Are proton pump inhibitors a new antidiabetic drug? A cross sectional study

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Abstract

AIM: To investigate the effect of proton pump inhibitors (PPIs) on glycemic control (HbA1c) in type 2 diabetic patients.

METHODS: A cross-sectional study of consecutive inpatients admitted to hospital in any department during the first semester of the year 2010 who had a recent HbA1c measurement. The study excluded those with a diagnosis of hyperglycemic decompensation, diabetic onset or pregnancy. It compared HbA1c levels of those taking PPIs and those not.

RESULTS: A total of 97 patients were recruited. The average HbA1c level was 7.0% ± 1.2%. Overall PPI consumption was 55.7%. HbA1c was significantly lower in individuals who took PPIs: -0.6%, 95% CI: -0.12 to -0.83. People who used PPIs with some type of insulin therapy had a HbA1c reduction by -0.8%, 95% CI: -0.12 to -1.48. For the rest of subgroup analysis based on the antidiabetic drug used, PPI consumption always exhibited lower HbA1c levels.

CONCLUSION: PPIs seems to be consistently associated with better glycemic control in type 2 diabetes. HbA1c reduction observed is similar to incretin-based therapies.

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Key words: Proton pump inhibitors; Diabetes mellitus; Drug therapy; Hypoglycemic agents; Incretins

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INTRODUCTION

Proton pump inhibitors (PPIs) have become one of the most commonly prescribed class of drugs whose overall safety profile is unquestionable[1].

PPIs are mainly used to treat symptoms of gastroesophageal reflux disease and gastritis, but also to treat peptic ulcers (duodenal and gastric), drug-induced ulcers and to promote healing of erosive esophagitis[2]. They decrease secretion of gastric acid by blocking
the last enzyme in the system that actively transports acid from gastric parietal cells into the gastrointestinal lumen, hydrogen-potassium adenosine triphosphatase, also known as the proton pump[3].

A physiological effect of acid suppression with PPIs is a mild/modest hypergastrinemia which occurs with all PPIs[3]. Gastrin is known to be the major endocrine regulator of the secretory response to a protein meal, while somatostatin (SST) is a potent inhibitor of gastrin and histamine synthesis and release and therefore, of gastric acid secretion[4].

In rodents, gastrin induces islet β-cell neogenesis[4,5] and in in vitro studies, this hormone increases the β-cells mass[6].

A few retrospective studies in adults with diabetes appear to show that PPIs are associated with better glycemic control. Mefford et al[7] compared HbA1c levels from type 2 diabetic patients taking PPIs (7.0%) and type 2 diabetics not taking them (7.6%), obtaining significant differences.

Boj-Carceller et al[8], in a personal communication, in a smaller study with diabetic in-patients with poor glycemic control (33.8% were type 1 diabetic patients), found that those who were using PPIs had lower HbA1c levels (average HbA1c of 9.5%) than patients not taking PPIs (average HbA1c of 8.8%). After this, Hove et al[9] conducted a case-control study to investigate whether treatment with esomeprazole (a type of PPI) improved HbA1c levels in a group of type 2 diabetic patients. They found a borderline significant reduction of HbA1c by 0.7%.

There are no more studies in the literature, so it would be cost-effective to conduct one in order to evaluate if PPIs are associated with better glycemic control in type 2 diabetic patients.

| MATERIALS AND METHODS |
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| This study was a cross-sectional study. From the electronic medical record database, the authors selected consecutive patients with type 2 diabetes who had been admitted to hospital in any department during the first semester of the year 2010 and had an HbA1c measurement during their hospital stay. The study excluded those with a diagnosis of hyperglycemic decompensation, diabetic onset or pregnancy. It compared HbA1c levels of those taking PPIs and those not taking PPIs by a two-sample t test. It also performed the same comparison according to the antidiabetic medication used (insulin, metformin, sulfonylurea and "others" for the rest of antidiabetic drugs) by the Mann-Whitney test. HbA1c levels were determined by a high-performance liquid chromatograph (Adams A1c HA-8160).

Data are presented as mean ± SD and as percentages for categorical data. P < 0.05 was considered statistically significant. All statistical analyses were carried out using the SPSS statistical package for Windows, version 17.0 (SPSS Inc., Chicago, IL, United States).

| RESULTS |
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| A total of 97 subjects were included. There were 43 (44.3%) women. The average age was 72 ± 10.8 years. Overall, PPI consumption was 55.7%. Glycemic control was acceptable (HbA1c ≤ 7%) in 54.6% and the prevalence ratio of acceptable good metabolic control was 1.81 (95% CI: 0.74-4.42), in favor of those taking PPIs.

Table 1 presents the main results. HbA1c was significantly lower in individuals who take PPIs: -0.6% (P = 0.018), 95% CI: -0.12 to -0.83. When the study subdivided these two groups based on diabetes treatment, those taking insulin and concurrent PPIs had better glycemic control; HbA1c of -0.8% points (P = 0.022), 95% CI: -0.12 to -1.48, compared with those taking insulin but not PPIs.

