Teneligliptin : A New DPP-4 inhibitor for Type 2 Diabetes

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ABSTRACT

Teneligliptin, a novel DPP-4 inhibitor, characterised by five consecutive rings, which produce a potent and long-lasting effecting glycemic control. It is currently used in cases showing insufficient improvement in glycemic control even after diet control and exercise or a combination of diet control, exercise, and sulfonylurea- or thiazolidine class drugs. In adults, teneligliptin is orally administered at a dosage of 20 mg once daily, which can be increased up to 40 mg per day. Because the metabolites of this drug are eliminated via renal and hepatic excretion, no dose adjustment is necessary in patients with renal impairment. The safety profile of teneligliptin is similar to those of other available DPP-4 inhibitors. However, caution needs to be exercised when administering teneligliptin to patients who are prone to QT prolongation. Although clinical data for this new drug are limited, this drug shows promise in stabilising glycemic fluctuations throughout the day and consequently suppressing the progression of diabetic complications.

Key words : teneligliptin, DPP-4 inhibitor, diabetes

Introduction :

Dipeptidyl peptidase IV inhibitors are a class of oral anti-hyperglycemic agents for the treatment of type 2 diabetes. The anti-glycemic effect of DPP-4 inhibitors is mediated by inhibiting the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1) and stimulating insulin release in response to increased blood glucose levels. Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), and have a very short half-life as a result. DPP-4 inhibitors increase the levels of active GLP-1 and GIP by inhibiting DPP-4 enzymatic activity thus, in patients with diabetes, these inhibitors improve hyperglycemia in a glucose-dependent manner by increasing serum insulin levels and decreasing serum glucagon levels.Among all DPP-4 inhibitors, vildagliptin, saxagliptin and teneligliptin are peptide mimetic compounds, which have been discovered by replacing segments of peptide-based substrates. Whereas, sitagliptin, alogliptin and linagliptin are non-peptide mimetic compounds, which Therefore, their chemical structures are diverse, suggesting that each of their binding modes in DPP-4 would be unique.[1,2]

On the basis of binding subsites all DPP4 inhibitors are categorized into 3 classes *(Table 1 & Fig. 1)*.[1]

Class	Criteria	Molecules
I	Binding to S1 & S2 only (interactions with the core S1 and S2 subsites and a covalent bond with Ser 630 in the catalytic triad)	Saxagliptin Vildagliptin
II	Binding to S1, S2 & S'1, S'2 (interactions with the S'1 and / or S'2 subsites in addition to the S1 and S2 subsites	Linagliptin Alogliptin
III	Binding to S1, S2 & S2 extensive subsites (interactions with the S1, S2 and S2 extensive subsites)	Sitagliptin Teneligliptin

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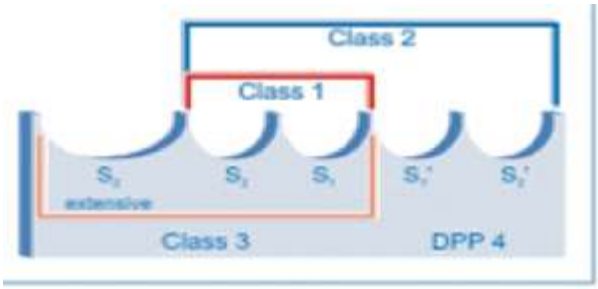

Fig. 1 : **The concept of 3 classes on the basis of the inhibitor's binding subsitesDPP4 inhibitor**

Teneligliptin bind to the S2 extensive subsite. Although both inhibitors appear to bind to the subsites in the same manner, teneligliptin has 5-fold higher activity. Following three potential reasons may be responsible for the difference.

Teneligliptin consists of a considerably rigid which are directly connected, the loss in entropy is small upon binding to DPP-4. [1,3]

1. The carbonyl group of teneligliptin, derived from the peptide mimetics, forms a hydrogen bond with the side chain of Asn710.
2. For teneligliptin, introduction of the "anchorlockdomain", which binds to the S2 extensive subsite, increased the activity by 1500-fold over the corresponding fragments that binds to S1 and S2 only.
3. Because of above mentioned unique features teneligliptin is one of the most potent DPP4 inhibitor ***(Table 2)***

Table 2 : **The DPP-4 inhibitory activity**

Compound	DPP-4 inhibition, IC50 (nmol/L)
Vildagliptin	29.2
Saxagliptin	6.3
Alogliptin	4.9
Linagliptin	0.6
Sitagliptin	10.3
Teneligliptin	1.9

Clinical Particulars :

Therapeutic indications[4,5,6]

Teneligliptin Tablets are indicated as a mono therapy adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In adults, 20 mg of teneligliptin may be orally administered once daily. If this dosage is insufficient, the dosage is increased to 40 mg once daily.

Effects on insulin :

The relative insulin concentrations were higher in the teneligliptin-treated groups because of the decreased blood glucose concentrations of the patients in these groups.

