PPI use >1 year is associated with a statically significant increased risk of hip fractures. The longer the treatment with PPIs, the greater the association with increased fracture risk. They also found that the fracture risk increased with higher doses of PPI therapy. The study also found that the interaction between PPI therapy and sex was statistically significant, with men being at a higher risk for fractures.
Critique: ***Strengths:*** A strength of this study was that it used a very large population size. Another strength of this study was that it used up to 10 very well-matched controls for each case. This study also used patients for a very large time period (1987-2003) which helped determine long term data. ***Limitations:*** One weakness of this study was that there was no way for them to determine if the patients had continued to take their prescriptions for the full time it was prescribed or if they had taken PPIs prior to being enrolled. They were also unable to determine if participants were taking over the counter calcium supplements during the study period.

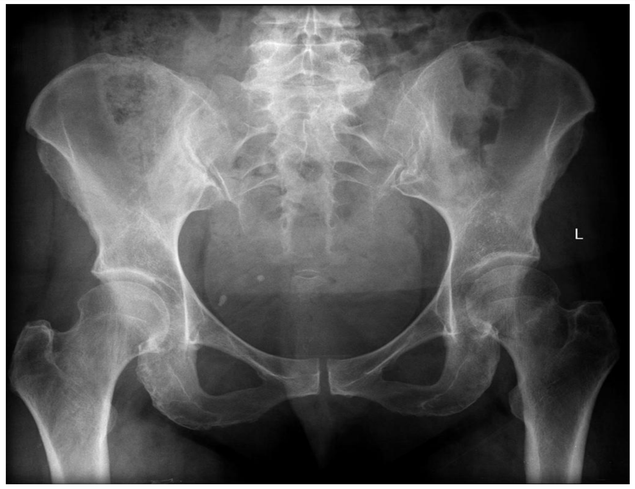


Image 1. Left femoral neck fracture [6]

CONCLUSIONS

Due to the high use of long-term PPI therapy in elderly women, and their overall risk of falling as a general population, the association between increased fall risk and PPI exposure is an extremely important relationship to investigate. All of the research articles compared in this study found a significantly increased association between long-term PPI use with falls and fractures. Even minor increases in fractures in this population may have permanent effects on the absolute risk of events and their associated cost to an individual and society. Physicians should be aware of this potential association when considering prescribing long-term PPIs to their patients, and only use them in the smallest doses possible, and only when they are extremely necessary and proven to be efficacious. Further study should be done to examine the possible mechanisms for this association including the effect of acid inhibition on calcium absorption and bone mineral density.

ACKNOWLEDGEMENTS

We would like to thank Dr. Erika Kancler, Carolyn Schubert, and the James Madison University's Graduate Writing & Communication Center for all the time they all gave us to help us complete this project.

REFERENCES

1. Wolfe M. Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders. UpToDate. https://www.uptodate.com/contents/proton-pump-inhibitors-overview-of-use-and-adverse-effects-in-the-treatment-of-acid-related-disorders?source=search_result&search=Overview%20and%20comparison%20of%20the%20proton%20pump%20inhibitors%20for%20the%20treatment%20of%20acid-related%20disorders&selectedTitle=1~150#topicContent. Published October 2017.
2. Lewis JR, Barre D, Zhu K, et al. Long-term proton pump inhibitor therapy and falls and fractures in elderly women: a prospective cohort study. J Bone Miner Res Off J Am Soc Bone Miner Res. 2014;29(11):2489-2497. doi:10.1002/jbmr.2279.
3. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ Can Med Assoc J. 2008;179(4):319-326. doi:10.1503/cmaj.071330.
4. Bo-linn G, Davis G, Buddrus D, Morawski S, Santa Ana C, Fordtran J. An evaluation of the Importance of gastric acid secretion in the absorption of dietary calcium. J Clin Invest. 1984;73(3):640-647.
5. Yang Y-X, Lewis JD, Epstein S, Metz DC. Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture. JAMA. 2006;296(24):2947-2953. doi:10.1001/jama.296.24.2947.
6. Murphy A, Gaillard F. Femoral Neck Fracture. Radiopaedia. https://radiopaedia.org/articles/femoral-neck-fracture. Published 2017.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097