e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(10); 60-65

Original Research Article

To Determine the Effect of Oral Pantoprazole and Rabeprazole on Blood Glucose Levels in Type 2 Diabetes Mellitus

Geetika Gupta[1], Puneeta Gupta[2], Bhavna Langer[3], Anil K. Gupta[4]

[1]Professor & Head, MBBS, MD Physiology, Department of Physiology, Acharya Shri Chander College of Medical Sciences & Hospital, Sidhra, Jammu, J&K, 180017 (ASCOMS & Hospital)
[2]Professor, MBBS, MD Medicine, Department of Medicine, Acharya Shri Chander College of Medical Sciences & Hospital, Sidhra, Jammu, J&K, 180017 (ASCOMS & Hospital)
[3]Associate Professor, MBBS, MD Medicine, Department of Community Medicine, Government Medical College, Jammu, J&K,180001
[4]Professor & Head, MBBS, MD Medicine, Department of Medicine, Acharya Shri Chander College of Medical Sciences & Hospital, Sidhra, Jammu, J&K, 180017 (ASCOMS & Hospital)

Received: 12-07-2023 / Revised 21-00-2023 / Accepted 20-09-2023
Corresponding author: Dr. Geetika Gupta
Conflict of interest: Nil

Abstract:

Background: Diabetes mellitus represents a spectrum of metabolic disorders which has become a major challenge worldwide. There is a plethora of drugs targeting the defects of DM. Recently, however the focus has been on strengthening the enteroinsular axis and incretins. Proton pump inhibitors used extensively for the treatment of gastritis and related symptoms, indirectly elevate gastrin levels which is reported by few studies to have the potential to improve glycemic control.

Material & Methods: 195 patients of T2DM satisfying the inclusion criteria were included in the study after taking informed consent. A prestructured questionnaire was used for data collection. Subjects who were prescribed pantoprazole 40mg or rabeprazole 20mg for 12 weeks for their acid related ailments were divided into two groups and those not taking PPI were considered as controls. Fasting blood glucose, HbA1c levels were noted at baseline and after 12 weeks.

Results: Comparison of fasting blood glucose and HbA1c at baseline and at 12 weeks for Group I and Group II using paired t test showed that in both the groups there was a statistically significant change for both these parameters (Group I=0.00 & 0.00 respectively; Group II=0.00 &0.00 respectively) thereby implying better glycemic control.

Conclusion: The study suggested of a possible role of PPI as an adjunctive therapy in achieving better glycemic control similar to incretin-based therapies in patients of T2DM but further studies are warranted to confirm the effect of combination therapy.

Keywords: Fasting Blood Glucose - Glycemic Control - Incretin Like Effect – Pantoprazole- Rabeprazole - T2DM.

Introduction

Type 2 diabetes (T2DM) is a complex heterogeneous group of metabolic conditions characterized by peripheral insulin resistance, impaired insulin secretion and excessive hepatic glucose production [1].The prevalence of diabetes is rapidly rising all over the globe at an alarming rate [2]. Patients with type 2 diabetes have an increased risk of developing both micro vascular and macro vascular complications [3]. By achieving better glycemic control, the incidence and progression of macro and microvascular complications can be decreased. At present the treatment of T2DM includes lifestyle modifications and list of many drugs like insulin, biguanides, sulfonylureas and thiazolidinediones which lower glycemia by various mechanisms [4]. Few of these have limited efficacy, limited tolerability and many side effects. Another problem is that many patients who respond initially become refractory to treatment over time because of progressive loss of β cell mass in type 2 diabetes with an increase in β-cell apoptosis as a result these drugs fail to maintain glycemic levels [5].

Proton pump inhibitors (PPIs) are widely used for the treatment of gastric acid-related diseases such as peptic ulcer disease and gastroesophageal reflux disease [6]. It acts by irreversibly binding to the H+/K+ ATP pump to inhibit the final step in gastric acid secretion and lead to consistent endogenous

hypergastrinemia via negative feedback effect [7]. Gastrin is reported to have incretin-like stimulating actions on beta cells and can influence glucose - insulin homeostasis [8]. Studies on animal model (rodents) and some in vitro studies have demonstrated that gastrin induces islet β-cell neogenesis [9,10] and increases the β-cells mass[11]. Tellez N et al [12] also reported gastrin effect on β cell regeneration, survival, increased beta cell mass and improved glucose tolerance in 95% pancreatectomised rats and thereby suggesting a potential role of gastrin in the treatment of diabetes. There are few studies on PPIs and diabetes, but their results are not consistent. Some clinical studies showed negative results on glycemic control by PPI in patients of T2DM [13], few studies have interestingly demonstrated an improvement of glycemic control by PPI [14,15]

Data on the relationship between PPI therapy and glycemic control is scanty in the literature, therefore present study is undertaken to see any possible role of PPI as adjunctive therapy in achieving better glycemic control in patients of T2DM.

