Proton pump inhibitors and Pharmacist only medicines
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The availability of Proton Pump inhibitors (PPIs) as Pharmacist only medicines has changed the management of patients requesting relief from short-term heartburn and other gastro-oesophageal reflux disease. Pharmacist only PPIs are intended for short-term use only and a person with recurring symptoms or alarm bells as listed below must be referred for further assessment. The availability of PPIs as Pharmacist only medicines also is convenient for those patients who have run out of their regular PPIs, or are away from home without supplies.

Diagnosis
Dyspepsia or indigestion or reflux as described by patients are difficult, sometimes vague symptoms to define or evaluate and requires very careful questioning to clarify the exact nature of the complaint. It may cover nausea, heartburn/regurgitation, upper abdominal discomfort, lower chest discomfort, acidity, epigastric fullness or unease, abdominal distension leading to wide and varied diagnoses such as reflux, functional dyspepsia, dysmotility, peptic ulcer, upper gastrointestinal tract (GIT) malignancies, hepatobiliary disease, pancreatitis, upper GIT inflammation, food allergy, irritable bowel syndrome; and non gastrointestinal disorders such as myocardial ischaemia, drug reaction, alcohol effect, somatisation, anxiety or stress, and depression. (1) Ischaemic heart disease must always be considered. When in doubt and when red flags are present pharmacists must refer.

About 15 to 20 percent of adults experience heartburn or regurgitation (the cardinal symptoms of reflux) at least once a week. (2) Most individuals have occasional symptoms, usually following dietary indiscretion, with a smaller proportion of the population, about 5% experiencing daily symptoms. (2)

Gastro-oesophageal reflux disease (GORD) is defined as recurring symptoms or mucosal damage resulting from exposure of the distal oesophagus to reflux of gastric contents (3). These symptoms should occur regularly, at least one day per week, for the diagnosis to be made. Relaxation of the lower oesophageal sphincter is the major determinant of reflux. Hiatus hernias are commonly found in reflux disease, but they are not the cause of GORD.

Gastro-oesophageal reflux disease may have a negative effect on quality of life. Complications of GORD include oesophagitis, iron-deficiency anaemia, stricture, respiratory symptoms eg chronic cough, asthma, hoarseness, dental erosions and Barrett’s oesophagus from prolonged reflux (1, 2). Barrett’s oesophagus is a premalignant condition prone to ulceration requiring regular endoscopies with biopsies (1, 2). It is therefore important that supply of PPIs by pharmacists be limited to short-term use only and patients with ongoing symptoms are referred for investigation.

Symptoms of reflux
The cardinal and typical symptoms of gastroesophageal reflux is heartburn, or a burning feeling which may begin in the epigastrium and rise retrosternally into the neck. It may be precipitated by meals, postural change, certain medications and stress, and is usually relieved by antacids. (1, 2)

Other symptoms include:
- regurgitation of food or acid contents of the stomach (especially when lying down at night)
- waterbrash (regurgitation of an excessive accumulation of saliva)

Some patients will experience atypical symptoms of:
- cardiac-like chest pain
• non-specific abdominal pain or discomfort,
• cough
• hoarseness,
• sore throat
• bloating, belching or nausea.

The Pharmaceutical Society of Australia (PSA) protocol for supply of pantoprazole (4,5) as Pharmacist only states that patients presenting with symptoms of heartburn and other gastro-oesophageal reflux disease, or requesting PPIs should be referred if they:

• Are under 18 or above 55 years of age
• Are pregnant or breast feeding
• Have non-specific atypical symptoms
• Have taken another OTC treatment for indigestion or heartburn continuously for 4 or more weeks
• Have jaundice or hepatic impairment, previous gastric ulcer or gastrointestinal surgery or other significant medical condition

