Is there an interaction between bisphosphonates and proton pump inhibitors?

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Background

Bisphosphonates are used for treatment and prophylaxis of osteoporosis, treatment of Paget's disease, hypercalcaemia of malignancy and bone metastases in breast cancer. A common side effect of bisphosphonates is upper gastro-intestinal (GI) disturbance e.g. dyspepsia, abdominal pain. (1-15) Observational cohort studies of adverse effects seen with risedronate and alendronate after starting therapy showed that dyspepsia is the most frequently reported adverse event in the first month of treatment and amongst the most frequently reported reasons for stopping risedronate and alendronate. (15-17) Gastric erosions or ulcers can develop in the first few weeks following initiation of alendronate and risedronate. (15) A case control study showed that bisphosphonate use appears to be associated with increased use of acid suppressant drugs within 6 weeks of the first bisphosphonate prescription. (18) Dyspepsia can be treated and prevented with a proton pump inhibitor (PPI). (19-38)

The National Institute for Health and Clinical Excellence (NICE) technology appraisal (TA) on secondary prevention of osteoporotic fragility fractures issued in October 2008 highlights an increased risk of fractures when PPIs and bisphosphonates are taken together. (39) The TA states that evidence from two cohort and two case-control studies suggests that fracture risk at some fracture sites may be increased in women taking acid-suppressive medication (PPIs or histamine 2 receptor antagonists (H2RAs)). (40-43)

None of the UK Summaries of Product Characteristics (SPCs) for bisphosphonates used for treatment and prevention of osteoporosis, or PPIs, list concomitant use as an interaction. (1-13, 19-37)

Answer

The product information for both bisphosphonates and PPIs (with a few exceptions) includes warnings about a risk of fractures. (1-13, 19-33, 35-37)

The UK SPCs for bisphosphonates state that atypical fractures of the femur have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. (1-13) The Medicines & Healthcare Regulatory Agency issued advice about the rare risk of atypical femoral fractures with bisphosphonates in June 2011. (14)

The UK SPCs for PPIs state that 'proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium'. (19-33, 35-37)

A retrospective cohort study used data from the UK General Practice Research Database (GPRD) to assess the fracture risk of patients taking concomitant bisphosphonate and acid suppressive medication (PPI & H2RAs) versus bisphosphonates alone. The incidence of GI effects after initiation of bisphosphonates was approximately 5 times that seen in comparable patients receiving other prescriptions. Of 67,309 patients on bisphosphonates, 20.1% received PPI therapy and 7.5% H2RAs. Concomitant use of bisphosphonates and PPIs was found to be associated with an increased risk of any fracture (adjusted relative risk (RR) 1.08) and hip fracture (adjusted RR 1.21) but not vertebral fracture compared to bisphosphonate use alone. In contrast, bisphosphonates and H2RAs versus bisphosphonates alone were associated with an increased risk of vertebral fractures (adjusted RR

1.48) but not any fracture or hip fracture. It should be noted that the information on patients included in the study was incomplete and adjustments for confounders were not reported. (39, 40)

A nested case control study using information from the GPRD (1987-2003), concluded that long term PPI therapy at high doses is associated with an increased risk of hip fractures. Significant hypochlorhydria (low production of gastric acid in the stomach) could theoretically result in calcium malabsorption. Limited animal and human studies have shown that PPI therapy may decrease insoluble calcium absorption or bone density. The hip fracture cases were more likely to have received medications or medical diagnoses that had known associations with osteoporosis or the risk of falling. The study suggests that physicians should use the lowest effective dose of PPI for appropriate indications. For elderly patients who require long term and particularly high dose PPI therapy, it may be prudent to re-emphasise increased calcium intake. (41)

A case control study looking at the effect of PPIs, H2RAs and other antacid drugs on fracture risk concluded that PPIs appeared to be associated with a limited increase in fracture risk while H2RAs were associated with a small decrease in fracture risk. In all cases, the changes in risk estimates were small and the clinical significance limited. (42)

A cohort study published in 2006 concluded that short term use of acid suppressive medication is associated with impaired intestinal absorption of calcium. The study included 3,432 women aged 65 or over given a PPI or H2RA. Women on bisphosphonates or other osteoporosis medication were excluded. Total hip BMD was measured at baseline and 4.9 years later. There was no significant difference between PPI/H2RA users and non-users in mean total hip BMD at baseline. With prolonged follow up there was an 18% increase in the risk of non-spine fracture among users of acid suppressive medications. There was also a non-significant increased risk of hip fracture among PPI/H2RA users. The study concluded that among postmenopausal women, use of acid suppressive medications may be associated with an increased risk of non-spine fracture, but there was no evidence of a detrimental effect on bone mass. (43)

A review published in 2015 summarises the evidence available on the relationship between long-term PPI therapy and skeletal frailty. Multiple observational studies have shown that PPIs increase the risk of fractures particularly hip fractures compared to non-users of PPIs. This review suggests that although the increased risk of fractures due to PPI use is quite modest (RR 1.30, 95% CI 1.19-1.43), this poses a significant impact on fracture risk on a population level as a result of a high prevalence of patients treated with a PPI that can often be overlooked. (44)

