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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Proton pump inhibitors and fracture risk

Proton pump inhibitors are very commonly prescribed in Australia and elsewhere, and are used for the management of peptic ulcer disease and gastro-oesophageal reflux disease. A number of observational studies have found an association between long term use of proton pump inhibitors (PPI) and increased osteoporotic fracture risk.

The most recent observational study was published by Targownik et al in the Canadian Medical Association Journal in August 2008. This retrospective cohort study extracted data from the Canadian Population Health Research Data Repository. In all, 15 792 cases of hip, wrist or vertebral fracture were identified between April 1996 and March 2004. Each case was matched for age, gender and comorbidity with three controls subjects with no fracture history. PPI exposure was then identified from prescription records and grouped according to use and non-use, in addition to continuous and non continuous PPI use. The primary outcome measure was the occurrence of osteoporotic fracture according to PPI duration of use.

In this study, PPI use for seven years or more was associated with a significant increase in risk for any osteoporotic fracture (adjusted OR 1.92; 95%CI 1.16 - 3.18; p=0.011). In addition, PPI use for five years or more was associated with an increase in hip fracture risk (adjusted OR 1.62; 95%CI 1.02 - 2.58; p=0.04) and significantly greater with seven or more years of PPI use (adjusted OR 4.55; 95%CI 1.68 - 12.29; p=0.002).

In December 2006 Yang et al published results of a nested case control study using the UK General Practice Research Database evaluating the association between hip fractures and PPI use. PPI therapy of more than one year was associated with increased risk of hip fracture (adjusted OR 1.44; 95% CI 1.3 - 1.59; P>0.001). The incidence rate of hip fracture among those prescribed one or more years of PPI therapy was 4.0 per 1000 patient years compared with 1.8 per 1000 patient years among persons not prescribed acid suppression therapy. The risk appeared greater at higher doses and the strength of the association increased with increasing duration of therapy.

Vestergaard et al also found that recent use of PPI (within one year) increased the fracture risk. Small but significant increases were seen for PPIs with regard overall fracture risk, hip fractures and spine fractures.

Limitations of these observational studies include confounding by unmeasured factors (i.e. calcium and vitamin D supplementation and status, smoking, alcohol intake, physical activity, falls risk etc).

Whilst the mechanism of the association is unclear, it has been proposed that hypochlorhydria induced by PPIs could result in calcium malabsorption (as an acidic environment in the gastrointestinal tract facilitates the release of ionized calcium from insoluble calcium salts).

Clinicians should be aware of this possible association, and use the lowest effective dose of PPI for patients with appropriate indications. In addition, it may be worth emphasising to elderly patients requiring long term PPI the need for adequate calcium intake, preferably from a dietary source, and co-ingestion of a meal when taking insoluble calcium supplements.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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