

Comparison of hypoglycaemia episodes in people with type-2 diabetes fasting in Ramazan, treated with vildagliptin or sulphonylurea: Results of the Pakistani cohort of the VIRTUE study

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Abstract

Objective: To assess the effect of vildagliptin in comparison to sulphonylurea (SU) on hypoglycaemia in Muslim patients with type 2 diabetes mellitus fasting during Ramadan.

Methods: VIRTUE was a multicenter, prospective, observational study, which enrolled 244 patients from Pakistan who were re-analysed. All included patients were treated with vildagliptin (n=121) or SU (n=121) as add-on to metformin or as monotherapy for 16 weeks. The primary outcome of interest was to compare the proportion of patients with ≥ 1 hypoglycaemic event (HE) during fasting between vildagliptin and SU cohort. Changes in HbA1c and body weight and treatment adherence were also measured.

Results: Of the 244 patients enrolled, 120 patients in the vildagliptin cohort (99.2%) and 119 patients in the SU cohort (98.3%) completed the study. Patients experiencing at least one HE were fewer with vildagliptin when compared with SUs (5.8% vs. 14.2%; $p < 0.033$). The reduction in HbA1c was 0.3% with vildagliptin from a baseline of 7.6% and 0.1% with SU from a baseline of 7.4% (between-treatment difference: -0.1% $p < 0.054$). A reduction of 0.3 kg was seen with vildagliptin treatment vs. 0.2 kg weight gain in the SU group. Adverse events were experienced by 15.7% in the vildagliptin cohort and 17.4% in the SU group.

Conclusion: The treatment with vildagliptin was associated with fewer hypoglycaemic events compared with SUs and was well tolerated with good glycaemic and weight control in patients with T2DM fasting during Ramadan.

Keywords: DPP-4 inhibitor, Fasting, Hypoglycaemia, Ramadan, Type 2 diabetes mellitus, Vildagliptin, Sulphonylurea. (JPMA 64: 1297; 2014)

Introduction

Ramadan is the ninth month of the Islamic lunar calendar and fasting in Ramadan is one of the five pillars of Islam. All healthy, adult Muslims are obligated to fast from sunrise to sunset in which food, fluids, medications, drugs and smoking are prohibited during the daylight hours which can extend from 13 to 18 hours a day, depending on the geographical location and season.¹ During Ramadan fasting, glucose homeostasis is maintained by meals taken during night time before dawn and by liver glycogen stores.² Major changes in dietary habits, daily physical activities and sleeping patterns during Ramadan have significant impact on the glycaemic control, lipid profile, body weight and dietary intake.³ Patients with

type 2 diabetes mellitus (T2DM) can develop complications like hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration and thrombosis.⁴ Epidemiologic data from the first large retrospective study Epidemiology of Diabetes and Ramadan (EPIDIAR) conducted in 13 Islamic countries reported that a vast majority of patients with T2DM (79%) fasted for at least 15 days during Ramadan with a 7.5 fold increase in the incidence of severe hypoglycaemia and 5-fold increase in hospitalization due to hypoglycaemia.⁵

Therefore, guidelines recommend a pre-Ramadan meeting between patients with diabetes and their physicians to review lifestyle and therapeutic regimens, treatment individualization, regular monitoring of blood glucose levels, tailoring nutritional advice and providing Ramadan-focused structured education.⁴

However, there is no consensus about the most appropriate oral antihyperglycaemic agent(s) for patients with T2DM to use during Ramadan, as there is limited data assessing the efficacy and safety of these agents during Ramadan. Thus, choosing an antidiabetes agent is of particular concern in the coming decade as

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Ramadan will fall during the summer months, increasing the number of fasting hours and eventually raising the risk of negative effects in patients with diabetes who wish to fast.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of drugs that enhance glucose-dependent insulin secretion from pancreatic β -cells by preventing DPP-4 mediated degradation of endogenously released incretin hormones, represent a new therapeutic approach to the management of T2DM.⁶

Vildagliptin, a selective DPP-4 inhibitor, has been shown to be effective and well tolerated with a low incidence of hypoglycaemia in clinical trials up to 2 years in duration.⁷ The risk of hypoglycaemia with vildagliptin in Muslim patients with T2DM fasting during Ramadan is less when compared with sulphonylureas (SUs).⁸

In a small sample-size study of 52 fasting patients in predominantly Pakistani population from UK, vildagliptin has demonstrated significant reduction in hypoglycaemia incidence compared with SUs.⁹ However, there is need for more data in a sizeable population, particularly in Pakistan.

The observational study, Vildagliptin experience compared with sulphonylureas observed during Ramadan (VIRTUE), evaluated the effect of vildagliptin on hypoglycaemia compared with SU in T2DM on 1333 patients who fast during Ramadan in 10 countries. The data of the Pakistan cohort has been analysed independently and is being presented.

