Universe International Journal of Interdisciplinary Research
(Peer Reviewed Refereed Journal)

© UIJIR | ISSN (O) – 2582-6417
OCTOBER 2022 | Vol. 3 Issue 5
www.uijir.com

"A COMPARATIVE STUDY TO ASSESS EFFECT OF DISCONTINUATION OF PROTON PUMP INHIBITORS (PPIs) AFTER 48 HOURS ON ADMISSION IN CRITICAL CARE UNIT ON INCIDENTS OF NOSOCOMIAL PNEUMONIA"

Author's Name: [1]Dr. Mahadeo B. Shinde, [2]Ms. Besty Varghes

Affiliation: [1]Professor, Specialty of Medical-Surgical Nursing, Krishna Institute of Medical Nursing Sciences, Karad, India

[2]Student, Krishna Institute of Medical Nursing Sciences, Karad, India

E-Mail ID: bestyvarghese08@gmail.com

DOI No. – **08.2020-25662434**

Abstract

The aim of this study was to determine whether the use of gastric acid-suppressive agents increases the risk of nosocomial pneumonia (NP) in the Critical care unit population. The methodology adopted for experimenting with the effectiveness of the use of proton pump inhibitors in two study groups and evaluated the result with the help of APACHE II and CPIS calculator.The researcher performed an experimental study with a non-probability purposive sampling technique in a multi-critical care unit that included 60 critically ill patients fromJanuary 2021 to October 2021 at Krishna Hospital, Karad. The researcher divided patients into two groups after initiation of enteral feeding on a random basis, one group of patients with PPI and another group without PPI. Both of the groups were evaluated the risk of suspected HAI with the guidance of medical classification tools,APACHE-II, GCS, and CPIS at the time of admission and followed by consequent times irrespective of their diagnosis and treatment. There was no significant difference between the two groups for any of the scores (P>0.05) indicates very few cases of nosocomial pneumonia in Krishna hospital, Karad. In short, prior use of a proton-pump inhibitor did not correlate with a significant increase in the risk of developing Nosocomial Pneumonia (NP).Apart from Proton Pump Inhibitors, there are a plethora of treatments, nursing care received by critical care patients with various physical illnesses & symptoms. It is also important to treat different pre-disposing and existing clinical conditions because those factors affect the functional outcome of the patient. Further studies are required for more clarification related to correlating the effect of PPIs and early detection of HAI. For this, a standard group selection is suggested on matching diagnoses with similar hemodynamic status.

Keywords: *Proton Pump Inhibitor, Clinical pulmonary infection score, nosocomial pneumonia, Hospital-acquired infection, Acute Physiology and Chronic Health Evaluation score.*

INTRODUCTION

Proton pump inhibitors (PPIs) are one of the most popularly prescribed drugs in India for conditions such as gastroesophageal reflux disease, peptic ulcer disease, and functional dyspepsia. Despite their good safety profile, PPIs have potential adverse effects, yet they are often overprescribed and without a clear indication. Nosocomial pneumonia refers to any pneumonia contracted by a patient in a hospital at least 48–72 hours after being admitted. It is thus distinguished from community-acquired pneumonia. It is usually caused by a bacterial infection, rather than a virus. Nosocomial pneumonia (NP) is the leading cause of mortality among patients who die from hospital-acquired infections.

Several studies have stated that pharmacological stress ulcer prophylaxis with sucralfate is safer than H2 blockers respecting VAP. Proton pump inhibitors are more effective in causing community-acquired pneumonia (CAP) and HAP in patients without mechanical ventilation. The aim of this study was to determine whether the use of gastric acid-suppressive agents increases the risk of nosocomial pneumonia (NP) in the Critical care unit population.

Prior use of a proton-pump inhibitor did not correlate with a significant increase in the risk of developing NP. This risk was higher with the administration of sedatives or neuromuscular blockers, increased disease severity, and placement of a central venous catheter.

OBJECTIVES

1. To assess patients who had an Acute Physiology and Chronic Health Evaluation score (APACHE II) of less than 25.
2. To calculate Clinical Pulmonary Infection Score (CPIS) need to be calculated to confirm VAP/NP(if a score of 7 out of 14 need to obtain).
3. To compare between patients with Proton Pump Inhibitors (PPI) till discharge and study group stopping of Proton Pump Inhibitors (PPI) after 48 hours on the incidence of Nosocomial Pneumonia (NP) or after initiation of enteral feeding.

MATERIAL AND METHODS

This study was conducted to find out Holding PPIs (Proton Pump Inhibitors) after 48 hours of hospitalization among patients admitted in Critical Care Unit of Krishna Hospital, Karad will help to reduce Nosocomial Pneumonia (NP)/VAP Rate. Stopping of PPIs will reduce adverse effects associated with Proton Pump Inhibitors.

Assessment of Acute Physiology and Chronic Health Evaluation score (APACHE II) is a severity-of-disease classification system (Knaus et al., 1985), one of several ICU scoring systems. It is applied within 24 hours of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. The advantage of the APACHE is that it can be used throughout the patient's hospital course in monitoring the patient's response to therapy, especially PPI drugs. The clinical pulmonary infection score evaluates objective data in patients suspected of ventilator-associated pneumonia (VAP) and stratifies risk of positive diagnosis.

Clinical pulmonary infection score - CPIS calculator helps the clinician decide whether the patient in question would benefit from a **pulmonary culture testing**. By using the CPIS, unnecessary antibiotic administration due to treatment of colonized patients is prevented and the incidence of misdiagnosed VAPs is lowered. The score also helps clinicians determine which patients may benefit from a pulmonary culture testing. This means that the administration of the score not only facilitates diagnosis but also helps reduce unnecessary tests and antibiotic administration, thus reducing the incidence of misdiagnosed VAP. Each of the six variables in the score is awarded a number of points, depending on its predictive value and contribution towards the risk of positive diagnosis. The total CPIS varies between 0 and 12, where 0 means normal function with little risk of VAP and 12 means high risk.

The original study introduces a cut-off value at 6 points, where scores below 6 indicate a low risk of pulmonary infection while scores of 6 and above indicate a high likelihood of VAP diagnosis.

