International Journal of Basic & Clinical Pharmacology
Butul M et al. Int J Basic Clin Pharmacol. 2020 Mar;9(3):498-505
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20200729

Original Research Article

Evaluation of the analgesic activity of single and multiple oral doses of teneligliptin (20 mg/day), using hot air analgesiometer in healthy human volunteers: a randomized, double blind, placebo controlled, cross over study

Maleha Butul, Usharani Pingali, Chandrasekhar Nutalapati*

Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Received: 13 January 2020
Revised: 13 February 2020
Accepted: 15 February 2020

***Correspondence:**
Dr. Chandrasekhar Nutalapati,
Email: csnpru@gmail.com

ABSTRACT

Background DPP-4 inhibitors showed analgesic and anti-inflammatory activity in human and animal-studies. DPP-4 inhibitors improved nerve function and thermal nociception in animal models. Aim of the study was to explore analgesic activity of single and multiple doses of teneligliptin 20 mg/day using hot air analgesiometer in healthy human volunteers.

Methods: After IEC approval and informed consent, subjects were randomized to receive either teneligliptin 20 mg or placebo in double-blinded manner with standard breakfast. Mean pain threshold and tolerance(sec) using hot air analgesiometer were recorded at baseline and 1 hr, 2 hrs post drug on day 1, for single dose study. Subsequently drugs were administered under supervision daily for 6 days and same procedure repeated on day8 for multiple-dose study. After 2 weeks washout, subjects crossed over in period 2 to receive other formulation and same procedure repeated to determine study parameters. Fasting blood-sugar (FBS) was monitored, ADRs recorded in CRF. Statistical analysis done with SPSS20.0.

Results: Twelve-healthy subjects (8 males, 4 females) with mean age 33.08±4.69 years, mean BMI 22.6±1.37kg/m^2 participated. Single dose teneligliptin produced significant increase in pain threshold (35.9%) and pain tolerance (25.1%) ($p<0.001$) at 1hour compared to baseline. With multiple doses, pain threshold increased by 37.1% and pain tolerance by 25.4% ($p<0.001$) at 1hour compared to baseline. The increase in pain threshold and tolerance values at 1 and 2 hours were similar. There was no significant change in pain threshold($p=0.4135$) and tolerance ($p=0.4476$) at baseline on day1 and day 8. Placebo showed non-significant change in study parameters. Both treatments well tolerated. FBS of volunteers within normal limits during treatment period and no hypoglycemia reported.

Conclusions: Results of our study suggest that teneligliptin20mg in healthy subjects demonstrated modest analgesic activity compared to baseline and placebo. Its role in painful diabetic conditions may be further explored.

Keywords: Analgesic, Teneligliptin, GLP-1, Thermal nociception, Healthy volunteers, Hot air analgesiometer

INTRODUCTION

Pain is an unpleasant experience following tissue damage. Early treatment offers an excellent relief of pain. Non-steroidal anti-inflammatory drugs are not well tolerated within majority of the patients due to its pro-hypertensive, gastrointestinal and renal effects.[1] Paracetamol and tramadol are the widely preferred analgesic drugs for moderate pain. However, their use is restricted to non-inflammatory pain.

DPP-4 inhibitors (DPP-4I) are antidiabetic agents that are known to have pleiotropic actions.[2] Selective DPP4 inhibition has been linked to immuno-modulation in both animal and human models of disease.[3,4] Because of its pleiotropic nature, DPP-4 inhibitors (gliptins) are considered as drugs for the treatment of non-alcoholic steatohepatitis and associated liver fibrosis and cardiovascular complications.[5] Both sitagliptin and vildagliptin have shown analgesic and anti-inflammatory activity in animals.[6] Teneligliptin is a potent DPP-4I and has efficacy and safety profile similar to other drugs in the same group. Comparative inhibition studies showed that teneligliptin exhibited more potent inhibition of the DPP-4 enzyme than sitagliptin, vildagliptin, and alogliptin.[7] Teneligliptin can increase GLP-1 concentrations and result in glucose-dependent insulin secretion with minimal risk of hypoglycemia. Animal studies demonstrated that toxicity may be caused by the inhibition of other enzymes, like DPP-8 and DPP-9 in this family.[8] Since teneligliptin shows higher relative selectivity for DPP-4, the risk of development of adverse effects due to inhibition of other enzymes is minimal. Teneligliptin at a dose of 20 mg/day achieves peak plasma concentration at 1 hour and has a half-life of 18.9 hours. Maximum (89.7%) inhibition in plasma DPP-4 activity was noted within 2 hours and this was maintained at > 60% at 24 hours.[9]