**Have any of the following red flags: (1, 4)**

- Unintentional weight loss
- Angina related symptoms - chest pain
- Anaemia
- Gastrointestinal bleeding (haematemesis/ melaena)
- Difficult swallowing (dysphagia)
- Painful swallowing (odynophagia)
- Haematemesis (spitting up blood)
- Persistent vomiting
- Choking attacks – especially at night

**Choice of treatment:**

When presented with the symptoms of indigestion/reflux a pharmacist now has the choice of:

- **Antacids or alginates.** Liquid antacids work better than tablets and can be taken when needed and 1 – 2 hours before meals and bedtime. Antacids should be separated by two hours from other medications due to reduction in absorption. Table 1 lists common antacids in use.
- **H2 antagonists.** Famotidine or ranitidine are appropriate for mild or intermittent symptoms. (1-3)
- **PPIs.**
  The SUSMP in September 2010 approved the following PPIs as Pharmacist only medicines (S3):
  - Lansoprazole in oral preparations containing 15 mg or less of lansoprazole per dosage unit
  - Omeprazole in oral preparations containing 20 mg or less of omeprazole per dosage unit
  - Pantoprazole in oral preparations containing 20 mg or less of pantoprazole per dosage unit
  - Rabeprazole in oral preparations containing 10 mg or less of rabeprazole per dosage unit
  - all for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply. (6)

For those with predominately daytime symptoms PPIs are best given 30 minutes before breakfast and those with predominately nocturnal symptoms they should be taken 30 minutes before dinner. PPIs have been shown to be superior to antacids, alginates and H2 receptor antagonists in the treatment of gastric reflux. (2)
Table 1: Antacids in common use (Adapted from 1)

<table>
<thead>
<tr>
<th>Antacid</th>
<th>Side effect</th>
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<tbody>
<tr>
<td>Aluminium hydroxide</td>
<td>May cause constipation</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>May cause alkalosis, constipation, milk-alkali syndrome*, hypercalcaemia</td>
</tr>
<tr>
<td>Magnesium trisilicate</td>
<td>May cause diarrhoea</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>May cause alkalosis, milk-alkali syndrome* aggravation hypertens ion</td>
</tr>
</tbody>
</table>

*Iron-alkali syndrome — the triad of hypercalcaemia, metabolic alkalosis and renal insufficiency — is associated with ingesting large amounts of calcium and absorbable alkali.

Management of GORD by medical practitioners

Patients with recurring upper gastrointestinal symptoms should be referred to their doctor for diagnosis and ongoing management. The access of effective acid suppression therapy has made gastro-oesophageal reflux disease easily treatable. When proton pump inhibitors were first introduced use was restricted to gastroscopy diagnosis. International management guidelines now recommend two alternatives to gastroscopy:

- empiric acid-suppression therapy;
- or *H. pylori* testing and treatment (2).

Acid-suppression therapy is effective treatment for gastro-oesophageal reflux disease (GORD), and the “omeprazole test” (a simple trial of omeprazole [40 mg twice daily for a week]) diagnoses GORD more accurately than endoscopy, and with a sensitivity of around 80 percent (2).

Treatment

Proton pump inhibitors provide rapid and effective control of the symptoms of gastro-oesophageal reflux disease and dyspepsia, with few adverse effects. These are now prescribed in most new cases of GORD (7). Continuous use at a standard dose is common practice, but may represent more intensive therapy than many patients require.

Although a step-up approach can be used with antacids followed by H2-receptor antagonists, and proton pump inhibitors there has been a change to favour a high level initial therapy with PPIs at standard dose then step-down. This has been based on grounds of outcomes, speed of response and total cost. Most GPs are aware of the step-down strategy, but it does not appear to be used widely.

Guidelines for prescribing PPIs are as follows (2, 5):

1. **Use a 4–8 week course of standard-dose PPI therapy to control symptoms of GORD**

   An initial 4-8 week course of standard-dose PPI is appropriate, either as empirical therapy if alarm symptoms are absent or if ulcer, malignancy and severe oesophagitis have been ruled out by endoscopy. The patient should return to the prescriber for review if symptoms persist or recur. After discontinuation, 20–40% of patients will not require another PPI prescription for 6–12 months. These patients may present for Pharmacist only PPIs.