A comparative study was carried out of total 65 samples from January 2021 to October 2021 by using random sampling method by using experimental design.

RESULTS

From table no. 2, it was clear that all patients from both groups 30 (100%) admitted in the critical care unit of selected hospital had APACHE II score <25. Table 3 depicts that according to CPIS I score, there were 1(3.3%) patient from PPI group and 2 (6.6%) patients from no PPI group who suffered from VAP/NP. Table 4 depicts that according to CPIS II score, there were 2(6.6%) patients from PPI group and 1 (3.3%) client from no PPI group who suffered from VAP/NP. Table 5 depicts that according to CPIS III score, there were 2(6.6%) patients from PPI group and 1 (3.3%) patient from no PPI group who suffered from VAP/NP.

Unpaired t test was done to compare between patients with Proton Pump Inhibitors (PPI) till discharge and study group stopping of Proton Pump Inhibitors (PPI) after 48 hours. There was no significant difference between two groups for any of the scores (P>0.05).

- Mean Pre-operative ICU mortality for patients from PPI group (11.13) was lower than patients from No PPI group (12.77).
- Mean Post-operative ICU mortality for patients from PPI group (5.43) was lower than patients from No PPI group (6.77).
- Mean APACHE II score for patients from PPI group (7.83) was lower than patients from No PPI group (9.13).
- Mean CPIS I score for patients from PPI group (1.83) was lower than patients from No PPI group (2.13).
- Mean CPIS II score for patients from PPI group (2.23) was higher than patients from No PPI group (1.90).
- Mean CPIS III score for patients from PPI group (2.20) was higher than patients from No PPI group (1.90).

LITERATURE REVIEW

MathieuBeaulieu MSc, et.al[2008] A study was conducted on total of 924 medical records, which included in the database during the study period of which 787 patients were included in the study. Out of this cohort,104 patients (13.2%) eventually developed a NP. The risk for patients who received proton-pump inhibitors (adjusted hazard ratio [AHR] 0.63; 95% CI 0.39-1.01) was not significantly different than in non-exposed patients. Variables most strongly associated with NP were the administration of sedatives or neuromuscular blockers for at least 2 consecutive days (AHR 3.39;95% CI 1.99-5.75), an Acute Physiology and Chronic Health Evaluation II (APACHE II) severity score greater than 15 (AHR, 3.34; 95% CI 1.82-6.50), and presence of a central venous catheter (AHR, 1.76; 95% CI 1.12-2.76). Prior use of a proton-pump inhibitor did not correlate with a significant increase in the risk of developing NP. This risk was higher with the administration of sedatives or neuromuscular blockers, increased disease severity, and placement of a central venous catheter.

Beaulieu M1, et.al [2008] The aim of this study was to determine whether the use of gastric acid-suppressive agents increases the risk of nosocomial pneumonia (NP) in a medical intensive care unit population. Retrospective cohort study in a medical intensive care unit of a 554-bed, university-affiliated, academic medical center.The result was a total of 924 medical records were included in the database during the study period of which 787 patients were included in the study. Out of this cohort,104 patients (13.2%) eventually developed a NP. The risk for patients who received proton-pump inhibitors (adjusted hazard ratio [AHR] 0.63; 95% CI 0.39-1.01) was not significantly different than in non-exposed patients. Variables most strongly associated with NP were the administration of sedatives or neuromuscular blockers for at least 2 consecutive days (AHR 3.39;95% CI 1.99-5.75), an Acute Physiology and Chronic Health Evaluation II (APACHE II) severity score greater than 15 (AHR, 3.34; 95% CI 1.82-6.50), and presence of a central venous catheter (AHR, 1.76; 95% CI 1.12-2.76). Conclusions were Prior use of a proton-pump inhibitor did not correlate with a significant increase in the risk of developing NP. This risk was higher with the administration of sedatives or neuromuscular blockers, increased disease severity, and placement of a central venous catheter.

Megan Jaynes, D, et.al [2019] Proton pump inhibitors (PPIs) are among the most frequently prescribed medications. Their use is likely even higher than estimated due to an increase in the number of PPIs available without a prescription. Appropriate indications for PPI use include *Helicobacter pylori* infection, erosive esophagitis, gastric ulcers, and stress ulcer prevention in high-risk critically ill patients. Unfortunately, PPIs are often used off-label for extended periods of time. This increase in PPI usage over the past two decades has called into question the long-term effects of these medications. The association between PPI use and infection, particularly *Clostridium difficile* and pneumonia, has been the subject of several studies. It's proposed that the alteration in gastrointestinal microflora by PPIs produces an environment conducive to development of these types of infections. At least one study has suggested that long-term PPI use increases the risk of dementia. Drug interactions are an important and often overlooked consideration when prescribing any medication. The potential interaction between PPIs and antiplatelet agents has been the subject of multiple studies. One of the more recent concerns with PPI use is their role in the development or progression of chronic kidney disease. There is also some literature suggesting that PPIs contribute to the development of various micronutrient deficiencies. Most of the literature examining the potential adverse effects of PPI use is composed of retrospective, observation studies. There is a need for higher quality studies exploring this relationship. We must be cautious about drawing broad conclusions on the current level of evidence with the long-term use of PPIs. This is especially important because the conclusions are overwhelmingly based on observational studies and meta-analyses, which frequently include the same observational studies. PPIs have had a profound impact on the outcomes of patients with acid peptic disease since their introduction into clinical practice in the late 1990s. They continue to have a strong positive impact when used appropriately for the recognized indications. The optimal strategy for PPI prescription at this time is for patients with clear indications, avoiding broad off-label use and to have a prudent time-limited endpoint of prescription.

