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A Concise Review on Extensive use of Proton Pump Inhibitors

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Abstract

Proton Pump inhibitors have been a landmark since their inception through their safe and efficacious use in inhibition of acid secretion. They superseded another class of drugs that serve the same purpose but with a different mode of action termed "H2 receptor antagonists". PPI's (Proton pump inhibitors) prescribing has been dramatically increased over the years owing to their role in treating acid related disorders like GERD (Gastro Esophageal Reflux Disease), Gastric and Duodenal Ulcers, NSAID (Non-Steroidal Anti Inflammatory Drugs) induced ulcers etc. They are available as over the counter medications in many countries. But, the long-term use of PPi's (Proton pump inhibitors) have certain limitations that has been extensively studied. Deprescribing has been suggested to reduce polypharmacy where the PPi (Proton pump inhibitors) use may be inappropriate or without indication. The present article emphasizes the need for PPi ((Proton pump inhibitors) use with possible indications along with various de-prescribing methods along with possible safety and acceptable efficacy profile of PPi's (Proton pump inhibitors) in long term use. Recent novel studies are being aimed at reducing nocturnal acid secretion4 that conventional PPi's (Proton pump inhibitors) couldn't address where Potassium Competitive acid blockers (PCAB) come into play.

Keywords: Proton pump inhibitors; Deprescribing; Polypharmacy

Introduction

Proton pump inhibitors account for the most sold medications worldwide. Their relative safety and acceptable efficacy has been considerable. PPi's are a class of drugs that work by inhibiting the H¬+-K+-ATPase pump along the baso-lateral membrane of the gastric parietal cells that secrete the acid. The drugs in this class differ in their pharmacokinetics and clinical indications but relative action remains similar (Table 1). The drugs are acid-labile, weak bases that were delivered by different mechanisms and routes be it enteric-coated tablets, powder for suspension or gelatin capsules. Intravenous formulations of PPi's were available that find their use in hospital setup to aid immediate acid reduction and where PPi's cannot be taken orally [1-5].

Of all the PPi's Lansoprazole, Dexlansoprazole, Pantoprazole have highest bio-availability, but rabeprazole is the most potent as it is most acid-sensitive and Pantoprazole is least potent. Various evaluation studies were performed to know whether if one PPi outweighs the other in terms of clinical outcomes but no single study was able to prove the same (Table 2).

General clinical indications of PPi's

- Healing of Peptic Ulcer Disease
- NSAID induced ulcers
- Eradication of *H.pylori* infection
- Zollinger-Ellison Syndrome
- Erosive Esophagitis
- GERD
- Functional Dyspepsia
- Prophylactic Considerations

Adverse Effects

PPi's are relatively safe and potent in their action, however they have certain shortcomings due to their long-term use that may be associated with the class of the drug that include head-ache, nausea, dry mouth etc [6]. it is as advised by the FDA that prolonged PPi usage may warrant bacterial colonization of *Clostridium difficale* as acid suppression reduces the gastric P^H.

Long-term use of PPI's

There is high risk associated with chronic long-term use of PPi's which is not suggested in otherwise serious clinical conditions where potential benefits of long term treatment outweigh the acceptable risks. They are commonly prescribed to regulate and prevent symptoms of a chronic condition, it is likely that the treatment may persist for more than four years [7]. This longevity in treatment is believed to hamper calcium and magnesium absorption in the small intestine. The ability of the small intestine to absorb calcium salts is highly pH dependent, and since proton pump inhibitors cause an increase in gastric pH, calcium salts are rendered insoluble and cannot be absorbed. This directly correlates with the fact that supports osteoporosis in patients with long-term use of PPi's. A study conducted in Canada determined that after seven years of continuous exposure to a PPI, there was a statistically significant increase in osteoporosis-related fractures, and an increase risk of hip fracture after five years. A study correlates that same is the case with magnesium hence the hypomagnesemia, warrants that prescribers/clinicians must be aware of this adverse effects whenever they prescribe & monitor Sr.Calcium & Sr.Magnesium levels on a regular basis [8,9]. Concurrent studies revealed an association between exposure to PPI and risk of Chronic kidney disease (CKD), kidney disease progression and end-stage renal disease.