Methods

This was a multicenter, prospective, observational study that enrolled 244 consecutively patients from different centers of Karachi and Lahore. Patients from Bangladesh, Egypt, India, Pakistan, Indonesia, Malaysia, United Arab Emirates, Kuwait, Lebanon, Oman and Saudi Arabia were recruited for VIRTUE study. This study presents the results for patients from Pakistan. Eligible patients included 18 years of age or older with T2DM for at least 12 months prior to the start of Ramadan fasting, HbA1c $\leq 8.5\%$ (measured within 6 weeks prior to study entry), treated with vildagliptin or SU as dual therapy with metformin or as monotherapy for at least 4 weeks but not more than 3 years before fasting commenced.

Patients were excluded if they had contraindications to the medications of interest; require three or more oral anti-diabetes therapies or insulin therapy at the time of

study entry. Use of any investigational drugs at the time, or within 30 days or five half-lives, of enrolment was also prohibited.

During the observational period of 16 weeks, data from at least two visits were recorded for each patient: at baseline (up to 6 weeks prior to the start of fasting), and at the end of the study (within 6 weeks after the end of fasting). Data collection was also permitted during the observational period if the patient made an interim visit during the fasting period.

Study Assessments and Endpoints

The primary assessment was the proportion of patients who experienced at least one hypoglycaemic event (HE). Hypoglycaemia was defined as any reported symptoms by the patient and/or any blood glucose measurement <70.2 mg/dl (grade 1 or mild), or the need for third-party assistance (grade 2 or severe). Secondary assessments were the change in HbA1c and body weight and from screening visit (baseline) to the end of observational period, and treatment adherence. Safety assessments included monitoring and treatment of emergent adverse events (AEs), serious adverse events (SAEs) by the physician. If a patient did not record HEs or glucose readings, the number of HEs experienced was recorded by the physician at the end of observational period, as recalled by the patient. For reporting drug exposure during fasting and hypoglycaemia, patients were provided a treatment diary.

Statistical Analysis

For the primary assessment variable, based on 90% power and a two-sided significance level of 0.05, a sample size of 41 patients per cohort would be sufficient to detect a 40% difference between the proportions of patients experiencing at least one HE, tested with a two-group continuity corrected chi-squared test. The difference estimate is based on published incidences of HEs for patients receiving SU (60%) and vildagliptin ($\leq 20\%$).⁹

Of the 244 patients enrolled from Pakistan, 121 patients in each group received vildagliptin and SU. This compensated the loss to follow-up and provided a representative number of participants from all centers. The primary study variable was analyzed using a two-sided Fisher's exact test performed on data from all patients who received one dose of the medication of interest at the beginning of Ramadan and had at least one efficacy assessment after the start of fasting. Apart from HbA1c assessments, other assessments were performed on the safety of the population, consisting of all patients

who received at least one dose of the medication of interest at the beginning of Ramadan and had at least one safety assessment. HbA1c and body weight data were analyzed using a paired t-test between the baseline and last observation. Data was analyzed by DATAMAP GmbH, Freiburg, Germany using SAS®, Release 9.3 (SAS Institute Inc, Cary, NC).

Ethical approval was taken from the Institutional Review Board of Baqai Institute of Diabetology & Endocrinology, Karachi, Pakistan. A written informed consent was taken from all patients before start of the study.

Results

Of the 244 patients enrolled from Pakistan, 121 patients in each group received vildagliptin and SU; 2 patients did not receive medication of interest and were excluded from the analysis. Overall, 120 patients in the vildagliptin cohort (99.2%) and 119 patients in the SU cohort (98.3%) completed the study. The only reason for discontinuation in the vildagliptin group was death (n=1, 0.8%). Discontinuations in the SU group were due to an unsatisfactory therapeutic effect (n=1, 0.8%) and lost to follow-up (n=1, 0.8%).

The demographic and baseline characteristics of the patients are presented in Table-1. Sixty eight (56%) patients were males in each group, the mean age of patients was 43±12.1 years and maximum age 63, 74 years respectively in vildagliptin and SU cohort, mean body weight was 75.1±12.1 kg, mean BMI was 27.8±4.6 kg/m² and mean HbA1c at baseline was 7.5±0.5%. The mean duration of T2DM was 3.7±3.5 years. Vildagliptin with metformin was given to 108/121 (89.3%) patients and 112/121 (92.6%) received SU and metformin. The mean duration of exposure to the study drug during Ramadan was 29.9±0.8 days in the vildagliptin group and 30.0 (0.1) days in the SU group. Patients fasted for a mean of 27.9±4.0 days in the vildagliptin group compared with

Table-1: Patient demographic and baseline characteristics (Safety set).