Alan B R Thomson, et.al [2010], The proton pump inhibitors (PPIs) as a class are remarkably safe and effective for persons with peptic ulcer disorders. Serious adverse events are extremely rare for PPIs, with case reports of interstitial nephritis with omeprazole, hepatitis with omeprazole and

lansoprazole, and disputed visual disturbances with pantoprazole and omeprazole. PPI use is associated with the development of fundic gland polyps (FGP); stopping PPIs is associated with regression of FGP. In the absence of Helicobacter pylori infection, the long-term use of PPIs has not been convincingly proven to cause or be associated with the progression of pre-existing chronic gastritis or gastric atrophy or intestinal metaplasia. Mild/modest hypergastrinemia is a physiological response to the reduction in gastric acid secretion due to any cause. The long-term use of PPIs has not been convincingly proven to cause enterochromaffin-like cell hyperplasia or carcinoid tumors. PPIs increase the risk of community acquired pneumonia, but not of hospital acquired (nosocomial) pneumonia. There is no data to support particular care in prescribing PPI therapy due to concerns about risk of hip fracture with the long-term use of PPIs. Long-term use of PPIs does not lead to vitamin B12 deficiencies, except possibly in the elderly, or in persons with Zollinger-Ellison Syndrome who are on high doses of PPI for prolonged periods of time. There is no convincingly proven data that PPIs increase the risk of Clostridium difficile-associated diarrhea in persons in the community. The discontinuation of PPIs may result in rebound symptoms requiring further and even continuous PPI use for suppression of symptoms. As with all medications, the key is to use PPIs only when clearly indicated, and to reassess continued use so that long-term therapy is used judiciously. Thus, in summary, the PPIs are a safe class of medications to use long-term in persons in whom there is a clear need for the maintenance of extensive acid inhibition.

Huan Song 1, Jianwei Zhu, et.al [2010] Proton pump inhibitors (PPIs) are the most effective drugs to reduce gastric acid secretion. PPIs are one of the most commonly prescribed classes of medications worldwide. Apart from short-term application, maintenance therapy with PPIs is recommended and increasingly used in certain diseases, such as Zollinger-Ellison syndrome and gastro-oesophageal reflux disease, especially for people with erosive oesophagitis or Barrett's oesophagus. Although PPIs are generally safe, their efficacy and safety of long-term use remains unclear. The question of whether the long-term use of PPIs could promote the development of gastric pre-malignant lesions has been widely investigated, but results are inconsistent. Limited insight on this problem leads to a dilemma in decision making for long-term PPI prescription. It was to compare the development or progression of gastric pre-malignant lesions, such as atrophic gastritis, intestinal metaplasia, enterochromaffin-like (ECL) cell hyperplasia, and dysplasia, in people taking long-term (six months or greater) PPI maintenance therapy.There is presently no clear evidence that the long-term use of PPIs can cause or accelerate the progression of corpus gastric atrophy or intestinal metaplasia, although results were imprecise. People with PPI maintenance treatment may have a higher possibility of experiencing either diffuse (simple) or linear/micronodular (focal) ECL cell hyperplasia. However, the clinical importance of this outcome is currently uncertain.

Br J Cancer, et.al[2020] Studies have shown increased gastric cancer risk in users of proton pump inhibitors (PPI) and histamine-2 receptor antagonists, questioning the safety of gastric acid suppression. Therefore, we conducted a case-control study within the Scottish Primary Care Clinical Informatics Unit (PCCIU) database and a cohort study in the UK Biobank.In PCCIU, five controls were matched to cases diagnosed in 1999-2011, and medications were determined from GP records. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression. In the UK Biobank, medications were self-reported at cohort entry 2006-2010,

and gastric cancer ascertained from cancer registries until 2014. Hazard ratios (HR) were calculated using Cox regression. The results found, PCCIU contained 1119 cases and 5394 controls. UK Biobank contained 250 cases in 471,779 participants. PPI users had a higher gastric cancer risk in PCCIU and UK Biobank when applying a 1-year lag (adjusted OR = 1.49, 95% CI 1.24, 1.80; adjusted HR = 1.28, 95% CI 0.86, 1.90, respectively), but these associations were attenuated when using a 2-year lag (adjusted OR = 1.13, 95% CI 0.91, 1.40; adjusted HR = 1.15, 95% CI 0.73, 1.82, respectively). Overall, it is observed little consistent evidence of an increased risk of gastric cancer with PPI use.

Blánaid Hicks, et.al [2018] Preclinical studies have suggested that proton pump inhibitors (PPIs) may increase pancreatic cancer risk; however, epidemiological studies are few, with conflicting results. This spurred us to evaluate whether PPI use is associated with an increased risk of pancreatic cancer in a large population-based study. They conducted a nationwide case-control study using data from Danish demographic and health care registries. All patients with a first cancer diagnosis of pancreatic cancer between 2000 and 2015 were identified from the Danish Cancer Registry and age-matched, sex-matched, and calendar-matched 1:20 to population controls using risk set sampling. Conditional logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer associated with PPI use, adjusting for potential confounders. Secondary analyses examined dose-response patterns and associations with individual PPIs as well as with histamine-2-receptor antagonists. They found ever use of PPIs occurred among 27.8% of 6921 pancreatic cancer cases and 25.4% of 34 695 matched controls, yielding a neutral adjusted OR of 1.04 (95% CI 0.97-1.11). Odds ratios were also close to unity in analyses of high use of PPIs (≥1000 DDDs; OR, 0.92 95% CI 0.80-1.07). There was no evidence of a dose-response relationship, with ORs close to unity across categories, including for those with the highest cumulative use (>2000 DDDs; OR, 1.03 95% CI 0.84-1.26). Analyses of subgroups as well as individual types of PPI and of histamine-2-receptor antagonists use also returned neutral associations. It concludes, in this large nationwide case-control study, PPI use was not associated with an increased risk of pancreatic cancer.

