Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Effect of Teneligliptin on QT Interval in Type II Diabetes Mellitus Patients: A Retrospective Evaluation

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Abstract

Background and Aim: According to a strict QT/QTc evaluation study and clinical studies for type 2 diabetes conducted in Japan and other countries, NO AEs related to QT prolongation were detected with 40 mg/day of teneligliptin, which is the maximal dosage used in clinical practice. So far, there are no data regarding the safety of teneligliptin in Indian type 2 diabetic patients with respect to QTc prolongation. Therefore, the study was conducted to evaluate the safety of teneligliptin in type 2 diabetic patients with respect to QT prolongation.

Methods: A retrospective data were collected from type 2 diabetes mellitus patients with electrocardiogram (ECG) records who were treated with teneligliptin along with ongoing treatment. Primary endpoint was to compare the change in the ECG at 3 months from the baseline from the collected data. Mean daily dose (MDD) of antidiabetic drugs, HbA1c, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) was also analyzed.

Results: A total of 49 patients' data were collected and analyzed with a mean age of 55.5 years and mean duration of diabetes 9.3 years. Hypertension was the most common comorbid disease (63.3%) along with diabetes for a mean duration of 10.0 years. Metformin plus glimepiride were the most prescribed dual drugs (63.3%) along with teneligliptin with an overall MDD of metformin (1065.2 mg) and glimepiride (2.1 mg). From the collected data, there was significant reduction in FPG and PPG at 3 months which were 49.6 mg/dL *(*$P < 0.0001$) and 100.5 mg/dL *(*$P < 0.0001$) reduction observed from the baseline, respectively. Significant changes were observed in the HbA1c from the baseline to 3 months (0.9%, $P < 0.0001$). There was no significant increase in the mean QTc interval from baseline to 3 months. No serious adverse events or hypoglycemia were reported.

Conclusion: Teneligliptin was well tolerated with no significant change in QTc prolongation and significantly effective in reducing the FPG, PPG, and HbA1c at 3 months from the baseline with no adverse events. There was no increase in the mean QT interval.

Key words: Diabetes, Teneligliptin, QT interval

INTRODUCTION

Diabetes mellitus, characterized by abnormally high blood sugar (glucose) level, is one of the leading global health issues of the 21st century.[1] Type 2 diabetes mellitus (T2DM) constitutes more than 95% of all the diabetic populations.[2] T2DM is a well-known risk factor for cardiovascular (CV) disease, with almost 50% of patients developing heart failure, and those with both diabetes and established heart failure have more severe outcomes.[3] Hence, selecting the optimal therapy for individuals with T2DM requires cautious consideration regarding CV safety of glucose lowering therapies.

There have been persistent concerns about potential adverse CV effects of oral hypoglycemic agents. In 2008, the US Food and Drug Administration responded to this need by issuing guidelines that mandate a thorough assessment of CV risk in glucose lowering drugs.[4] Apart from glucose-lowering effect, dipeptidyl peptidase-4 (DPP4) inhibitors have a diverse impact on CV system. This impact is due

Access this article online

www.ijss-sn.com

Month of Submission : 11-2018
Month of Peer Review : 12-2018
Month of Acceptance : 12-2018
Month of Publishing : 01-2019

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to the presence of glucagon-like peptide-1 receptors in human cardiac myocytes which is well documented for the past two decades.[5]

Teneligliptin, a DPP4 inhibitor, was approved for the management of T2DM in Japan (2012), South Korea (2014), and India (2015).[1] In addition to effective glycemic control, the results of various clinical trials also suggested that teneligliptin, as monotherapy or add-on therapy, was generally well tolerated in patients with T2DM.[1] It was associated with improvements in left ventricular function - particularly diastolic - and endothelial functions, as well as with an increase in serum adiponectin levels.[6] No CV side effects were ever reported with the molecule at a normal therapeutic dose, but mild QTc transient prolongation was documented while using teneligliptin in supraclinical dosages of 160 mg per day.[7] Significant QTc prolongation has not been reported with teneligliptin 20 as well as 40 mg in various Japanese studies. However, there are no studies for QTc prolongation in Indian diabetic patients.

Therefore, the present retrospective analysis was undertaken to evaluate the effect of teneligliptin on QT interval in T2DM patients in real-world setting.

METHODS

This was a retrospective, single-centric study conducted in T2DM patients who were prescribed teneligliptin 20 mg once daily as a monotherapy or add-on therapy with other OADs for at least 3 months. Patients with available data for fasting plasma glucose (FPG), postprandial plasma glucose (PPG), HbA1C, and electrocardiogram (ECG) at baseline, 1st month, and 3rd month were enrolled in the study. QT interval in the ECG is a measure of cardiac repolarization and any drug that increases the QT interval may increase the risk of CV events, and hence, QT interval was focused in ECG in the present study. Confidentiality of the data was maintained throughout the study period. The data were captured and compiled in Microsoft Excel version 2013. Categorical data were expressed in percentage and mean ± SD; paired *t*-test was used to look for the statistical difference at baseline and $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 49 patients were enrolled for data analysis, to evaluate the effect of teneligliptin on QT interval. The average age of patients was 55.5 years with the mean duration of diabetes being 9.3 years. Hypertension was the most common comorbidity in 63.3% of patients followed by dyslipidemia (32.7%) and stroke (10.2%) [Table 1]. Metformin and glimepiride were the two most common drugs prescribed along with teneligliptin. The average daily dose of metformin and glimepiride prescribed was 1065.2 mg and 2.1 mg, respectively [Table 2]. Metformin and glimepiride was the most common fixed-dose combination prescribed along with teneligliptin in 63.3% of patients [Table 3].