   In endoscopy-confirmed oesophagitis, healing rates are increased from about 75% to around 90% if therapy is extended to 8 weeks. If symptomatic oesophagitis persists, a further 4 weeks of double-dose therapy is indicated. In the minority of patients with severe or complicated oesophagitis, continuous standard-dose therapy is indicated.

2. **Communicate to patients that adopting lifestyle changes can help reduce the need for PPI therapy**

   Lifestyle changes for general health benefits and avoidance of dyspepsia triggers are points that should be discussed with patients by medical practitioners and pharmacists.
Table 2: Some suggested lifestyle changes (1-5)

<table>
<thead>
<tr>
<th>Consider:</th>
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<tbody>
<tr>
<td>• weight reduction- if overweight- this may decrease symptoms</td>
</tr>
<tr>
<td>• smoking cessation</td>
</tr>
<tr>
<td>• alcohol reduction especially with dinner</td>
</tr>
<tr>
<td>• avoid acidic foods (citrus and tomato-based products), spicy foods, onions, garlic and peppermint</td>
</tr>
<tr>
<td>• decrease dietary fat intake e.g. pastries, French fries</td>
</tr>
<tr>
<td>• reduction of coffee, tea, chocolate</td>
</tr>
<tr>
<td>• avoid coffee and alcohol late at night</td>
</tr>
<tr>
<td>• avoid gaseous drinks</td>
</tr>
<tr>
<td>• have at least 3 hours between evening meal and retiring</td>
</tr>
<tr>
<td>• increase fibre intake</td>
</tr>
<tr>
<td>• eat slowly and chew food well</td>
</tr>
<tr>
<td>• sleep on the left side</td>
</tr>
<tr>
<td>• elevation of head of bed or wedge pillow</td>
</tr>
<tr>
<td>• avoid tight clothing around waist (1,4,5).</td>
</tr>
</tbody>
</table>

3 Step-down to the lowest dose and frequency of PPI that is effective

If continuous maintenance therapy is needed, a low-dose PPI should be used. The standard dose should be reverted to if symptoms are not controlled or in case of relapse. There is no evidence that double-dose PPIs are more effective than standard dose in maintenance of healed oesophagitis, but a few patients may require titration to a high dose to control symptoms. There is no evidence showing differences in efficacy between the various proton pump inhibitors.

As mentioned above an antacid/alginate or an H2 antagonist, i.e. famotidine or ranitidine is appropriate for mild or intermittent symptoms.

Non-responders to these treatments often have non-ulcer or functional dyspepsia and treatment is unrewarding. Prescribed and complementary medications, a frequent cause, should be reviewed. Delayed gastric emptying affects up to 40% of non-ulcer dyspepsia patients. Functional dyspepsia is particularly frequent in patients with acute or chronic stress (2). Previous gastroenteritis is a recently identified cause of non-ulcer dyspepsia. Prokinetic therapy (with drugs that increase the contractility of the smooth muscle of the upper gut, such as domperidone, metoclopramide) may be of benefit if the main symptoms are a feeling of discomfort and bloating and/or the PPI if there is burning epigastric pain. (2) Eosinophilic oesophagitis, an isolated eosinophilic inflammation of the oesophagus, is the most common of the eosinophilic gastrointestinal disorders and is linked to atopic disorders, including asthma and eczema (8).

