

Stopping medicines – proton pump inhibitors

Proton pump inhibitors (PPIs) are used in a number of settings for:

- the short-term treatment of duodenal and gastric ulcers (for 4 to 8 weeks).
- eradicating *H pylori* when given in combination with appropriate antibacterials (1 to 2 weeks).
- the prevention and treatment of NSAID-associated ulcers.
- controlling excessive gastric acid secretion in *Zollinger-Ellison syndrome*.
- treating dyspepsia and gastro-oesophageal reflux disease (GORD) (if medication review and lifestyle advice prove ineffective).
 - for uninvestigated dyspepsia (continuously for 4 weeks or intermittently to control symptoms long-term).
 - for symptomatic functional dyspepsia, after *H pylori* eradication (for 4 weeks).
 - as an option for mild GORD.
 - for severe GORD (for 4 to 6 weeks before titrating down to maintain remission).¹

Other uses (including unlicensed uses) that are more common in hospital settings include:

- the reduction of re-bleeding episodes after treatment of severe peptic ulcer bleeding.¹
- prophylaxis of acid aspiration during general anaesthesia.¹
- stress ulcer prophylaxis^{2,3} (for example, in intensive care patients requiring mechanical ventilation, those with multiple trauma, sepsis, acute renal failure, or patients on corticosteroids).

There may be several reasons for stopping a PPI:

- An adverse drug reaction (ADR).

These medicines are generally well tolerated; the incidence of short-term adverse events is relatively low. However, information about long-term use is less consistent and there are studies that suggest some serious adverse clinical effects may be linked with PPI use. These adverse effects have been identified predominantly from retrospective observational studies that have some conflicting findings.⁴ Nevertheless, they have raised safety concerns.

There is some evidence that both long-term and high-dose use of PPIs are associated with an increased risk of fractures of the hip, wrist, and spine.⁵ Use of PPIs has also been reported to increase the risk of *Clostridium difficile* infection^{6,7} and hospital-associated pneumonia (commonly linked with gastric bacterial overgrowth and aspiration).⁸ A possible association with community-acquired pneumonia⁹ and with colorectal cancer¹⁰ has been investigated.

- An intercurrent illness or concomitant medication may impact PPI treatment.

Potential interactions, such as those with warfarin, phenytoin, and clopidogrel, may negate the intended benefit from co-administration.¹

- Remission has been achieved for the desired period or the response has been inadequate.

Guidelines recommend that patients receiving PPIs should be offered an annual review, and encouraged to step down or stop treatment.¹¹ Stepping down treatment may involve using a lower dose, intermittent doses, or changing to antacid and/or alginate therapy. The need for any maintenance therapy must be established.

- The PPI is not indicated.

It is becoming evident that one of the biggest problems with PPIs, and a possible cause of their rapid and continuously increasing use, is that they are often used in patients in whom they were never or are no longer indicated.¹² The relative safety of PPIs, and their reducing cost as more agents become available generically, is leading to their use for a variety of gastrointestinal complaints that are not known to be acid-induced.¹³ The effectiveness of PPIs in appropriate high-risk patients should not be considered support for more widespread use in patients for whom the risk/benefit ratio is lower. Such use is a particular problem when 'defensive medicine' is practiced, and when issuing a prescription is considered easier than explaining alternative approaches.¹⁴

The use of PPIs for mild or vague symptoms, and any 'diagnostic' use, must be short-term, especially in view of the potential for these agents to produce the type of disease they are designed to treat (see the discussion below regarding rebound acid hypersecretion). There is a risk that patients with no justifiable prior need may end up on continued treatment.¹³

Also a problem is the inappropriate continuation of prophylactic use in hospital. Risk should be reassessed during the course of a hospital stay, and if it is necessary to issue a supply at discharge, the intended duration of treatment should be specified.

The main problems with stopping are:

- ♦ Relapse, recurrence, and an increased risk of bleeding (depending on the indication).

Stopping or reducing therapy may not be appropriate for some patients, for example those taking PPIs for the prevention of NSAID-associated ulcers, Barrett's oesophagitis, or some of those patients with oesophagitis complicated by past strictures, ulcers, or haemorrhage.¹⁵

- ♦ Possible rebound acid hypersecretion.

Rebound acid hypersecretion (an increase in gastric acid secretion above pre-treatment levels) does occur after PPI therapy. The clinical relevance of this has recently been investigated in a 12 week trial of 120 healthy volunteers.¹⁶ Eight weeks of PPI therapy was found to induce acid-related symptoms within two weeks, and for at least four weeks, after withdrawal. If a similar increase in gastric symptoms occurs in patients in clinical practice when discontinuing PPIs, there is the potential for increased reliance on these medicines.

How to discontinue therapy

Apart from those patients in whom stopping therapy is not appropriate (see above), the only barrier to discontinuing PPIs abruptly is the anticipation of persisting symptoms, typically in patients with dyspepsia or GORD. A step down approach can be followed in those patients in whom symptoms are thought likely to persist and become troublesome below a certain threshold of acid suppression.¹¹

Summary

The best way to avoid excess problems when stopping PPIs is to ensure they are only initiated where indicated, and that they are used for the shortest possible time. Guidelines suggest a step down approach can be employed for certain patients, alongside recommendations for appropriate trials of antacids or alginates and lifestyle changes. If further evidence reinforces the importance of rebound acid hypersecretion, the appropriateness of using PPIs first-line for particular indications might be questioned in some patients. For example, the risk/benefit ratio might favour H₂ antagonists in more cases if the rebound acid hypersecretion associated with these agents does not persist for as long.¹⁷

References

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