

January 2016

Long term PPIs Part 2

Prescribing...

- ✚ This bulletin looks at unusual side effects that may be caused by long term proton pump inhibitor or PPI use.
- ✚ The causes of dyspepsia should be identified and avoided and PPIs only used for the shortest possible duration.
- ✚ It is imperative that long term PPI use be reviewed particularly in frail elderly patients.
- ✚ PPI prescribing data at doctor level is being distributed to each GP practice with this bulletin.

There is emerging evidence that PPIs when used long term may increase the risk of *C Diff* and bone fractures, the evidence base for which was covered in December's bulletin. Other rarer potential side effects have been shown in smaller studies and trials.

Colleagues will be aware that industry-sponsored clinical trials are invariably short term, have multiple exclusions and include highly selected patients. Trial design and intensive support from investigators mean that participants have near-perfect concordance. So the results may demonstrate maximum benefit and minimum harm. Frail elderly people with multiple co-morbidities are rarely if ever included in clinical studies. There is therefore a danger that what is an extremely rare side effect of a drug, or an interaction between drugs may be accepted as part of normal ageing.

The evidence base on the latest concerns is as follows:

✚ Acute interstitial nephritis or AIN

This is a rare complication of PPI use. Drug treatment accounts for 60% of all AIN, including antibiotics, NSAIDs, diuretics and PPIs. All PPIs have been implicated. However data is limited to case reports. The standard treatment for AIN is withdrawing the causative drug, administering steroids depending on the degree of kidney injury and a clinical assessment. This is intended to avoid the development of chronic kidney disease and its consequences. PPIs can be replaced by lifestyle measures, antacids and ranitidine in patients at particular risk of AIN.

✚ Higher mortality in older patients

A study in 2013 found that long term PPI use may be associated with higher mortality in older people. The risk increases with higher doses, but no RCT data including frail older people is available. PPIs may interfere with the absorption of nutrients, exacerbating the risk of malnutrition, which is common in older people. More recent studies have shown that PPIs may be inappropriately prescribed in 50 to 80% of patients admitted to geriatric and internal medicine wards.

✚ Community acquired pneumonia

A small but significant increase in hospitalisation from pneumonia due to PPI exposure was found. The estimated 30-day fatality rate among older people hospitalised with CAP was 18% and again the

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widespread use of PPIs means that many people could be affected. However GORD itself may be a risk factor for pneumonia from stomach content aspiration so a balanced approach is necessary.

✚ Hypomagnesaemia

Following a number of case reports of hypomagnesaemia in people on long term PPIs, a Drug Safety Update was issued in 2012. Some cases occurred after 3 months of PPI therapy, but most occurred after 1 year of treatment. Colleagues will be aware that hypomagnesaemia can result in potentially serious problems: fatigue, tetani, delirium, convulsions, dizziness and ventricular arrhythmias. However initially they can be subtle and overlooked as a result. In most cases in the literature the condition improved after magnesium replacement and discontinuation of the PPI. If PPI long term is truly unavoidable monitoring magnesium levels may be considered, especially for people also taking digoxin or diuretics.

✚ Vitamin B₁₂ deficiency

Mixed results have been found from studies of PPI use and vitamin B₁₂ deficiency. Data are from small retrospective studies or case reports with varying methods of B₁₂ level measurements. From the information available at present, a normal diet should safeguard against a clinical deficiency.

✚ Rebound acid hypersecretion syndrome or RAHS

A 2013 systematic review concluded that RAHS following PPI therapy induces reflux-like symptoms in asymptomatic volunteers. There is not yet enough evidence to conclude that there is a link in the general population and even less that this is clinically significant. However RAHS does need to be considered in patients treated with a PPI for a longer period, especially those who previously experienced rapid recurrence of symptoms after PPIs were withdrawn. A gradual step-down of PPI treatments would be wise in these patients, or alternate day therapy for 1 to 2 weeks before discontinuation.

Conclusions and recommendations

NICE and other bodies recommend that lifestyle advice should be offered in the first instance to manage dyspepsia e.g. healthy eating, weight reduction and smoking cessation. Patients should be advised to manage symptoms by avoiding causes and treating with PPIs only when needed and at the lowest possible dose.

Medication, such as calcium channel blockers, nitrates, theophyllines, bisphosphonates, corticosteroids or NSAIDs, is frequently the cause of dyspepsia.

People with dyspepsia on prescribed PPIs should be offered an annual review. They should be encouraged to try stepping down or to take one dose on alternate days. Rebound symptoms are not unexpected and should be self-treated with antacids and/or alginates when required.

Long terms PPIs should be reviewed to reduce the potential risk of *C Difficile*, bone fractures and to a lesser extent the risk of higher mortality in older people, acute interstitial nephritis, community acquired pneumonia, hypomagnesaemia, vitamin B₁₂ deficiency and rebound acid hypersecretion.