The multiple mechanisms of pain generation could offer potential targets for development of new analgesics. Many human experimental pain models have been validated to evaluate the analgesic activity of drugs.[10] Evaluation of analgesic action by experimental pain models in healthy volunteers may thus eliminate the confounding factors which may be present in a diseased patient. The hot air pain model is a thermal pain model used for the evaluation of analgesics in humans.[11,12]

Clinically, pain can be reduced by the use of available drugs like NSAIDs and opioids but they are associated with side effects which may sometimes be serious. Therefore, there is a need to explore the therapeutic potential of available drugs for their analgesic activity.

There is limited data available on the evaluation of analgesic activity of teneligliptin in human subjects. Analgesic potential of teneligliptin was thus explored in the present study by hot air pain model. Teneligliptin inhibits the degradation of GLP-1 and GIP, improves fasting and postprandial hyperglycemia. It also has a wide range of pleiotropic actions like anti-inflammation as well as anti-oxidant effects, which are Incretin independent.[13] It achieves maximum plasma concentrations at 1hour, which is suitable to demonstrate the analgesic action at 1 and 2 hours.[8]

The present study was thus done to evaluate the analgesic effect of teneligliptin in comparison to placebo in healthy human volunteers by using validated hot air pain model.

METHODS

The study was conducted during the period august 2018 to January 2019 in the Pharmacodynamics Research Laboratory of Clinical Pharmacology and Therapeutics Department, NIMS after taking institutional ethics committee approval. The protocol was executed in accordance with the Good Clinical Practice guidelines and the principles in the Declaration of Helsinki. Written informed consent was provided by all the subjects prior to study enrolment.

Study medications

Teneligliptin Tablet: Teneligliptin hydrobromide hydrate IP equivalent to teneligliptin 20mg (Ziten, Glenmark Pharmaceuticals LTD) and Placebo Tablet: Identical to teneligliptin tablets having Inactive ingredients: 49.7% microcrystalline cellulose, 49.5% lactose and 0.8% Magnesium stearate

Selection criteria

The study included both male and female participants, between 18-45yrs of age and having BMI-18.5-24.9 kg/m^2. Participants had normal screening lab values and were able to comprehend and perform the test and comply with all study-related procedures. Participants with finger deformities and prior wounds or fractures on the tested extremity, pre-existing dyspepsia, gastritis, peptic ulcer, any acute or chronic drug or alcohol abuse, diabetes mellitus were excluded. Those whose hot air pain threshold value was < 30sec and pain tolerance value > 180sec, or who were receiving drugs known to alter pain sensation within 2 weeks prior to the study or having hypersensitivity to test drug or not willing to participate were also excluded (Figure 1).

Study methodology

The study was a randomized, double-blind, placebo-controlled, two sequences, and two treatments crossover study, with a washout period of 14 days. After obtaining written informed consent, twelve healthy volunteers, as evidenced by history, medical examination, and lab investigations (Fasting blood sugar, complete blood picture, complete urine examination, liver function test, renal function test, ECG, Chest X-ray, Screening for viral markers – HIV, HbsAg & HCV) participated in the study.

Participants received training of study procedures on two different days prior to participation in the study to reduce variability. Enrolled participants were asked to come in fasting state to the study site at 8 AM after good overnight sleep.

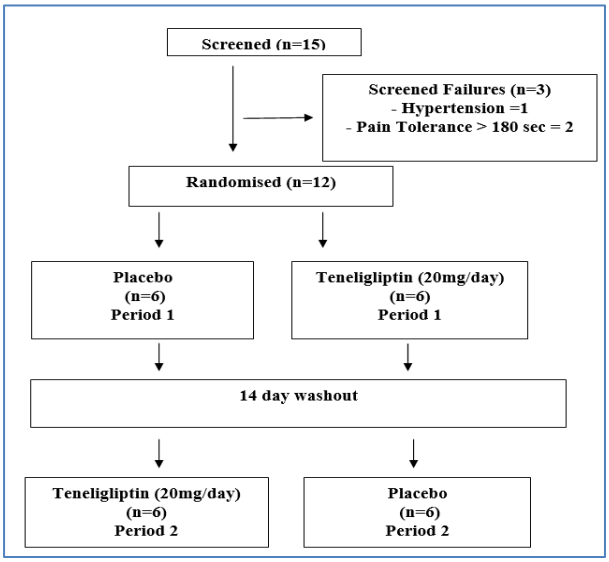

Figure 1: Study flow diagram.