Methods: An observational study was conducted in settings of tertiary care hospital from period May 2018 to April 2019. Ethical approval was obtained from the Institutional Ethics Committee for conducting the study. Subjects with type 2 diabetes (According to the American Diabetes Association [16] venous blood glucose values higher than or equal to 7 mmol/l ≥126 mg/dl) visiting the department of medicine during their outpatient visits or admitted in medicine ward for some complaint, during the 12-month study period were screened. 195 subjectsof T2DM, aged 40 years and above, maintained on oral anti diabetic therapy and satisfying the inclusion criteria were included randomly in the study. After selecting the subjects, the purpose of the study was explained to each subject and written informed consent was taken. The selected subjects for the study were interviewed so as to ensure privacy and all the information collected was incorporated on a pretested, predesigned semi structured questionnaire prepared for the study purpose. History regarding demographic profile, personal history, history of PPI intake, its type, any significant past medical history was enquired. Subjects were divided into three groups, consisting of two study groups and one control group. The study groups were further divided according to the type of PPI they were prescribed for their acid related ailments. Group I on Pantoprazole 40mg /day orally & group II on Rabeprazole 20mg /day orally for 12weeks. The defined daily dose (DDD) recommended by the World Health Organization of 40mg per day was used to quantify usage for pantoprazole; and 20mg per day for rabeprazole usage. Those taking 80% of the drug were considered compliant. T2DM subjects with no PPI intake were included in the control group.

Subjects were reviewed for no new change in dose of drug, addition of new drugs or change in lifestyle and dietary habits. Clinical records were screened for values of fasting blood sugar & glycosylated haemoglobin (HbA1c) at baseline i.e., before the start of study & after 12 weeks. Fasting blood glucose was measured by glucose oxidase method and HbA1c levels by a high-performance liquid chromatography.An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. The HbA1c is now recommended as a standard of care for testing and monitoring diabetes, and for assessing the efficacy of anti-diabetic medications specifically the type 2 diabetes [17].

Exclusion criteria: Past and current users of insulin, subjects with history of liver disease, renal disease, or any complication of diabetes were excluded from the study.

Statistical Analysis: The information collected was compiled, tabulated and analysed. Descriptive statistics were used for the demographic and anthropometric measurements. Data was analysed using open epi info. Data presented as mean ± SD. Statistical tests like chi-square tests (for qualitative data) and ANOVA (quantitative data) were applied. It compared glucose & HbA1c levels of those taking PPIs and those not taking PPIs by paired t tests to find the significance of difference between the groups. $p< 0.05$ was considered as statistically significant.

Results: Following observations were made from the study of glycemic levels in the study groups and the control group. A total of 221 subjects of T2DM were enrolled for the study. Out of these, 195 subjects were included in the study who met the inclusion criteria. 65 subjects who were prescribed pantoprazole were included in group I, 64 subjects who were prescribed rabeprazole were included in group II and 66 were included in the control group/comparative group.

Table 1: Comparison of various physical parameters among study groups (Group I &II) & controls

Physical parameters	Pantoprazole users(n=65) Grp I	Rabeprazole users (n=64) Grp II	No PPI intake (n=66) Controls	F	p
Age (years)	63 .16 ± 8.82	60.25 ± 11.24	61.69± 11.81	F = 0.452	0.638
Gender					
Male	34	31	32	X^2 =0.25	0.87
Female	31	33	34		
Weight (kg)	71.60 ± 9.85	70.54 ± 7.44	70.69 ± 8.30	F = 0.110	0.896

*p<0.05 - statistically significant

On comparison of various physical parameters among study groups (Group I & II) & controls, the mean age of the subjects taking pantoprazole in years is 63.16 ± 8.82, rabeprazole users 60.25 ± 11.24 & control group is 61.69± 11.81. There was no difference among the three groups based on mean age and mean weight. Further the distribution of males and females in the three groups were random and the difference was not significantly significant . (Table 1).

Table 2: Comparison of blood parameters among study groups (Group I & II) & controls at Baseline i.e., at the start of the study.

