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Association Between Proton Pump Inhibitor Use & Dementia: A Two-Fold Approach

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Abstract

❖ An observational study of data derived from the German Study on Aging, Cognition and Dementia indicated that proton pump inhibitor use was associated with dementia risk (Benmassaoud, McDonald, & Lee, 2016). The purpose of this study is to explore a two-fold approach between proton pump inhibitor use and dementia. This two-fold approach will first investigate the association between dementia and proton pump inhibitor use and secondly, the proposed pathophysiology behind it. This approach to proton pump inhibitor use and dementia will allow for providers to utilize the association and make decisions to avoid chronic proton pump inhibitor use in effort to reduce or prevent dementia. Research methods include reviewing peer reviewed journal that were obtained from Pubmed, ClinicalKey and PsycINFO. Gomm et al. (2016) found that their study participants prescribed proton pump inhibitors had a significant increase in risk of dementia (HR, 1.44 [95% CI, 1.04-1.83]). Haenisch et al. (2015) found that the use of proton pump inhibitor medication increased the risk of any dementia (HR 1.38, [95% CI, 1.04-1.83]) compared to no proton pump inhibitor use. Akter et al. (2015) utilized the CANTAB software which provided multiple significant findings in several different testable areas among proton pump inhibitor users. Badiola et al. (2013) used materials and methods such as cell culture, drug treatments, analysis of amyloid-beta peptides by ELISA, mass spectrometry of amyloid-beta species, animals and treatments, brain soluble amyloid-beta extraction and western blotting to provide one-way ANOVA and t-test to report the effect of proton pump inhibitors have on amyloid-beta degeneration in mice. Jung et al. (2015) found statistical significance between chronic acid lowering agents and vitamin B12 deficiency with a hazard ratio of 1.83 [95% CI: 1.36-2.46], p-value <0.0001. Additionally, Dharmarajan et al. (2008) reported a relationship between serum B12 levels and the duration of proton pump inhibitor use. Their study revealed a diminishing serum B12 level that correlated with an increase in length of proton pump inhibitor use (P<.0005).

Introduction

- It is estimated that over 15 million patients were prescribed proton pump inhibitors with the cost estimated at \$79 billion between the years of 2007 and 2011 (Benmassaoud, McDonald, & Lee, 2016).
- Proton pump inhibitors are not only available via prescription, but also over-the-counter. Therefore, the extent into which proton pump inhibitors are used are not really known.
- Hamzat et al. found 61% of patients were inappropriately prescribed proton pump inhibitors in their 440 patient study (Hamzat et al., 2012).
- With the over-prescribing and long-term use of proton pump inhibitors, the elderly patients receiving these drugs may be at the highest risk of complications.
- The therapies and care related to a dementia diagnosis have an enormously high price association; it is estimated that in the year 2010 the worldwide cost was \$604 billion (Gomm et al., 2016).

Statement of the Problem

•As our national population continues to age, the diagnosis of dementia will increase.

•Establishing an association between proton pump inhibitors and dementia could alter the clinician's decision when considering risk versus benefit of treatment for diagnoses requiring acid lowering drugs.

•The information gained from this literature review would allow for clinicians to make an educated decision for treatment of diseases requiring acid lowering drugs.

Research Question

- ▶ In elderly patients with dementia, is there a significant difference in the proportion of patients using proton pump inhibitors versus no proton pump inhibitor use?
- ▶ What proposed pathophysiology links dementia to proton pump inhibitor use?

