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REVIEW ARTICLE

PHARMACOLOGY

LINAGLIPTIN- A NOVEL DPP-IV INHIBITOR

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ABSTRACT

Although glycemic control is an important and effective way to prevent and minimize the worsening of diabetes-related complications, type 2 diabetes is a progressive disease which often proves difficult to manage. Most affected patients will eventually require therapy with multiple medications in order to reach appropriate glycemic targets. The dipeptidyl peptidase-4 (DPP-4) inhibitors constitute a relatively new class of oral medications for the treatment of type 2 diabetes, which has become widely incorporated into clinical practice. Linagliptin is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor in clinical development for the treatment of type 2 diabetes. It exhibits non-linear pharmacokinetics and shows concentration-dependent plasma protein binding to its target, DPP-4.

KEYWORDS

Type 2 diabetes, DPP-4 inhibitor, non-linear pharmacokinetics, Linagliptin, DPP-4, protein binding

INTRODUCTION

Dipeptidyl peptidase-4 (DPP4), also known as adenosine deaminase complexing protein 2 or CD26 (cluster of differentiation 26) is a protein that, in humans, is encoded by the DPP4 gene.

The protein encoded by the DPP4 gene is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis. It is an intrinsic membrane glycoprotein and a serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides. It is a rather indiscriminate enzyme for which a diverse range of substrates are known. The substrates of CD26/DPPIV are proline(or alanine)-containing peptides and include growth factors, chemokines, neuropeptides, and vasoactive peptides.

DPP4 is related to FAP, DPP8 and DPP9.DPP-4 plays a major role in glucose metabolism. It is responsible for the degradation of incretins such as GLP-1.Furthermore, it appears to work as a suppressor in the development of cancer and tumours.CD26/DPPIV plays an important role in tumor biology, and is useful as a marker for various cancers, with its levels either on the cell surface or in the serum increased in some neoplasms and decreased in others. DPP-4 also binds the enzyme adenosine deaminase specifically and with high affinity. The significance of this interaction has yet to be established. [1]

Role Of DPP-4 in Diabetes

Glucagon-like peptide-1 (GLP-1) is a hormone, which is released following meals and stimulates insulin release from the pancreas. Its effects are terminated by breakdown by the enzyme dipeptidyl peptidase IV (DPP-IV). Therefore, inhibition of DPP-IV increases GLP-1 levels in the circulation and, hence, insulin release under conditions when it is needed, i.e. after a meal but not during fasting. Consequently, inhibition of GLP-1 inactivation is an insulinotropic principle, which is unlikely to cause hypoglycemia between meals. The lower risk for hypoglycemic events as compared with other insulinotropic or insulin-sensitizing agents makes DPP-IV inhibitors very promising candidates for a more physiological treatment of type 2 diabetes. [2]

In individuals with type 2 diabetes, the incretin effect appears to be blunted. This blunting has been attributed to 2 factors: GLP-1 levels are lower and GIP exerts a lesser physiologic effect than seen in normoglycemic individuals. Responsiveness to GLP-1 is generally preserved; infusion of GLP-1 to individuals with diabetes has been shown to lower both postprandial and fasting blood glucose levels. Conversely, there appear to be relatively normal levels of GIP in persons with type 2 diabetes, but their physiologic response to GIP is diminished. Whether or not abnormalities in DPP-4 levels or degradative activity exist in patients with diabetes is still unclear. [3]

Dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes:

Inhibitors of Dipeptidyl peptidase 4 , also DPP-4 inhibitors or glyptins, are a class of oral hypoglycemic that block DPP-4. They can be used to treat diabetes mellitus type 2.The first agent of the class - sitagliptin - was approved

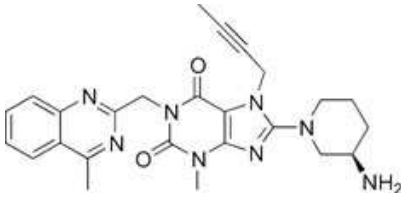
by the FDA in 2006. Sitagliptin entered the Australian drug market in late 2007 for the treatment of difficult-to-control diabetes mellitus type 2. Another DPP-4 inhibitor, vildagliptin, was added to the PBS listings in 2010 on the basis of a similar cost-minimisation basis to sitagliptin. Their mechanism of action is thought to result from increased Incretin levels (GLP-1 and GIP), which inhibit glucagon release which increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.

Drugs belonging to this class are:

- Sitagliptin (FDA approved 2006, marketed by Merck & Co. under the trade name Januvia),
- Vildagliptin (marketed in the EU by Novartis under the trade name Galvus),
- Saxagliptin (FDA approved in 2009, marketed under the trade name Onglyza),
- Linagliptin (being developed by Boehringer Ingelheim),
- Dutogliptin (being developed by Phenomix Corporation),Phase III
- Gemigliptin (being developed by LG Life Sciences,Korea)
- Alogliptin (developed by Takeda Pharmaceutical Company, whose FDA application for the product is currently suspended as of June 2009). [1]

The administration of DPP-4 inhibitors to individuals with type 2 diabetes has been shown to raise levels of endogenous GLP-1 and GIP, which in turn results in a glucose-appropriate increase in insulin secretion and suppression of glucagon release. In patients with type 2 diabetes, administration of DPP-4 inhibitors has been shown to improve markers of insulin processing, including homeostasis model assessment of beta cell function (HOMA-β) and the proinsulin: insulin ratio. Furthermore, there are animal data to suggest that pancreatic beta cell mass may be preserved; beta cells may even be stimulated to grow and proliferate in the presence of these agents. However, no comparable anatomic data in humans are available. [3]

