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DPP-4-inhibitors – What are the similarities, where are the differences?

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Abstract
With the increasing prevalence of type 2 diabetes and its complications throughout the world, there is a need for efficient and safe therapeutic strategies. The dipeptidyl peptidase-4 (DPP-4) inhibitors have become important oral glucose lowering drugs for the management of patients with type 2 diabetes. All DPP-4-inhibitors act on the incretin system to lower hyperglycemia, have a similar safety profile, are well tolerated, do not cause significant weight gain and have a relatively low risk of hypoglycemia. However, there are clinical differences among the four agents, sitagliptin, vildagliptin, saxagliptin, and linagliptin which are currently approved by the US Food and Drug Administration or the European Medicines Agency. This review article discusses similarities and differences in efficacy, safety and tolerability of these four DPP-4-inhibitors.

Key words: DPP-4-inhibitors – vildagliptin – sitagliptin – saxagliptin – linagliptin – type 2 diabetes – incretin system – GLP-1

Introduction

Nutrient intake stimulates the release of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) into the circulation [1,2]. Important functions of both incretins include potentiating glucose-dependent insulin secretion from pancreatic beta-cells and inhibiting glucagon secretion, which in turn reduces hepatic gluconeogenesis [2]. The effect of incretins is significantly reduced in patients with type 2 diabetes (T2D) and contributes to impaired insulin secretion and chronic hyperglycemia [3]. Under normal physiological conditions, dipeptidyl peptidase-4 (DPP-4) rapidly degrades GIP and GLP-1 [2]. Inhibition of DPP-4 is a therapeutic option to lower hyperglycemia in patients with T2D. DPP-4 is a 766 amino acid membrane-associated, serine-protease enzyme [4]. The enzyme is widely detected in numerous tissues such as kidney, liver, intestine, spleen, lymphocytic organs, placenta, adrenal glands, and vascular endothelium [4]. DPP-4-inhibitors are relatively new class of oral glucose lowering drugs. DPP-4-inhibitors exert their hypoglycemic effect indirectly by increasing plasma concentration, duration and action of incretins [2,4]. DPP-4-inhibitors are orally active, small molecular weight drugs that can inhibit more than 90% of plasma DPP-4 activity for over 24 h period [4]. These agents increase active GLP-1 levels by preventing their rapid degradation. Therefore, DPP-4-inhibitors are dependent on endogenous incretin secretion and could thus be effectively used in early stages of T2D development, when pancreatic beta cell function is not completely exhausted [1,2,4].

Sitagliptin, vildagliptin, saxagliptin, and linagliptin are DPP-4-inhibitors currently approved by the US Food and Drug Administration or the European Medicines Agency, while others are awaiting approval or are in development. In addition, alogliptin is approved in Japan only and several other DPP-4-inhibitors including denagliptin and dutogliptin are in clinical testing [4]. DPP-4-inhibitors are orally active, small molecular weight drugs that can inhibit more than 90% of plasma DPP-4 activity for over 24 h period [4]. These agents increase active incretin levels by preventing their rapid degradation. Thus, DPP-4-inhibitors are dependent on endogenous incretin secretion and could thus be effectively used early in T2DM, when pancreatic beta-cell store of insulin is not completely exhausted [4]. DPP-4-inhibitors have demonstrated a favorable safety and tolerability profile in clinical studies of patients with T2D [4]. Other beneficial effects observed in animal and *in vitro* studies include inhibition of beta-cells apoptosis [5] caused by glucotoxicity and/or lipotoxicity [6] and modulation of beta-cell mass and islet cell proliferation [7].

In a recent meta-analysis of 19 studies including 7 136 patients randomized to a DPP-4-inhibitor and 6 745 patients randomized to another hypoglycemic drug it was reported that in monotherapy, metformin is superior to DPP-4-inhibitors in reducing HbA_{1c} and body weight but is associated with a higher incidence

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of diarrhoea, nausea, and vomiting [8]. In combination with metformin, DPP-4-inhibitors seem to have similar glycemic efficacy to sulfonylureas but without the risk of body weight gain and hypoglycemia [8]. Therefore, DPP-4-inhibitors can be used as second line treatment in patients with type 2 diabetes who do not achieve their glycemic targets with metformin alone or as monotherapy in patients who do not tolerate metformin [8]. The long term safety of all DPP-4-inhibitors remains to be answered from ongoing trials.