Literature Review

- ❖ Research methods include reviewing peer reviewed journal that were obtained from Pubmed, ClinicalKey and PsycINFO.
- ❖ Gomm et al. (2016) study showed that the 2,950 patients prescribed proton pump inhibitors had a significant increase in risk of dementia (HR, 1.44 [95% CI, 1.04-1.83])
- ❖ Haenisch et al. (2015) found that the use of proton pump inhibitor medication increased the risk of any dementia (HR 1.38, [95% CI, 1.04-1.83]) compared to no proton pump inhibitor use.
- ❖ Wijarnpreecha et al. (2016) established an increased risk of dementia among proton pump inhibitor users.
- ❖ Akter et al. (2015) addressed the degree of association with each proton pump inhibitor and cognitive impact. The results of the study found a statistically and clinically significant impairment in visual memory, attention, executive function, working and planning function. The mean error from baseline to 7 days of treatment with omeprazole (p<0.05) was significant. Overall, the study found that the omeprazole group had more errors in the motor screening test and paired associates learning test
- ❖ Ravaglia et al. (2005) conducted a cohort study to investigate the relation between high plasma levels of total homocysteine and the risk for dementia. Hyperhomocysteinemia was present in 26.6% of participants that were more likely to have low vitamin B12 levels and more likely to develop dementia.
- ❖ Badiola et al. (2013) investigated the effects of lansoprazole and other proton pump inhibitors on the amyloid beta production in cellular and animal models. The study establishes the plausible connection between proton pump inhibitors and the amyloid-beta theory in mice. Extracellular deposition of amyloid beta peptides in the brain that results in oxidative and inflammatory is one type of lesion found in dementia. This can lead to energy failure and synaptic dysfunction.
- ❖ Lam et al. (2013) noted that the use of proton pump inhibitors for two or more years is associated with a new diagnosis of vitamin B12 deficiency. They also found that the higher dosage of proton pump inhibitors correlated with a stronger association of vitamin B12 deficiency.
- ❖ Kivipelto et al. (2009) produced a study to address vitamin B12 deficiency using hyperhomocysteinemia and holo-transcobalamin to associate a relationship in the development of dementia. The conclusion of this study indicated that high total homocysteine levels were found to increase the risk of dementia, surprisingly, holotranscobalmin was found to be an unrelated to the risk of dementia
- ❖ Jung et al. (2015) used systematic review of 57 studies and found statistical significant between chronic acid lowering agents and the vitamin B12 deficiency with a hazard ratio of 1.83, 95% CI: 1.36-2.46, p-value <0.0001.
- ❖ Dharmarajan et al. (2008) also examined the relationship between serum vitamin B12 levels in older adults on proton pump inhibitors or histamine-2 receptor antagonists. The relationship between serum B12 levels and duration of proton pump inhibitors was significant for a pattern in diminishing serum B12 levels with increasing duration of proton pump inhibitor use (P<.0005).

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Discussion

- Based upon the results of the studies examined in this literature review, there is a significant difference in the proportion of patients with dementia who use proton pump inhibitors. The results of Gomm et al. (2016) study showed that the 2,950 patients prescribed proton pump inhibitors had a significant increase in the risk of dementia. However, in this study the participants were never directly involved, only a review of their information. Nevertheless, this study implied that the duration of proton pump inhibitor use was significant. Therefore, it can be interpreted that the longer a person uses a proton pump inhibitor, the risk of them developing dementia also increases. Haenisch et al. (2015) found that the use of proton pump inhibitor medication increased the risk of any dementia compared to no proton pump inhibitor use. Yet, this study was an epidemiological study. Consequently, fundamental biological mechanisms were not explored. However, this study remains significant due to the association found between proton pump inhibitor use and the increasing risk of dementia. Both studies provide a statistical association between proton pump inhibitors and dementia. Therefore, elderly patients who are already at risk for developing dementia due to their age will have an additional risk in developing dementia if they use proton pump inhibitors chronically.
- The study by Wijarnpreecha et al. (2016) established an increased risk of dementia among proton pump inhibitor users, however, it was performed via literature search. A total of four studies were included in their analysis. Wijarnpreecha et al. (2016) included studies that were either case-control, cross-sectional or cohort studies that were designed to evaluate proton pump inhibitor users related to non-users. Their study did establish a link between proton pump inhibitors and dementia that was non-biased and based upon previously published studies.
- Akter et al. (2015) addressed the degree of association that each proton pump inhibitor had on cognition by using the CANTAB software. This software allowed for actual results to be assigned to the different proton pump inhibitor groups and provided insight to the mechanisms of their properties. The results of the study found a statistically and clinically significant impairment in visual memory, attention, executive function, working and planning function. Yet, this study is a short-term study. If Akter et al. (2015) could produce these profound results in a short-term study, it would be valuable to invest in a long-term study. A long-term study, utilizing the CANTAB software, has the potential to provide more awareness into this association.

