



Evaluation of the Effectiveness of the use of Pantoprazole and the Risks

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Authors' contributions

This work was carried out in collaboration between both two authors. Authors RV and PDR have contributed to the conception, design, data collection and analysis. The manuscript was written by author RV. Both authors read and approved the final manuscript

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ABSTRACT

Drug use evaluation (DUE) is a systematic approach to study the utilization of marketed drugs. These studies are proved invaluable for policy makers to get inputs on the use of drugs so that they can review their strategies. In this prospective observational study, we have conducted a DUE of Acid suppressant drugs in Outpatient department (OPD) of a tertiary care teaching hospital in Kadapa, Andhra Pradesh. In the armamentarium of acid suppressants Proton pump inhibitors (PPIs) occupied a special space owing to their superiority to others like H₂ receptor blockers. PPIs are in the market for the last 40 years and their safety and efficacy is impeccable till now. These are the most commonly used drugs and tend to be used for long-term to manage acidity problems. But unregulated usage of PPIs over long term could pose very significant health problems ranging from electrolyte imbalance to cognitive impairment. Our study identified some issues in prescribing PPIs suggesting there is generous use of PPIs without considering their risks. And their safety also taken for granted, it appears.

Keywords: *Acid suppressants; proton pump inhibitors; pantoprazole; drug utilization evaluation.*

ABBREVIATIONS

DUE : Drug use evaluation
GERD : Gastroesophageal reflux disease
H2RAs : H2 receptor antagonists
OPD : Out patient department
PPI : Proton pump inhibitor
NSAID : Non steroidal anti-inflammatory drug
OTC : Over the counter drugs
IFA : Iron Folic Acid

1. INTRODUCTION

Drug utilization studies are invaluable to the stake holders and policy makers to review their strategies in dealing with public health problems and to bring new policies. While doing DUE studies, one needs to be specific about what should be collected as there is huge data are available. Indications, dosage details, comorbidities, drug interactions and other relevant information should be collected.[1] The drugs often picked up for drug utilization studies are most commonly prescribed drugs, narrow therapeutic index drugs, drugs associated with severe adverse effects and high cost drugs [2].

In this study, acid suppressing drugs have been selected for their wide usage. Mainly 2 classes of acid suppressants are widely used in practice. Those are H2 receptor antagonists (H2RAs) and Proton pump inhibitors (PPIs).

PPIs are authenticated by FDA for treatment of erosive esophagitis associated with GERD, and for treatment of hyper secretory conditions like Zollinger-Ellison syndrome. And also they have various off-label uses to treat H pylori bacteria, to prevent peptic ulcer re-bleeding, NSAID induced ulcers and stress ulcer prophylaxis [3] PPIs are marketed 40 years ago and till now their safety and efficacy are impeccable. But emerging literature causes concern for PPI safety over long term usage. These concerns include risk of bone fractures, unproven cognitive impairment, hypomagnesaemia and respiratory tract infection [4]

PPIs have superior efficacy over H2 receptor antagonists owing to their irreversible inhibition of H⁺/K⁺ ATPase. And their prescribing rate is also increasing. People are also increasingly using these as OTC drugs. And as people tend to use them for long term, all these causes worry as they may cause unexpected adverse drug reactions [5]. Known adverse effects of PPIs like bone fractures, Vit B12 deficiency, enteric infections are directly explained by acid inhibition property of these drugs but some adverse effects

are not related to this. Increased amyloid beta production is one of the effects due to long term use of PPIs, which predisposes patients to Alzheimer's disease [6]. In recent years PPI usage has been increased dramatically. In 2014, 7.4% of all adult population of Denmark used PPIs. Two studies conducted in Germany stated potential association between PPI use and Dementia [7]. This caused a worry since these are mostly used by older individuals in whom risk of dementia is more. Till date, all studies are inconclusive about the association.

Risk of Pneumonia is higher for Dementia patients who use PPIs, judicious use of PPIs is required for dementia patients [8]. There is a strong association between PPI use and hypomagnesaemia. Hypomagnesaemia is often developed secondary to hypocalcaemia and hyperparathyroidism due to PPI usage [9]. These levels should be monitored regularly and if required supplementation should be given. One observational study found that, among all the adverse drug events in PPI users reported to FDA, prevalence of Hypomagnesaemia is about 1% but the causality is not assured. And also they found that hypomagnesaemia is more prevalent in older population [10]. In view of the above concerns, these types of drug utilization studies are more warranted.

