Neuroprotection and Side Effects of Proton Pump Inhibitors: A Comprehensive Review

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ABSTRACT

Proton pump inhibitors [PPIs] are extensively used drugs for various indications. They are not approved for long term use by regulatory authorities. PPIs are also available as over the counter drugs which can lead to their inappropriate use. Amongst the adverse drug reactions [ADRs] of PPIs, dementia and Alzheimers disease [AD] are the recent ones. Inappropriate long term use of PPIs can lead to serious ADRs like myocardial infarction, nephropathy along with dementia. The possible mechanisms for PPIs induced dementia and AD are endothelial dysfunction, its aging and senescence. Effect on lysosomal function and proteostasis, shortening of telomere length, and inhibition of vacuolar ATPases [V-ATPases] of microglial lysosomal membrane also contribute for this pathology. Increased generation of beta amyloid [Aβ] peptide by inverse gama secretase modulation and augmentation of beta secretase are responsible for the generation and accumulation of Aβ along with its decreased degradation as a result of inhibition of V-ATPases in the microglia. Vitamin B 12 absorption is decreased due to long term use of PPIs. This also contributes for nerve damage as a result of impaired DNA synthesis, methylation and homocysteine neurotoxicity along with cognition impairment. Seizure like condition can be the result of hypomagnesemia induced by long term PPIs use. Thus long term, inappropriate use of PPIs invite serious and life threatening conditions which need to be kept in mind by the clinician before prescribing them.

Keywords: Alzheimers disease, Proton pump inhibitors, hypomagnesemia.

INTRODUCTION

Proton pump inhibitors [PPIs] are extensively used drugs in gastroesophageal reflux and acid peptic disorders, erosive oesophagitis, non steroidal anti inflammatory drug induced gastritis, Helicobactor pylori infection and Zollinger-Ellison syndrome[1,2]. They inhibit the release of gastric acid from parietal cells by blocking hydrogen potassium adenosine triphosphatase [H^+K^+ATPase] pump-proton pump[3,4]. Along with blocking H^+K^+ATPase they also block vacuolar ATPases at various sites including those in the brain microglial cells. PPIs are observed to cross blood brain barrier[5,6].

In countries like United states PPIs are available as over the counter drugs. They are not approved for long term use by regulatory authorities. Available evidence suggests that there is an inappropriate use of these drugs[7,8,9]. Though PPIs are considered safe drugs and enjoy eighth position in the list of commonly prescribed drugs, studies have shown that about 25-70% of patients taking PPIs have no appropriate and confirmed indications[10-12] .

Along with other adverse drug reactions, PPIs are found to have serious reactions like myocardial infarction, dementia and renal failure[13-16]. Out of these ADRs of PPI dementia is quite a recently observed one. Elderly patients are exposed to PPIs therapy to prevent or counteract gastrointestinal adverse effects of concurrent **Author for Correspondence: drpatiltr@gmail.com*

drugs used. This overuse of PPIs can invite serious adverse drug reactions like dementia and alzheimers disease [AD] [17,18].

Number of PPI prescriptions have shown four-fold increase in last 10 years[19]. Significant inappropriate prescriptions of PPIs were noted in the aged patients having dementia where they were used in maximum therapeutic doses for more than 8 weeks[20].

Dementia is characterized by decline in cognitive function mainly seen old people. Diabetes mellitus, obesity hypertension and smoking are the potential risk factors for dementia[21,22]. Recent studies have suggested that PPIs could be another potential risk factor for dementia and cognitive decline. It was found that there was a small increased risk of dementia in chronic PPI users than nonusers[16,23-25].

The global prevalence of dementia is likely to increase to more than 80 million people in 2040 as compared to 35 million in year 2016[26,27]. Dementia creates a huge burden on the health care system and financial status[28]. Hence the reduction in the incidence of dementia in terms of primary prevention is important[29]. Finding out the causative and precipitating factors including the drugs, deserves special attention.

PPIs like lansoprazole and omeprazole have been reported to cross blood brain barrier and hence can have action on brain cells[30,31,32].