Mr. ThawinSrinutta, et.al [Nov 2019] A meta-analysishas suggested that there might be an association between the use of proton pump inhibitors (PPIs) and the development of hypomagnesemia, although the conclusions were no definitive. The methods followed to provide an update on this topic, we performed a meta-analysis of all observational studies that examined the association between the use of PPIs and the development of hypomagnesemia. A literature search was conducted in MEDLINE, Scopus and Cochrane Central Register of Controlled Trials (January 1970 to June 2018) to identify observational studies that examined the association between the use of PPIs and the incidence and prevalence of hypomagnesemia.In the absence of randomized controlled trials, they focused primarily on observational studies, including cross-sectional, case-control, retrospective, and prospective cohort studies. There was no limitation on sample size or study duration. Random-effect models meta-analyses were used to compute pooled unadjusted and adjusted odds ratios (ORs) for binary variables. The results includes sixteen observational studies were identified, including 13 cross-sectional studies, 2 case-control studies, and 1 cohort study, with a total of 131,507 patients. The pooled percentage of PPI users was 43.6% (95% confidence interval [CI] 25.0%, 64.0%). Among PPI users, 19.4% (95% CI 13.8%, 26.5%) had hypomagnesemia compared to 13.5% (95% CI 7.9%, 22.2%) among nonusers. By meta-analysis,

PPI use was significantly associated with hypomagnesemia, with a pooled unadjusted OR of 1.83 (95% CI 1.26, 2.67; P = .002) and a pooled adjusted OR of 1.71 (95% CI 1.33, 2.19; P < .001). In subgroup analyses, high-dose PPI use was associated with higher odds for hypomagnesemia relative to low-dose PPI use (pooled adjusted OR 2.13; 95% CI 1.26, 3.59; P = .005). They concluded in support of the results of the previous meta-analyses. Furthermore, we found a dose-response between the PPI use and development of hypomagnesemia.

Mr. Jinqiu Yuan, et.al. [2020] An observational study was conducted by Aliment Pharmacol Ther on 2020 Aug with subject to Regular use of proton pump inhibitor and risk of rheumatoid arthritis in women.Proton pump inhibitors (PPIs) have a significant impact on the gut microbiome, which in turn, might increase the risk of rheumatoid arthritis (RA). The main aim is to evaluate regular use of PPIs and risk of RA. It was a prospective analysis of the US nurses who reported PPI use data, and were free of RA from the Nurses' Health Study (NHS 2002-2014) and NHS II (2003-2015). The exposure was regular use of PPI in the past 2 years, which was repeatedly evaluated in biennial surveys. RA was confirmed by the 1987 or 2010 American College of Rheumatology criteria. We estimated the hazard ratios (HRs) and confidence interval (CIs) with time-dependent Cox regression adjusting for potential confounders. In the results they documented 421 cases of RA over 1 753 879 person-years of follow-up. Regular PPI users had a 44% higher risk of RA as compared with non-regular users (adjusted HR = 1.44; 95%CI, 1.10-1.89). The risk of RA increased with the total duration of PPI use (P-trend = 0.008). Compared with non-regular users, the adjusted HRs were 1.22 (95%CI, 0.93-1.62) for women with >0 to 4 years' use and 1.73 (95% CI, 1.14 to 2.61) for >4 years' use. It concluded a regular use of PPI was associated with increased risk of RA in women, with a higher risk observed in individuals with a longer duration of PPI use. Due to the observational study design, large prospective trials are still required to confirm their finding.

Mr. Paul Moayyedi, et.al [2019] Proton pump inhibitors (PPIs) are effective at treating acid-related disorders. These drugs are well tolerated in the short term, but long-term treatment was associated with adverse events in observational studies. We aimed to confirm these findings in an adequately powered randomized trial. They performed a 3 × 2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease randomly assigned to groups given pantoprazole (40 mg daily, n = 8791) or placebo (n = 8807). Participants were also randomly assigned to groups that received rivaroxaban (2.5 mg twice daily) with aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg) alone. We collected data on development of pneumonia, C*lostridium difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every 6 months. Patients were followed up for a median of 3.01 years, with 53,152 patient-years of follow-up. The results it found there was no statistically significant difference between the pantoprazole and placebo groups in safety events except for enteric infections (1.4% vs 1.0% in the placebo group; odds ratio, 1.33; 95% confidence interval, 1.01–1.75). For all other safety outcomes, proportions were similar between groups except for *C difficile* infection, which was approximately twice as common in the pantoprazole vs the placebo group, although there were only 13 events, so this difference was not statistically significant.Finally it found in a large placebo-controlled randomized trial, we found that pantoprazole is not associated with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections.

Signal Mining, et.al [Nov 2021] Mounting evidence demonstrates that proton pump inhibitors (PPIs) are associated with a number of adverse effects. However, the literatures about hepatotoxicity-related adverse effects (HRAEs) of PPIs are mostly case reports and a few clinical studies. Methods: We evaluated the association between PPIs and HAREs using the reporting odd ratio (ROR) for mining the adverse event report signals in the FDA Adverse Event Reporting System (FAERS) database. Results: There were 23,825 reports of PPIs as primary suspect drug or second suspect drug, of which 3,253 reports were HRAEs. The top five HRAE signals caused by PPIs were hepatitis cholestatic, cholestasis, fulminant hepatitis, subacute hepatic failure, and acute hepatitis. They also summarized the signals of the HRAEs caused by each PPI. The simultaneous signals were cholestasis and hepatitis cholestatic. For the cholestasis signal, esomeprazole showed an ROR of 21.556 (95% CI 17.592–26.413); pantoprazole showed the highest ROR of 22.611 (95% CI 17.794–28.733) in the hepatic cholestatic signal; lansoprazole was the only PPI with expression in the coma hepatic signal, with an ROR of 10.424 (95% CI 3.340–32.532). By analyzing the reports of pantoprazole-induced hepatic encephalopathy, we found that patients aged over 65 years and males reported the highest rate. And from the combination of drugs and indications of drugs, no significant results were obtained. Conclusions: The RORs of signals of "cholestasis" were generally higher than those of "hepatocellular injury." And the signals about "cholestasis" in HRAE caused by PPIs are more reported.