For the rest of comparisons there was a lack of statistical significance but the trend for lower HbA1c was constant in all groups taking a PPI.

| DISCUSSION |
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| The present study found a significant reduction of HbA1c by 0.6% in patients with type 2 diabetes who were taking a PPI. In patients who were taking insulin with a PPI, the reduction, also statistically significant, was 0.8%.

To date, three other studies have commented on a beneficial effect of PPIs on the glycemic control in patients with diabetes. The results of the current study are similar to Mefford et al[7] performed in a primary care context with a bigger population sample and have the same significant overall HbA1c reduction of -0.6% associated with PPI consumption. Although Hove et al[9] and the group did not obtain statistically significant differences, the reduction of HbA1c of those taking PPIs was identical 0.7%. The observation of these figures could provide interesting insights into the potential mode of action of PPIs since it is inside the range that Dipeptidyl peptidase-4 (Dpp-4) inhibitors and glucagon-like peptide-1 agonists (exenatide) appear to lower A1c levels -0.5% to -1%[10,11]. Actually, gastrin is a cousin of incretin.
hormones since they are both gastrointestinal peptides, so PPIs could lower glycemia by a mechanism similar to incretin-based therapies. In fact, it is known that PPIs slow gastric emptying,\textsuperscript{[12,13,14]} which could decrease postprandial hyperglycemic excursions, as glucagon-like peptide 1 does.

Other underlying mechanisms could be considered. Acid secretion from parietal cells in the stomach is highly regulated by a complex network of paracrine and endocrine effects. For instance, the effect of PPIs on glycemia could be explained by SST decrease. Several studies seem to show that administration of omeprazole decreased the antral SST content significantly.\textsuperscript{[14,15]} SST is an inhibitory hormone that regulates numerous biological processes. SST inhibits the secretion of glucagon and insulin. Although the relationship between SST and diabetes is not clear, the rare somatostatinoma\textsuperscript{[16]} and SST analogs are followed frequently by a glucose metabolism imbalance\textsuperscript{[17]}. There are no studies that assess SST plasmatic concentration before and after PPI use.

In summary, PPIs may share most of the glucoregulatory effects of incretin-based therapies: increase islet-cell mass, slow gastric emptying, decrease glucagon levels, no weight gain and even adverse events such as concerns about immune function.

The authors recognize that the study has several limitations. Patient specific data were limited to that recorded in the database. Incomplete data collection about medication is possible (including doses). PPIs are commonly used among the population and sometimes not declared during anamnesis so the effect found may be underestimated.

In our hospital, the determination of gastrin is not available; this is the main reason it was not measured. Nevertheless, it is known that it is higher in patients taking PPIs.

Lastly, the analysis probably lacked power to compare HbA1c between specific diabetes treatment groups.

Close observation of the data imply that patients retrieved for this study had good glycemic control (in terms of target HbA1c). Previously the group has found also a positive effect on HbA1c in diabetic in-patients with poor glycemic control. This may be an independent effect of the severity of disease.

Despite the inherent limitations of the study design, PPIs appears to be strongly and consistently associated with better glycemic control in type 2 diabetes in the four published studies on the subject to date. The pharmacology of these drugs implies several gastrointestinal peptides, gastrin mainly, so it is not strange that the HbA1c reduction observed is similar to DPP-4 inhibitors and glucagon-like peptide-1 agonists.

Randomized clinical trials are required to evaluate the efficacy of this possible new antidiabetic drug and elucidate its mechanism of action.

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COMMENTS

Background
Type 2 diabetes mellitus is a complex disease whose physiopathology includes a progressive loss of islet β-cell function. More than one medication will be necessary for the majority of patients over time. Choices of therapies are usually made according to efficacy, safety, tolerability, cost of medications, simplicity and anticipated degree of patient adherence. New treatment strategies that take into account these characteristics will be welcome. Gastrin has been said to have trophic effects on β-cell mass. Theoretically it is similar to an incretin, a hormone released in the intestine associated with oral intake. Proton pump inhibitors (PPIs) are known to increase gastrin levels so they could be associated with better glycemic control in diabetes.

Research frontiers
PPIs are widely used, safe and not very expensive medicines. In the area of type 2 diabetes therapeutics, the research hotspot is the development of new treatment targets and new therapies. Treatments targeting the incretin system have recently generated interest. PPIs enhance gastrin, a gastrointestinal peptide close to glucagon-like peptide 1, so it would be appropriate to explore the antidiabetic properties of these drugs.

Innovations and breakthroughs
This study supports the hypothesis that PPIs are associated with better glycemic control in type 2 diabetes patients. To date, this hypothesis has been explored by three other groups, including the authors, in different clinical contexts (primary and hospital care) with positive and similar results in terms of decrease of HbA1c. This article also speculates about the underlying mechanisms, considering an incretin-like effect.

Applications
If these results are demonstrated in randomized clinical trials, PPIs could be a new antidiabetic drug with a good profile: no hypoglycemia events, good tolerability and safety, and with a limited price.

Terminology
PPIs are drugs used to treat symptoms of acid-related disorders and for primary prevention of gastroduodenal toxicity mainly. They include five agents: omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole.

Peer review
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