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Corresponding Author
Maaz Hussain Syed,
Department of Pharmacology, Indian Institute of Medical Science and Research and Noor Hospital, Jalna, India
dr_maaz_Syed@yahoo.com

Author Designation
[1]Assistant Professor
[2,4,5]Professor
[3]Associate Professor

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To Evaluate the Efficacy and Safety of Canagliflozin in Patients of Type 2 Diabetes Mellitus Inadequately Controlled on Maximum Dose of Three Oral Hypoglycemic Agents

[1]Quazi Zubair Zafar, [2]Maaz Hussain Syed, [3]Shaikh Huzaif, [4]Imran Nawaz Khan and [5]Shaikh Ubedullah
[1-5]Department of Pharmacology, Indian Institute of Medical Science and Research and Noor Hospital, Jalna, India

ABSTRACT
Control over hyperglycemia is essential in type 2 DM management to reduce the complications. Many patients with type 2 diabetes are over-weight or obese at the time of diagnosis. Weight reduction leads to improvement in glycemic control, lowers the HbA1c and risk of complications in patients with T2DM. SGLT-2 inhibitor Canagliflozin demonstrated reduction in blood sugar, HbA1c and body weight in clinical studies. It was a prospective, open label, single arm, single centre, interventional study in which each patient treated for 24 weeks. Patients with age between 18-65 years, have type 2 diabetes mellitus with HbA1c >8.5% and BMI > 25kg/m2 and on maximum dose of three OHA but inadequate response and willing to give written informed consent were included in the study. After 24 weeks of treatment, compared to baseline, mean HbA1c was decreased by -1.565% at 3 months and -3.02% at the end of 6 months interval. Mean FBS was reduced by 25.15mg/dL and 46.76mg/dL and mean PPBS was decreased by -54.34mg/dL and -87.41mg/dL after 3 and 6 months respectively. Mean change in HbA1c and fasting and postprandial blood sugar are statistically significant (P< 0.0001). We found significant reduction in mean weight (-4.313 Kg) at the end of 6 months treatment. Canagliflozin is effective and safe drug to decrease HBA1c, blood sugar and weight in type 2 Diabetes mellitus patients failed to respond triple drug therapy of oral hypoglycemic drugs.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease that develops due to defective insulin secretion and is frequently associated with insulin resistance[1]. It is characterized by progressively decreasing beta-cell function over a period of time[2]. It contributes to about 90-95% of all diagnosed cases of DM in adults and currently affects more than 61[3]. million Indian people that is more than 8% of the adult population[3,4]. Control over hyperglycemia is essential in T2DM management to reduce the complications and the target glycemic goals must be set different for every patient considering overall patient's risk factors and associated comorbidities[5,6]. At the time of diagnosis, many patients with type 2 diabetes are obese or fall in the category of over- weight. Obesity is a risk factor for worsening the disease and leads to complications like coronary heart disease (CHD). It is said that 1% HbA1c reduction benefit can be offset by 3 kg of weight gain this concept is known as kgA1c paradox. On the contrary, weight reduction has demonstrated improvement in glycaemic control and also lowers the risk of CAD in patients with T2DM[7-9]. Administration of insulin secretagogues and glitazones has also been associated with weight gain. It is observed that drugs which causes release of the insulin results in early sapping of ß cells and after sometime response to these drugs gradually decreased and insulin resistance increased[7-9]. As ß-cell dysfunction progress many patients ultimately required insulin therapy to control blood sugar level[10,11]. Usually, patient are not in favour to take the insulin treatment and hold up it for remarkable time leads to worsening of the disease[12,13]. Sodium glucose co-transporter 2 (SGLT2) and Sodium glucose co-transporter 1(SGLT1) reabsorb the glucose in the kidney, inhibition of these transporters results in decrease reabsorption of glucose in Kidney which ultimately reduces the blood glucose level[14]. In a normal healthy individual, 180 g of glucose is filtered and is reabsorbed on a daily basis with a maximum transport rate of 300 mg/min and this rate increases by about 20% in uncontrolled T2DM patients[15,16]. SGLT2 inhibitors work with an insulin-independent mechanism and have an advantage of increase glucose excretion via urine without inducing hypoglycemia and it also promotes weight loss because of excretion of glucose leading to loss of around 300-400 kcal/day[17-19]. These agents were approved for their use in diabetes in 2006 by US Food and Drug Administration (FDA). In phase-3 studies, SGLT2 inhibitor Canagliflozin along with reduction in HbA1c and body weight was well tolerated by most of the patients with T2DM[20]. We planned this study to evaluate the efficacy and tolerability of Canagliflozin in patients of type 2 Diabetes mellitus inadequately controlled on maximum dose of three oral hypoglycemic agents.