Study methodology

The study was a randomized, double-blind, placebo-controlled, two sequences, and two treatments crossover study, with a washout period of 14 days. After obtaining written informed consent, twelve healthy volunteers, as evidenced by history, medical examination, and lab investigations (Fasting blood sugar, complete blood picture, complete urine examination, liver function test, renal function test, ECG, Chest X-ray, Screening for viral markers – HIV, HbsAg & HCV) participated in the study. Participants received training of study procedures on two different days prior to participation in the study to reduce variability. Enrolled participants were asked to come in fasting state to the study site at 8 AM after good overnight sleep.

On study day-1

Single dose study

On participant arrival to the study site, study procedure was explained to the volunteers. After 30 minutes rest, their baseline vitals and the fasting blood sugar (FBS) by using one-touch glucometer were recorded. Participants were blindfolded during the recordings. The investigator then helped the participants to place their non-dominant forearm exposing the volar surface in the lower chamber A of the hot air analgesiometer. This apparatus was developed to deliver variable, quantifiable and reproducible heat stimulus via hot air to induce thermal pain stimulus on the volar surface of the forearm. Height of chamber B was adjusted to short level of 36.5 cm (level 1). Heat stimulus was given by turning on the hot air and blowing air at high speed.

The participants were instructed to indicate as soon as they perceive the heat sensation as painful (pain threshold), and when the pain becomes intolerable (pain tolerance) by raising their index finger of the other hand. On indication of intolerable pain, the hair drier was immediately turned off (Figure 2).

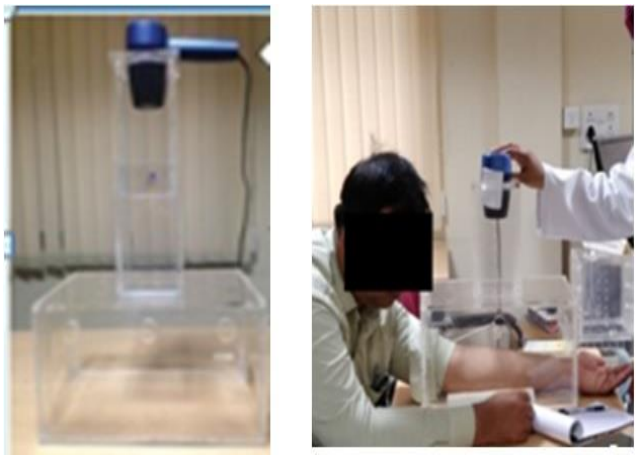

Figure 2: Hot air analgesiometer to deliver heat stimulus to participants.

Three baseline readings to determine pain threshold and pain tolerance time were recorded with an interval of 5 minutes in between the readings. After taking baseline readings, the participants were provided with standard breakfast. After half an hour of breakfast, they received either teneligliptin 20mg or placebo as per their randomization schedule which was according to computer-generated random sequences. They were asked to take their respective study medication with 240ml of water. The allocation of treatment was not known to the investigator or participant. After taking the drug, the participants were asked to sit upright in the chair. The same procedure was repeated at 1 and 2 hours of post-drug administration. The mean of the three measurements for pain threshold and tolerance for analysis was determined. Participants were asked to report any side effects during the study. Vitals were recorded periodically thereafter and random blood sugar (RBS) by using glucometer was recorded at the time of discharge.

Multiple dose study

Subsequently from next day (day-2) participants were asked to come to study site for 6 consecutive days in fasting state. Their vitals were recorded and study drugs were dispensed under supervision daily for the next 6 days. They were instructed to report any new symptoms to the investigator.

On arrival on day-8, same procedure was repeated as on day-1 to determine pain threshold and tolerance. After 14 days of washout period, participants were crossed over in

period 2 to receive other study medications and the same procedures for single dose and multiple dose study were repeated to determine pain threshold and tolerance. Subjects were monitored for any ADRs during the study.

Study endpoints

The primary endpoint was the change in pain threshold and pain tolerance time (sec) at 1 hour and 2 hours after single and multiple doses of study drugs and the secondary endpoint was the incidence of adverse events.

Statistical analysis

Sample size calculation

A total of 15 healthy volunteers were screened. About 12 subjects were found to be adequate to detect an effect size of 7.63 sec and SD of 3.72 considering 90% power at a 5% level of significance with a screen failure rate and drop-out rate of 20% each.