Mr. Francisco Torres-Bondia, et.al [3rd Dec 2020] Proton pump inhibitors (PPIs) are among the most prescribed medications. Previous epidemiological studies have presented contradictory results about PPIs and the risk of dementia. Their objective was to investigate the association between the use of PPIs and an increasing risk of incident AD or non-AD dementias. A community-based retrospective cohort study was conducted based on the data available from 1st January 2002 to 31st December 2015 in the Catalan health service (CatSalut) system. This cohort included all PPI users (N = 36,360) and non-users (N = 99,362). A lag window of 5 years was considered between the beginning of the PPI treatment and the diagnosis of dementia. PPI use was not associated with the risk of AD (adjusted odds ratio (OR) 1.06) (95% CI 0.93–1.21; p = 0.408). A weakly but significantly increased risk of non-AD dementias was observed among PPI users (adjusted OR 1.20, 95% CI 1.05–1.37; p = 0.007). A higher dose of PPIs was not associated with an increased risk of either AD or non-AD dementias (OR 1.20; 95% CI 0.91–1.61 and OR 0.95; 95% CI 0.74–1.22, respectively). Regarding the number of PPIs used, we observed an increased risk of AD (OR 1.47; 95% CI 1.18–1.83) and non-AD dementias (OR 1.38; 95% CI 1.12–1.70) in users of two types of PPIs compared with those who used only one type. We did not find a higher incidence of AD among PPI users, but a weak increase in the risk of non-AD dementias among PPI users was observed.In conclusion, we found that the incidence of AD was not higher among PPI users, and a slight increase in the risk of non-AD dementia was observed. As the consumption of PPIs is a useful variable for identifying patients with dementia according to the random forest tree, presence of some chronic and co-morbid pathologies and the resulted polypharmacy, including the increased consumption of PPIs, probably give rise to the increased risk of dementia observed in previous studies.

Emmae N Ramsay, et.al[24 June 2013] The main aim was to compare the results of a new-user cohort study design and the self-controlled case series (SCCS) design using the risk of hospitalisation for pneumonia in those dispensed proton pump inhibitors compared to those unexposed as a case study.The Australian Government Department of Veterans' Affairs

administrative claims database was used. Exposure to proton pump inhibitors and hospitalisations for pneumonia were identified over a 4 year study period 01 Jul 2007 -30 Jun 2011. The same inclusion and exclusion criteria were applied to both studies, however, the SCCS study included subjects with a least one hospitalization for pneumonia.There were 105,467 subjects included in the cohort study and 6775 in the SCCS. Both studies showed an increased risk of hospitalisations for pneumonia in the three defined risk periods following initiation of proton pump inhibitors compared to baseline. With the highest risk in the first 1 to 7 days (Cohort RR, 3.24; 95% CI (2.50, 4.19): SCCS: RR, 3.07; 95% CI (2.69, 3.50)).This study has shown that the self-controlled case series method produces similar risk estimates to a new-users cohort study design when applied to the association of proton pump inhibitors and pneumonia. Exposure to a proton pump inhibitor increases the likelihood of being admitted to hospital for pneumonia, with the risk highest in the first week of treatment.

Yoon Hee Park, et.al [1st Dec 2019] A hospital-based cohort studies on the association between use of proton pump inhibitors (PPIs) and increased Clostridium difficile infection (CDI) risk, detailed studies analyzing the effects of PPI use on CDI risk are lacking. The present study investigated the association of the dose, duration, and types of PPIs with CDI risk. Methods: A single-center, cohort study was conducted on patients admitted to a hospital. The exposed cohort comprised patients who were prescribed PPIs at least once during the study period, and a control cohort was prepared by randomly assigning an index date to patients who did not use PPIs ensuring the same distribution of index dates as in the exposed cohort and matching sex, age, hospitalization period, and date of admission. Results: PPI use increased the risk of CDI by 1.8-fold [95% confidence interval (CI) 1.5–2.2]. CDI risk increased by 1.8-fold with esomeprazole (95% CI 1.4–2.2) and 2.0-fold with pantoprazole (95% CI 1.5–2.8). Patients who used a high dose had a higher risk than those who used a medium dose [adjusted hazard ratio (HR) 2.0 vs 1.3]. The risk of CDI increased 4.2-fold when the PPI exposure period was 6 days or shorter than 6 days. Conclusions: Our study showed that PPI use was associated with an increased risk of developing CDI and the risk of CDI was dose dependent. Therefore, PPIs should only be used at proper doses and only for the necessary indications to avoid CDI Risk.

Beaulieu M1, et.al [2008] The aim of this study was to determine whether the use of gastric acid-suppressive agents increases the risk of nosocomial pneumonia (NP) in a medical intensive care unit population. Retrospective cohort study in a medical intensive care unit of a 554-bed, university-affiliated, academic medical center.The result was a total of 924 medical records were included in the database during the study period of which 787 patients were included in the study. Out of this cohort,104 patients (13.2%) eventually developed a NP. The risk for patients who received proton-pump inhibitors (adjusted hazard ratio [AHR] 0.63; 95% CI 0.39-1.01) was not significantly different than in non-exposed patients. Variables most strongly associated with NP were the administration of sedatives or neuromuscular blockers for at least 2 consecutive days (AHR 3.39;95% CI 1.99-5.75), an Acute Physiology and Chronic Health Evaluation II (APACHE II) severity score greater than 15 (AHR, 3.34; 95% CI 1.82-6.50), and presence of a central venous catheter (AHR, 1.76; 95% CI 1.12-2.76). Conclusions were prior use of a proton-pump inhibitor did not correlate with a significant increase in the risk of developing NP. This risk was higher with the administration of sedatives or neuromuscular blockers, increased disease severity, and placement

of a central venous catheter.

Megan Jaynes, D, et.al [2019] Proton pump inhibitors (PPIs) are among the most frequently prescribed medications. Their use is likely even higher than estimated due to an increase in the number of PPIs available without a prescription. Appropriate indications for PPI use include *Helicobacter pylori* infection, erosive esophagitis, gastric ulcers, and stress ulcer prevention in high-risk critically ill patients. Unfortunately, PPIs are often used off-label for extended periods of time. This increase in PPI usage over the past two decades has called into question the long-term effects of these medications. The association between PPI use and infection, particularly *Clostridium difficile* and pneumonia, has been the subject of several studies. It's proposed that the alteration in gastrointestinal microflora by PPIs produces an environment conducive to development of these types of infections. At least one study has suggested that long-term PPI use increases the risk of dementia. Drug interactions are an important and often overlooked consideration when prescribing any medication. The potential interaction between PPIs and antiplatelet agents has been the subject of multiple studies. One of the more recent concerns with PPI use is their role in the development or progression of chronic kidney disease. There is also some literature suggesting that PPIs contribute to the development of various micronutrient deficiencies. Most of the literature examining the potential adverse effects of PPI use is composed of retrospective, observation studies. There is a need for higher quality studies exploring this relationship. We must be cautious about drawing broad conclusions on the current level of evidence with the long-term use of PPIs. This is especially important because the conclusions are overwhelmingly based on observational studies and meta-analyses, which frequently include the same observational studies. PPIs have had a profound impact on the outcomes of patients with acid peptic disease since their introduction into clinical practice in the late 1990s. They continue to have a strong positive impact when used appropriately for the recognized indications. The optimal strategy for PPI prescription at this time is for patients with clear indications, avoiding broad off-label use and to have a prudent time-limited endpoint of prescription.