MATERIALS AND METHODS

The present study was performed in department of general medicine in collaboration with pharmacology department at a tertiary health care hospital in Aurangabad, Maharashtra. The study was open label, prospective, single arm, single center, interventional study in which each patient treated for 24 weeks. Study was started in November 2016 and continued for one and half year. Patients presented to the medicine OPD with type -2 DM were screened to enrol in the study. Both male and female patients, age between 18 to 65 years and diagnosed with Type 2 diabetes mellitus with HbA1c >8.5% and BMI >25kg/m2 and on maximum dose of three OHA but inadequate response and willing to give written informed consent were included in the study. Patients with Type 1 diabetes mellitus, newly diagnosed Type 2 DM and GDM were excluded from the study, Patients with history of IHD, CVA, CKD, hepatic disease and uncontrolled hypertension were excluded from the study. Patient with known allergy or hypersensitivity to study drugs and lactating ladies were also not included in the study.

Sample Size: Sample size (n) for the study was calculated using the following formula.

$$n = \frac{Z^2\, p\,(1-p)}{D^2}$$

Where, 'n' is the sample size, the value of Z is set to 1.96, which represent the level of errors of 5% (95% level of confidence), 'p' denotes the prevalence of the disease in given population, here prevalence is taken as 8%, 'D' is the margin of error (5%). So after putting the values, Z=1.96, p= 0.08, D=0.05, therefore, sample size came to be114 patients.

Methodology: After getting approval from the IEC, the present study was performed according to the protocol, Good Clinical Practice (GCP) guidelines, ICH, ICMR guidelines for Biomedical Research on Human Subjects and Declaration of Helsinki. After fulfilling the eligibility criteria, details of the study procedure explained to the patients in language best understood by them. Before enrolment in the study, each patient provided a written informed consent and the patients were given choice to withdraw at any time. Each patient received Tab Canagliflozin 100 mg once in a day for 6 months along with their ongoing oral hypoglycemic agents. The assessment of patients take place at baseline, 3 and 6 months. To evaluate the efficacy of the drug, these investigations were carried out, blood glucose (both fasting and post meal), glycosylated haemoglobin (HbA1C), mean change in BMI and serum creatinine. At the time of each visit, patients were instructed to came in OPD in morning after observing fast of 8-10 hours and blood samples were collected and above-mentioned laboratory tests

were performed. At the time of each visit all patients were asked for the occurrence of any adverse drug reaction (ADR). The objectives of the study are.

Primary Objective: To evaluate the efficacy of Tab Canagliflozin 100 mg in type 2 Diabetes mellitus patients failed to respond high dose of three oral hypoglycemic drugs.

Secondary Objective:

- To evaluate the effect of Tablet Canagliflozin 100 mg on mean change in BMI.
- To assess the safety of Tablet Canagliflozin 100mg.

Statistical Analysis: All the data entered into Microsoft Excel from case record form for analysis. For comparing quantitative data within the study groups repeated measures ANOVA were used. Fisher's exact test was performed to compare qualitative data between the study groups. 'Graph pad Prism 9' used for statistical analysis. The p value of <0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

Total 164 patients were screened to enrol the 125 patients according to sample size. 11 patients didn't come after the first visit. A total 114 patients completed the study. The assessment of patients take place at baseline, 3 and 6 months for fasting and post prandial blood sugar level, HbA1c, body weight and serum creatinine levels. In present study maximum number of patients have age between 41-50 years (33.3%) followed by age between 51-60% (30.7%). Mean age of the patients were 48.56 years (Table No 1). 55 patients were male and 59 patients were female, male to female ratio is 1: 1.07. At baseline mean fasting and post prandial blood sugar were 193.03 mg/dl and 299.50 mg/dl respectively. Mean HbA1c was 11.907%, mean weight of the patients was 87.094 Kg and mean serum creatinine was 0.9157mg/dL at baseline (Table No 2).

SGLT2 inhibitors work with an insulin-independent mechanism and have an advantage of increase glucose excretion via urine without inducing hypoglycemia and it also promotes weight loss because of excretion of glucose[17-20]. In the present study compared to baseline, mean HbA1c was decreased by -1.565% at 3 months interval and -3.02% at the end of 6 months and it was statistically significant (P<0.0001). HbA1c was more decreased in initial 3 months of treatment (-1.56% Vs-1.46%). In our study mean fasting blood sugar was reduced by 25.15mg/dL at 3 months and it was further decreased by 46.76 mg/dL at the end of 6 months treatment and this reduction was statistically significant (P<0.0001). Fasting plasma sugar value was more decreases in first 3 months of therapy as compared to 3-6 months (-25.15mg/dL Vs -23.61 mg/dL). Similarly, mean post-meal blood sugar was decreased by -54.34 mg/dL at 3 months and it was further reduced by -87.41 mg/dL at the end of 6 months treatment and this reduction was also statistically significant (P<0.0001). Post prandial blood sugar reduction more in initial 3 months (-54.34 mg/dL Vs -33.07mg/dL). We found significant reduction in mean weight of the patients at the end of 6 months treatment and this reduction is 4.313 Kg. Reduction was observed more in later 3 months period., -1.94 as compared to -1.89 kg from baseline to 3 months (P=0.0398). In our study mean serum creatinine was reduced by -0.057 mg/dL at 3 months and it was further decreased by -0.0961 mg/dL at the end of 6 months treatment and this reduction was statistically significant (P=0.0056). Canagliflozin inhibits SGLT2 in kidneys leads to increase excretion of sugar in urine results in decreased blood sugar and HbA1c level. Urinary excretion of glucose responsible for the calories loss which ultimately results in decrease weight of the patients.