Data analysis

Data was presented as mean±SD, numbers, and percentages. Study parameters were analysed by paired t-test for within-group and unpaired t-test between-group comparisons using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

RESULTS

A total of 15 healthy subjects were screened of which 12 subjects (8 males, 4 females) participated in the study. The mean age and mean BMI of the volunteers were 23±2.4 years and 22.6±1.37 kg/m^2 respectively (Table 1).

Teneligliptin in single dose significantly increased the mean pain threshold and tolerance time compared to baseline and placebo. The mean pain threshold rose from 64.64±1.77 sec at baseline to 87.85±2.6 sec at 1 and 87.5±2.67 sec at 2 hours respectively (p<0.001). Likewise, the meantime for pain tolerance rose from 103.58 ±2.23 sec to 128.74 ±3.53 sec and 129.3 ±4.18 sec (p<0.001) (Table 2).

Table 1: Demographic characteristics of study groups.

Parameters	(n=12)
Age (years)	23±2.4
Gender (males or females)	8/4
Height (cm)	170±1.23
Weight (kg)	65.3±3.1
BMI (kg/m^2)	22.6±1.37

In multiple-dose study pain threshold was increased from 66.55 ±1.95 sec at baseline to 91.22±3.05 sec and 90.64±2.99 sec (p<0.001) at 1 and 2 hours respectively. Pain tolerance was increased from 103.33 ±2.26 sec at 0 hour to 129.6 ±3.62 sec and 129.83 ±3.3 sec (p<0.001) at 1 and 2 hours respectively (Table 3).

When compared to placebo, there was an increase in mean percentage change in pain threshold and tolerance time at 1 hour and 2 hours post-drug with single and multiple doses of teneligliptin (Figure 3 and 4).

The shift observed in pain threshold and tolerance with placebo was noticeable but statistically non-significant (p>0.05).

There was no change in pain threshold (p=0.4135) and tolerance (p=0.4476) at baseline on day-1 and day-8 between the groups with single and after multiple doses of teneligliptin.

When we compared pain threshold and tolerance values with placebo, teneligliptin in both single and multiple-dose studies resulted in a significant increase in pain threshold time and pain tolerance time (p<0.001).

Fasting blood sugar values of the study participants were within normal limits and no signs & symptoms of hypoglycemia were reported. Both treatments were tolerated well. No ADRs were reported. Compliance was assured because of the supervised administration of drugs. All safety lab parameters (haemogram, renal function tests, hepatic function tests, ECG, random blood sugar) were repeated after the test procedure and found to be within normal limits.

Table 2: Comparison of pain threshold and tolerance values after administration of single dose of teneligliptin and placebo.

Single dose	Placebo				Teneligliptin			
	0 hr	1 hr	2 hrs	P value	0 hr	1 hr	2 hrs	P value
Pain threshold (sec)								
Values	63.97 ±2.58	65.19 ±2.13	64.21±2.19	0 Vs.1=>0.05 0 Vs.2=>0.05 1Vs.2=>0.05	64.64±1.77	87.85±2.6	87.5±2.67	0 Vs.1=<0.05 0 Vs.2=<0.05 1Vs.2=>0.05
Pain tolerance (sec)								
Values	101.6±2.33	102.47 ±2.16	102.27 ±3.97	0 Vs.1=>0.05 0 Vs.2=>0.05 1Vs.2=>0.05	103.58 ±2.23	128.74 ±3.53	129.3 ±4.18	0 Vs.1=<0.05 0 Vs.2=<0.05 1Vs.2=>0.05

Table 3. Comparison of pain threshold and tolerance values after administration of multiple dose of teneligliptin and placebo.

Multiple dose	Placebo				Teneligliptin			
	0 hr	1 hr	2 hrs	P value	0 hr	1 hr	2 hrs	P value
Pain threshold (sec)								
Values	65.16 ±2.1	65.3±1.97	65.64 ±1.44	0 Vs.1=>0.05 0 Vs.2=>0.05 1Vs.2=>0.05	66.55 ±1.95	0 vs. 0=>0.05	91.22±3.05	90.64±2.99	0 Vs.1=<0.05 0 Vs.2=<0.05 1 Vs.2=>0.05
Pain tolerance (sec)								
Values	101.72 ±3.04	102.05 ±1.95	102.1 ±3.13	0 Vs.1=>0.05 0 Vs.2=>0.05 1Vs.2=>0.05	103.33±2.26	0 vs.0=>0.05	129.6 ±3.62	129.83 ±3.3	0 Vs.1=<0.05 0 Vs.2=<0.05 1 Vs.2=>0.05