Among the enrolled patients, baseline mean FPG level was 147.9 ± 38.4 mg/dl, which decreased to 115.7 ± 19 mg/dl at the end of 1st month and 98.3 ± 5.8 mg/dl at the end of 3rd month. A significant difference was seen in the mean FPG at baseline and at the end of 1st month ($P \leq 0.0001$) and 3rd month ($P \leq 0.0001$). The mean PPG level was 256.2 ± 63.3 mg/dl at baseline which decreased to 184 ± 18.3 mg/dl and 155.7 ± 13.9 mg/dl at the end of 1st month and 3rd month, respectively. A significant difference was seen in the mean PPG at baseline and 1st month ($P \leq 0.0001$) and 3rd month ($P \leq 0.0001$). Mean HbA1C level was 7.6 % ± 0.9 % at baseline and decreased significantly ($P \leq 0.0001$) to 6.7% ± 0.9% at the end of 3rd month. Mean QT interval was 407.1 ± 27.8 ms at baseline and 407.1 ± 29.3 ms and 407.8 ± 27.6 ms at the end of 1st month and 3rd month, respectively. No significant difference was seen in the mean QTc at

Table 1: Comorbidities among enrolled patients

Comorbidities	Mean (years)	Number of patients (%)
Hypertension	10.0	31 (63.3)
Dyslipidemia	8.3	16 (32.7)
Stroke	7.6	5 (10.2)
CAD/ACS/IHD*	5	2 (4.1)

*CAD: Coronary artery disease; ACS: Acute coronary syndrome; IHD: Ischemic heart disease

Table 2: Concurrent medication prescribed among enrolled patients

Concurrent medication	Mean dose	Number of patients (%)
Metformin	1065.2	46 (93.9)
Glimepiride	2.1	35 (71.4)
Gliclazide	67.5	4 (8.2)
Pioglitazone	12.9	7 (14.3)
Dapagliflozin	5	4 (8.2)
Miglitol	10	1 (2.0)
Voglibose	0.6	3 (15.0)

Table 3: Combinations prescribed among study participants

Combination	Number of patients (%)
Metformin+Glimepiride	31 (63.3)
Metformin+Glimepiride+Dapagliflozin	2 (4.1)
Metformin+Glimepiride+Dapagliflozin+Voglibose	1 (2.0)
Metformin+Glimepiride+Voglibose	1 (2.0)

Table 4: FPG, PPG, HbA1C, and ECG at baseline, 1st month, and 3rd month

Parameters	FPG	PPG	HbA1C	QTc
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Baseline visit	147.9±38.4	256.2±63.3	7.6±0.9	407.1±27.8
Follow-up visit at 1 month	115.7±19	184±18.3	NA	407.1±29.3
Changes from baseline	32.2±19.4*	72.2±45*	NA	0±1.5#
Follow-up visit at 3 months	98.3±5.8	155.7±13.9	6.7±0.5	407.8±27.6
Changes from baseline	49.6±32.6*	100.5±49.4*	0.9±0.4*	0.7±0.2@

*P<0.0001; #P=0.99; @P=0.69. SD: Standard deviation, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, ECG: Electrocardiogram

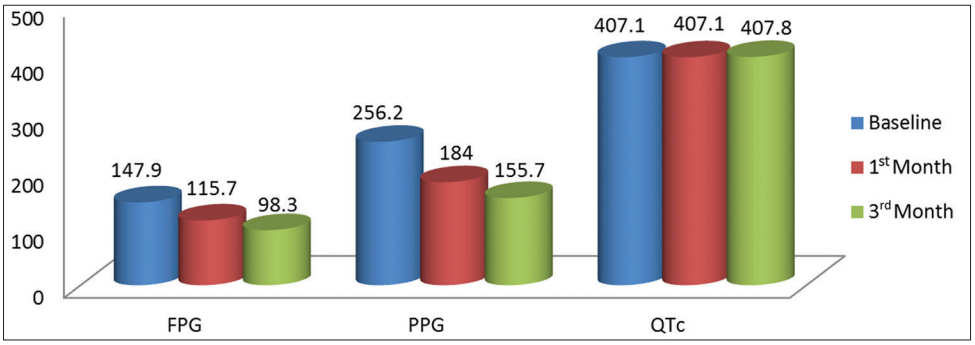

Figure 1: Fasting plasma glucose, postprandial plasma glucose, and electrocardiogram at baseline, 1st month, and 3rd month

baseline and 1st month (P = 0.99) and 3rd month (P = 0.69) [Table 4 and Figures 1 and 2]. There were no clinically relevant drug–drug interactions reported when teneligliptin was coadministered with other antidiabetic drugs.