4. Review the need for ongoing maintenance therapy as rare, but serious, PPI side effects can occur.

PPIs are well tolerated and most adverse effects are mild and transient. Common adverse effects, observed in up to 10% of patients, are headache, diarrhoea, gastrointestinal upset, constipation and flatulence. Rare but important adverse events include acute interstitial nephritis, hyponatraemia, hypokalaemia, hypomagnesaemia, pancreatitis and Stevens-Johnson syndrome. There are reports of an increased risk of pneumonia and Clostridium difficile colitis in long-term users of PPIs. (9) Patients taking PPIs on short term Pharmacist only basis would be unlikely to experience these effects.
**Decrease in Vitamin B12:** Utilisation of vitamin B12 from dietary sources requires gastric acid. This issue remains controversial as to clinical significance but current evidence suggests it is wise to check B12 levels with chronic gastric acid suppression therapy (10).

**Increase in C difficile:** A number of studies have found a 2–3-fold increase in risk of *Clostridium difficile* infection in patients using a PPI. Risk factors for *C. difficile* infection include using antibiotics, age over 5 years and renal failure (11, 12). *C. difficile* infection should be distinguished from the symptoms of diarrhoea that occur at a rate of around 5–15 per 100 patient-years of PPI use and from the uncommon cases of microscopic colitis that appear to be specifically associated with lansoprazole (2).

**Increase in community-acquired pneumonia:** The risk was greatest in patients who started treatment within the previous 7 days. Those with a longer history of PPI use had a modest, or no increased risk. (5)

**Interstitial nephritis:** Acute interstitial nephritis is a rare but serious hypersensitivity reaction that has been reported with all PPIs. The symptoms of PPI-related interstitial nephritis are non-specific (e.g. weight loss, malaise, fever and nausea). Laboratory investigation confirms the presence of renal dysfunction and urine examination, including microscopy, may show haematuria and proteinuria but may be unremarkable. Case reports describe an onset as soon as 12 days or as late as 12 months after starting PPI therapy (13).

**Fractures- increase in risk:** The biological mechanism underlying this possible association is unknown. One explanation may be that the absorption of dietary calcium is dependent on a low pH in the stomach and as PPIs are potent inhibitors of acid secretion from the gastric parietal cells, there will be an increase in pH. However the effect of this, if any, on bone density in the long term is still unknown and it is certainly possible that other factors contribute to the observed increase in fracture risk. Recent papers have concluded that the risk of hip fracture increased with duration of therapy when patients took high doses of PPI greater than one year. (14, 15)

**Magnesium & PPIs:** Long term use proton-pump inhibitors may cause low serum magnesium levels. The Food and Drug Administration (FDA) says there is little risk from over-the-counter PPIs when taken as directed for 14 days. *FDA Safety March 2011*

**Use in combination with NSAIDS:** In patients who require an NSAID the use of PPIs to prevent NSAID- induced ulcers or NSAID- induced dyspepsia may be considered in high risk patients but rates of recurrent bleeding may still be high. This is also not a PBS indication for the PPI nor an indication for the sale of Pharmacist only PPIs.

**Drugs/Diseases which may aggravate GORD**
Drugs may aggravate GORD by relaxation of the lower oesophageal sphincter (LOS) or may be irritant to the oesophagus as shown in Table 3. In addition alcohol and smoking reduce lower oesophageal pressure. Identification of these agents which may aggravate should be bought to the person’s general practitioner by the pharmacist.

People with asthma also often have GORD. Reflux is very common in people with asthma. It may be a trigger for asthma, or alternatively, asthma may trigger reflux. This review of trials found that using reflux treatments does not generally help ease asthma symptoms. While asthma may be improved in some people, it was not possible to predict who might benefit.
Table 3: Drugs which may aggravate GORD (1-4)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphablockers</td>
<td>Nicotine*</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Nitrates*</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Non-steroidal-anti-inflammatory drugs (NSAIDS)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Opioids</td>
</tr>
<tr>
<td>Beta-agonists</td>
<td>Phosphodiesterase inhibitors</td>
</tr>
<tr>
<td>Bisphosphonates (alendronate, risedronate)</td>
<td>Potassium chloride</td>
</tr>
<tr>
<td>Corticosteroids (oral)</td>
<td>SSRI antidepressants</td>
</tr>
<tr>
<td>Calcium channel blockers*</td>
<td>Tetracyclines (doxycycline, minomycin)</td>
</tr>
<tr>
<td>Hormone replacement therapy*</td>
<td>Theophylline*</td>
</tr>
<tr>
<td>Iron supplements</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td>* reduce LOS pressure</td>
<td></td>
</tr>
</tbody>
</table>