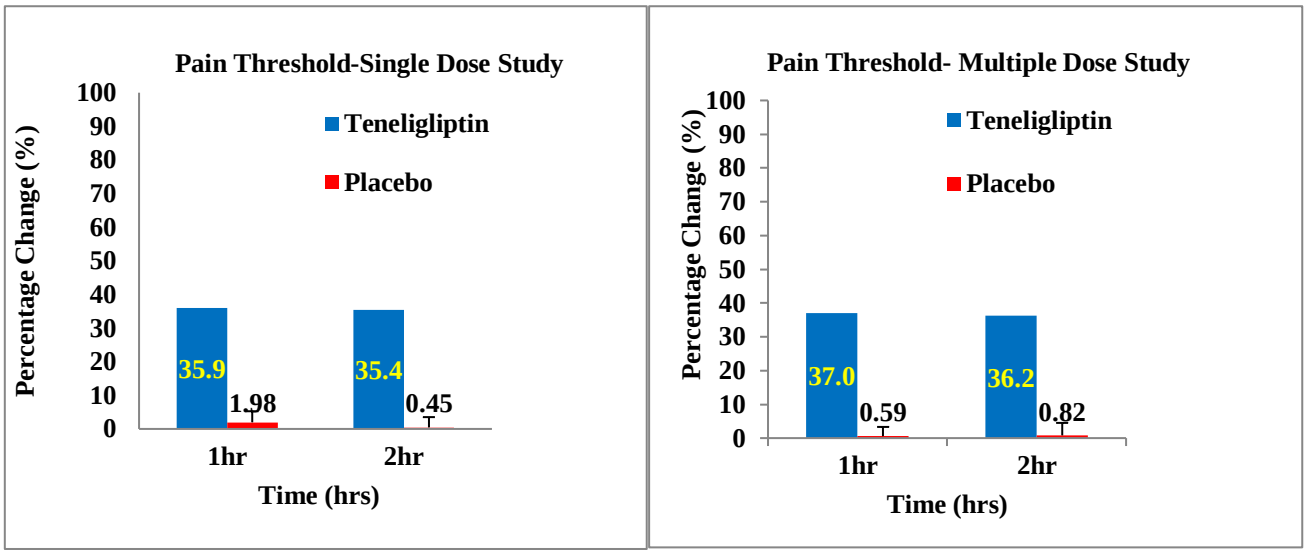

Figure 3 (A and B): Percentage change in pain threshold values after administration of single and multiple doses of placebo and teneligliptin at 1 and 2 hrs.

Data presented as percentages.

