

## Use of proton pump inhibitors in primary care

Proton pump inhibitors (PPIs) are one of several groups of drugs used to treat dyspepsia. They cause profound and prolonged suppression of gastric acid production and are clearly more effective at controlling dyspeptic symptoms than antacids or the other group of acid-suppressing agents, the histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub> antagonists).

The widespread use of PPIs and their relatively high cost has raised questions regarding the cost-effectiveness of their use for different conditions. There are also questions about their long-term safety and whether there are any clinically significant differences between the PPIs available (esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole).

In this bulletin, dyspepsia (as defined by the British Society of Gastroenterology<sup>1</sup>) refers to a group of symptoms that may indicate a disease of the upper gastrointestinal tract. These symptoms include heartburn, epigastric pain, abdominal discomfort, bloating, early satiety, nausea and vomiting.<sup>1</sup> Several different illnesses may cause dyspepsia but, because the symptoms are variable and not discriminatory, diagnosis may be difficult without specific investigations. An endoscopy will identify patients with gastric cancer, peptic ulcers and oesophageal pathology (for example, oesophagitis) but is not always considered to be cost-effective.

Testing for *Helicobacter pylori* is commonly done because infection with this bacterium is strongly associated with peptic ulcers. However, it is not always clear when investigations are necessary and when treatment should commence without testing.

### Summary

Proton pump inhibitors (PPIs) are used in primary care for a variety of conditions associated with dyspepsia.

- ♦ General issues relating to the prescribing of PPIs are discussed on pages 2 and 3.

The choice of PPI is likely to depend on licensed indications and cost, because differences between the PPIs in clinical efficacy and safety are minimal.

An initial four-to-eight week course of treatment with a PPI should be followed by review before any prolonged (continuous or intermittent) therapy is prescribed.

- ♦ The management of peptic ulcers, including NSAID-induced ulcers, and eradication of *H. pylori* is reviewed on page 3.
- ♦ For the role of PPIs in gastro-oesophageal reflux disorder, see page 4.
- ♦ For the controversies surrounding management of patients with non-ulcer dyspepsia or dyspepsia of unknown cause, see pages 4 and 5.
- ♦ Tables 1 and 2 in the accompanying Supplement present the comparative costs, and the licensed indications and usual doses of PPIs.

**See the Supplement accompanying this Bulletin**

In this bulletin, we discuss the use of PPIs for gastrointestinal conditions commonly treated in primary care. More serious conditions that are normally treated under specialist care, such as Barrett's oesophagus, Zollinger-Ellison syndrome and cancer, are excluded.

### Safety

PPIs have been in common use for at least ten years worldwide.<sup>2</sup> They have few known adverse effects and are generally well tolerated. Possible adverse consequences of long-term acid suppression have been suggested, including atrophic gastritis in *H. pylori*-positive patients.<sup>3</sup> However, an international study of 230 patients with reflux oesophagitis taking omeprazole for up to 11 years, amounting to almost 1500 patient-years of follow-up, found no evidence of any serious adverse effects.<sup>4</sup> Rebound gastric acid secretion after stopping PPIs has also been reported<sup>5</sup> but its clinical importance is not clear.

Another concern is that the use of PPIs may mask the “alarm” symptoms that warn of serious illness such as gastric cancer (especially weight loss, dysphagia, anaemia or progressively worsening symptoms).<sup>6</sup> Patients presenting with “alarm” symptoms should always be referred promptly.<sup>1</sup>

### Dosing

The PPIs are pro-drugs for active forms that bind irreversibly to the proton pump enzyme in the gastric parietal cell; synthesis of new enzyme is required to restore acid secretion. This explains the prolonged action of PPIs and the lack of correlation of effect with the plasma half-life. PPIs bind only to active pumps and because not all pumps are active at any one time, several days are required to reach a steady-state of pump inhibition.<sup>2</sup>

On theoretical grounds, PPIs should be taken before breakfast for greatest effect.<sup>2</sup> It is recommended that all drug treatment should be stopped if possible four weeks before endoscopy because the diagnosis of oesophagitis (and potentially gastric cancer) is easier if a patient is not on acid-suppressing therapy.<sup>1,6,7</sup> In general, an initial four-to-eight-week course of treatment should be prescribed, followed by review of the patient before deciding whether prolonged (continuous or intermittent) therapy is appropriate. Maintenance doses should be the minimum required to control or prevent symptoms.