Blood parameters	Pantoprazole users Grp I	Rabeprazole Users Grp II	No PPI Intake Controls	F	p
Fasting blood glucose	142.63 ± 14.29	140.27 ± 17.72	141.01 ± 13.54	0.155	0.857
HbA1c	6.92 ± 0.49	6.72 ± 0.61	6.69 ± 0.49	1.417	0.249

*p<0.05 - statistically significant

At the base line the mean fasting blood glucose of those in group I (142.63 ± 14.29) was slightly more than those in group II and controls however this difference among three groups failed to achieve statistical significance (p=0.857). Those included in group I had HbA1c, 6.92 ± 0.49 followed by in group II and controls, but this difference among the three groups was not statistically significant (p=0.24) (Table 2).

Table 3: Comparison of blood parameters among study group (Group I & II) & controls after 12 weeks.

Blood parameters	Pantoprazole users Grp I	Rabeprazole users Grp II	No PPI intake Controls	F	p
Fasting blood glucose	135.75 ± 11.9	135.17 ± 13.7	140.29 ±14.8	1.085	0.343
HbA1c	6.55 ± 0.54	6.45 ± 0.62	6.61 ± 0.54	0.452	0.638

*p<0.05 - statistically significant.

On analysis of various parameters after 12 weeks, it was found that the fasting blood glucose was more in control group (140.29 ±14.8) followed by almost similar values of blood glucose in group I and II. Similar trend was seen for HbA1c where the controls had highest values (6.61 ± 0.54) followed by those in group I and II. For both these parameters using Anova, the difference among groups was not statistically significant (p=0.343, 0.638) (Table 3).

Table 4: Comparison of blood parameters at base line & at 12 weeks within the three groups- Grp I, Grp II & controls.

Blood parameters	Pantoprazole users Grp I	Rabeprazole users Grp II	No PPI intake Controls
Comparison of FBS at base-line & at 12 weeks	Change=6.88±5.53 t = 6.215 p = 0.000*	Change=5.10±0.26 t =3.327 p = 0.003*	Change= 0.71±8.49 t=0.432 p=0.670
Comparison of HbA1c at baseline & at 12 weeks	Change=0.37±0.40 t = 4.660 p = 0.000*	Change=7.50±0.33 t = 3.891 p = 0.001*	Change= 0.08±0.29 t = 1.382 p = 0.179

*p<0.05 - statistically significant.

Table 4 provides the details of comparison of blood parameters at base line & at 12 weeks within the three groups - Grp I, Grp II & controls. Comparison of fasting blood glucose and HbA1c at baseline and at 12 weeks for group I and group II using paired t test showed that in both the groups there was a statistically significant change for both these parameters (group I=0.00 & 0.00 respectively; group II=0.00 &0.00 respectively.) thereby implying better blood glucose control. In the control group comparison of values at base line and at 12 weeks for fasting blood glucose and HbA1c did not show any statistically significant difference (p=o.67, 0.17 respectively) thus indicating not much improvement.

Discussion

T2DM is a progressive disease characterised by increasing dysfunction of pancreatic beta cells through inactivation or apoptosis with worsening glycemia over time. Successfully managing diabetes is a great challenge since current treatments do not achieve long term adequate glycemic control leading to annoyance, disappointment and patient usually become non compliaint. New therapeutic entities that can halt the progress of disease and increase the functional activity of beta cells have recently gained interest and are the centre of research hotspot in area of Type 2 diabetes therapeutics.

The present study was undertaken to see the beneficial effect of PPI on glycaemic control in patients of T2DM. In our study on 195 Type 2

diabetic subjects, 129 T2DM subjects with PPI intake showed improvement in fasting blood glucose and HbA1c levels. On comparison between the three groups after 12 weeks, it was found that fasting blood glucose & HbA1c levels were more in the control group followed by decrease in the values of these parameters in the study groups. But the difference among the groups was not statistically significant (p=0.343, 0.638). Hove et al [18] also reported decrease in HbA1c levels in their study but the difference was not statistically significant. Comparison of values at base line and at 12 weeks in both the study groups (among PPI users) were significant. The change in the levels of fasting blood glucose of 6.88±5.53 (p= 0.000*) & HbA1c of 0.37±0.40 (p= 0.000*) were seen in subjects with pantoprazole intake. Significant change in fasting blood glucose levels of 5.10 ± 0.26 (p = 0.003*) & HbA1c levels of 7.50 ± 0.3 (p=0.001*) was also observed in subjects who took rabeprazole. The results of our study are in consistent with Singh et al [19] who evaluated the effect of pantoprazole therapy on glucose-insulin homeostasis in patients with T2DM and showed that 12 weeks of pantoprazole therapy significantly reduced HbA1c levels and increased gastrin and insulin levels. Mefford and Wade's [20] also reported significantly lower mean glycosylated hemoglobin in patients with type 2 diabetes who previously had been prescribed PPI vs those not taking PPI. Similarly, Boj-Carceller et al [21] reported that HbA1c was significantly different in T2DM patients who received PPI compared with those who did not received PPIs. On the contrary, Han N et al [22], Hove et al [23] reported negative results on glycemic control by PPI & did not obtain statistically significant differences in their study.