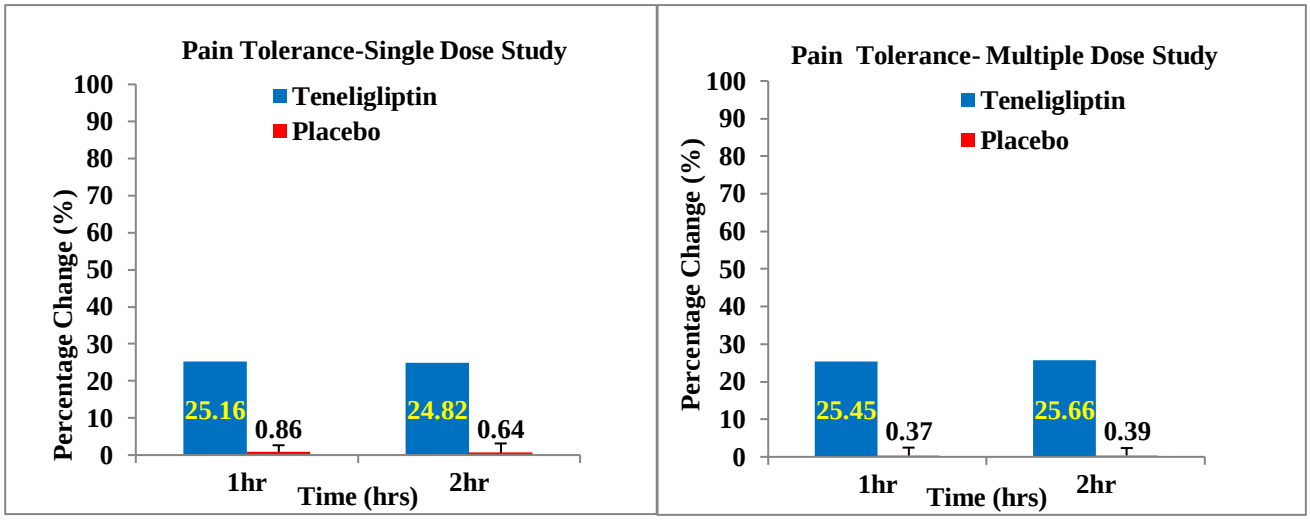

Figure 4 (A and B): Percentage change in pain tolerance values after administration of single and multiple doses of placebo and teneligliptin at 1 and 2 hrs.

Data presented as percentages.

DISCUSSION

The present study was a randomized double-blind placebo-controlled, crossover study, evaluating the analgesic activity of teneligliptin 20 mg/day. In our study, we used hot air to induce acute pain in healthy volunteers before and after administration of single and multiple doses of teneligliptin. It was found that both single and multiple oral doses of teneligliptin produced a significant ($p<0.001$) increase in pain threshold and tolerance time compared to baseline and placebo at 1 hour and 2 hours.

DPP-4 inhibitors (gliptins) have shown analgesic and anti-inflammatory activity in humans and in different experimental models in mice. These drugs increase the temperature threshold in hot-plate tests in animal models showing improved nerve function. Neurotrophic and neuroprotective potential of GLP-1 and GLP-1R stimulation in cellular and animal neuro-degeneration models is also evidenced by studies.[14] There are very few reports about the proven effects of DPP4 or DPP4 inhibitors in pain modulation, despite its assumed role in this area.

According to a study by Byrne et al, the antidiabetic drugs linagliptin and metformin prevented the decreases in mechanical withdrawal thresholds in high-fat diet/streptozotocin (HFD/STZ) rats. The effects of linagliptin on pain behaviour in the HFD/STZ model reported that DPP-4 inhibitors can improve thermal nociception and reduce mechanical hypersensitivity in the STZ model, without affecting glucose and insulin levels. Putative mechanisms include the effects of linagliptin arising from inhibition of DPP-4 and the resultant beneficial effects of increasing plasma levels of GLP-1 on nerve function, supporting a mechanism independent of glycemic control.[15]

In another study by Sharma et al, the sensory function of animals was assessed by evaluating the pain threshold. There was a significant difference (5.5±0.54 vs 13.67±1.38) in paw jumping response 14-day post-induction of diabetic neuropathy in rats, but there was no significant difference found in the control group in which diabetes was not induced (5.33±0.51 vs 5.83±0.75). However, the paw jumping responses of all treated rats with sitagliptin and in combination with metformin or amitriptyline on days 21, 28 and 35 were reduced significantly compared with the diabetic control group. They reported that the improvement in hot-plate response was related to the increased pain threshold of diabetic animals treated with sitagliptin, metformin or amitriptyline combinations.[16]

A study by Judit Ujhelyi et al, has demonstrated that sitagliptin and vildagliptin significantly increased the threshold temperature, compared to the control group. The study concluded that DPP4I had a dose-dependent anti-inflammatory effect in in-vivo mouse models. The applied methods were sensitive enough to detect the action of gliptins.[6]

Elevated plasma GLP-1 levels, as a result of inhibition of DPP4-enzyme by DPP4 inhibitors, have shown a beneficial effect on nerve function, improvement in thermal-nociception and reduction of mechanical hypersensitivity in the animal models, without affecting glucose and insulin levels. These effects may thus reflect a peripheral site of action, as improvements in sensory thresholds and nerve fibre loss have been reported.[15]

In a study by Davidson et al, it was observed that DPP4 activity in diabetic untreated rats reduced from 35.4±5.1 to 18.3 ± 3.4 ng/mL on treatment with alogliptin (DPP-4 inhibitor) when compared to control group -untreated nondiabetic rats.

They also demonstrated that treatment with alogliptin in diabetic rats, improved thermal nociceptive response in the hind paw when measured using the Hargreaves method.