### Intermittent use

For conditions that are known to recur, such as gastro-oesophageal reflux disorder (GORD), there is a need for therapy that can be used intermittently. The H<sub>2</sub> antagonists are already used in this way for dyspepsia and several formulations are available without a prescription. They relieve symptoms quickly, but are not as effective in suppressing acid secretion as the PPIs.

Patients taking PPIs often use them on an “as-needed” basis. One study indicated that at least 30% of patients on long-term PPIs did not take their medication regularly.<sup>8</sup> Several studies have shown that such intermittent use is clinically effective as well as cost-effective, and it is considered to be safe.<sup>9,10</sup> Considering the mechanism of action of PPIs, short courses of two to four weeks of treatment would be expected to be more effective than single doses. Lansoprazole is licensed for intermittent courses of two to four weeks for acid-related dyspepsia.<sup>11</sup> Esomeprazole is licensed for use “when needed” for GORD without oesophagitis, once initial symptom control has been achieved. However, no duration of therapy is specified in the prescribing recommendations.<sup>12</sup>

### Which PPI?

Comparative studies of the PPIs have found marginal or no differences in clinical efficacy between them when used to treat GORD and other acid-related diseases.<sup>13-16</sup> In one study esomeprazole 40 mg was found to be more effective than omeprazole 20 mg for healing reflux oesophagitis,<sup>16</sup> but these doses are not considered equipotent. A subgroup analysis of another study suggested that esomeprazole 40 mg may be preferable to lansoprazole 30 mg in treating the severest forms of oesophagitis.<sup>13</sup>

The PPIs are predominantly metabolised by the CYP2C19 and CYP3A4 isoforms of cytochrome P450 and, theoretically, could interact with other drugs metabolised by these enzymes or by inducers or inhibitors of these enzymes. The metabolism of rabeprazole is less dependent on enzyme-mediated metabolism and may therefore be less affected.<sup>17</sup> However, clinically important

drug interactions with the PPIs are rare.<sup>18</sup> For example, there are only a few case and anecdotal reports that omeprazole may interact with phenytoin (omeprazole 40 mg but not 20 mg), warfarin and diazepam; close monitoring is recommended when starting therapy.<sup>18</sup> Lansoprazole, pantoprazole and rabeprazole have not been found to interact with these drugs.<sup>18,19</sup> These findings suggest that the potential for clinically important drug interactions involving PPIs based on metabolic pathways may be exaggerated.

In summary, there is currently no clear evidence to suggest that any particular PPI is preferable in most situations, and choice is more likely to depend on licensed indications and cost (see the accompanying Supplement, Tables 1 and 2). Guidance from the National Institute for Clinical Excellence (NICE) also reflects this view.<sup>20</sup>

### The importance of lifestyle

Are PPIs used to support an unhealthy lifestyle that predisposes patients to gastric problems? This question was addressed by a qualitative comparative study based on semi-structured interviews.<sup>21</sup> It found that GPs generally felt that PPIs were used in this way and that patients were “demanding” with regard to PPIs, but this impression was modified when GPs spoke of their own patients. GPs also overemphasised the importance of lifestyle factors in causing dyspepsia-related disorders. The survey found that more than two-thirds of patients had modified their life-style, especially with regard to diet, and some had to continue dietary restrictions even while taking PPIs. The authors warn that legitimate use of PPIs may be hampered by labelling patients as having a poor lifestyle or being irresponsible.<sup>21</sup>

## Gastric and duodenal ulcer

The major cause of gastric and duodenal ulcers (apart from drug-induced cases) is infection of the gastro-intestinal mucosa by *H. pylori*, and its eradication leads to long-term healing of the ulcer in the majority of cases.<sup>22,23</sup> Testing for *H. pylori* before or after eradication therapy is recommended in the case of gastric ulcers, about 70% of which are associated with infection.<sup>1</sup> (The preferred test is the <sup>13</sup>C-urea breath test.) However, in the case of uncomplicated duodenal ulcer, testing may not be considered necessary because about 95% of duodenal ulcers are associated with infection.<sup>1,23</sup> Because idiopathic ulcer disease may be increasing, these recommendations could change.<sup>24</sup>