Alan B R Thomson, et.al [2010] The proton pump inhibitors (PPIs) as a class are remarkably safe and effective for persons with peptic ulcer disorders. Serious adverse events are extremely rare for PPIs, with case reports of interstitial nephritis with omeprazole, hepatitis with omeprazole and lansoprazole, and disputed visual disturbances with pantoprazole and omeprazole. PPI use is associated with the development of fundic gland polyps (FGP); stopping PPIs is associated with regression of FGP. In the absence of Helicobacter pylori infection, the long-term use of PPIs has not been convincingly proven to cause or be associated with the progression of pre-existing chronic gastritis or gastric atrophy or intestinal metaplasia. Mild/modest hypergastrinemia is a physiological response to the reduction in gastric acid secretion due to any cause. The long-term use of PPIs has not been convincingly proven to cause enterochromaffin-like cell hyperplasia or carcinoid tumors. PPIs increase the risk of community acquired pneumonia, but not of hospital acquired (nosocomial) pneumonia. There is no data to support particular care in prescribing PPI therapy due to concerns about risk of hip fracture with the long-term use of PPIs. Long-term use of PPIs does not lead to vitamin B12 deficiencies, except possibly in the elderly, or in persons with Zollinger-Ellison Syndrome who are on high doses of PPI for prolonged periods of time. There is no convincingly proven data that PPIs increase the risk of Clostridium difficile-associated diarrhea in persons in the community. The discontinuation of PPIs may result in rebound symptoms

requiring further and even continuous PPI use for suppression of symptoms. As with all medications, the key is to use PPIs only when clearly indicated, and to reassess continued use so that long-term therapy is used judiciously. Thus, in summary, the PPIs are a safe class of medications to use long-term in persons in whom there is a clear need for the maintenance of extensive acid inhibition.

Huan Song 1, Jianwei Zhu, et.al [2010] Proton pump inhibitors (PPIs) are the most effective drugs to reduce gastric acid secretion. PPIs are one of the most commonly prescribed classes of medications worldwide. Apart from short-term application, maintenance therapy with PPIs is recommended and increasingly used in certain diseases, such as Zollinger-Ellison syndrome and gastro-oesophageal reflux disease, especially for people with erosive oesophagitis or Barrett's oesophagus. Although PPIs are generally safe, their efficacy and safety of long-term use remains unclear. The question of whether the long-term use of PPIs could promote the development of gastric pre-malignant lesions has been widely investigated, but results are inconsistent. Limited insight on this problem leads to a dilemma in decision making for long-term PPI prescription. It was to compare the development or progression of gastric pre-malignant lesions, such as atrophic gastritis, intestinal metaplasia, enterochromaffin-like (ECL) cell hyperplasia, and dysplasia, in people taking long-term (six months or greater) PPI maintenance therapy.There is presently no clear evidence that the long-term use of PPIs can cause or accelerate the progression of corpus gastric atrophy or intestinal metaplasia, although results were imprecise. People with PPI maintenance treatment may have a higher possibility of experiencing either diffuse (simple) or linear/micronodular (focal) ECL cell hyperplasia. However, the clinical importance of this outcome is currently uncertain.

Br J Cancer, et.al[2020] Studies have shown increased gastric cancer risk in users of proton pump inhibitors (PPI) and histamine-2 receptor antagonists, questioning the safety of gastric acid suppression. Therefore, we conducted a case-control study within the Scottish Primary Care Clinical Informatics Unit (PCCIU) database and a cohort study in the UK Biobank.In PCCIU, five controls were matched to cases diagnosed in 1999-2011, and medications were determined from GP records. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression. In the UK Biobank, medications were self-reported at cohort entry 2006-2010, and gastric cancer ascertained from cancer registries until 2014. Hazard ratios (HR) were calculated using Cox regression. The results found, PCCIU contained 1119 cases and 5394 controls. UK Biobank contained 250 cases in 471,779 participants. PPI users had a higher gastric cancer risk in PCCIU and UK Biobank when applying a 1-year lag (adjusted OR = 1.49, 95% CI 1.24, 1.80; adjusted HR = 1.28, 95% CI 0.86, 1.90, respectively), but these associations were attenuated when using a 2-year lag (adjusted OR = 1.13, 95% CI 0.91, 1.40; adjusted HR = 1.15, 95% CI 0.73, 1.82, respectively). Overall, it is observed little consistent evidence of an increased risk of gastric cancer with PPI use.

Blánaid Hicks, et.al [2018] Preclinical studies have suggested that proton pump inhibitors (PPIs) may increase pancreatic cancer risk; however, epidemiological studies are few, with conflicting results. This spurred us to evaluate whether PPI use is associated with an increased risk of pancreatic cancer in a large population-based study. They conducted a nationwide case-control study using data from Danish demographic and health care registries. All patients with a first cancer

diagnosis of pancreatic cancer between 2000 and 2015 were identified from the Danish Cancer Registry and age-matched, sex-matched, and calendar-matched 1:20 to population controls using risk set sampling. Conditional logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer associated with PPI use, adjusting for potential confounders. Secondary analyses examined dose-response patterns and associations with individual PPIs as well as with histamine-2-receptor antagonists. They found ever use of PPIs occurred among 27.8% of 6921 pancreatic cancer cases and 25.4% of 34 695 matched controls, yielding a neutral adjusted OR of 1.04 (95% CI 0.97-1.11). Odds ratios were also close to unity in analyses of high use of PPIs (≥1000 DDDs; OR, 0.92 95% CI 0.80-1.07). There was no evidence of a dose-response relationship, with ORs close to unity across categories, including for those with the highest cumulative use (>2000 DDDs; OR, 1.03 95% CI 0.84-1.26). Analyses of subgroups as well as individual types of PPI and of histamine-2-receptor antagonists use also returned neutral associations. It concludes, in this large nationwide case-control study, PPI use was not associated with an increased risk of pancreatic cancer.