2. METHODOLOGY

This is a prospective drug utilization study conducted in the outpatient department of a tertiary care teaching hospital in Kadapa, Andhra Pradesh, India. Duration of the study is 3 months and the number of prescriptions studied is 200 (n=200). A customised data collection form had prepared before the initiation of the study (Fig. 1). In this study adult patients of both genders are included. All prescriptions collected contain at least one acid suppressant drug. Pregnants and uncooperative patients are excluded as pregnant women require special medical needs for their altered physiology. Relevant data was collected and analysed for appropriateness of PPI usage.

3. RESULTS

Out of the total 200 prescriptions analysed in this study, 102 were happened to be female and 98 were belonged to male patients (Fig. 2).

And further age analysis tells that 54 patients are less than 30 years old and 98 were in between 30 to 60 years and 48 patients were more than 60 years old (Fig. 3).

DUE of Acid suppressing agents

Drug to be evaluated:

Date:

Initials of Data Collector:

Patient ID / Initials:

Age & sex

Diagnosis

Medical and medication history

Criteria and indicators

- 1) Whether patient having any gastric or duodenal ulcers
- 2) Is the patient suffering from hyperacidity that is resistant to H2 receptor blockers
- 3) Whether patient using any medicines that warrant the use of acid suppression drugs.

Process criteria

- 4) Whether Dose and duration of the therapy is appropriate or not
- 5) Whether the risk of fractures is assessed or not before initiating the treatment.
- 6) Whether the drug-drug interactions are taken cared or not.
- 7) Whether dose tapering recommended for withdrawal or not