Based on the five studies detailed above (40-44), the NICE TA concludes that acid-suppressive medication leads to a small increase in fracture risk and that co-administration of acid-suppressive medication and bisphosphonates may lead to an increased fracture risk compared with bisphosphonate administration alone. It was noted that the data are observational and tentative, and different for various fracture sites and for different acid suppressors. However, because the various studies show a trend, caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates. (39)

Further studies have been published since the NICE TA which explore the link between acid suppressive medication, bisphosphonates and fractures. (45-50)

A retrospective cohort study using data from the GPRD (1988-2007) was conducted in patients aged 40 years and older starting PPIs (n=234,144), H2RA (n=166,798) or bisphosphonates (n=67,309). In the 6 months before initiating bisphosphonate therapy, 20.1% of patients received a PPI and 7.5% an H2RA. Current PPI use was associated with an increased risk of any fracture (adjusted relative rate (ARR) 1.15, 95% CI 1.10-1.20), hip fracture (ARR 1.22, 95% CI 1.10-1.37), and vertebral fracture (ARR 1.40, 95% CI 1.11-1.78); and concomitant bisphosphonates and PPIs with an increased risk of

any fracture (ARR 1.08, 95% CI 1.01-1.16) and hip fracture (ARR 1.24, 95% CI 1.08-1.42). The authors concluded that acid-suppressive medication is associated with an increased risk of fracture when taken alone or in combination with bisphosphonates. (45)

A retrospective cohort study using data from the Irish Health Services Executive Primary Care Reimbursement Services pharmacy database (2003-2007) aimed to determine an association between prescribing anti-osteoporotic therapies following the use of PPIs in general practice. 442,341 patients were identified, 209,175 were PPI users and 233,166 were used as the comparison group. The odds ratio (OR) for the prescribing of anti-osteoporotic therapies following the prescribing of PPIs was 1.69 (95% CI, 1.66 1.72) compared to not receiving any PPI therapy, when adjusted for age and sex. When adjustments were made for other confounders; the OR decreased to 1.26 (95% CI, 1.23-1.28). The strength of the association increased with increasing duration of PPI therapy; 6-12 months, OR = 1.19 (95% CI, 1.15-1.23) and for longer than 24 months, OR = 2.09 (95% CI, 2.04, 2.13) compared to less than 3 months. The OR also increased with increase in dose of therapy. The authors of the study suggested the results may be clinically relevant. (46)

A population based, national register based, open cohort study conducted in Denmark followed up 38,088 adult new alendronate users over a 3.5 year period who also had prescriptions for PPIs, H2RAs or systemic corticosteroids. 2,071 people had a hip fracture, and 1,110 had a non-hip osteoporotic fracture. High compliance with alendronate therapy was associated with a significant reduction (39%) in the risk of fracture in those who were not taking a PPI (hazard ratio [HR] 0.61; 95% CI 0.52 to 0.71; P<0.001). Concurrent PPI use was associated with a significant reduction in protection against a fracture compared to alendronate alone (19% vs. 39%; HR 0.81; 95% CI, 0.64 to 1.01; P =0.06). No difference in response was seen in those who used concomitant alendronate and PPI for up to1 year. When concomitant use continued for more than 1 year the risk increased. Concurrent H2RA use had no effect on alendronate effectiveness and there was no difference in alendronate effectiveness for corticosteroid users vs. non-users. The authors conclude that additional research is needed to verify the interaction with PPIs and explain its mechanism. PPIs are often prescribed inappropriately, and the study provides support for discouraging the use of these drugs in patients on alendronate wherever possible. (47)

A retrospective case control study published in 2013 used data from the Korean Health Insurance Review and Assessment Service database between January 2005 and June 2006 to identify patients with hip fractures and up to four controls matched by age, gender and osteoporosis diagnosis. 24,710 cases of hip fracture were found and 98,642 controls were matched to the cases. The adjusted odds ratio (aOR) and the 95% CI of hip fractures related to the use of PPIs was 1.34 (95% CI 1.24-1.44). When the study participants were stratified according to bisphosphonate use, the aOR was 1.30 (95% CI 1.19-1.42) in non-users of bisphosphonates, and 1.71 (95% CI 1.31-2.23) for bisphosphonate users. Patients who used bisphosphonates showed a decreasing tendency toward fracture risk as exposure to PPI became less recent, and a trend of increasing risk with increasing cumulative doses. The study authors concluded that the results suggest that the mechanism for increased risk of hip fracture by PPIs may arise mainly from an interaction of bisphosphonates and PPIs, however further research is needed to identify the mechanism of the interaction. (48)

