

SAFER MEDICATION USE

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Can Proton Pump Inhibitors Increase the Risk of Osteoporotic Fracture?

Recent case-control studies have suggested an association between proton pump inhibitor (PPI) use and fracture risk. This is potentially important, as millions of people worldwide use these medications. At present there is no evidence that PPI therapy should be discontinued when it is used for an appropriate indication, but the doses and durations of therapy used should be kept to a minimum. There are no data indicating differences in risk between individual PPIs. Recipients should be advised to maintain an adequate dietary intake of calcium during long term PPI therapy. This can be supplemented with calcium salts as required.

Background

Proton pump inhibitors (PPIs) suppress the secretion of gastric acid by inhibiting the “proton pump” of the gastric parietal cell. Indications include peptic ulcer disease, gastro-oesophageal disease and dyspepsia. Prolonged treatment is sometimes required for conditions such as severe gastro-oesophageal reflux or Zollinger-Ellison syndrome.¹ This article examines the possible link between PPI therapy and incidence of osteoporotic fractures.

Why are PPIs being associated with osteoporotic fracture?

A large retrospective, case-control study using the General Practice Research Database comparing data (e.g. age, gender, BMI, factors related to falling e.g. stroke and medications) between 13,556 patients with a hip fracture and 135,386 controls was published in 2006. The majority of participants were female (80%) and the average age was 77 years. The adjusted odds ratio (AOR) for hip fracture in those taking a PPI for more than one year was 1.44 (95% confidence interval (CI) 1.30 to 1.59) and was 2.65 (95% CI 1.8 to 3.9) in those prescribed long-term, high-dose PPIs. Risk was also increased with duration of use (AORs for hip fracture: one year: 1.22 (95% CI 1.15 to 1.30); two years: 1.41 (95% CI 1.28 to 1.56); three years: 1.54 (95% CI 1.37 to 1.73); four years: 1.59 (95% CI 1.39 to 1.80).² A Danish case-control study looking at all fractures in Denmark during 2000 provided similar results. The incidence of

hip (AOR 1.45 [95%CI 1.28 to 1.65]) and vertebral (AOR 1.60 [95%CI 1.25 to 2.04]), fractures were increased in patients receiving PPI therapy, although there was no dose response association found in this study.³

A third retrospective case-control study using an administrative database (Manitoba Health) studied assessed cases of vertebral, wrist or hip fractures in subjects over the age of 50 years. Although there was no significant association between the overall risk of osteoporotic fracture and the use of PPIs for less than six years, exposure for seven or more years was associated with an increase in risk of an osteoporosis-related fracture (AOR 1.92, 95% CI, 1.16 to 3.18).

An increased risk was also seen for hip-fracture (AOR 1.62, 95%CI 1.02 to 2.58) after five or more year's exposure, with an even greater risk after seven or more years (AOR 4.55, 95%CI 1.68 to 12.29).⁴

Proposed mechanism of development of fractures

PPIs may increase the risk of fracture by increasing gastrointestinal pH which may reduce gastrointestinal calcium absorption by impairing ionized calcium release from calcium salts.⁵ This can lead to secondary hyperparathyroidism, an increase in osteoclastic bone resorption and, in time, a reduction in bone mass and an increased risk of fracture.⁶ Further studies are needed to clarify to what extent calcium absorption is affected by PPIs and what action if any would need to be taken to overcome this possible PPI – calcium interaction.

Prevention of fracture in patients receiving PPIs

Long term PPI therapy should only be continued when there is an appropriate indication. The current NICE guidance on dyspepsia suggests initial PPI therapy for one or two months, thereafter treatment should be at the lowest possible dose on a limited repeat prescription, long-term patients should be reviewed at least annually and step-down therapy or cessation of therapy should be encouraged.⁷ Patients who have been receiving divided-dose PPI therapy for gastro-oesophageal reflux disease (GORD) may be stepped down to a once-daily dosing regime.⁸ Over half of patients in whom step-down is implemented actually cease PPI treatment or use an alternative agent.⁹

When should adverse drug reactions be reported to the MHRA?

All serious suspected adverse reactions to any PPI should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk). This includes fractures suspected to be related to PPI use. All suspected adverse reactions to black triangle drugs should be reported (regardless of seriousness), as should all serious suspected reactions to any drug, herbal or OTC medicine. The Yellow Card Centre Northern and Yorkshire can provide support and guidance on any adverse reaction related enquiry or completion of a Yellow Card. Information is available via our website (www.nyrdtc.nhs.uk).

Practice Points:

The research to date identifies a probable increased risk of fracture in patients taking PPIs for longer than one year, although the absolute risk to the individual patient remains low.

- The clinician should weigh the proven benefits of PPI use against the potential risk of osteoporotic fracture.
- Long term PPI therapy should be prescribed at the lowest dose for the shortest time necessary to achieve the desired treatment outcomes.¹⁰
- Patients using long-term (>1 year) PPI therapy should be advised to maintain an adequate calcium in-take, which may involve a calcium supplement in some patients.¹¹

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Key: **CCS** - case-control study, **CS** - cohort study, **G** - guidance, **R** - review, **RCT** - randomised controlled trial

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