Mr. ThawinSrinutta, et.al[Nov 2019] A meta-analysishas suggested that there might be an association between the use of proton pump inhibitors (PPIs) and the development of hypomagnesemia, although the conclusions were no definitive. The methods followed to provide an update on this topic, we performed a meta-analysis of all observational studies that examined the association between the use of PPIs and the development of hypomagnesemia. A literature search was conducted in MEDLINE, Scopus and Cochrane Central Register of Controlled Trials (January 1970 to June 2018) to identify observational studies that examined the association between the use of PPIs and the incidence and prevalence of hypomagnesemia.In the absence of randomized controlled trials, they focused primarily on observational studies, including cross-sectional, case-control, retrospective, and prospective cohort studies. There was no limitation on sample size or study duration. Random-effect models meta-analyses were used to compute pooled unadjusted and adjusted odds ratios (ORs) for binary variables. The results includes sixteen observational studies were identified, including 13 cross-sectional studies, 2 case-control studies, and 1 cohort study, with a total of 131,507 patients. The pooled percentage of PPI users was 43.6% (95% confidence interval [CI] 25.0%, 64.0%). Among PPI users, 19.4% (95% CI 13.8%, 26.5%) had hypomagnesemia compared to 13.5% (95% CI 7.9%, 22.2%) among nonusers. By meta-analysis, PPI use was significantly associated with hypomagnesemia, with a pooled unadjusted OR of 1.83 (95% CI 1.26, 2.67; P = .002) and a pooled adjusted OR of 1.71 (95% CI 1.33, 2.19; P < .001). In subgroup analyses, high-dose PPI use was associated with higher odds for hypomagnesemia relative to low-dose PPI use (pooled adjusted OR 2.13; 95% CI 1.26, 3.59; P = .005). They concluded in support of the results of the previous meta-analyses. Furthermore, we found a dose-response between the PPI use and development of hypomagnesemia.

Mr. Jinqiu Yuan, et.al. [2020] An observational study was conducted by Aliment Pharmacol Ther on 2020 Aug with subject to Regular use of proton pump inhibitor and risk of rheumatoid arthritis in women.Proton pump inhibitors (PPIs) have a significant impact on the gut microbiome, which in turn, might increase the risk of rheumatoid arthritis (RA). The main aim is to evaluate regular use of PPIs and risk of RA. It was a prospective analysis of the US nurses who reported PPI use data, and were free of RA from the Nurses' Health Study (NHS 2002-2014) and NHS II (2003-2015). The exposure was regular use of PPI in the past 2 years, which was repeatedly evaluated in biennial

surveys. RA was confirmed by the 1987 or 2010 American College of Rheumatology criteria. We estimated the hazard ratios (HRs) and confidence interval (CIs) with time-dependent Cox regression adjusting for potential confounders. In the results they documented 421 cases of RA over 1 753 879 person-years of follow-up. Regular PPI users had a 44% higher risk of RA as compared with non-regular users (adjusted HR = 1.44; 95%CI, 1.10-1.89). The risk of RA increased with the total duration of PPI use (P-trend = 0.008). Compared with non-regular users, the adjusted HRs were 1.22 (95%CI, 0.93-1.62) for women with >0 to 4 years' use and 1.73 (95% CI, 1.14 to 2.61) for >4 years' use. It concluded a regular use of PPI was associated with increased risk of RA in women, with a higher risk observed in individuals with a longer duration of PPI use. Due to the observational study design, large prospective trials are still required to confirm their finding.

Mr. Paul Moayyedi, et.al[2019] Proton pump inhibitors (PPIs) are effective at treating acid-related disorders. These drugs are well tolerated in the short term, but long-term treatment was associated with adverse events in observational studies. We aimed to confirm these findings in an adequately powered randomized trial. They performed a 3 × 2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease randomly assigned to groups given pantoprazole (40 mg daily, n = 8791) or placebo (n = 8807). Participants were also randomly assigned to groups that received rivaroxaban (2.5 mg twice daily) with aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg) alone. We collected data on development of pneumonia, C*lostridium difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every 6 months. Patients were followed up for a median of 3.01 years, with 53,152 patient-years of follow-up. The results it found there was no statistically significant difference between the pantoprazole and placebo groups in safety events except for enteric infections (1.4% vs 1.0% in the placebo group; odds ratio, 1.33; 95% confidence interval, 1.01–1.75). For all other safety outcomes, proportions were similar between groups except for *C difficile* infection, which was approximately twice as common in the pantoprazole vs the placebo group, although there were only 13 events, so this difference was not statistically significant.Finally it found in a large placebo-controlled randomized trial, we found that pantoprazole is not associated with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections.

Signal Mining, et.al [Nov 2021] Mounting evidence demonstrates that proton pump inhibitors (PPIs) are associated with a number of adverse effects. However, the literatures about hepatotoxicity-related adverse effects (HRAEs) of PPIs are mostly case reports and a few clinical studies. Methods: We evaluated the association between PPIs and HAREs using the reporting odd ratio (ROR) for mining the adverse event report signals in the FDA Adverse Event Reporting System (FAERS) database. Results: There were 23,825 reports of PPIs as primary suspect drug or second suspect drug, of which 3,253 reports were HRAEs. The top five HRAE signals caused by PPIs were hepatitis cholestatic, cholestasis, fulminant hepatitis, subacute hepatic failure, and acute hepatitis. They also summarized the signals of the HRAEs caused by each PPI. The simultaneous signals were cholestasis and hepatitis cholestatic. For the cholestasis signal, esomeprazole showed an ROR of 21.556 (95% CI 17.592–26.413); pantoprazole showed the highest ROR of 22.611 (95% CI 17.794–28.733) in the hepatic cholestatic signal; lansoprazole was the only PPI with expression in the coma hepatic signal, with an ROR of 10.424 (95% CI 3.340–32.532). By analyzing the reports of

pantoprazole-induced hepatic encephalopathy, we found that patients aged over 65 years and males reported the highest rate. And from the combination of drugs and indications of drugs, no significant results were obtained. Conclusions: The RORs of signals of "cholestasis" were generally higher than those of "hepatocellular injury." And the signals about "cholestasis" in HRAE caused by PPIs are more reported.