Effects on glucagon :

There were no significant differences in the glucagon concentrations between the two teneligliptin-dosage groups, although glucagon secretion was lower with teneligliptin treatment at 20 mg, particularly after dinner.

Contraindications :

Teneligliptin Tablets are contraindicated in patients with Hypersensitivity to the drug or any of its components. Severe ketosis, diabetic coma or pre-coma and also for immediate remedy in type 1 diabetes. Severe trauma, before and after surgery and when the blood glucose has to be controlled with insulin injection.

Pregnancy and lactation :

Teneligliptin should be used in pregnant women or in women who may possibly be pregnant only if of this product in pregnant women has not been established. Breast-feeding must be discontinued during administration of this product in lactating women (transfer to milk in animal studies (rats) has been reported.).

Undesirable effects :[8]

In clinical trials conducted in Japan, 232 adverse reactions to this drug (including abnormal laboratory tests) were reported in 156 patients (9.5%) of total 1645 patients. The most frequently observed adverse reactions were hypoglycemia in 43 patients (2.6%) and constipation in 14 patients (0.9%).

a) Hypoglycemia

b) Intestinal Obstruction (0.1%)

c) Liver dysfunction (unknown frequency)

d) Interstitial pneumonia (frequency unknown)

Overdose

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Clinical Pharmacology[6]

Mechanism of Action

The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal in response to meal that promotes insulin secretion from pancreas and regulates blood sugar post meal by controlling glucagon secretion. Teneligliptin exhibits a hypoglycemic effect by controlling the degradation of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity and thereby increasing blood concentration of active GLP-1.

Metabolism :

The unaltered substance and the metabolites M1, M2, M3, M4, and M5 were observed in the blood plasma. Furthermore, the ratio of AUC of teneligliptin, M1, M2, M3, M4, and M5 with respect to AUC calculated from the plasma radioactive concentration up to 72 hours after administration was 71.1%, 14.7%, 1.3%, 1.3%, 0.3%, and 1.1%.

Excretion :

When a single oral dose of 20 mg and 40 mg teneligliptin was given to the healthy adults on empty stomach, about 21.0 to 22.1% of dose was excreted as unaltered substance in urine, and the renal clearance was 37 to 39 mL/hr/kg. Dosage radioactivity was excreted in urine and 46.5% was excreted in faeces up to 216 hours after administration. Furthermore, with respect to the dosage up to 120 hours after administration, the accumulated urinary excretion rate of unaltered substance, M1,M2, and M3 was 14.8%, 17.7%, 1.4%, and 1.9%, respectively and the accumulated faeces excretion rate of unaltered substance, M1, M3, M4, and M5 was 26.1%, 4.0%, 1.6%,0.3%, and 1.3%, respectively.

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Table 3 : **Precautions for co-administration of teneligliptin tablets with other drugs**[7]

Drug name	Clinical condition / Measures	Mechanism / risk factors
Drugs for diabetes Sulfonylurea fast-acting insulin secretagogueglucosidase inhibitor BiguanideThiazolidinediones GLP-1 analog preparation SGLT2 inhibitor Insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully observing the patient's condition. Particularly, when co administered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia.	Hypoglycemic action is increased.
Drugs increasing hypoglycemic action-blocking agents Salicylic acid Monoamine oxidase inhibitor	Since the blood sugar may further decrease, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is increased.
Drugs decreasing hypoglycemic action Adrenalin adrenocortical hormone	Since the blood sugar may increase, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is decreased.
Drugs known to cause QT Prolongation Class IA antiarrhythmic drug Quinidine sulfate hydrate, procainamide hydrochloride Class III antiarrhythmic drugs amiodarone hydrochloride, sotalol hydrochloride	QT prolongation might occur.	QT prolongation is with single administration of these drugs

Table 4 : **Other adverse reactions**

Incidence/Types	0.1% ~ 1%	<0.1%
Digestive system	Constipation, abdominal swelling, abdominal discomfort, nausea, increased amylase, increased lipase, acute pancreatitis	
Liver	Increased AST (SGOT), increased ALT (SGPT), and increased -GTP	Rise in ALP
Kidney and urinary system	Albuminuria, positive ketone body in urine, increased uric acid in blood	
Skin	Eczema, Wet rash, pruritus, allergic dermatitis	
Others	Increased CK (CPK), increased serum potassium, fatigue, allergic Rhinitis, and increased serum uric acid	

Table 5 : **Pharmacokinetic parameters at the time of single dose oral drug administration in healthy adults**

Strengths	Cmax (ng/mL)	AUC0-inf (ng.hr/mL)	tmax (hr)	t1/2 (hr)
20 mg	187.20 ± 44.70	2028.9 ± 459.5	1.8 (1.0-2.0)	24.2 ± 5.0
40 mg	382.40 ± 89.83	3705.0 ± 787.0	1.0 (0.5-3.0)	20.8 ± 3.2