The use of a PPI without eradication of *H. pylori* will also heal an ulcer but recurrence is common upon discontinuation of the drug.<sup>20</sup> Patients who test negative for *H. pylori* should be treated with a healing course of a PPI, followed by the lowest dose of PPI that provides effective symptom relief.<sup>20</sup>

### *H. pylori* eradication

Several drug regimens can be used for eradication (see the BNF). Triple therapy including a PPI and two antibiotics for one week is highly effective, resulting in a cure rate of 80-90%.<sup>23,25</sup>

There is usually no need to continue acid suppression after eradication in cases of duodenal ulcer uncomplicated by haemorrhage or

perforation.<sup>1,23</sup> However, in the case of gastric ulcer, continuing antisecretory therapy is recommended for two months or until healing is confirmed at endoscopy.<sup>1</sup> In those cases where persistent symptoms require continuation of therapy, the lowest dose of PPI that provides effective relief should be used.

### NSAID-induced ulcer

Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, may cause gastro-intestinal bleeding and ulceration. Patients who have a known NSAID-induced ulcer and who must continue therapy, for example if they have severe rheumatoid arthritis, should take an acid-suppressing drug. This is usually a PPI.<sup>20</sup> (PPIs licensed for this indication are listed in Table 2 of the Supplement.) PPIs are more effective than H<sub>2</sub> antagonists and misoprostol for the treatment and prophylaxis of NSAID-induced ulcers.<sup>2</sup>

*H. pylori* eradication was previously not recommended in patients taking NSAIDs because *H. pylori* infection and NSAIDs are considered to be independent risk factors for gastrointestinal bleeding or ulceration.<sup>23,26</sup> However, several

studies have recently suggested some synergy between these factors, at least in a subgroup of patients.<sup>26,27</sup> These have led to suggestions that

eradication therapy should be offered to *H. pylori*-positive patients with known gastric ulceration on long-term NSAIDs.<sup>28</sup>

## Gastro-oesophageal reflux disorder

It has been estimated that lifestyle modification to minimise acid reflux, with or without antacids, is likely to fail in successfully treating 80% of patients with GORD.<sup>29</sup> Acid suppression with a PPI is considered to be the most effective treatment both for healing and maintenance of remission.<sup>30,31</sup> The mean healing rate of erosive oesophagitis at eight weeks for omeprazole in ten trials was 78%.<sup>31</sup>

NICE guidance recommends treatment with a healing dose of a PPI for patients with **severe GORD** or proven pathology (such as oesophagitis or oesophageal ulceration) until symptoms have been controlled.<sup>20</sup> Symptoms can then be prevented in most patients with a lower maintenance dose or intermittent short courses. Where oesophagitis is complicated by haemorrhage, ulcer or stricture, the patient should be kept on the full healing dose.<sup>20</sup>

Cases of **mild GORD** (mild or moderate symptoms with mild or no oesophagitis) can initially be treated with less potent therapies, and, if necessary, a “step-up” strategy (trying antacids, then H<sub>2</sub> antagonists, then a PPI) can be used.<sup>20,30</sup> An alternative is a “step-down” strategy (therapy in reverse order, as control of symptoms allows).<sup>20</sup>

Currently, routine eradication of *H. pylori* is not recommended in patients with GORD but this is controversial. In one study, patients who were infected with *H. pylori* relapsed sooner than those who tested negative or those in whom *H. pylori* had been eradicated.<sup>32</sup> However, it has been suggested that some strains of *H. pylori* may protect against oesophageal disease.<sup>33</sup> In other studies infection with *H. pylori* had no bearing on outcome<sup>4,10</sup> and eradication did not worsen reflux symptoms.<sup>34</sup>

## Non-ulcer dyspepsia

The term non-ulcer dyspepsia (NUD) (or “functional” dyspepsia) is used to describe patients with no obvious pathology on investigation (that is, no obvious signs of cancer, ulceration or GORD).<sup>35</sup> Other conditions that may be associated with nonspecific symptoms, such as hiatus hernia, have also been included in this category.<sup>36</sup>

An analysis of studies of the use of various therapies for NUD showed that there was little robust evidence for effectiveness of any particular therapy in primary care.<sup>36</sup> In one study in which omeprazole was compared with placebo, acid suppression was associated with a modest beneficial effect.<sup>37</sup> This finding may be related to the fact that in a subgroup of patients with NUD the symptoms are acid-related. A trial of a PPI at a therapeutic dose for four weeks

should identify such patients.<sup>7</sup> NICE guidance concludes that patients with NUD should not routinely be treated with PPIs unless the symptoms appear to be acid-related, in which case the lowest dose of an acid suppressor that controls symptoms should be used.<sup>20</sup> If PPIs are not effective, treatment with a prokinetic agent such as domperidone should be tried.<sup>1,7</sup>