Proton pump inhibitors (PPIs) are among the most prescribed drugs worldwide. The effects of PPIs on blood glucose levels & HbA1c could be by a mechanism similar to incretin-based therapies. PPIs may share most of the glucoregulatory effects of incretin-based therapies by increasing gastrin levels which in turn stimulates β-cell growth and neogenesis and enhances glucose-stimulated insulin release, i.e., exerts an incretin-like effect [24]. Additionally, PPI's also delays gastric emptying, thereby providing conducive ambience for incretin hormone secretion and thereby resulting into decrease postprandrial glucose levels [25,26]. F. Incietal [27] in his study observed increased in beta cell function with reduction in values of fasting blood glucose, HbA1c and increase in log-HOMA-B, c-peptide & proinsulin levels. Results of PPI are somewhat milder or similar compared with antidiabetic drugs such as Dipeptidyl dipeptidase-4 (DDP-4) inhibitors or sodium-glucose transporter 2 inhibitors [28,29]. This suggest PPI have the potential to achieve better glycemic control in patients of T2DM already on oral hypoglycaemics. Lifestyle modifications with focus on healthy dietary habits, exercise for weight management, diabetes education should be incultated in diabetic subjects for better glycemic control.

Limitation of our study:

The limitation of our study is that we could not measure serum gastrin and serum insulin levels due to resource constraints as these tests are not done in our hospital. Although PPIs may be possible candidates for a new approach in the therapy of T2DM, a prospective, long-term, randomised double-blind controlled clinical study on large number of patients is warranted to establish the effect of PPIs on glycemic control.

Conclusion

This study provides insight into the potential of PPI for improvement in glycemic control when taken for 12wks in subjects of Type 2 DM for their acid related ailment & could be a new therapeutic approach with a good profile- no hypoglycemia events, good tolerability and safety in patients of T2DM.

Acknowledgements: Authors would like to thank all the participants for their kind cooperation in conducting the study and all those who directly or indirectly were helpful in the study.

Financial Support & sponsorship: Nil

References

1. Expert Committee on the Diagnosis and classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis & Classification of Diabetes Mellitus. Diabetes care 1997; 20: 1183-1197.
2. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res, 2007;125: 217-230.
3. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ. 2000; 321(7258):405-12.
4. Powers AC. Diabetes Mellitus in: Longo DL, Kasper DL, Jameson JL, Fauci AS,Hauser SL, LoscalzoJ. (Eds) 18th edition. Harrison's Principles of Internal Medicine. The Mc Graw Hill Companies, USA, 2012; 2968-3009.
5. David EM. New drug targets for type 2 diabetes and the metabolic syndrome. Nature, 2001;414:821-827.
6. Zhag JX, Ji MY, Song J, Lei HB, Qiu S, Wang J, Ai MH, Wang J, Lv XG, Yang ZR, Dong WG etal. Proton pump inhibitor for non-