A retrospective case control study investigated the factors associated with the development of atypical femoral fractures (AFF) and typical femoral fractures (TFF) among Korean females. Between 2003 and 2013, thirty patients with AFF and 577 patients with TFF were identified. More patients in the AFF group were treated with bisphosphonates (p<0.01) or PPIs (p=0.02). The authors concluded that the use of a bisphosphonate was an important risk factor for AFF with a high odds ratio; in addition longer duration of treatment with bisphosphonates was associated with greater risk of AFF, although any period of bisphosphonate use could lead to AFF. Since they recruited patients who had femoral fractures irrespective of bisphosphonate use, the number of patients that used bisphosphonates in this population was not large. Moreover, it was not possible to determine total exposure to the bisphosphonate or the compliance of each patient. Therefore it is difficult to draw solid conclusions with the lack of detailed information regarding bisphosphonate use in this study. Further research is needed including male and female patients to acquire stronger conclusions regarding risk factors for AFF among patients of Asian ethnicity. (49)

The authors of a meta-analysis conducted a PubMed database, Ovid database and Cochrane Library search (up to July 2014) for studies assessing the association between fractures and bisphosphonates or/and PPIs. From a total of 323 potentially relevant reports identified, four studies including 57259 patients and 5 comparisons were available for this meta-analysis. Pooled analysis of overall fracture risk of bisphosphonate + PPI group versus bisphosphonate group showed a significant increase in risk of fractures (OR = 1.52, 95% CI 1.05-2.19, P = 0.025). The findings of this meta-analysis suggest that there is an interaction associated with increased fracture risk (particularly for spine fractures and Asian race) between bisphosphonates and PPI use. Clinicians should carefully evaluate such risk factors for osteoporosis in patients taking bisphosphonates before routinely prescribing PPIs, and make a careful judgement as to whether PPIs may be safe for patients at high risk of fractures. (50)

A case series of 18 cases were retrospectively identified from June 2006 to January 2018. Patients with features suggestive of AFF were identified after presenting to the fracture liaison service at Yeovil District Hospital NHS Foundation Trust. The objective was to identify other risk factors contributing to the development of AFF. There were 22 patient episodes; female to male ratio was 21:1, and median age of presentation was 71. 86% cases had either concurrent or previous bisphosphonate therapy. Duration of bisphosphonate therapy was variable from 12 months to 30 years. 54% were taking PPIs and 41% were on long term glucocorticoids. 9% were active smokers. 50% episodes were in patients having two or more risk factors, and 3 patients had no risk factors identified. From these cases the authors concluded that exposure to bisphosphonates remains a major risk factor for the development of AFF but other risk factors do play an important part e.g. prolonged courses of glucocorticoids and PPI therapy. The risk appears to be greater with multiple risk factors. The temporal relationship of fractures with relation to bisphosphonate therapy cannot be determined as it can happen even after the cessation of therapy. (51)

Summary

- There is not a recognized interaction between bisphosphonates and PPIs.
- A common side effect of bisphosphonates is gastro-intestinal (GI) disturbance, which may commonly be treated with acid suppressive therapy such as a PPI or H2RA.
- The SPCs for bisphosphonates and PPIs highlight an increased risk of fractures, primarily in patients receiving long-term treatment for osteoporosis.
- There is conflicting information on H2RAs, as they have been associated with both small increases and decreases in fracture risk.
- The mechanism for PPIs increasing fracture risk in patients also taking a bisphosphonate is unknown and requires further research.
- Patients on PPI therapy for a valid reason should continue on the lowest effective dose for the shortest possible duration.

Limitations

This Q&A only looks at the evidence for concomitant use of oral PPIs and bisphosphonates when used for osteoporosis. It does not address co-administration of acid suppressive therapy and bisphosphonates for other conditions.

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Search strategy

- **Embase:**
- exp BISPHOSPHONIC ACID DERIVATIVE/it [it=Drug Interaction] AND exp PROTON PUMP INHIBITOR/it [it=Drug Interaction] [Limit to: Human and English Language and Publication Year 2017-2019]
- [exp OMEPRAZOLE/it [it=Drug Interaction] OR exp ESOMEPRAZOLE/it [it=Drug Interaction] OR exp LANSOPRAZOLE/it [it=Drug Interaction] OR exp PANTOPRAZOLE/it [it=Drug Interaction] OR exp RABEPRAZOLE/it [it=Drug Interaction]] AND [exp ALENDRONIC ACID/it [it=Drug Interaction] OR exp RISEDRONIC ACID/it [it=Drug Interaction] OR exp IBANDRONIC ACID/it [it=Drug Interaction]; OR exp ZOLEDRONIC ACID/it [it=Drug Interaction] [Limit to: Human and English Language and Publication Year 2017-2019]
- **Medline**: [exp DIPHOSPHONATES/ AND exp PROTON PUMP INHIBITORS/] AND exp DRUG INTERACTIONS/ [Limit to: English Language and Humans and Publication Year 2014-2016]
- Electronic Medicines Compendium: search terms used = alendronate, risedronate, ibandronate, pamidronate, zoledronate, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole
- NICE Evidence: search terms used = bisphosphonates, proton pump inhibitors, fractures, interaction
- NICE: osteoporosis
- Other database/resources: BNF online, Cochrane Library, Stockleys Drug Interactions