The effect of eradication of *H. pylori* in patients with NUD is not clear.<sup>1,34,36,38</sup> A meta-analysis of studies showed evidence of a small benefit of *H. pylori* eradication (15 patients would need to be treated to cure one extra case of NUD; NNT=15).<sup>39</sup> The estimated incremental cost (compared with antacid treatment) was £56 per dyspepsia-free month during the first year of treatment.<sup>39</sup> The British Society of Gastroenterology considers a “test and treat” strategy to be acceptable.<sup>1</sup>

## Dyspepsia of unknown cause

Initial management of these patients is controversial because diagnostic investigations are expensive and may not be cost-effective.<sup>35</sup> In those patients over 55 years or those with “alarm” symptoms, an endoscopy is recommended to confirm a diagnosis and check for the presence of cancer; this is considered to be cost-effective.<sup>1,20,40</sup> In those under 45 years, serious disease such as gastric cancer is rare and endoscopy is considered not to be cost-effective.<sup>20</sup> In patients aged 45 to 55 the value of endoscopy is unclear.<sup>1,20</sup> Local recommendations for this age group might vary and may change as evidence emerges.

With regard to treatment, it is difficult to draw conclusions from studies in this category because of variation in the inclusion and exclusion criteria used in the different trials.

NICE guidance suggests treating patients with mild symptoms of dyspepsia with either a “step-up” or a “step-down” approach.<sup>20</sup> Meta-analyses have shown that PPIs are significantly more effective than H<sub>2</sub> antagonists or antacids in treating patients in this category.<sup>36</sup> However, NICE guidance recommends that generally PPI treatment should not be continued long-term without a confirmed diagnosis.<sup>20</sup>

Routine use of PPIs in patients with dyspepsia would result in benefit for those with GORD or acid-related NUD. It would lead to improvement (but no cure) for those with an

ulcer but will not benefit those with non-acid-related NUD. Whilst this approach may in fact be cost-effective overall<sup>36</sup> (especially if PPIs are used intermittently) it clearly does not provide optimal treatment for all patients.

The value of *H. pylori* testing or eradication in dyspepsia of unknown cause is debated,<sup>1,24,36</sup> especially as the prevalence of *H. pylori* infection varies geographically and is generally decreasing.<sup>33</sup> In one study that included 1017 patients with dyspepsia who were *H. pylori*-positive, eradication led to a 5% reduction in dyspepsia and no impact on quality of life.<sup>34</sup> In another study, treating *H. pylori* significantly reduced symptoms of dyspepsia at the end of one year (NNT=7), and improved quality of life.<sup>41</sup>

Eradication in all infected patients may not be the best strategy because it may lead to higher acid concentrations in some patients with NUD, and therefore increase the risk of GORD and possibly certain oesophageal cancers,<sup>33</sup> although this risk may be exaggerated.<sup>24</sup>

It has been suggested that only those patients who are at high risk of having peptic ulcer disease (those with a history of the disease or who smoke) should be tested and treated.<sup>42</sup> Others, including the British Society of Gastroenterology,<sup>1</sup> currently favour testing and treating *H. pylori* infection until its prevalence becomes minimal.<sup>24</sup>

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Summaries of Product Characteristics should be consulted for full prescribing information.

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**Table 1 Comparative costs of proton pump inhibitors (PPIs)**