De-Prescribing

Deprescribing' involves slow withdrawal but not abrupt stopping of medicines which can be similar to tapering therapy as with other drugs. Also, the most sought-after idea is to start taking medications

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Drug	Dosages, mg	IV	Liquid (or) suspension	Generic	Over- the- counter
Omeprazole	10,20,40	Yes	No	Yes	Yes
Esomeprazole	20,40	Yes	Yes	Yes	Yes
Lansoprazole	15,30	Yes	Yes	Yes	Yes
Dexlansoprazole	30,60	No	No	No	No
Pantoprazole	20,40	Yes	Yes	Yes	No
Rebeprazole	20	No	No	Yes	No

Table 1: Different marketed products of PPI's.

FDA approved Indications	Pantoprazole	Rabeprazole	Esomeprazole	Dexlansoprazole	Omeprazole	Lansoprazole
Healing of erosive esophagitis	X	X	X	X	X	X
Maintenance of healing of erosive esophagitis	X	X	X	X	X	X
Symptomatic gasteroesophaegeal reflux diseases	X	X	X	X	X	X
H. pylori eradication in combination with antibiotics		X	X		X	X
Short-term treatment of active gastric ulcers					X	X
Short-term treatment of active duodenal ulcers		X			X	X
Maintenance of healed duodenal ulcer						X
Healing of NSAID-associated gastric ulcer						X
Risk reduction of NSAID-associated gastric ulcer			X			X
Risk reduction of upper gastrointestinal bleeding in critically ill patients					X	
Pathological hypersecretory conditions incl. Zollinger-Ellison Syndrome	X	X	X		X	X
Symptomatic gasteroesophaegeal reflux diseases/erosive esophagitis in children		X	X		X	X

Table 2: FDA approved indications.

only when the symptoms start to appear or already have (heartburn begins). The main aim of de-prescribing is to reduce poly pharmacy by PPi's and minimize drug related adverse effects.

Deprescribing was defined as one or more of the following interventions:

Stopping PPI therapy

Either via abrupt discontinuation or a tapering regimen.

Step down

Following abrupt discontinuation or tapering of PPI, an H2RA was prescribed (any H2RA at any approved dose and dosing interval per drug monograph).

Reduction in PPI, which included the following subcategories

i) intermittent PPI use as previously defined by the Canadian Consensus (Armstrong 2005);

ii) on-demand PPI use as previously defined by the Canadian Consensus (Armstrong 2005);

iii) lower dose: continuous daily PPI therapy at a lower dose

Treatment of H

Followed by four to eight weeks of PPI maintenance therapy for bleeding or non-bleeding PUD and then PPI discontinuation.

The above interventions are mostly followed in various studies and deemed successful in assessing PPi usage patterns and relevant prescriptions that give PPi's without indication.

Patient Satisfaction with PPI's

Satisfaction with PPI's

A study was conducted to assess the patient satisfaction with proton pump inhibitors and a rating scale was developed ranging from 1-10 that depicts the level of satisfaction with their PPIs with 0 (not at all satisfied) to 10 (extremely satisfied). Overall, 59% of the 400 subjects indicated that they were extremely satisfied with their PPI's. On the contrary, subjects experiencing acid breakthrough symptoms expressed that PPi's have no effect in curtailing acid secretions [10,11].

Conclusion

Proton pump inhibitors have largely been used in clinical settings in accordance with maximal efficacy and minimal risks. However, they were also used inappropriately as a "Drug Without Indication" promoting polypharmacy and increase treatment costs. It is reported in a study that the correctness of PPI prescriptions in some hospitals is as low as 19%. Several factors must be taken into consideration before prescribing a proton pump inhibitor with primary being the assessment of appropriateness of treatment. Also see the use of H_2-receptor antagonists if they are plausible before commencing treatment with a proton pump inhibitor.

Limitations

It is common practice that PPi's are over used in FDA approved or undocumented clinical indications. This unchecked drug use has its toll on economy of the patient in the long term. If the rate at which non-FDA compliant prescriptions were being dispensed could be controlled, this would result in an immense cost savings to both the government and the general public. Long-term use of PPi's have their own problems with acid break through symptoms and the nocturnal acid secretion that negates PPi's use. Deprescribing tends to promote fair use and reduce economic burden only if the appropriate interventions are followed.

Recent Trends

Owing to their long-term complications say break through acid release, studies are in a full swing to counter PPi's, even the altered release formulations that are found to be less advantageous than with

conventional PPi's, Potassium competitive acid blockers (PCAB) were the choice though they were not wide in use with the only drug being "VONAPRAZAN" which has superseded conventional PPi's in reducing nocturnal acid secretion and thus it may be helpful in addressing the unmet medical need of acid secretion.

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