They have attributed this to DPP4 inhibition which in turn preserves GLP-1 and thus may have preventive effect on peripheral nerve degeneration.[17]

Kiraly et al reported that the expression of the DPP4 protein was increased by peripheral inflammation in astrocytes and also after neural injury (partial ligation of the sciatic nerve) in microglia suggesting that in pathological painful situations the role of DPP4 becomes more pronounced, therefore the effect of DPP4 inhibitors on nociception could also increase.[18] They reported that DPP4 inhibitors could activate the endogenous opioid system and cause an opioid-mediated anti-hyperalgesic effect in subacute inflammatory pain. Similarly, Balogh et al, in their study on rat inflammatory pain models reported that the anti-hyperalgesic effect of DPP4 inhibitors can be attributed to the activation of endogenous opioid system especially the delta opioid receptor.[19]

In our study, in addition to an increase in pain threshold and tolerance time, we also observed similar baseline values on day-1 and day-8 between the groups for pain threshold and pain tolerance time. Similar baselines values could due to the fact that GLP-1 concentrations are normal in the fasting state in healthy individuals, and increases only in response to high glucose levels after a meal. The findings also reflect that there was no carryover effect of the study medication after the washout period as evidenced by similar baseline values between the groups on both the study days.

The results in the present study are similar to other studies done in our department, where we have reported an increase in pain threshold and tolerance using thermal or mechanical pain models.[20-22]

In our study, the observed analgesic activity could be attributed to increased GLP-1 concentrations due to inhibition of DPP4 enzyme by teneligliptin and probably to resultant activation of GLP-1 Rs in spinal microglia and release of endogenous endorphins as mentioned in the studies quoted above. The endorphins in turn may activate the peripheral opioid receptors resulting in analgesic activity of teneligliptin as evidenced by an increase in pain threshold and tolerance time.

In the present study, teneligliptin was tolerated well by all the participants without producing signs and symptoms of hypoglycemia.

To the best of our knowledge, there is no published data on the evaluation of the analgesic activity of teneligliptin compared to placebo in human subjects. Also, our study was the first of its kind to evaluate the analgesic activity of teneligliptin using hot air pain model. The use of a hot-air analgesiometer in our study was a validated apparatus that have been proven to detect the efficacy of analgesics by the use of quantifiable and reproducible heat stimulus.[23] Also, our efficacy time points were well planned according to the maximum concentration of teneligliptin achieved at 1 hour and thus matched the analgesic effect of teneligliptin. All these add to the strength of our study. Limitation of our study was that analgesic activity as early as half an hour could also have been evaluated in order to know the onset of the time of analgesic activity.

CONCLUSION

Teneligliptin in healthy volunteers demonstrated significant analgesic activity with single and multiple oral doses, compared to baseline and placebo with hot air analgesiometer. Its role in relieving painful diabetic conditions may be explored further.

ACKNOWLEDGEMENTS

The authors thank ICMR Advanced Center for Clinical Pharmacodynamics, NIMS, Hyderabad for supporting the development of pain models.

Funding: Department of clinical pharmacology and therapeutics, Nizam's institute of medical sciences, Hyderabad
Conflict of interest: None declared
Ethical approval: The study was approved by the NIMS Institutional Ethics Committee

REFERENCES

1. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Internal Med. 1993;153(4):477-84.
2. Balakumar P, Dhanaraj SA. Cardiovascular pleiotropic actions of DPP-4 inhibitors: a step at the cutting edge in understanding their additional therapeutic potentials. Cellular signalling 2013;25(9):1799-803.
3. Kim SJ, Nian C, Doudet DJ, McIntosh CH. Dipeptidyl peptidase IV inhibition with MK0431 improves islet graft survival in diabetic NOD mice partially via T-cell modulation. Diabetes. 2009;58(3):641-51.
4. Makdissi A, Ghanim H, Vora M, Green K, Abuaysheh S, Chaudhuri A, et al. Sitagliptin exerts an antinflammatory action. The J Clin Endocrinol Metabol. 2012;97(9):3333-41.
5. Wang X, Hausding M, Weng SY, Kim YO, Steven S, Klein T, et al. Gliptins suppress inflammatory macrophage activation to mitigate inflammation, fibrosis, oxidative stress, and vascular dysfunction in models of nonalcoholic steatohepatitis and liver fibrosis. Antioxidants Redox Signaling. 2018;28(2):87-109.
6. Újhelyi J, Újhelyi Z, Szalai A, László JF, Cayasso M, Vecsernyés M, et al. Analgesic and anti-inflammatory effectiveness of sitagliptin and vildagliptin in mice. Regulatory Peptides. 2014;194:23-9.
7. Nabeno M, Akahoshi F, Kishida H, Miyaguchi I, Tanaka Y, Ishii S, et al. A comparative study of the binding modes of recently launched dipeptidyl peptidase IV inhibitors in the active site. Biochem Biophy Res Communications 2013;434(2):191-6.
8. Sharma SK, Panneerselvam A, Singh KP, Parmar G, Gadge P, Swami O.C. Teneligliptin in management of type 2 diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets Therap. 2016;9:251-60.
9. Erin E, Mulvihill, Daniel J. Drucker. Pharmacology, Physiology, and Mechanisms of Action of Dipeptidyl Peptidase-4 Inhibitors. Endocrine Rev. 2014;35:992-1019.
10. Staahl C, Drewes AM. Experimental Human Pain Models: A Review of Standardised Methods for Preclinical Testing of Analgesics. Basic Clin Pharmacol Toxicol. 2004;95:97-111.
11. Reddy KSK, Naidu MUR, Rani PU, Rao TRK. Human experimental pain models: A review of standardized methods in drug development. J Res Med Sci. 2012;17:587-95.
12. Usharani P, Nalini P, Manjunath N, Reddy S. Evaluation of the analgesic activity of standardized aqueous extract of Withania somnifera in healthy human volunteers using Hot Air Pain Model. Res J Life Sci. 2013;1:1-6.
13. Renate VG, Diane MG, Daniel VR, Diamant M. Extra-pancreatic effects of incretin-based therapies: potential benefit for cardiovascular-risk management in type 2 diabetes. Diabetes Obesity Metabol. 2013;15(7):593-606.
14. Kamble M, Gupta R, Rehan HS, Gupta LK. Neurobehavioral effects of liraglutide and sitagliptin in experimental models. Euro J Pharmacol. 2016.

