Te Awakairangi Health NETWORK

Clinical Pharmacy Bulletin August 2015

Proton Pump Inhibitors: too much of a good thing?

Proton pump inhibitors (PPIs) are one of the most widely used medicines in New Zealand and have changed the management of acid-related upper gastrointestinal disorders.[1]

Empirical treatment is often used in general practice for managing un-investigated dyspepsia. While there is a significant placebo response when treating dyspepsia, initiating anti-secretory treatment for an uncertain indication for more than a few weeks may lead to unnecessary long-term use.[2]

PPIs are very effective and are generally well tolerated, but concerns about adverse effects such as increased risk of fractures, and vitamin and mineral deficiencies means they should not be prescribed indefinitely, without review.[1]

Key points:

- ✓ **When starting patients on a PPI, discuss expected duration of treatment, including plan for stepping down or stopping treatment.**
- ✓ **Review patients taking long-term PPIs and assess whether the indication for treatment remains. Consider whether 'as needed' dosing would be more appropriate for individual patients.**
- ✓ **Advise patients of the possibility of rebound acid secretion when PPIs are withdrawn, even after periods as short as four weeks.**
- ✓ **Recommend antacids as 'rescue' therapy if necessary.**
- ✓ **Rebound hyperacidity does not always mean a return of original symptoms.**
- ✓ **PPIs may be associated with a 16% increased risk of MI, independent of clopidogrel use.**

Review long-term PPI patients regularly

Some patients do require PPIs long-term, and withdrawal will be inappropriate eg patients with Barrett's oesophagus, or patients taking non-steroidal anti-inflammatory drugs long-term.

However, a substantial number of patients treated with PPIs, without a clear indication can step down or stop treatment without experiencing deteriorating symptom control.

Tapering, rather than abrupt discontinuation seems to be the most effective way of doing this.

Discontinuation without worsening symptom control can occur for up to 64% of patients, with discontinuation persisting for more than a year.

Other studies have shown that 30–50% of patients are able to lower their PPI dose without an increase in symptoms.[3] Patients may also be able to switch to 'as needed' dosing, although this may not be effective for all patients because of the lag time to peak anti-secretory effectiveness.[3]

Use the **STOPP/START** tool to help when reviewing older patients. Consider:

- clinical appropriateness and benefit,
- duration of use,
- adherence,
- wishes of the patient, and
- the prescribing cascade.[4]

General tapering guide for acid suppressants[4]	Withdrawal effects
Halve the dose for four to eight weeks then stop (or step down to a less potent agent). Consider providing an antacid for dyspepsia symptoms	Recurrence of oesophagitis and indigestion symptoms
PPIs - consider alternate day dosing. Capsules cannot be halved. Consider stepping down to an H_2RA if a more gradual taper is required	Stopping PPIs suddenly can cause rebound hypersecretion of acid
Histamine receptor antagonists (H_2RA) - taper gradually	Rebound dyspepsia has been described after stopping H_2RA therapy abruptly

Rebound acid secretion

Some patients may experience rebound hyperacidity when PPIs are stopped after one month or more continuous use. Serum markers suggest that acid secretion one week following PPI cessation can be significantly elevated above pre-treatment levels but should return to normal within two weeks.[1]

Other studies suggest gastric acid secretion returns to baseline over a three to five day period.[4]

If rebound hyperacidity is mistaken for a return of the underlying condition, acid suppressants may be restarted unnecessarily.[5]

PPIs linked to increased risk of heart attack[5]

Proton pump inhibitors have previously been associated with adverse clinical outcomes in patients concurrently treated with clopidogrel.

New research using a novel, validated approach for assessing clinical data for pharmacovigilance, queried 16 million clinical documents representing 2.9 million individuals treated for gastro-oesophageal reflux disease (GORD). The investigation was to determine whether PPI use was associated with an increased cardiovascular risk in patients without any history of cardiovascular disease.

Patients who were exposed to PPIs had a 1.16-fold (95% CI 1.09–1.24) increased association with myocardial infarction (MI) and a 2-fold (95% CI 1.07–3.78; p=0.031) increased association with cardiovascular mortality regardless of clopidogrel use. The findings are also independent of high-risk (elderly) patients.

This study suggests that there may be a general adverse effect of PPIs independent of other therapy, although the results cannot eliminate possible confounding. By comparison, no association was found between H_2RAs such as ranitidine and increased MI risk.[5]

References:

1. Best Practice Journal. Proton pump inhibitors: when is enough enough? BPJ. 2014;61:8-15
2. Haastrup P, Paulsen MS, Begtrup LB, Hansen JM, Jarbøl DE. Strategies for discontinuation of proton pump inhibitors: a systematic review. Family Practice. 2014;31(6):625–630.
3. Hauser SC, Pardi DS et al. Mayo Clinic Gastroenterology and Hepatology Board Review. Mayo Clinic Scientific Press. 2005; 58.
4. Best Practice Journal. A practical guide to stopping medicines in older people. BPJ. 2010;27:10-23.
5. Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, et al. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. PLoS ONE 2015;10(6): e0124653. doi:10.1371/journal.pone.0124653