❑ *Pathophysiology behind the association between proton pump inhibitors and dementia:*

- Badiola et al. (2013) studied cellular and animal models. This study suggests a relationship between proton pump inhibitors and an increase in the extracellular depositing of amyloid beta peptides in the brain which the deposits can result in oxidative and inflammatory lesions. These lesions can lead to synaptic dysfunction. This study makes a reasonable association, but more evidence is needed to investigate the relationship. Studies investigating this particular theory are few. It would be valuable to have further studies that investigate this theory.
- The study completed by Lam et al. (2013) verified the association vitamin B12 deficiency and chronic use of proton pump inhibitors by using a review of information which found that the higher dosage of proton pump inhibitors correlated with a *stronger* association of vitamin B12 deficiency. Jung et al. (2015) performed a systematic review of existing studies, which found an association between proton pump inhibitor use and vitamin B12 deficiency. These studies provided an association between proton pump inhibitors and dementia by examining previously assembled data.
- Dharmarajan et al. (2008) monitored proton pump inhibitor users and histamine-2 receptor antagonist users and their serum vitamin B12 levels were monitored. This study was interesting because it found a relationship between serum B12 levels and the *duration* of proton pump inhibitor use. The increased duration of proton pump inhibitor use was significant for a pattern of diminishing serum B12 levels. This evidence can be understood that the chronic use of proton pump inhibitors contributes to the lowering serum B12 levels. It is important to monitor chronic users of proton pump inhibitors for vitamin B12 deficiency or stop the use of proton pump inhibitors. The problem with diminishing serum vitamin B12 levels only become pertinent after long-term use. It can also be assumed that short-term use of proton pump inhibitors is acceptable. Similarly, Dharmarajan et al. (2008) found that the serum B12 levels *did not* decrease for those who used histamine-2 receptor antagonists.
- Originally, it was thought that the association between proton pump inhibitors and dementia was due to the vitamin B12 deficiency. However, Kivipelto et al. (2009) and Ravaglia et al. (2005) found that there are other risk factors that contribute to this association. The results of these two studies provided awareness into other sensible mechanisms behind dementia and proton pump inhibitors. Continued studies into these mechanisms would be of benefit to gain a greater understanding of the association of proton pump inhibitors and dementia. Exploring the biological mechanisms further into the association would not only provide a greater understanding, but also more awareness for preventive responsibilities.

Applicability to Clinical Practice

- Naturally elderly patients are of historic increased risk for developing dementia, thus, chronic proton pump inhibitor use should be restricted to patients with suitable indications. Attempt to prescribe the lowest effective dose and discontinue proton pump inhibitors if able
- A diagnosis of dementia requires an increase in demand for therapies and specialized care as the cumulative cognitive declines in the patient. These particular treatments are costly (Haenisch et al., 2015).
- The prevalence of dementia does increase with the normal aging of the brain and about one percent of people will have dementia at age 65. At age 90, it is estimated that around one-third of the population will be diagnosed with dementia (Haenisch et al., 2015). The most important method in treating dementia is establishing a cause.
- Proton pump inhibitors have been found to effectively increase gastric pH, which decreases the amount of vitamin B12 being absorbed.
- Prevention or risk reduction is a priority for reducing the occurrence of dementia. If a specific cause is acknowledged, such as nutritional deficiencies, treatment can be added. There is no exact treatment for dementia, but establishing a cause and providing a specific treatment produces the expectations of reversing or halting the progression. Health care providers should monitor cognitive decline and serum vitamin B12 when they have a patient on prolong prescriptions of proton pump inhibitors.
- Providers becoming aware of the possible side effects of chronic proton pump inhibitors in the elderly is an adaptable intervention to reducing a patient's risk of dementia.
- Providers may be able to discontinue unnecessary proton pump inhibitor prescriptions, provide close follow-up in patients requiring proton pump inhibitors, monitor serum B12 status in those taking proton pump inhibitors, monitor mental decline, or provide treatment before a dementia diagnosis.
- When practitioners are prescribing proton pump inhibitors to the elderly, it is import to be cognizant of the risk that is associated with dementia.

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