Haenisch et al observed that patients receiving long term PPIs therapy had significantly increased risk of dementia as well as AD[24]. AD is a progressive neurodegenerative disorder characterized by dementia, impairment of memory, language and general intellectual activity[27]. Accumulation of amyloid beta[Aβ] oligomers form insoluble plaques in the brain cells triggering the formation of cytotoxic inflammatory cytokines and reactive oxygen species. This results in neurodegeneration and hamper the brain function[33]. Possible pathogenesis of dementia and AD induced by PPIs could be as follows.

Effect of PPI on lysosomal function and proteostasis

Studies have shown that PPIs impaired endothelial

lysosomal acidification, proteostasis and enzyme activity[34]. Disturbed proteostasis results in to deteriorated cell function and accelerated cell aging[35-37]. To complete the process of autophagy the binding of lysosome to autosome is needed[38]. This helps in degradation and elimination of unwanted cellular products including misfolded proteins[39]. Impaired lysosomal acidification and reduced lysosomal enzyme activity results in to an accumulation of protein aggregate. The accumulation of protein aggregate is associated with endothelial dysfunction, increased oxidative stress and endothelial cell senescence[40-42]. *Effect of PPI on endothelial function*

Endothelial cell [EC] dysfunction plays a major role in the pathogenesis of disorders like myocardial infarction, renal damage and dementia[40-42]. Decrease in nitric oxide [NO] production by endothelial cells and generation of superoxide anions are the features of endothelial dysfunctions[43-45]. Vascular senescence provides rational explaination for vascular pathologies involved in cardiovascular and renal diseases and also for dementia[13-16].

PPI like esomeprazole [ESO] could produce decreased endothelial NO generation, DDAH 1 and 2, eNOS and iNOS. NO dependent angiogenesis and cell proliferation is impaired by long term use of ESO in dose dependent manner. It also increased the expression of cell cycle inhibition gene p21. Thus, PPIs affect various functions adversely[34].

PPI enhance endothelial ageing and senesence

Hallmark of cellular senescence are reduced cell proliferation and impaired proteostsis[37,46]. When cells were treated chronically with ESO and were observed for senescence, it was found that beta galactosidase [SAbeta-gal] positive cells were increased with decrease in total cell count per microscopic field. Cell morphology was changed to that of fried egg appearance which is a characteristic of EC senescence. Expression of genes related to senescence of EC were increased. These were the increased expression of genes involved in endothelial to mesenchymal transition [EndoMT], inflammation and increased oxidative stress. Genes associated with EndoMT including TWIST 1, COLIA 1 and SMAD 3 were upregulated. After treatment with ESO, plasminogen activator inhibitor 1 [PAI-1], a well known marker of endothelial dysfunction characterized by increased thrombogenecity, immune activation, oxidative stress and cellular senescence, was upregulated. Thus chronic exposure of PPIs induce endothelial dysfunction consistent with EndoMT and senescence[34].

Effect of PPI on telomere length

Attrition of telomere length is suggestive of endothelial senescence[46]. In ESO treated group there was significant decrease in telomere length as compared to the control. This was associated with downregulation of genes like TRF 1, TRF 2, POT 1, RAP 1 and TIN 2 of shelterin complex involved in the maintenance of telomere length and function[34].

Thus, long term use of PPIs impairs acidification of lysosomes and enzyme activity associated with accumulation of protein aggregates, impair endothelial NO release and increase the generation of reactive oxygen species. There is an acceleration of telomere erosion with downregulation of genes of shelterin complex. It also enhances endothelial aging suggested by impaired angiogenesis and cell proliferation along with histological markers of EndoMT and endothelial senescence. EndoMT is a measure of endothelial cell senescence and plays an important role in diseases characterized by fibrosis and loss of vasculature like those of cardiovascular and other disorders. Long term exposure to PPIs upregulate the genes involved in EndoMT.

Role of vacuolar ATPase proton pumps in AD

Abnormal generation of amyloid beta peptide plays an important role in the pathogenesis of AD[47]. Microglia in the brain are the mononuclear phagocytic cells[48]. They have acidic lysosomes and can engulf and digest amyloid beta peptides[48]. For optimal function, lysosomal proteases should have acidic environment. But in patients of AD lysosomes of microglia are less acidic than that of the normal one. Thereby they have less capacity to clear ABP. Lyosomal pH in the microglia is regulated by vacuolar proton pumps [V-ATPase] which pump protons from cytoplasm to the lumen of the vacuoles or in to the extracellular space. The B and E subunits of the VATPase present in the microglia and macrophages play an important role in the acidification of lysosomes of these cells.

