ORIGINAL ARTICLE

Synergistic Effects of Omeprazole and Metformin on Glycemic Control in Type 2 Diabetic Patients. A Randomized Clinical Study

Fizzah Ali[1], Moosa Khan[2], Kausar Aamir[1] and Muhammad Azhar Mughal[2]

ABSTRACT

Objective: To evaluate the synergistic effects of omeprazole and metformin on glycemic control among patients with type 2 diabetes.
Method: This randomized interventional clinical study was conducted in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah post graduate medical Centre Karachi. Total study period was 10 months (august 2014-June2015) with individual study period of 3 months (90 days), Eighty(80) type 2 diabetic patients (40 in each group) of either sex, ages ranged from 30 to 60 years without any known co-morbidities were included. Group-A was treated with metformin alone and Group-B was treated with metformin plus omeprazole. Efficacy was evaluated by means of FBG, and HbA1C.
Results: Out of 80 patients, 74 had completed the study. Group B showed significant reduction (P=0.001) in terms of FBS and HbA1c level when comparison was done on day 90 with Group A and within group as compared to day 0.
Conclusion:-Addition of proton pump inhibitor with metformin was found effective in achieving better glycemic control in type 2 diabetic patients.

Key words: Proton pump inhibitor, omeprazole, metformin, HbA1C, FBG, SGPT.

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INTRODUCTION

Diabetes mellitus is a heterogeneous multifactorial /endocrinological disorder having defect in pancreatic beta cells leading to absolute or relative deficiency of insulin. Globally approximately 285 million people in the age bracket 20-79 have diabetes with 70% of burden in developing countries. This number will probably rise to 438 million by 2030. Diabetes mellitus is one of the serious health issues worldwide with higher prevalence of type 2 diabetes in developing countries[1]. Pakistan ranked on 7th position globally with 7.6% to 11% population suffering from diabetes which will increase to around 15% by 2030[2].

The underlying cause behind this aggression of diabetes is sedentary life style, ageing, urbanization and eating habits. Environmental factors and genetic components can influence the disease[3]. Management of diabetes can not be achieved using pharmacotherapy only, rather should be done on broad spectrum. Patient should be educated regarding nutritional requirements, exercise plans, acute & chronic complications and blood glucose monitoring.[4] Different oral hypoglycemic drugs have been used, in order to achieve an optimal HbA1C level and to avoid long term complications combination therapies should be used. Medications that can act synergistically are preferred. Individual therapies alone can not improve pathophysiological effects. According to the UK Prospective Diabetes Study (UKPDS) after certain time an adjunctive treatment is always needed to normalize HbA1C level and in such cases add on therapies should be started.[5]

1 Department of Pharmacology & Therapeutics, Basic Medical Sciences Institute Jinnah Postgraduate Medical Centre Karachi, Pakistan.

2 Basic Medical Sciences Institute Jinnah Postgraduate Medical Centre Karachi, Pakistan.

Correspondence: Dr. Fizzah Ali, Department of Pharmacology & Therapeutics, Basic Medsical Sciences Institute Jinnah Postgraduate Medical Centre Karachi.

Email: fizzah.saqib@gmail.com

Proton pump inhibitors are widely used in acid peptic diseases with good safety profile[6]. They are indicated in acid peptic diseases. It can influence the plasma insulin level by unknown mechanism and improve glycemic control in diabetic patients.[7] Some studies have suggested their role via gastrin secretion. Gastrin resembles to incretin hormone and has stimulating effects on Pancreatic β-cells causing insulin secretion so proton pump inhibitors can reduce glycemia just like incretin based therapy i.e. increase islet-cell mass, slow gastric emptying, and decrease glucagon level.[8]

Few studies have been conducted to evaluate the role of proton pump inhibitors as antidiabetic drug. Most of the researches have been done on retrospective data. Furthermore, despite both drugs are widely used literature review failed to show details regarding their safety profile.

Therefore a prospective clinical trial was needed to explore the synergistic effects of metformin and omeprazole along with their safety profiles.

MATERIAL & METHODS

This randomized interventional clinical study was conducted in the Department of Pharmacology and Therapeutics Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre Karachi in collaboration with a diabetic clinic 'Memon Diabetic Center, Karachi' and Medical Unit (Ward-7), Jinnah Postgraduate Medical Centre, Karachi after duly approved by Ethical Committee. All diagnosed type 2 diabetic patients of both sexes with age ranging from 30 to 60 years having HbA1C between 7% to 8% were included.[9] The exclusion criteria included all decompensated diabetic patients, type 1 diabetics and patients with co-morbidities like cardiovascular disorder, liver disease, kidney diseases or pregnancy. Patients having symptoms of gastric discomfort were included in group B. Gastric discomfort was evaluated on behalf of questionnaire. Questions regarding symptoms of abdominal bloating, abdominal pain, indigestion, burning with empty stomach and loss of appetite were evaluated. Sample size was calculated on the basis of previous study[9] using computer program "Open Epi version 2"[10]. Formal consent was also obtained from all the study participants. Patients fulfilling the study criteria were selected and randomly assigned to two groups of 40 subjects (group A and B). The personal data of the patients, history of disease and baseline investigations were collected before starting the medications.