| PPI  | Preparations<br>(= daily dose)* | Cost of 28 days supply (= 1 original pack) <sup>†</sup><br>£0 _____ £80 |
|--|---------------------------------|---|
| esomeprazole ( <i>Nexium</i> <sup>®</sup> ) tablets<br>(AstraZeneca)   | 20 mg                           | £18.50  |
|  | 40 mg                           | £28.56  |
| lansoprazole ( <i>Zoton</i> <sup>®</sup> ) capsules<br>(Wyeth/Lederle)   | 15 mg                           | £12.98  |
|  | 30 mg                           | £23.75  |
| Omeprazole capsules<br>(generic prices given <sup>#</sup> )<br><br>also available as <i>Losec</i> <sup>®</sup> &<br><i>Losec</i> <sup>®</sup> <i>MUPS</i> <sup>®</sup> (AstraZeneca) | 10 mg                           | £18.18  |
|  | 20 mg                           | £27.42  |
|  | 40 mg                           | £54.40 (four original packs)  |
| pantoprazole ( <i>Protium</i> <sup>®</sup> ) tablets<br>(Knoll)  | 20 mg                           | £12.88  |
|  | 40 mg                           | £23.65  |
| rabeprazole ( <i>Pariet</i> <sup>®</sup> ) tablets<br>(Janssen-Cilag/Eisai)  | 10 mg                           | £12.43  |
|  | 20 mg                           | £22.75  |

\* Dose information is taken from the BNF (Volume 43, March 2002) and Summaries of Product Characteristics (SPCs).

† Costs are calculated from the Drug Tariff and Chemist & Druggist, August 2002.

# Generic products recently available; prices likely to change.

**Table 2 Licensed indications and dosing for proton pump inhibitors\***

| PPI   | Duodenal ulcer                              |             | Benign gastric ulcer                        | <i>H. Pylori</i> eradication <sup>#</sup> | NSAID-associated peptic ulcer   | Gastro-oesophageal reflux disease (GORD)                             |                                       | Acid-related Dyspepsia | Other <sup>‡</sup> |
|---|---|-------------|---|---|---|--|---------------------------------------|------------------------|--------------------|
|   | treatment                                   | prophylaxis | treatment                                   |   |   | treatment  | maintenance                           |                        |                    |
| esomeprazole<br><i>Nexium</i> <sup>o</sup>  |   |             |   | 20 mg bd                                  |   | 40 mg<br>4 weeks,<br>repeat if<br>necessary <sup>†</sup>             | 20 mg <sup>†</sup>                    |                        |                    |
|   |   |             |   |   |   | 20 mg<br>4 weeks <sup>§</sup>  | 20 mg when<br>needed                  |                        |                    |
| lansoprazole<br><i>Zoton</i> <sup>o</sup>   | 30 mg<br>4 weeks                            | 15 mg       | 30 mg<br>8 weeks                            | 30 mg bd                                  | 15-30 mg<br>4 weeks treatment,<br>repeat if necessary<br><br>prophylaxis:<br>15-30 mg | 30 mg<br>4 weeks,<br>repeat if<br>necessary                          | 15-30 mg                              | 15-30 mg<br>2-4 weeks  | ✓                  |
| omeprazole<br>generics<br><i>Losec</i> <sup>o</sup><br><i>Losec</i> <sup>o</sup> <i>MUPS</i> <sup>o</sup> | 20-40 mg<br>4 weeks                         | 10-20 mg    | 20-40 mg<br>8 weeks                         | 40 mg<br>or 20 mg bd                      | 20 mg<br>4 weeks treatment,<br>repeat if necessary<br><br>prophylaxis: 20 mg          | 20-40 mg<br>4 weeks,<br>repeat<br>4-8 weeks<br>if necessary          | 10-20 mg                              | 10-20 mg<br>2-4 weeks  | ✓                  |
| pantoprazole<br><i>Protium</i> <sup>o</sup>   | 40 mg<br>2 weeks,<br>repeat if<br>necessary |             | 40 mg<br>4 weeks,<br>repeat if<br>necessary | 40 mg bd                                  | prophylaxis: 20 mg  | 20-40 mg<br>4 weeks,<br>repeat if<br>necessary                       | 20-40 mg,<br>reassess after<br>1 year |                        |                    |
| rabeprazole<br><i>Pariet</i> <sup>o</sup>   | 20 mg<br>4 weeks,<br>repeat if<br>necessary |             | 20 mg<br>6 weeks,<br>repeat if<br>necessary | 20 mg bd                                  |   | 20 mg<br>4-8 weeks <sup>†</sup><br><br>10 mg<br>4 weeks <sup>§</sup> | 10-20 mg <sup>†</sup>                 |                        |                    |

\* dosing is daily unless otherwise indicated (bd = twice daily).

# in combination with antibacterials for healing and prevention of relapse of peptic ulcer disease (see the BNF for prescribing details).

‡ see SPCs for other indications.

† for erosive reflux oesophagitis.

§ for symptomatic GORD; investigate if symptoms are not controlled after 4 weeks.