Currently available DPP-4-inhibitors

Several DPP-4-inhibitors have been developed including vildagliptin, sitagliptin, saxagliptin and linagliptin. DPP-4-inhibitors are rapidly absorbed when given orally and the maximal concentration is observed within 1–2 h of administration [4]. Bioavailability of DPP-4-inhibitors is said to be more than 80% after oral dosage [4]. Vildagliptin is hydrolyzed to an inactive compound excreted via the kidney into urine and approximately 20% of vildagliptin is disposed from our body unchanged [4]. In contrast, sitagliptin is primarily excreted as molecule by the kidney and, therefore, renal insufficiency may increase the circulating level of sitagliptin [9] leading to abnormal plasma levels of the drug. An overdose of sitagliptin may possibly lead to hypoglycaemia [4,9]. Saxagliptin is mainly metabolised in the liver, whereas the active compound and unconverted saxagliptin and other metabolites are released via the kidney [4]. Hepatic insufficiency does not seem, therefore, to alter the pharmacokinetics of these compounds. The risk for drug-drug interaction does not seem to be an major problem for patients taking DPP-4-inhibitors [4,9]. Linagliptin is a xanthine-based, DPP-4-inhibitor, mainly excreted in the feces [10].

Vildagliptin

Vildagliptin was the first developed DPP-4-inhibitor, which has been approved as second DPP-4-inhibitor (following sitagliptin) in the Europe Union in 2008 [4]. Vildagliptin has a high affinity for DPP-4, increases fasting and postprandial GLP-1 level, and induces pancreatic beta-cell sensitivity to glucose and insulin [11]. Vildagliptin also significantly lowers postprandial lipaemia and increases insulin release with a simultaneous reduction in glucagon levels especially in the post-meal period [4,12]. It causes a reduction in glucagon/insulin ratio and significantly lowers endogenous glucose production during both the postprandial and post-absorptive phases [12]. In the largest clinical trial program of the class of DPP-4-inhibitors, vildagliptin has been shown to induce significant improvements in glycemic control in patients with T2D when used alone or in combination with other hypoglycemic agents such as metformin [4]. Without the risk of weight gain, vildagliptin improves pancreatic beta-cell function in patients with T2D [4]. Moreover, plasma concentrations of proinsulin are significantly reduced in patients treated with vildagliptin [11]. Vildagliptin can reduce lipolysis as well as postprandial hypertriglyceridemia [4]. Importantly, in a recent human pilot study, vildagliptin has been shown to improved peripheral glucose utilization and insulin sensitivity [13].

Sitagliptin

Sitagliptin is the first FDA approved DPP-4-inhibitor for monotherapy of T2D and can also be given in combination with metformin or glitazone, when glycemic goals can not be achieved by metformin plus life style modifications [4]. Recent reports suggested that sitagliptin can be added to either metformin, or glitazone, or a sulfonylurea, or in a triple combination with both metformin and a sulfonylurea, but not with a glinide [4]. Given as monotherapy, sitagliptin induces a significant up 80% to 96% inhibition of DPP-4 activity resulting in an increased GLP-1 response to oral glucose tolerance testing [4]. Administration of sitagliptin to streptozocin-induced diabetic rats, fed on high-fat diet caused large and significant increases in the number of pancreatic beta-cell in the islets of Langerhans, resulting in improved beta-cell mass and beta-cell-to-alpha-cell ratio [4,14]. In addition, sitagliptin prevents the development of metabolic and hormonal disturbances, increased beta-cell apoptosis and liver steatosis induced by a fructose-rich diet in normal rats [14].

Taken together, sitagliptin reduces HbA_{1c}, triglyceride and free fatty acid serum concentration in patients with T2D.

Saxagliptin

Saxagliptin is a more recently approved selective and reversible DPP-4-inhibitor. Saxagliptin is another potent DPP-4-inhibitor, requiring about 10 times lower doses than vildagliptin or sitagliptin [4]. As for the other DPP-4-inhibitors, saxagliptin has been shown to effectively reduce hyperglycemia in drug-naive patients with T2D, but also in combination treatment strategies [4,8].