Fig. 1. Data collection form

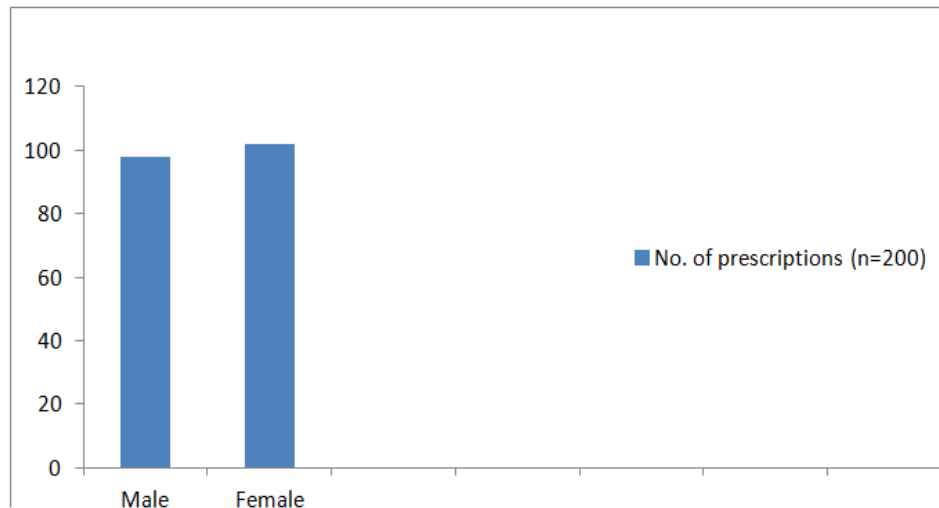


Fig. 2. No. of Prescriptions based on gender

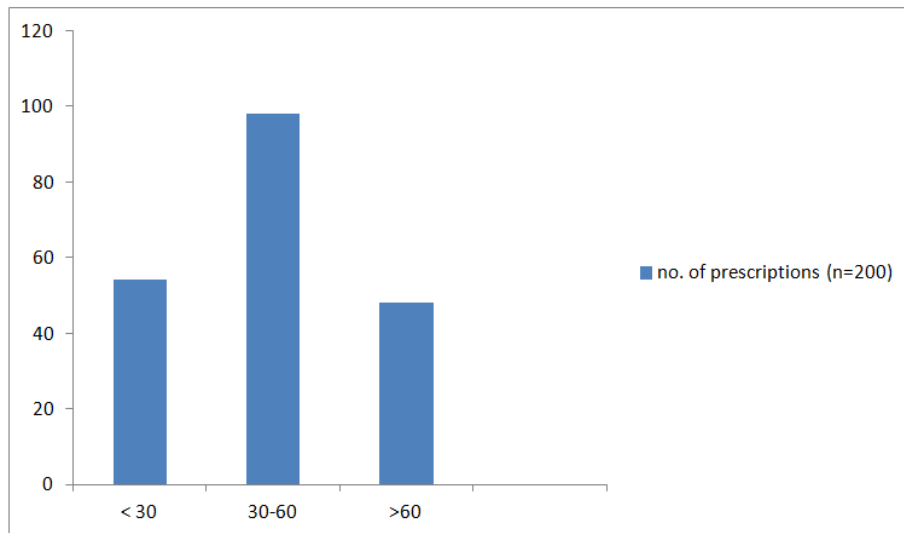


Fig. 3. Sample distribution based on age

Pantoprazole (Pantop) was the only PPI found in the study and it is present in 197 prescriptions, and in the remaining 3 prescriptions Ranitidine (Rantac) a H2 receptor antagonist (H2RA) was found (Fig. 4).

About 90 patients were given acid suppressants for Esophagitis associated with GERD and Peptic ulcer disease treatment (Table 1). In these

90 patients the indication is a labelled one according to regulatory guidelines (FDA source document for Pantoprazole). And 108 patients were given for prophylactic treatment because of other prescribed drugs, which is off-label use for PPIs (off-label use means using a licensed drug in a condition for which it is not approved). But in a minimal 2 patients the rationale for PPI use is not identified.

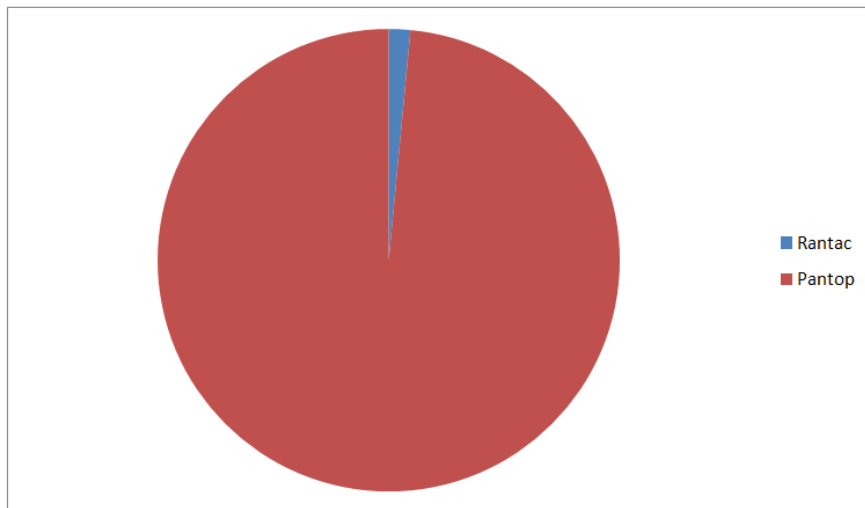


Fig. 4. Different acid suppressants found in the study

Table 1. Conditions warranted the use of acid suppressants

S.No.	Indication	Patients	Percentage
1	GI disorders (Labelled use)	90	45
2	Prophylaxis (Off-label use)	108	54
3	Unidentified reason	2	1

The drugs in most cases, which prompted the PPI usage in 108 patients, are Paracetamol, Ceftriaxone, Hydrocortisone, Cefixime, Iron Folic Acid (IFA), Diclofenac, and Augmentin (Fig. 5). The gastric adverse effects of the above drugs are well known and required precautionary treatment was taken care of.

Prescribed dose of Pantoprazole was 40 mg and frequency was once daily in all the 197 patients (For Pantoprazole defined daily dose (DDD) is given as 40 mg by WHO).

And some drug interactions are also identified in the study. The severity ranges from minor to moderate and some needs close monitoring. The following table summarizes the drug interactions found in the study.

4. DISCUSSION

In this study it is observed that PPIs prescription rate is way higher than H2RAs owing to their superior efficacy. But one should note that the higher efficacy of PPIs is bundled with higher risk also. According to a study, risk of death in people

who takes PPIs is 24% more compared to people taking H2RAs. Further the risk is increased to 50% for people who are taking PPIs for more than one year.[11] Thus choosing acid suppressing drug should be more judicious and based on logical reasoning but not simply owing to the superior efficacy of one over other.