Group-A included diabetic patients without gastric symptoms and were treated with metformin 500 mg twice daily half an hour before meal. Group-B included diabetic patients with gastric discomfort symptoms and were dispensed with metformin 500 mg twice daily and omeprazole 20 mg twice daily. Glycemic control of each group was evaluated and compared on the basis of HbA1C and blood sugar levels. Blood samples were collected at the time of enrollment and follow-up visits, fasting blood glucose were assessed on day 0, day 30, day 60 and day 90 by the glucose oxidase method. Serum HbA1C (by using HPLC (Bio-Rad D10), Serum creatinine and liver function tests were assessed at day 0 and day 90.

The data was recorded and analyzed by using SPSS computer software version 16.0. The results were given in the text as Mean and Standard Deviation for quantitative variables (FBG, HbA1C,) and percentage/proportion for qualitative variables like gender, symptoms, adverse effect etc, and an analysis of variance (ANOVA) was used for quantitative variables. P-value < 0.05 was considered as significant.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

RESULTS

Eighty patients were initially enrolled and were divided into two groups. Six (6) patients were dropped out due to loss of follow up. The study revealed no significant difference (P>0.05) between two groups in term of demographic data (age, sex, weight, height and BMI).

Table 1 shows fasting blood sugar levels & glycated hemoglobin levels at day 90 which were comparable at baseline. There was no significant difference between both groups regarding fasting blood sugar levels and glycated hemoglobin (HbA1C) at day 0. After 3 months of treatment mean fasting blood sugar level (mean±S.D) in group B was 115±9.6 mg/dl and in group A was 135±14.9 mg/dl with significant P value of 0.001. Similarly the mean level of HbA1c (mean±S.D) in group B was 7.40±0.36 as compared to group A 7.75±0.23 with P value of 0.001 at day 90. When safety profile were compared no significant differences (P>0.05) were found in serum creatinine, serum

bilirubin, alkaline phosphatase and SGPT levels at day 0 and at the end of therapy as shown in Table-2. Symptoms and adverse effects at day 0 and day 90 are depicted in Table-3. There was a gross percentage reduction of symptoms in combination therapy at the end of the study except reduction in appetite was noticed with the omeprazole therapy.

Table 1: Comparison of treatment effect on Fasting Blood Glucose in Group-A and Group-B

Variables	Group A (Metformin) (n=35) Mean ± S.D	Group B (Metformin+PPI) (n=39) Mean ± S.D
Fasting Blood Sugar		
Day 0	140 ± 12.4	141 ± 7.9
Day 90	135 ± 14.9	115 ± 9.6*?
P-value	0.144	0.001
HbA1c		
Day 0	7.77 ± 0.21	7.72 ± 0.24
Day 90	7.75 ± 0.23	7.40 ± 0.36 *
P-value	0.614	0.001

* Statistically significant (p<0.05)

Table 2: Safety Profile of Treatment Drugs In Group A & B

Variables	Group A (Metformin) (n=35) Mean ± S.D	Group B (Metformin+PPI) (n=39) Mean ± S.D	P-value
Creatinine			
Day 0	10.72 ± 0.13	0.76 ± 0.09	0.152
Day 90	0.72 ± 0.14	0.77 ± 0.10	0.069
P-value	0.921	0.058	-
Bilirubin			
Day 0	0.68 ± 0.08	0.72 ± 0.10	0.052
Day 90	0.67 ± 0.09	0.71 ± 0.11	0.074
P-value	0.133	0.355	-
Alkaline Phosphates			
Day 0	212 ± 28.9	221 ± 22.9	0.120
Day 90	209 ± 27.1	219 ± 21.8	0.085
P-value	0.154	0.317	-
SGPT			
Day 0	33.3 ± 5.82	36.4 ± 9.64	0.107
Day 90	32.9 ± 6.08	36.1 ± 9.07	0.081
P-value	0.481	0.671	-

* Statistically significant (p<0.05)

Table 3: Comparison In Improvement In Diabeti Symptoms And Adverse Effects In Group A And B

	Group A (Metformin) (n=35)		Group B (Metformin+PPI) (n=39)	
Adverse effect	Day 0	Day 90	Day 90	Day 0
Intense thirst	5(14.3%)	3(8.6%)	-	5(12.8%)
Decrease appetite	4(11.4%)	1(2.9%)	6(15.4%)	2(5.1%)
Nausea/vomiting	4(11.4%)	1(2.9%)	-	-
Abdominal pain	-	4(11.4%)	5(12.8%)	38(97.4%)
Frequent urination	7(20.0%)	2(5.7%)	3(7.7%)	3(7.7%)
Blood sugar >300mg/dl	2(5.7%)	-	-	2(5.1%)
Light headedness	7(20.0%)	-	-	8(20.5%)
Weakness	8(22.9%)	-	-	4(10.4%)
Intense hunger	6(17.1%)	5(14.3%)	-	5(12.8%)
Loss of consciousness	-	-	-	-