Variable	Vildagliptin N=121	Sulphonylurea N=121	p-value
Age, years	40.1±11.8	45.9±11.8	<0.001*
<65, n (%)	121 (100)	117 (96.7)	>0.05**
Men, n (%)	68 (56.2)	68 (56.2)	>0.5**
Weight, kg	76.6±12.3	73.6±11.8	0.054*
BMI, kg/m ²	28.2±5.0	27.3±4.0	0.123*
Duration of T2DM, years	3.2±3.3	4.2±3.8	0.03*
HbA1c, %	7.5±0.51	7.5±0.6	0.999*

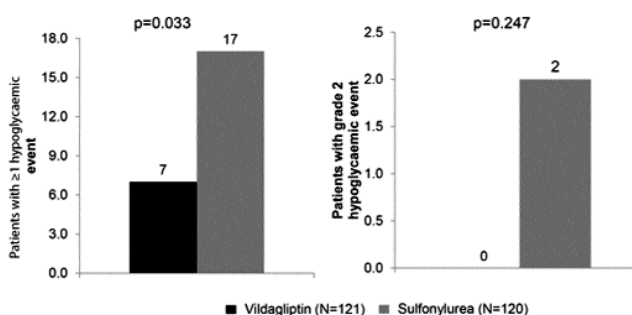
Values are mean±SD unless indicated otherwise. BMI, body mass index; HbA1c, haemoglobin A1c; SD, standard deviation; T2DM, type 2 diabetes mellitus.

* Two sample t-test **Chi-square test.

Table-2: Overall summary of adverse events (Safety set).

Event, n (%)	Vildagliptin N=121	Sulphonylurea N=121	p-value
Any AE	19 (15.7)	21 (17.4)	0.729
Any SAE	1 (0.8)	3 (2.5)	
Discontinuation due to AEs	0 (0.0)	0 (0.0)	
Deaths	1 (0.8)	0 (0.0)	
Most common AEs by preferred term*			
Hypoglycaemia	6 (5.0)	16 (13.2)	0.024
Nausea	5 (4.1)	2 (1.7)	
Abdominal pain	3 (2.5)	0 (0.0)	
Vomiting	3 (2.5)	0 (0.0)	
Abdominal discomfort	2 (1.7)	1 (0.8)	

AE, adverse event; SAE, serious adverse event. *≥1.7% in any group.



*Includes patients with a post baseline assessment of hypoglycaemic events

Figure-1: Number of patients with hypoglycaemic events (HEs) during Ramadan fasting (Primary analysis set)*.

28.0±3.5 days in the SU group.

The proportion of patients experiencing at least one hypoglycaemic event were fewer with vildagliptin (n=7/121, 5.8%) than in patients receiving SUs [n=17/120, 14.2%; individual SU drug types: glibenclamide (n=6/22, 27.3%), gliclazide (n=5/17, 29.4%), glimepiride (n=5/81, 6.2%) and glipizide (n=1/2, 50.0%)] (p<0.033) (Figure-1). No patient in the vildagliptin group experienced a severe (grade 2) hypoglycaemic event compared with two patients in the SU group (p<0.247).

The mean changes in HbA1c were -0.3% in the vildagliptin cohort (baseline 7.6%) and -0.1% in the SU cohort (baseline 7.4%), with a between-treatment difference of -0.1% (p=0.054). The change in body weight was -0.3 kg from a baseline of 76.6 kg in the vildagliptin group compared with 0.2 kg weight gain from a baseline of 73.6 kg in the SU group (between-treatment difference: -0.5 kg; p<0.08).

Treatment Adherence

The mean missed number of doses was similar between the two groups with 1.5 ± 3.2 and 1.9 ± 3.0 in the vildagliptin group and the SU group, respectively ($p < 0.318$). A lesser number of patients in the vildagliptin group required medication changes during Ramadan compared with the SU group (0.8% vs. 3.3%).

Safety

In this study, a total of 19 (15.7%) patients in the vildagliptin cohort and 21 (17.4%) patients in the SU group experienced AEs (Table-2). This was mainly driven by hypoglycaemia (vildagliptin: 6, 5.0% and SU: 16, 13.2%). The SAEs were reported in four patients in both the groups; myocardial infarction in one patient in the vildagliptin group and a transient ischaemic attack in one patient and hypoglycaemia in two patients in the SU group. However, none of the non-hypoglycaemic SAEs were suspected to be drug-related. One patient died in the vildagliptin group due to myocardial infarction and was not suspected to be related to the study drug.