Structure of Linagliptin



Linagliptin (BI 1356, Ondero) is a novel, orally DPP-4 inhibitor currently in development by Boehringer Ingelheim. Unlike the other inhibitors, linagliptin is extensively protein-bound (>80% at the therapeutic dose). Because DPP-4 is expressed in various tissues but soluble DPP-4 is also present in plasma, binding to soluble DPP-4 may influence the PK of linagliptin. High affinity, but readily saturable binding of linagliptin to its target DPP-4 accounted primarily for the concentration-dependent plasma protein binding at therapeutic plasma concentrations of linagliptin. As the DPP-4 binding capacity is saturated already at low doses, accumulation of linagliptin in tissues is unlikely, despite the long persistence of low amounts in the body.

Healthy Subjects

Linagliptin was rapidly absorbed, with *t*max values ranging from 0.7 to 3 h across doses from 2.5 to 600 mg linagliptin given orally once daily. Exposure of linagliptin

increased less than proportionally from 2.5 to 5 mg (estimated therapeutic dose), more than proportionally from 25 to 100 mg and approximately proportionally for doses 100–600 mg.

Patients with Type 2 Diabetes Mellitus

The PK and PD properties of multiple oral doses of linagliptin in patients with T2DM were studied. Linagliptin 1, 2.5, 5 or 10 mg, or placebo, once daily for 12 days administered to 47 male patients. Linagliptin exposure (AUC and *C*max) increased less than proportionally with dose. Accumulation *t*1/2 was rather short (8.6–23.9 h), resulting in rapid attainment of steady state (2–5 days) and little accumulation (range: 1.18–2.03). The long terminal *t*1/2 (113–131 h) led to a sustained inhibition of DPP-4 activity. Renal excretion was only a minor route of linagliptin elimination (overall less than 7%).

Subjects with Renal Impairment

Renal excretion of unchanged linagliptin was below 1% after administration of 5 mg of the DPP-4 inhibitor. As absolute bioavailability was determined to be around 30%,renal excretion is a minor elimination pathway of linagliptin at therapeutic dose levels (in contrast to other DPP-4 inhibitors), and accordingly, a dose adjustment in patients with RI is not anticipated for linagliptin. [5]

Main clinically relevant pharmacokinetics differences between the five dipeptidylpeptidase-4 inhibitors [6]

Characteristics	Sitagliptin	Vildagliptin	Saxagliptin	Alogliptin	Linagliptin
Therapeutic dose(mg/day)	100	2×50	5	12.5-25	5
Half life	Long	Short	Short (but active metabolite)	Long	Very long
Administration	Once daily	Twice daily	Once daily	Once daily	Once daily
Active metabolite	No	No	Yes (BMS-510849)	No	No
Fraction bound to protein(%)	Intermediate	Low	Very low	Rather low	High
Renal excretion	Predominant	Interrmediate	Predominant	Predominant	Low
Dose reduction with renal impairment	Yes (25-50mg)	No	Yes (2.5mg)	Probably yes	Probabl no
Drug drug interactions	No	No	Yes	No	No
Dose reduction with CYP 3A4 inhibitors	No	No	Yes (2.5mg)	No	No

Effects of Other Drugs on Linagliptin Pharmacokinetics

Potential pharmacokinetic or pharmacodynamic interactions between linagliptin and metformin shows that coadministration of metformin did not significantly affect the Cmax of linagliptin but did increase the AUCt by 20%.

Effects of Linagliptin on the Pharmacokinetics of Other Drugs

Linagliptin (10 mg/day) and metformin (850 mg three times daily) administered alone and concomitantly or coadministration of linagliptin had no apparent effect on metformin exposure. Linagliptin has shown no clinically significant pharmacokinetic interactions with commonly prescribed oral glucose lowering agents (metformin, pioglitazone, glibenclamide) and with drugs commonly used in patients with cardiac disorders (warfarin, digoxin). Potential effect of linagliptin (10 mg/day) on the pharmacokinetics of simvastatin (40 mg/day). Plasma concentrations of simvastatin and its active metabolite simvastatin beta-hydroxy acid were determined. The GMRs (90%CIs) of the AUC values were 134.2%(119.4, 150.7) for simvastatin and 133.3% (118.1, 150.3) for simvastatin acid following coadministration of linagliptin with simvastatin, compared with administration of simvastatin alone. [5]

CONCLUSION

As HbA1c and FPG levels are key diagnostic indicators for effective management of Type 2 diabetes, the drug Linagliptin a dipeptidyl peptidase (DPP)-4 inhibitor, achieved significant, sustained and clinically meaningful reductions in blood glucose as measured by haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) concentrations. All doses of linagliptin showed superior HbA1c reduction compared to metformin alone.

Apart from it Linagliptin showed an excellent tolerability, weight neutrality, showed no increased risk of drug-drug interactions and, importantly, there was no increased risk of hypoglycaemia attributed to linagliptin use in monotherapy, or combination therapy with metformin or pioglitazone. The significant efficacy results together with the favourable safety profile shown by the drug linagliptin proves to be a Novel (DPP)-4 inhibitor.

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