REVIEW ARTICLE

Proton Pump Inhibitors : The Controversies to Consider

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Heartburn is ailing the masses. By one estimate, 20% of the Western population experiences acid reflux at least once a week and shelling out buckets of cash $25.6 billion worldwide in 2008 to alleviate those hot, sour, acidic pains in the chest. Proton pump inhibitors (PPIs) are one of the most commonly prescribed classes of medications in the primary care setting and are considered a major advance in the treatment of acid-peptic diseases. Since the introduction of omeprazole in 1989, several other PPIs have become available in combating various acid-peptic disorders, including gastroesophageal reflux disease, peptic ulcer disease, and nonsteroidal anti-inflammatory drug–induced gastropathy. The intravenous form of pantoprazole is now available, and the U.S. Food and Drug Administration (FDA) approved the newest dexlansoprazole in 2012.

Although H_2 blockers are less expensive than PPIs, but PPIs provide superior acid suppression, healing rates and symptom relief. Therefore, PPIs may be more cost-effective than H_2 blockers, especially in patients with more severe acid-peptic disorders, because of their lower and less frequent dosing requirements and their comparatively shorter duration of required therapy. When deciding which PPI to use, physicians should consider the patient's age, medications, and diagnosis, as well as the expense of therapy.

All five PPIs appear to have similar efficacy in the treatment of various acid-peptic disorders. PPIs are inactivated by exposure to gastric juice and are delivered in delayed-release gelatin capsules containing enteric-coated granules (omeprazole and lansoprazole) or in delayed-release enteric-coated tablets (rabeprazole and pantoprazole). The newer agents, rabeprazole and pantoprazole, seem to have fewer drug interactions[1]. This is a particularly important consideration in older patients who are already taking several other medications. While the average wholesale prices of all agents in this class are similar, pantoprazole is the least expensive. For patients who are unable to swallow intact capsules. The capsules may be opened and the granules sprinkled over a tablespoon of applesauce, pudding, yogurt, or cottage cheese; the food must be swallowed immediately without stirring, crushing, or chewing. In patients with nasogastric or gastrostomy tubes, the granules in one capsule may be mixed with 40 mL of apple juice and injected through the tube, which should be flushed with additional juice to clear the tube. The newly approved dexlansoprazole is the R-isomer of lansoprazole. It's formulated as a "dual delayed release" capsule, to release drug in two phases, and thus prolong acid suppression. For now, there's no proof that

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dexlansoprazole is clinically superior to other PPIs.

Rabeprazole should be taken after meals, but pantoprazole may be taken without regard to meals. Antacids may be administered concomitantly with all PPIs. Co-administration of other acid suppressing agents like H_2-receptor blockers may diminish the efficacy of PPIs. Since not all pumps or all parietal cells are functional at the same time[2]. Dosage adjustments for PPIs are not necessary in elderly patients or those with renal failure or mild hepatic impairment.

The FDA has not approved pantoprazole for maintenance therapy because safety has not been established beyond 16 weeks. At this time, pantoprazole is indicated by the FDA only for the treatment of erosive esophagitis in a dosage of 40 mg daily for eight to 16 weeks. It is the only PPI available for intravenous administration and has recently been approved by the FDA for the short-term intravenous treatment (seven to 10 days) of GERD in hospital inpatients who are unable to take an oral PPI. The intravenous dosage is the same as the oral dosage (40 mg) and should be administered slowly over two to 15 minutes[3].

Available for about two decades now, PPIs are perceived to be very safe. But research over the last four to five years has suggested patients and doctors shouldn't get complacent about this prescription, particularly over the long term. In fact, only about 1 to 3 percent of people will stop their PPI treatment because of side effects. However, all medications have risks and benefits. PPIs may have long-term side effects that should be taken into account when considering treatment. PPIs are well-tolerated, and some side effects may go away with continued use of the drug. However, contact your health care provider if any side effect becomes bothersome. Sometimes a change in dose or switch to another PPI may alleviate the problem. The side effects of all the different PPIs are very similar. The most common side effects include headache, stomach pain, nausea, diarrhea, vomiting, constipation. Sometimes myopathy, arthralgia and skin rashes also have been reported[2].

Some controversies

There are some controversies regarding the need to endoscopically evaluate patients before prescribing PPIs. It would be prudent to consider endoscopic evaluation before initiating PPI therapy in patients 45 years or older and in those with atypical symptoms because pre-endoscopy treatment with a PPI could mask gastric cancer. While some authorities recommend that the *H. pylori* status of all patients requiring long-term PPI therapy be determined and that those who are positive for *H. pylori* receive appropriate treatment to eradicate the infection, the FDA's gastrointestinal drug advisory committee has issued assurances regarding the absence of the risk of atrophic gastritis and gastric carcinoma in these patients. Esomeprazole may have increased bioavailability when compared with omeprazole, but otherwise it appears to be similar; omeprazole will soon be available in generic form.

Leads to broken bones? Sometimes it has been heard that PPIs can cause fractures. In May 2010, the U.S. Food and Drug Administration (FDA) warned about the possible increased risk of fractures with PPI use.