DISCUSSION

This clinical trial was conducted to evaluate the role of a proton pump inhibitor (omeprazole) on glycemic levels along with metformin therapy. Three months of omeprazole therapy significantly improved fasting blood glucose levels and HbA1c levels. Many authors have suggested beneficial role of proton pump inhibitors on glycemic levels. [7 -8]

Inci et al found improvement in fasting blood glucose and HbA1c levels when proton pump inhibitors were given to type 2 diabetic patients receiving only metformin therapy.[11] In the study of and similar[7] results were observed. Patients receiving metformin plus proton pump inhibitor had better HbA1C levels (6.6%) as compared to metformin monotherapy (7.3%), [12] Singh et al and Barchetta et al in their studies also demonstrated role of proton pump inhibitors and found improvement in HbA1c levels[13,8] Similar decline was also seen when proton pump inhibitors were initiated on diabetic rodents with the mean HbA1C level (7.7±0.6%) as compared to other group (10.3±0.5%,p<0.05).[14]

Boj-Carceller D, et al and Crouch MA, et al found insignificant changes with the synergistic use of proton pump inhibitors and metformin therapy despite of achieving decline in glycated hemoglobin in combination therapy.[15, 9]

In contrast to present study, Han N, et al found an inverse relationship. Increased HbA1c levels were noticed when metformin was given in combination with a PPI (7.34%) as compared to metformin monotherapy (6.97%).[16]

The results obtained from present clinical trial and previous studies suggest that proton pump inhibitors can influence the glycemic levels by unknown mechanisms. They probably act by binding covalently with hydrogen potassium ATPase pump (H+/K+-ATPase pump) and suppress gastric acid secretion,[6] when gastric acid suppresses, as a negative feedback mechanism gastrin levels increases.[17, 13] This mild to modest hypergastrenemia is somehow related with better glycemic control.[18] In rodents increase in gastrin levels was found associated with beta-cell neogenesis [14, 18], though in human beings this role is still unclear. Hypergastrenemia is also related with delayed in gastric emptying seen with PPI use.[19] Delayed emptying is related with decrease appetite, which is more obvious with use of PPI's. When symptoms and adverse events were monitored only mild adverse effects were noticed without any serious event in both groups. Majority of the symptoms are reflection of glycemic control. After achieving better glycemic levels symptoms also get improved in the combination therapy but decrease appetite was noticed profoundly. Hirst et al concluded more adverse effects including gastrointestinal events such as nausea, vomiting, diarrhea, flatulence and abdominal pain associated with metformin monotherapy as compared to other agents. [20] These findings are consistent with present study. We found frequent gastrointestinal complains in group A as compared to group B. Decrease in appetite was found among omeprazole users, this decrease in appetite is probably due to ghrelin suppression that is inversely correlated with rise in gastrin. Ghrelin is a gastric, hunger hormone which is responsible for appetite control.[21] Proton pump inhibitors most probably suppress appetite via this mechanism. Hypergastrenemia can also stimulate the secretion of GLP-1 (Glucagon-like peptide) from intestinal L-cells and can influence glucose homeostasis[22] In addition to these mechanisms; Proton pump inhibitor acts by increasing the PH thus provides an appropriate environment for the absorption of metformin resulting in better Area Under the Curve (AUC) and Cmax value[23]. Probably both drugs are showing synergism as this can be another reason for achieving good glycemic reduction.

There are very few studies on the combination of metformin and omeprazole therapy. Literature regarding their safety profile is very scanty. Proton pump inhibitors are overall perceived as safe drugs .In majority cases their safety profile is similar to control .[12] Some studies revealed positive correlation of proton pump therapy with increase creatinine levels .[24,25] In our study, we analyzed creatinine levels and found non significant increase in serum creatinine levels with the use of omeprazole therapy. Probably long term monitoring is needed. Up to our knowledge safety profile of this combination is not been analyzed. In current study no significant changes in liver function tests were noticed. Serum glutamic pyruvic transaminase, serum bilirubin, serum alkaline phosphates were found unaltered after adding proton pump inhibitors. On behalf of this present study results, this combination apparently do not alter hepatic profile.

Limitations of the study:

Authors recommend further randomized clinical trialsto be undertaken for longer duration on bigger population, so that long term efficacy and safety could be evaluated.

CONCLUSION

Despite of inherent limitations we conclude that adding a proton pump inhibitor with metformin can augment it effects without producing any additional side effects.

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