Osteoporos Int (2016) 27:1671–1672
DOI 10.1007/s00198-016-3497-7

LETTER

Proton pump inhibitors and fracture: do they do what it says on the tin?

O. F. Uzoigwe[1]

Received: 11 January 2016 / Accepted: 18 January 2016 / Published online: 4 February 2016

Dear Editor,

Zhou et al. and Sugiyama et al. provide an engaging exchange [1, 2]. Large studies and meta-analyses continue to show a strong connection between long-term use of high-dose proton pump inhibitors (PPIs) and the risk of fracture, in even young populations [1, 3–5]. The US Food and Drug Administration also raise awareness to this potential hazard (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm). The link is important as PPIs are widely used. However, what is perhaps most surprising is that the mechanism by which PPIs predispose to fracture apparently continues to baffle [1, 2]. PPIs inhibit the gastric parietal proton pump (H^+/K^+-ATPase) by irreversible covalent bonding. Bone osteoclasts also possess a proton pump, critical to their function. It serves to acidify the osteoclast micro-milieu (Howship's lacuna) thereby facilitating the action of enzymes responsible for bone resorption, a process germane to bone remodelling and turnover [6, 7]. The most parsimonious explanation for the tendency of PPIs to predispose to fracture is via inhibition of the osteoclast proton pump (H^+-ATPase), thereby impairing bone remodelling and turnover. This in turn renders the bone vulnerable to fracture [4, 5]. There is strong clinical and experimental evidence for this model.

Heritable mutations which cause a loss of function of the osteoclast proton pump result in osteopetrosis [7]. In this condition, failure to acidify the Howship's lacuna renders osteoclasts unable to resorb bone. Hence, osteoblastic action occurs unchallenged. Radiographically, the bone appears sclerotic and radio-dense. However, a lack of remodelling results in much more fragile bone which is prone to fractures [7, 8]. It is conceivable that partial blockade of the osteoclast proton pump by PPI renders bone vulnerable to fracture in an analogous manner. However, the inhibition is not to a degree that sclerosis is evident, but in this model, neither is there osteoporosis. This is significant, as it appears PPIs tend not reduce bone mineral density [1, 2]. Indeed the putative calcium malabsorption and hypomagnesaemia associated with PPI use may temper the osteoblast response, counteracting the tendency for bone ostesclerosis.

Mutations in the *TCIRG1* gene are responsible for almost 50 % of cases of osteopetrosis [8, 9]. The gene encodes for the a3 isoform of the V_0 (transmembrane) subunit of the proton pump, which is found almost exclusively in the osteoclast and gastric parietal cell proton pumps [8]. It is one site of PPI action on the gastric proton pump [10]. The direct inhibition of the osteoclast proton pump by PPIs has been demonstrated, although, tellingly, at higher doses than that required for inhibition of the gastric proton pump. PPI-mediated inhibition of osteoclast bone resorption has also been observed [11].

PPIs are pro-drugs. They are only activated by very acidic environments. The gastric parietal cell secretory canaliculi and osteoclast resorption vacuole are possibly the only two sites in the human body where pHs are

✉ O. F. Uzoigwe
ofuzoigwe@yahoo.co.uk

[1] University of Sheffield, Sheffield, UK

sufficiently low for activation to occur [4]. There may be no mystery in the action of PPIs on bone. Indeed, inhibition of the osteoclast proton pump would simply mean that PPIs "do what it says on the tin".

Compliance with ethical standards

Conflict of interest None.

References

1. Zhou B, Huang Y, Li H, Sun W, Liu J (2016) Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 27:339–347. doi:10.1007/s00198-015-3365-x
2. Sugiyama T, Torio T, Miyajima T, Kim YT, Oda H (2016) Calcium, proton pump inhibitors, and fracture risk. Osteoporos Int 27: 349–350. doi:10.1007/s00198-015-3403-8
3. Yu EW, Bauer SR, Bain PA, Bauer DC (2011) Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. Am J Med 124:519–526
4. Yang YX, Lewis JD, Epstein S, Metz DC (2006) Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 296:2947–5
5. Freedberg DE, Haynes K, Denburg MR, Zemel BS, Leonard MB, Abrams JA, Yang YX (2015) Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. Osteoporos Int 26:2501–2507
6. Rachner TD, Khosla S, Hofbauer LC (2011) Osteoporosis: now and the future. Lancet 377:1276–1278
7. Tolar J, Teitelbaum SL, Orchard PJ (2004) Osteopetrosis. N Engl J Med 351:2839–2849
8. Sobacchi C, Schulz A, Coxon FP, Villa A, Helfrich MH (2013) Osteopetrosis: genetics, treatment and new insights into osteoclast function. Nat Rev Endocrinol 9:522–536
9. Sachs G, Shin JM, Howden CW (2006) Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 23(Suppl 2):2–8
10. Osteopetrosis - Consensus Guidelines of the European Society for Immunodeficiencies (ESID) and the European Society for Bone and Marrow Transplantation (EBMT) Working Party Inborn Errors https://www.ebmt.org/Contents/About-EBMT/Who-We-Are/ScientificCouncil/Documents/00_OP_Guidelines_02122011.pdf
11. Costa-Rodrigues J, Reis S, Teixeira S, Lopes S, Fernandes MH (2013) Dose-dependent inhibitory effects of proton pump inhibitors on human osteoclastic and osteoblastic cell activity. FEBS J 280: 5052–5064