Physiologically it makes sense; if you decrease your gastric acid [by taking a PPI], you're likely to absorb less calcium. Gastric acid can help

cleave calcium from food, and suppression of gastric acid may lead to relative malabsorption. Research has shown that the rates of fractures appear to correspond to both the length of time that you're on the PPI as well as dose. Information from studies suggests that PPIs may be associated with an increased risk of hip, wrist, and spine fractures[4]. People who were at the greatest risk were those on high doses or used PPIs for at least one year or more. The FDA is recommending that prescribers consider shorter courses of treatment and lower doses as appropriate to treat a person's condition. People at risk for osteoporosis should be monitored by their health care provider and take adequate calcium and vitamin D supplements.

Long-term use of proton pump inhibitors has been less studied. A study of 135,000 people 50 or older found that those taking high doses of PPIs for longer than one year were 2.6 times more likely to break a hip. Those taking smaller doses for 1 to 4 years were 1.2 to 1.6 times more likely to break a hip, and the risk of a fracture increased with the length of time taking PPIs. However, in 2010 data from the same source (the UK General Practice Research Database) was analyzed a second time, and reported a different trend: risk of fracture more than doubled immediately after initiation of medication, but dropped to slightly less than double baseline with prolonged use. This information was not taken into account in the 25 May 2010 FDA labeling change because it wouldn't be published until a year later - May, 2011 and it wasn't even published online. Furthermore, of the seven studies the FDA did make note of, all but the smallest study found marked increased risks of fractures. Theories as to the cause of the increase are the possibility that the reduction of stomach acid reduces the amount of calcium dissolved in the stomach or that PPIs may interfere with the breakdown and rebuilding of bone by interfering with the acid production of osteoclasts. The reduction of vitamin B_{12} may also increase bone fragility by raising homocysteine). A recent study also suggested that proton pump inhibitors significantly decreased the effect of clopidogrel on platelets, as tested by VASP phosphorylation. The clinical impact of these results must be assessed by further investigations, but a PPI treatment should not be added to the antiplatelet dual therapy without formal indication[5].

The FDA is revising both the prescription and the over-the-counter (OTC) labels for PPIs to include the possible increased risk of fractures. This new information is based upon FDA review of several long-term studies that reported an increased risk of fractures of the hip, wrist, and spine with PPI use. Some studies found a greater risk for these fractures from higher doses of PPI or use for one year or more. Most studies evaluated individuals aged 50 or older and the increased risk of fractures was primarily in this group.

Reduces Magnesium levels? In March 2011, the FDA warned that using PPIs for more than a year may cause low magnesium levels. Symptoms of low magnesium include muscle spasms, tremors, irregular heartbeats, and seizures. However, not everyone with low magnesium will experience these symptoms. It is recommended that health care professionals consider checking magnesium levels prior to therapy in people i) Expected to be on long-term PPI therapy ii) On PPI therapy plus Digoxin, diuretics, or other medications that lower magnesium

Reduces vitamin B_{12} ? Stomach acid is needed to release vitamin B_{12} from the foods we eat. Because PPIs reduce stomach acid, it has been thought that PPIs may cause vitamin B_{12} deficiency. Symptoms of vitamin B12 deficiency may include weakness, anemia, numbness or tingling of hands or feet, memory problems, poor balance, soreness of the tongue or mouth.

The information available is conflicting on whether this is a true side effect of PPI use. It appears that long-term use of PPIs may be most likely to lead to vitamin B_{12} deficiency in the elderly or in people with Zollinger-Ellison syndrome who are on high doses.

Prevent or causes cancer? People who have uncontrolled GERD may be at risk for Barrett's esophagus — a condition in which the cells in the esophagus change. Although it is rare, a small number of people with Barrett's esophagus may develop esophageal cancer. PPIs are used to treat acid reflux associated with Barrett's esophagus and may lower the risk of cellular changes in the esophagus that can lead to cancer.

On the other hand, there has been speculation that long-term treatment with PPIs may increase the risk of cancer. However, the evidence is not conclusive. More research needs to be done regarding PPI therapy and the link to cancer. However, people on long-term PPIs should be reassessed periodically to make certain the benefits from the medication continue to outweigh the risks.

Hypergastrinemia (>500ng/L) occurs in approximately 5-10% of long term omeprazole users[2]. Gastrin is a tropic factor for epithelial cells and may cause hyperplasia of entero-chromaffin like cells in prolong users of PPIs predisposing rebound hypeproduction of acid following discontinuation of PPIs.

Points of precaution: FDA has determined an osteoporosis and fracture warning on the over-the-counter (OTC) proton pump inhibitor (PPI) medication "Drug Facts" label. Following a thorough review of available safety data, FDA has concluded that fracture risk with short-term, low dose PPI use is unlikely.

The available data show that patients at highest risk for fractures received high doses of prescription PPIs (higher than OTC PPI doses) and/or used a PPI for one year or more.

In contrast to prescription PPIs, OTC PPIs are marketed at low doses and are only intended for a 14 day course of treatment up to 3 times per year[5].

Individuals at risk for osteoporosis should have their bone status managed according to current clinical practice, and should take adequate vitamin D, calcium and bisphosphonate supplementation.

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