Mr. Francisco Torres-Bondia, et.al[3rd Dec 2020] Proton pump inhibitors (PPIs) are among the most prescribed medications. Previous epidemiological studies have presented contradictory results about PPIs and the risk of dementia. Their objective was to investigate the association between the use of PPIs and an increasing risk of incident AD or non-AD dementias. A community-based retrospective cohort study was conducted based on the data available from 1st January 2002 to 31st December 2015 in the Catalan health service (CatSalut) system. This cohort included all PPI users (N = 36,360) and non-users (N = 99,362). A lag window of 5 years was considered between the beginning of the PPI treatment and the diagnosis of dementia. PPI use was not associated with the risk of AD (adjusted odds ratio (OR) 1.06) (95% CI 0.93–1.21; p = 0.408). A weakly but significantly increased risk of non-AD dementias was observed among PPI users (adjusted OR 1.20, 95% CI 1.05–1.37; p = 0.007). A higher dose of PPIs was not associated with an increased risk of either AD or non-AD dementias (OR 1.20; 95% CI 0.91–1.61 and OR 0.95; 95% CI 0.74–1.22, respectively). Regarding the number of PPIs used, we observed an increased risk of AD (OR 1.47; 95% CI 1.18–1.83) and non-AD dementias (OR 1.38; 95% CI 1.12–1.70) in users of two types of PPIs compared with those who used only one type. We did not find a higher incidence of AD among PPI users, but a weak increase in the risk of non-AD dementias among PPI users was observed.In conclusion, we found that the incidence of AD was not higher among PPI users, and a slight increase in the risk of non-AD dementia was observed. As the consumption of PPIs is a useful variable for identifying patients with dementia according to the random forest tree, presence of some chronic and co-morbid pathologies and the resulted polypharmacy, including the increased consumption of PPIs, probably give rise to the increased risk of dementia observed in previous studies.

Emmae N Ramsay, et.al[24 June 2013] The main aim was to compare the results of a new-user cohort study design and the self-controlled case series (SCCS) design using the risk of hospitalisation for pneumonia in those dispensed proton pump inhibitors compared to those unexposed as a case study.The Australian Government Department of Veterans' Affairs administrative claims database was used. Exposure to proton pump inhibitors and hospitalisations for pneumonia were identified over a 4 year study period 01 Jul 2007 -30 Jun 2011. The same inclusion and exclusion criteria were applied to both studies, however, the SCCS study included subjects with a least one hospitalization for pneumonia.There were 105,467 subjects included in the cohort study and 6775 in the SCCS. Both studies showed an increased risk of hospitalisations for pneumonia in the three defined risk periods following initiation of proton pump inhibitors compared to baseline. With the highest risk in the first 1 to 7 days (Cohort RR, 3.24; 95% CI (2.50, 4.19): SCCS: RR, 3.07; 95% CI (2.69, 3.50)).This study has shown that the self-controlled case series method produces similar risk estimates to a new-users cohort study design when applied to the association of proton pump inhibitors and pneumonia. Exposure to a proton pump inhibitor increases the likelihood of being admitted to hospital for pneumonia, with the risk highest in the first week of treatment.

Yoon Hee Park, et.al [1st Dec 2019] A hospital-based cohort studies on the association between

use of proton pump inhibitors (PPIs) and increased Clostridium difficile infection (CDI) risk, detailed studies analyzing the effects of PPI use on CDI risk are lacking. The present study investigated the association of the dose, duration, and types of PPIs with CDI risk. Methods: A single-center, cohort study was conducted on patients admitted to a hospital. The exposed cohort comprised patients who were prescribed PPIs at least once during the study period, and a control cohort was prepared by randomly assigning an index date to patients who did not use PPIs ensuring the same distribution of index dates as in the exposed cohort and matching sex, age, hospitalization period, and date of admission. Results: PPI use increased the risk of CDI by 1.8-fold [95% confidence interval (CI) 1.5–2.2]. CDI risk increased by 1.8-fold with esomeprazole (95% CI 1.4–2.2) and 2.0-fold with pantoprazole (95% CI 1.5–2.8). Patients who used a high dose had a higher risk than those who used a medium dose [adjusted hazard ratio (HR) 2.0 vs 1.3]. The risk of CDI increased 4.2-fold when the PPI exposure period was 6 days or shorter than 6 days. Conclusions: Our study showed that PPI use was associated with an increased risk of developing CDI and the risk of CDI was dose dependent. Therefore, PPIs should only be used at proper doses and only for the necessary indications to avoid CDI risk.

CONCLUSION

Apart from Proton Pump Inhibitors, there are plethora of treatments, nursing care received by critical care patients with various physical illness & symptoms. It is also important to treat different pre-disposing and existing clinical conditions because those factors delay social and functional outcome of the patient. Due to ineffective focused history taking and physical examination, it affects proper diagnosing of critical care patient in appropriate time which delays to identify the risk factors, understanding the clinical features for better treatment of the patient. Ultimately, it affects the optimum outcome and increase hospital mortality along with Hospital Acquired Infection

It is difficult to predict the risk of co morbidity and also found it has no relationship with severity and laterally of lesions consistency. Treatment of the illness involves a multi-disciplinary approach with different specialist consultations along with care of medical- paramedical experts. Medication and managing should follow from a clearly articulated diagnostic scheme and should be time-limited. Thereafter it should be re- evaluated in the presence of poor or incomplete response.

This study dealt with the Methodology adopted for the study and presented the research approach, research design, setting, population, sample and sampling techniques, development and validation of the tool, procedure for data collection and data analysis plan. The selected tool was reliable and valid as per the data from pilot study. This chapter gives direction for the analysis and interpretation of data.

The risk for patients who received proton-pump inhibitors (adjusted hazard ratio [AHR] 0.63; 95% CI 0.39-1.01) was not significantly different than in non-exposed patients.

Prior use of a proton-pump inhibitor did not correlate with a significant increase in the risk of developing Nosocomial Pneumonia (NP). This risk was higher with the administration of sedatives or neuromuscular blockers, increased disease severity, and placement of various invasive medical treatment like central venous catheter.

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