Drug interactions
Before prescribing PPIs either as pharmacist only medicines or as prescription medicines possible drug interactions should be checked as summarised in Table 4.

The decreased intragastric acidity during treatment with PPIs may increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity.

There has been considerable debate about the clinical significance of the drug interaction between clopidogrel and PPIs. Clinical decisions about the use of the combination need to assess risks and benefits of cardiovascular and gastrointestinal complications. Latest evidence suggests that the interaction is of minor significance. (18) The decision whether to use a PPI as a pharmacy only medicine in a patient taking clopidogrel is difficult. Most evidence suggests that the use of pantoprazole is preferable however a safer option may be the use of an H2-receptor antagonist. Table 4 lists some common drug interactions.

Table 4: Some drug interactions with some common proton pump inhibitors (19-21),

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole, itraconazole</td>
<td>Absorption of antifungal agent may decrease due to increase in gastric pH</td>
</tr>
<tr>
<td>Drugs metabolised by CYP2C19 eg amitriptyline, citalopram diazepam, moclobemide, phenytoin, propanolol warfarin</td>
<td>May cause increase in plasma concentration of drug metabolised by CYP2C19</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Levels of PPI are increased during use of clarithromycin with omeprazole only</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Possible decrease in clozapine concentration</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Possible increase in methotrexate concentration reported with omeprazole, pantoprazole with high dose methotrexate therapy</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>Levels of PPI are decreased</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Concern about small increased risk of cardiovascular events - controversial?</td>
</tr>
</tbody>
</table>
Questions:
Indicate incorrect answer (one only)

1. Symptoms of Gastro-oesophageal reflux disease usually include
   a) heartburn
   b) acid brash
   c) regurgitation
   d) anorexia
   e) regurgitation of food

2. Alarm symptoms which require urgent investigation for patients with GORD may include
   a) odynophagia
   b) dysphagia
   c) angina
   d) weight loss
   e) cough

3. a) H2 receptor antagonists may offer sufficient relief for some patients
    b) Antacids offer sufficient relief for some patients
    c) PPIs prescribed as pharmacist only should be used for not more than 14 days.
    d) Gastroscopy should be used to diagnose all cases of GORD prior to commencing PPIs for long term treatment
    e) There is no evidence showing differences in efficacy between the various PPIs

4. a) PPIs must always be taken regularly not prn.
    b) Low dose PPIs are recommended for maintenance therapy
    c) If oesophagitis has healed some patients may still require ongoing therapy
Calcium carbonate may cause constipation
Smoking and alcohol may increase GORD
Alendronate may aggravate GORD
Calcium channel blockers may decrease lower oesophageal sphincter pressure increasing reflux
Patients should be take PPIs half an hour before either breakfast or dinner depending on symptoms
Patients reporting symptoms after 14 days of a PPI supplied by a pharmacist as a Pharmacist-only medicine should consult their medical practitioner
Serum levels of diazepam may be decreased by omeprazole

References:
4. Pharmaceutical Society of Australia protocol — Provision of pantoprazole as a pharmacist only medicine Available on members only section of the website www.psa.org.au
5. NPS Prescribing Practice Review 45: Proton pump inhibitors: step-down to symptom control May 2009
7. BEACH data, Australian General Practice Statistics and Classification Centre, a collaborating unit of the Family Medicine Research Centre, University of Sydney and the Australian Institute of Health and Welfare, 2006
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