DISCUSSION

An undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, an effect that can be measured as prolongation of the QT interval on the surface ECG. There is a qualitative relationship between QT prolongation and the risk of TdP (polymorphic ventricular tachyarrhythmia), especially for drugs that cause substantial prolongation of the QT interval. The "thorough QT/QTc study" is thus intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation.[8] The threshold level of regulatory concern is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.[8] Drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause TdP, while drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic. The data on drugs that prolong the mean QT/QTc interval by more than around 5 and <20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk.[8]

In the present QTc study, data from 49 T2DM patients on teneligliptin monotherapy or combination therapy

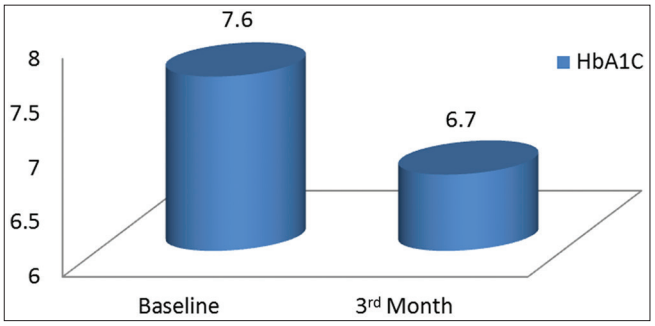

Figure 2: HbA1C at baseline and 3rd monthx

with other OADs were analyzed. ECG pattern was recorded at baseline and at the end of 1st month and 3rd month of therapy, to determine changes in the QT interval. The average change in the mean QT interval was 0 ± 1.5 ms at the end of 1st month and 0.7 ± 0.2 ms at the end of 3rd month. No significant change in the mean QT interval at baseline and 1st month (P = 0.99) and at baseline and 3rd month (P = 0.69) was seen. Thus, 20 mg dose of teneligliptin was relatively safe in study population. A thorough QT/QTc evaluation study was also conducted by Kishimoto in Japan[9] where teneligliptin 40 and 160 mg were actively compared to moxifloxacin. Teneligliptin 40 mg/day which is currently the maximal recommended dose prolonged the QTc by 4.9 ms after 3 h. 160 mg/day of teneligliptin significantly increased the QT by 11.2 ms after 1.5 h, almost similar to 12.1 ms of QTc prolongation as observed 2 h after moxifloxacin. While teneligliptin 160 mg (although not recommended

for clinical use) is clearly associated with a prolonged QTc, teneligliptin 40 mg does not cross the critical threshold of 5 ms. The threshold for QT prolongation will become more important when teneligliptin will be prescribed with several other drugs which tend to prolong QTc including antibiotics (azithromycin), antihistaminics (astemizole and terfenadine), diuretics (thiazide), selective serotonin uptake inhibitors, haloperidol, and obviously antiarrhythmic drugs (amiodarone and sotalol).[10] Moreover, hypoglycemia being one of the strong QTc prolongation, combination with other hypoglycemic drug, may need strict pharmacovigilance.[10]

Apart from its favorable effect on QT interval, teneligliptin was also associated with significant improvement in FPG, PPG, and HbA1C at the end of 1st month and 3rd month, with average decrease in FPG, PPG, and HbA1C at the end of 3rd month as 49.6 ±32.6 mg/dl, 100.5 ± 49.4 mg/dl, and 0.9 % ± 0.4%, respectively. Similar results were reported in Treat India study,[11] where mean HbA1c, FPG, and PPG were significantly reduced by 1.37% ± 1.15%, 51.29 ± 35.41 mg/dL, and 80.89 ± 54.27 mg/dL, respectively, at the end of 3 months of teneligliptin therapy. The above results were in line with the study conducted by Chatterjee[12] where 12-week teneligliptin showed significant change in HbA1c (9.6 ± 2.1–8.4 ± 1.2%, $P < 0.001$), FPG (181.4 ± 54.5–140.9 ± 27.1 mg/dL, $P < 0.001$), and PPG (273.7 ± 75.6–201.1 ± 47.7 mg/dL, $P < 0.001$).

Our study was limited by retrospective nature and small sample size, which warrants further need of a large-scale real-world randomized trial with longer follow-up period. In addition, taking into account that there are diabetic patients who have concurrent diseases such as arrhythmia and ischemia and that teneligliptin may be administered to such patients for a long period of time, it is deemed necessary to collect information on the safety data through post-marketing surveillance study.

CONCLUSION

At therapeutic dose (20 mg once daily) usually prescribed in clinical practice, teneligliptin was not associated with significant change in QT interval and was associated with significant decrease in HbA1c, FPG, and PPG during the study period.

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How to cite this article: Sengupta S, Rathod A, Suryawanshi S, Barkate H, Pethare A. Effect of Teneligliptin on QT Interval in Type II Diabetes Mellitus Patients: A Retrospective Evaluation. Int J Sci Stud 2019;6(10):88-91.

Source of Support: Nil, **Conflict of Interest:** None declared.