Discussion

Majority of Muslim subjects with T2DM wish to fast during Ramadan, and therefore fasting has to be made as safe as possible for them. Studies conducted in Baqai Institute of Diabetology and Endocrinology to assess the glycaemic control and management of fasting in patients with diabetes during Ramadan have demonstrated that composite effect of modifications in active glucose monitoring, alteration of drug dosage and timing, dietary counseling, pattern of physical activity and patient education can enable patients to fast without major complications and reduce any serious complications associated with fasting during Ramadan.^{10,11} Another study conducted in Brent, UK, in 2008 showed that a structured pre-Ramadan education programme led to better metabolic control, through weight loss and significant decrease in HbA1c, whilst ensuring safer fasting by decreasing the risk of hypoglycaemia.¹²

The results from this prospective, observational study demonstrated that fewer patients with vildagliptin experienced hypoglycaemia compared with SU in patients with T2DM. The treatment with vildagliptin lowered HbA1c, was well adhered and had no effect on body weight. Hanif W et al. reported that during Ramadan fasting, treatment with vildagliptin resulted in better treatment adherence compared with SU in Muslim patients with type 2 diabetes mellitus.¹³

The low incidence of hypoglycaemia is consistent with findings reported previously with vildagliptin in a pooled

analysis of the VIRTUE study.⁸ This study also supports the results observed in the VECTOR study conducted in Muslim patients with T2DM from the UK which showed that the incidence of HEs was significantly lower in the vildagliptin group than in the SU group during Ramadan.¹⁴ VERDI study also showed the frequency of more severe and better-documented episodes (AE, severe event, event leading to unscheduled medical visit) were much lower, with consistently less events with vildagliptin therapy.¹⁵ Furthermore, the results of the present study support the findings from a UK retrospective audit conducted in North West London with Muslim patients of mostly Pakistani and Middle Eastern origins. The confirmed hypoglycaemic events (defined as blood glucose < 63 mg/dl with or without symptoms) recorded during Ramadan were much lower in patients receiving vildagliptin (7.7%) than in patients receiving gliclazide (61.5%).⁹ In addition to this, a study comparing sitagliptin and SU in patients with T2DM during Ramadan has been published. In an open-label study performed in Egypt, Israel, Jordan, Lebanon, Saudi Arabia and the UAE, the lower incidence of hypoglycaemia was observed in patients receiving sitagliptin ($n=507$, 8.5%) versus SU ($n=514$, 17.9%).¹⁶

The low risk of hypoglycaemia with vildagliptin is most likely due to the increased sensitivity and improved α - and β -cell responsiveness to glucose.¹⁷ Vildagliptin improves glucose-dependent insulin secretion and β -cell function¹⁸⁻²² and reduces meal-dependent glucagon secretion and increases hypoglycaemia-dependent glucagon secretion.²³

Treatment with vildagliptin resulted in slight reduction in HbA1c and body weight from baseline in the vildagliptin cohort. Although there was slight reduction in HbA1c with SU, it was associated with weight gain. However, it is difficult to draw a more definitive conclusion from this result because of the short duration of the study. A study from India on Muslim diabetes patients fasting during Ramadan reported greater reductions in HbA1c in vildagliptin group compared with the sulfonylurea group, although the mean FPG and PPG levels decreased significantly in both the groups.²⁴ Although hypoglycaemia is a significant barrier to treatment adherence,²⁵ the self-reported adherence in the present study was high in both the treatment cohorts ($> 96\%$).

There are certain limitations to the study. Firstly, as this was an observational study, there are inherent limitations and bias which are integral components of observational studies. The subjective reporting of HE and recording of HEs in the diary due to recall bias was a major limitation,

which can potentially under or overestimate the number of events due to subjectivity in perceiving symptoms of hypoglycaemia. The results of this study should be further verified by daily monitoring of glucose level to quantify hypoglycaemia. Other factors, which limits inferring of results are, varied eating practices among different cultures during Ramadan (2-4 meals).

Conclusion

The treatment with vildagliptin was associated with fewer hypoglycaemic events compared with SUs and both drugs were well tolerated with good glycaemic and weight control during Ramadan.

Authors' Contribution

All authors participated equally and substantially contributed to the acquisition and data collection; AND drafting the work or revising it; AND final approval of the manuscript; AND accountable for all aspects of the work. Dr. Athar Khan was involved in the review of the questionnaire, manuscript writing, drafting, final review and approval of manuscript especially the results and discussion part and also for the questions related to the accuracy. Three authors of pharmaceutical company were not involved in the data collection and analysis part that could be considered as conflict of interest.. They were responsible for designing, drafting, critical review and final review of manuscript.

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Conflict of Interest

Dr. Saeed A. Mahar, Dr. Imtiaz Hasan, Dr. Imran Hasan Khan, Dr. Asher Fawwad and Dr. Shakir Hussain have received honorariums and had consultancy agreement with Novartis Pharma Pakistan for conducting this trial. Dr. Athar Khan has received honorariums and had consultancy agreement with Novartis Pharma Pakistan for the initial manuscript drafting of this trial. Dr. Ahson Siddiqi, Dr. Kishore Kumar and Dr. Neeta Maheshwary are employees of Novartis Pharma Pakistan.

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