erosive reflux disease: a meta-analysis. World J Gastroenterol. 2013 Dec 7; 19(45):8408-19.
7. Sanders SW, Tolman KG, Greski PA, Jennings DE, Hoyos PA, Page JG. The effects of lansoprazole, a new H+, K(+)-ATPase inhibitor, on gastric pH and serum gastrin. Aliment PharmacolTher. 1992; 6:359–372.
8. Rehfeld JF, Stadil F. The effect of gastrin on basal- and glucose stimulated insulin secretion in man. J Clin Invest 1973; 52:1415-26.
9. Rooman I, Lardon J, Bouwens L. Gastrin stimulates beta-cell neogenesis and increases islet mass from transdifferentiated but not from normal exocrine pancreas tissue. Diabetes, 2002; 51:686–690.
10. Suarez-Pinzon WL, Yan Y, Power R, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin increases beta-cell mass and reverses hyperglycaemia in diabetic NOD mice. Diabetes. 2005; 54:2596–2601.
11. Suarez-Pinzon WL, Lakey JR, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin induces neogenesis of human islet {beta}-cells from pancreatic duct cells and an increase in functional {beta}-cell mass. J Clin Endocrinol Metab.2005; 90: 3401– 3409.
12. Téllez N, Joanny G, Escoriza J, Vilaseca M, Montanya E. Gastrin Treatment stimulates β-cell regeneration and improves glucose tolerance in 95%pancreatectomized rats. Endocrinology,2011;152:2580–2588.
13. Hove KD, Brøns C, Færch K, Lund SS, Petersen JS, Karlsen AE, Rossing P, Rehfeld JF, Vaag A. Effects of 12 weeks' treatment with a proton pump inhibitor on insulin secretion, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes: a randomised double-blind prospective placebo-controlled study. Diabetologia. 2013; 56:22–30.
14. Barchetta I, Guglielmi C, Bertoccini L, Calella D, Manfrini S, Secchi C, Pozzilli P, Cavallo MG. Therapy with proton pump inhibitors in patients with type 2 diabetes is independently associated with improved glycometabolic control Acta Diabetol 2015 Oct;52(5):873-80.
15. Crouch MA, Mefford IN, Wade EU. Proton pump inhibitor therapy associated with lower glycosylated hemoglobin levels in type 2 diabetes. J Am Board Fam Med. 2012; 25:50–54.
16. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes care. Jan 2002; 25(Suppl 1):S5-20.
17. World Health Organization (WHO) Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus Abbreviated Report of a WHO Consultation. Geneva: WHO; 2011.
18. Hove KD, Færch K, Bödvarsdóttir TB, Karlsen AE, Petersen JS, Vaag A. Treatment with a proton pump inhibitor improves glycaemic control in type 2 diabetic patients - a retrospective analysis. Diabetes Res Clin Pract. 2010; 90: e72–e74.
19. Singh PK, Hota D, Dutta P, Sachdeva N, Chakrabarti A, Srinivasan A. Pantoprazole improves glycemic control in type 2 diabetes: A randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2012; 97: 2105-8.
20. MeffordIN, WadeEU. Proton pump inhibitors as a treatment method for type II diabetes. Medl Hypotheses 2009; 73: 29–32.
21. Boj-Carceller D, Bocos-Terraz P, Moreno-Vernis M, et al. Are proton pump inhibitors a new antidiabetic drug? A cross sectional study. World J Diabetes 2011; 2:217–220.
22. Han N, Oh M, Park SM, Kim YJ, Lee EJ, Kim TK, Kim TN, Kwon MJ, Kim MK, Lee SH, et al. The effect of proton pump inhibitors on glycated hemoglobin levels in patients with type 2 diabetes mellitus. Can J Diabetes. 2015; 39:24–28.
23. Hove KD, Brøns C, Færch K, Lund SS, Petersen JS, Karlsen AE, et al. Effects of 12 weeks' treatment with a proton pump inhibitor on insulin secretion, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes: A randomised double-blind prospective placebo-controlled study. Diabetologia 2013; 56:22-30.
24. Wang TC, Bonner-Weir S, Oates PS, et al. Pancreatic gastrin stimulates islet differentiation of transforming growth factor alpha-induced ductular precursor cells. J Clin Invest.1993; 92: 1349-1356.
25. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care.2009; 32:193–203.
26. Peters A. Incretin-based therapies: review of current clinical trial data. Am J Med. 2010; 123: S28–S37.
27. F.Inci, M. Atmaca, M. Ozturk, S. Yildiz, R. Koceroglu, R. Sekeroglu, S. H. Ipekci & L. Kebapcilar. Pantoprazole may improve beta cell function and diabetes mellitus. Journal of Endocrinological Investigation volume 37, 201 4: 449-454.
28. Nauck MA, Vilsboll T, Gallwitz B, Garber A, Madsbad S. Incretin-based therapies: viewpoints on the way to consensus. Diabetes care. 2009; 32 Suppl 2: S223-S231.

29. Whalen K, miller s, Onge ES. The Role of Sodium-Glucose Co - Transporter 2 Inhibitors in the Treatment of Type 2 Diabetes. Clin Ther. 2015; 37: 1150-1166.