Prescribing...

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Long term PPIs Part 1

- There were 79,411 prescriptions for Proton Pump Inhibitors or PPIs dispensed on the islands in all of 2014.
- Long term use may be unavoidable in people on regular NSAIDs, but some studies have shown that there may be a link between their use and increased risk of *Clostridium Difficile* and bone fractures.
- This bulletin reminds colleagues of the national advice on PPI use and the background to these risks.
- A second bulletin will look at concerns regarding possible links with higher mortality in older patients, acute interstitial nephritis, community acquired pneumonia, hypomagnesaemia and vitamin B_{12} deficiency.

Background

PBAC agreed a Deprescribing Policy earlier in the year and for cost and safety reasons long term PPIs were identified as a key area for review. As has happened elsewhere prescribing has greatly increased in recent years, from 41,839 items in 2005 to 79,411 in 2014. Due to reduced cost of generic versions, the first line of the best value drug across primary and secondary care and extremely high rates of generic perscribing , costs have fallen dramatically, from £760 K per annum in 2005 to £160K in 2014.

NICE advice on the care of people with dyspepsia is as follows

- Lifestyle advice should be offered e.g. healthy eating, weight reduction, smoking cessation and managing symptoms by avoiding the causes and using treatment only intermittently.
- Medication should be reviewed for possible causes of dyspepsia. These include calcium channel blockers, nitrates, theophylines , bisphosphonates, corticosteroids or NSAIDs.
- Low-acquisition cost PPIs should be used first line, as there is no evidence that one PPI is better than another.
- An annual review should be conducted to people needing long term management of dyspepsia considering intermittent use, steeping down or stopping altogether.
- Long term PPI use should be reviewed to reduce the risk of adverse effects.

The strongest evidence is for a link between long term PPI use and *Clostridium Difficile* Infection (CDI) and increased risk of bone fractures, as follows. However it should be noted that some studies showed no risk.

1. Clostridium Difficile Infection

A National Prescribing Centre Rapid Review in 2010 highlighted two US studies investigating PPI use and CDI. It stated that gastric acid suppression has been a suggested risk factor for CDI. Gastric juices that have a greater acidity are more effective at killing the bacterium and neutralising its toxin than less acidic gastric juices. Although C Diff spores are acid-resistant, vegetative forms are susceptible to acidity. Elevated gastric pH levels may allow or facilitate conversion from spore to

vegetative forms of *C diff* in the upper GI tract. Other mechanisms include impairment of leucocytes and other immune responses.
Evidence comes from the following sources

- GPRD data from 2005 found that people with CDI were three times more likely to have been prescribed a PPI in the previous three months than people without.
- Other studies found that hospital inpatients taking daily PPIs were 70% more likley to develop CDI than non-users. People who had received more frequent PPIs had more than a doubling of the risk. PPI use with treatment for CDI was associated with a 42% increased relative risk of recurrent infection 15 to 90 days after.The risk seemed to be higher in people aged over 80 years and those receiving antibiotics not targeted to CDI. The authors calculated that one additional case of CDI should be expected for every 533 patients who receive a daily PPI. This might seem a very high NNH. But given the extent of use, PPI use could be the cause of a number of CDI cases each year in the Bailiwick.

It would therefore seem wise for secondary care clinicians to

- Prescribe the least intensive acid-suppressive for a patient's clinical condition
- Limit exposure in low risk , non-critically ill patients for stress ulceration prophylaxis and
- Always stop prophylactic PPIs on discharge .

2. Increased risk of bone fractures

PPIs work by inhibiting gastric proton pumps at physiologic concentrations. However they also inhibit osteoclast proton pumps in the bones and the association appears to be greatest for spine fractures. There is at present no known link between increased fracture risk and use of H2RAs .

Trials available assessing fracture risk have generally lasted only six months. Given the very wide use of PPIs , even a modest increase in risks mean a substantial amount of patient harm at a population level.

Two meta-analyses suggested that the risk of fractures increased by 10 to 40% above baseline, especially if PPIs are used in high doses and for longer than one year. This was mainly observed in elderly people , where other factors may contribute to the increased risk.

One small RCT found that even taking a PPI for 8 weeks might alter calcium and bone metabolism in the elderly especially in the obese and in males.

A systematic review found a significant association between regular use of PPIs and risk of hip fractures. This risk increased with a longer duration of PPI use in post-menopausal women with a history of smoking , which is known to inhibit calcium absorbtion. So smoking and PPI use may have a synergistic effect on fracture risk mediated by impaired calcium absorbtion. The estimated absolute risk associated with PPI use is 5 hip fractures per 10,000 years, which suggests a potential for a high burden of fractures across the population attributable to PPI use. The increased rate of fractures was no longer evident two years after stopping.

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References : NICE CG 184, Presquipp : Safety of Long term PPIs May 2015 , Epact.net