15. Byrne FM, Cheetham S, Vickers S, and Chapman V. Characterisation of Pain Responses in the High Fat Diet/Streptozotocin Model of Diabetes and the Analgesic Effects of Antidiabetic Treatments. J Diabetes Res. 2015;1-13.
16. Sharmaa AK, Sharmaa A, Kumaria R, Kishorea K, Sharmaa D, Srinivasan BP, et al. Sitagliptin, sitagliptin and metformin, or sitagliptin and amitriptyline attenuate streptozotocin-nicotinamide induced diabetic neuropathy in rats. J Biomed Res 2012;26(3):200-10.
17. Davidson EP, Coppey LJ, Dake B, and Yorek MA. Treatment of Streptozotocin-Induced Diabetic Rats with Alogliptin: Effect on Vascular and Neural Complications. Exp Diabetes Res. 2011: 1- 7.
18. Király K, Kozsurek M, Lukácsi E, Barta B, Alpár A, Balázsa T, et al. Glial cell type-specific changes in spinal dipeptidyl peptidase 4 expression and effects of its inhibitors in inflammatory and neuropathic pain. Sci Reports. 2018;8:3490.
19. Balogha M, Vargaa BK, Karádia DA, Ribaa P, Puskárb Z, Kozsurekb M, et al. Similarity and dissimilarity in antinociceptive effects of dipeptidyl-peptidase 4 inhibitors, Diprotin A and vildagliptin in rat inflammatory pain models following spinal administration. Brain Res Bulletin. 2019;147:78-85.
20. Kumar CU, Pokuri VK, Pingali U. Evaluation of the Analgesic Activity of Standardized Aqueous Extract of Terminalia chebula in Healthy Human Participants Using Hot Air Pain Model. J Clin Diagnostic Res. 2015;9(5):1-4.
21. Prabhavathi K, Chandra USJ, Soanker R, Rani PU. A randomized, double blind, placebo controlled, cross over study to evaluate the analgesic activity of Boswellia serrata in healthy volunteers using mechanical pain model. Indian J Pharmacol. 2014;46(5):475.
22. Nalini P, Manjunath NK, Reddy KSK, Usharani P. Evaluation of the analgesic activity of standardized aqueous extract of Withania somnifera in healthy human volunteers using hot air pain model. Res J Life Sci. 2013;1(2):1-6.
23. Reddy KSK, Naidu MUR, Usha RP, Rao TRK. A simple thermal pain model for the evaluation of analgesic activity in healthy subjects. J Anaesth Clin Pharmacol. 2012;28:214-20.

Cite this article as: Butul M, Pingali U, Nutalapati C. Evaluation of the analgesic activity of single and multiple oral doses of teneligliptin (20 mg/day), using hot air analgesiometer in healthy human volunteers: a randomized, double blind, placebo controlled, cross over study. Int J Basic Clin Pharmacol 2020;9:498-505.