Pattanaik[21,22] conducted a prospective study in 51 patients who received Tablet Canagliflozin 100 mg daily for the period of 3 months along with their ongoing 3 drugs treatment of Metformin, Glimepride and Teneligliptin. In their study HbA1c was decreased by 1.1 %, FBS decreased by 32.5 mg/dl, PPBS decreased by 109 mg/dl, BW reduced by 0.62 kg and mean serum creatinine reduced by 0.1 mg/dL and the decrease in HbA1c, FBS, PPBS, BW and serum creatinine were statistically significant. The results of our study are in accordance with the study of **Pattanaik**[22]. **Panikar**[23] conducted a study by adding Canagliflozin as a fifth drug to the ongoing four oral hypoglycemic agents in Asian Indian patients. They observed that the mean reduction in HbA1c value at 6 months was -1.63% (P<0.001), mean reduction in fasting blood sugar was -63.65 mg/dL (p<0.001) and PPBS was -79.28 mg/dL (P<0.001) and mean reduction in body weight was -3.03 kg (P<0.001). The results of their study are similar to our study[23]. In Phase-3, double blind RCT conducted by **Stenlof**[24] on 584 subjects by administering Canagliflozin 100mg/300mg/placebo once a day in three different groups for 26 weeks. HbA1c reduced by -0.77%, -1.03% and -0.14% at 26 weeks in these three groups respectively. HbA1c significantly reduced in patients who received Canagliflozin 100 or 300[24]. CANTATA-M and CANTATA-D were the RCT performed, to find out the effects of canagliflozin, between 2010-2012, found that HbA1c decreased by -0.77% and -0.73% respectively, in patients unable to manage on diet and exercise (P<0.001)[25]. In phase-3 double blind RCT performed by **Wilding**[26] on 469 subjects by administration of Canagliflozin 100 mg and 300 mg in addition to metformin and sulfonylurea. They found that HbA1c, FBS and PPBS and BW was significantly decreased as

Table No 1: Distribution of Patients According to Age

Sr. No	Age-Group	No of patients	Percentage
1.	30-40	27	23.7%
2.	41-50	38	33.3%
3.	51-60	35	30.7%
4.	>60	14	12.3%
	Total	**114**	100%
	Mean age in the study ±SD*	**48.56 ± 9.75**	

Table No 2: Efficacy Parameters at Baseline, Week 12 and Week 24

Sr. No	Investigations	Baseline (Mean±SD)	Week 12 (Mean ± SD)	Week 24 (Mean±SD)	'P' value
1.	Fasting blood sugar (mg/dl)	193.03±61.428	167.88±43.764	146.27±31.661	<0.0001*
2.	Post-prandial blood sugar (mg/dl)	299.50±95.520	245.16±59.902	212.09±45.669	<0.0001*
3.	HbA1c	11.907±2.1600	10.342±1.7141	8.8859±1.3409	<0.0001*
4.	Weight (Kg)	87.094±13.135	85.207±12.865	82.781±12.200	0.0398*
5.	Serum Creatinine	0.9157±0.2334	0.8587±0.2266	0.8196±0.2076	0.0056*

('P' value: Repeated measure ANOVA, *: <0.05 statistically significant)

compared to placebo[26]. In meta-analysis done by **Sinclair**[27] four phase-3 RCT on Canagliflozin demonstrated that Canagliflozin improved metabolic parameters like blood glucose level, blood pressure and body weight in type-2 DM patients[27]. In the present study we found that 11 patients suffered from adverse drug reactions. Out of the 11 ADR, 8 ADRs were recorded in female and 3 in male. Among female 5 ADRs were simple urinary tract infections which subsided on primary treatment. 2 females suffered from vulvovaginitis and 1 form genital mycotic infection. All 3 males patients suffered from simple urinary tract infection. In rest of the patients the drug was well tolerated. The probable mechanism for development of urinary tract infection and genital mycotic infections is, not maintaining personal hygiene and the presence of increased amount of sugar in urine favored the growth of bacteria. Similar ADR were reported in CANTATA-M, CANTATA-D study and many other studied[25].

CONCLUSION

Canagliflozin is effective and safe drug to decrease HBA1c, blood sugar and weight in type 2 Diabetes mellitus patients failed to respond triple drug therapy of oral hypoglycemic drugs.

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