In this study Pantop has been prescribed for off-label use in more than half of the patients (n=108, 54%). All patients were given Pantoprazole 40 mg once daily (for Pantoprazole Defined Daily Dose (DDD) given by WHO is 40 mg which is not necessarily the therapeutic dose). Pantoprazole 40 mg o.d., is safe and effective compared to placebo for Rheumatic disease patients in preventing NSAID induced gastric lesions.[12] Pantoprazole 40 mg o.d., Omeprazole 20 mg o.d., provide effective, equivalent protection against gastric lesions caused by NSAIDS.[13]

Multiple Drug-Drug Interactions were also found in the prescriptions. The severity ranges from minor to moderate in nature. They need close monitoring or change of administration timings.

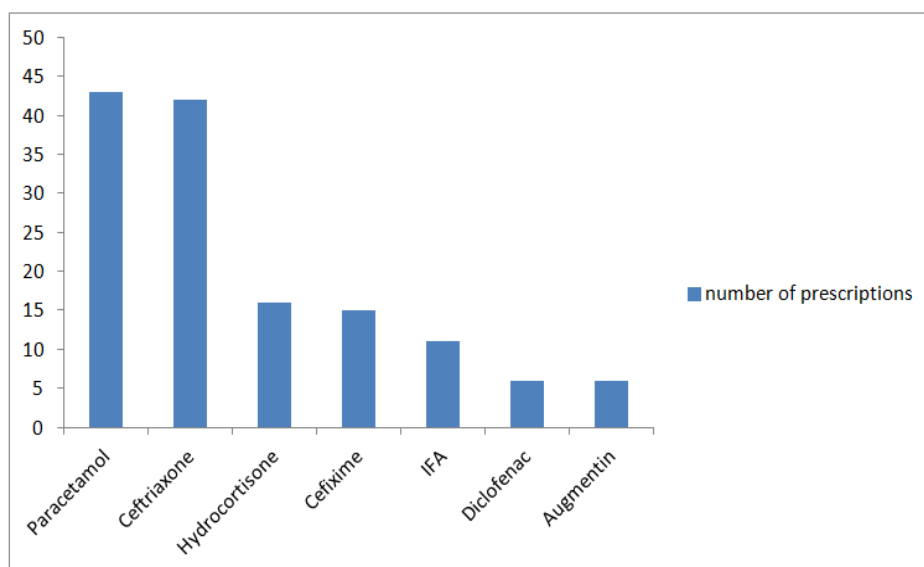


Fig. 5. Drugs which needed the Prophylaxis

Table 2. Drugs found interacting with Pantoprazole in the study

S.No.	Interacting drug	Severity	Number of instances
1	Digoxin	Serious	1
2	Phenytoin	Moderate	1
3	Clopidogrel	Moderate	8
4	Vit B12	Minor	1
5	Fluconazole	Minor	1

Some of the other observations in this study are dose tapering is not recommended for withdrawing the acid suppression therapy. Dose tapering of PPIs should be followed otherwise rebound hyperacidity would follow after discontinuation of PPIs. People in residential care setting are more prone to rebound hyperacidity after abrupt stoppage of PPIs, thus dose tapering should be followed for discontinuation of PPIs, both to find out the minimal effective dose and to control the rebound symptoms[14]. Significant number of elderly patients was also prescribed Pantoprazole generously. Caution should be taken and risk of adverse effects should be assessed while prescribing these drugs to elderly people since they are more vulnerable to dementia, bone fractures, Kidney failures and electrolyte imbalance.

Small sample size and time constraints are some of the limitations for this study.

5. CONCLUSION

Acid suppressant drugs are widely prescribed for their off-label use. And in the armamentarium of acid suppressants, PPIs are mostly chosen while ignoring the H2RAs. Of course PPIs are superior to H2RAs in their pharmacological action because of irreversible blockade of proton pump but the risks associated with PPIs are also more. Before prescribing PPIs risks should be assessed since evidences are emerging for PPI associated dementia, kidney problems, hypomagnesaemia. One should have drug discontinuation strategies like dose tapering to avoid rebound hyperacidity. Drug interactions should be taken into consideration and patients should be instructed to not to continue PPIs for more than recommended period.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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