PPIs have been shown to cross the blood brain barrier and enter CNS[30,31]. It has been demonstrated that PPIs can block V- ATPase of lysosomal membranes and make lysosomal pH less acidic. PPIs given for long term inhibit V-ATPases on the lysosomal membranes of microglia, decrease acidification of lysosomes and hinder the process of degradation of abnormal ABP. Acidic vacuolar pH is essential for degradation and clearance of AB peptide[49,50]. Thus chronic PPI therapy proves to be a potential risk factor for AD.

Increased Aβ generation by PPI

Lansoprazole and other PPIs could increase Aβ levels not only in cell culture but in mice also. PPIs like lansoprazole have been reported to cross the blood brain barrier and affect brain tissue[32].

Badiole et al showed that PPIs can interact with the brain enzyme and observed the increased Aβ levels in the brains of mice treated with these drugs[51]. It was suggested that inverse gama secretase modulation and augmentation of beta secretase BACE 1 activity can lead to accumulation of Aβ peptide[51].

Alzheimers disease is a neurodegenerative disorder characterized by extracellular deposition of amyloid beta [Aβ] peptide in the brain leading to oxidative stress and inflammatory damage resulting into synaptic dysfunction and energy failure[52,49].

Proteases like beta and gama secretases sequentially cleave amyloid precursor protein [APP] and produce Aβ 42 and Aβ 40.In the pathogenesis of AD, Aβ 42 is the main pathological species[51,53]. Severity of dementia is correlated to the soluble form of Aβ than the fibriller one[54-57]. Brain oligomeric Aβ correlates with the neuronal loss and astrocyte inflammatory response than total amyloid plaque burden[58]. Aβ oiligomers are found to alter dendritic spine density and affect synaptic plasticity of hippocampus[59-63].

Direct association between oligomers and cognitive impairment is strongly observed[64-66]. In the experimental studies conducted, it was observed that production of Aβ 37, Aβ 40 and Aβ 42 were increased by pantaprazole in AD like cell model. It was hypothesized that lansoprazole could inversely modulate the gama secretase activity resulting in to higher Aβ 42 and lower Aβ 38 levels due to shifting of cleavage site[67].

Effect of PPI on vitamin B12 absorption:

Lam et al considered possible association between decreased cognition due to PPIs induced deficiency of vitamin B 12[68]. Chronic use of PPI can lead to suboptimal GI absorption of vitamin B12 resulting in to its deficiency[68]. Vitamin B12 deficiency is known to decrease cognition by impairing DNA synthesis, methylation and homocysteine neurotoxicity[69,70]. Vitamin B12 level in the blood is reduced as result of its decreased absorption due to chronic PPIs therapy. PPIs increase intragastric pH, inhibit intragastric proteolysis and the release of vitamin B 12 from food which is required prior to its binding to R proteins and gastric intrinsic factor for its adequate absorption. Risk of hypovitaminosis of B 12 is more in elderly and malnourished[68,71,72].

PPI induced Hypomagnesemia

PPI induced Hypomagnesemia was noted with long term use of PPIs and warning was also released by FDA in March 2011[73]. The symptoms of hypomagnesemia include seizure, tetany, cardiac arrhythmias and hypotension which can prove fatal sometimes[74]. Decreased absorption of magnesium was observed with all PPIs. Hypomagnesemia was more common with older patients having mean age of 64.4 years and mean time for the onset of hypomagnesemia was 5.5 years after the initiation of PPIs therapy. Hypomagnesemia was found to be associated with hypokalemia and hypocalcemia also[75] Withdrawal of PPIs was found to correct this deficiency[76]. Concurrent use of diuretics can potentiate the risk of hypomagnesemia[74]. Hence it is recommended that patients on chronic PPIs therapy should have regular monitoring of serum magnesium and also that of potassium and calcium.

Now there is a serious need to propogate the knowledge about the rational use of PPI as they are being used by millions of people for indications which are often never confirmed and the duration which were never tested and approved. It is the responsibility of prescriber and manufacturer of PPIs to stress the measures for the safety of the patients on PPIs therapy.

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