Some studies have examined the efficacy of saxagliptin and other drugs in inadequately controlled patients with T2DM in terms of the degree of reductions in HbA_{1c}. The administration of saxagliptin at dosages of 2.5–10 mg, once-daily, in combination with metformin provided significant reductions in HbA_{1c} level when compared to placebo [4]. It has been reported that patients tolerate saxagliptin well, as it does not cause significant hypoglycaemia and weight gain and is therefore similar to the other approved DPP-4-inhibitors [4].

Linagliptin

Linagliptin, a xanthine-based, highly potent and long-acting non-peptidomimetic DPP-4-inhibitor, was recently approved in the United States for the treatment of T2D [4]. In animal and *in vitro* studies, linagliptin demonstrated a greater inhibition of DPP-4 than alogliptin, saxagliptin, sitagliptin, or vildagliptin [14]. After absorption, linagliptin binds to plasma proteins in a concentration-dependent manner, giving the drug

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a nonlinear pharmacokinetic profile [14]. Unlike other DPP-4-inhibitors that are cleared by the kidney, linagliptin is mainly excreted in the feces [10]. The high therapeutic index and a placebo-like safety profile support once-daily dosing with linagliptin in patients with T2D, with no requirement for dose adjustment in patients with renal impairment [15].

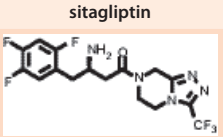
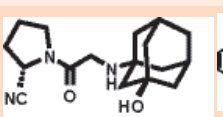
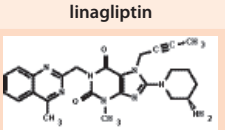
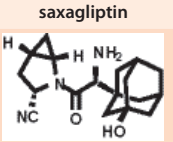
Differences in DPP-4 inhibition between DPP-4-inhibitors

DPP-4-inhibitors show significant structural heterogeneity, which could translate into different pharmacological properties [15]. At the pharmacokinetic level, DPP-4-inhibitors have important differences, including half-life, systemic exposure, bioavailability, protein binding, metabolism, presence of active metabolites and excretion routes (Table). These differences could be relevant, especially in patients with renal or hepatic impairment, and when considering combination therapy. At the pharmacodynamic level, the data available so far indicate a similar glucose-lowering efficacy of DPP-4-inhibitors [15,16], either as monotherapy or in combination with other hypoglycaemic drugs, a similar weight-neutral effect, and a comparable safety and tolerability profile [17]. Data on non-glycemic parameters including effects on blood pressure, endothelial function, lipid parameters, liver steatosis and inflammation are scant at present and do not allow a comparison among DPP-4-inhibitors [17].

The molecular structures and pharmacokinetics of DPP-4-inhibitors are different (Table). However, the mechanism of action of the various DPP-4-inhibitors appears to be similar. All of the named therapies inhibit DPP-4 activity by greater than 80%, which is the level of inhibition at which maximal glucose lowering is seen. Sitagliptin and linagliptin are competitive antagonists of DPP-4 while vildagliptin, as well as saxagliptin are substrates for DPP-4, thereby inhibiting the target molecule [4]. DPP-4-inhibitors may also be differentiated by their metabolism and mode of excretion. Vildagliptin is metabolized at the kidney prior to excretion, saxagliptin is partially metabolized by the liver, and sitagliptin is largely unmetabolized prior to excretion by the kidney [15,16]. Sitagliptin is approved for use in patients with renal insufficiency, although a dose reduction is necessary in patients with moderate or severe renal dysfunction. Sitagliptin should be reduced to 50 mg daily for creatinine clearance 30 to < 50 mL/min and to 25 mg daily for creatinine clearance < 30 mL/min [16]. Sitagliptin does not induce the CYP3A4 system and is not expected to interact with drugs metabolized through this pathway [16]. Moreover, adverse drug–drug interactions have not been seen in studies evaluating combinations with glyburide, metformin, rosiglitazone, and pioglitazone [15]. Drug metabolism does not differ between obese and lean subjects as well as in patients with diverse ethnic backgrounds, including Japanese, Korean, Chinese, and Indian subjects, with similar activity in all of these groups [16].

Vildagliptin is may be prescribed at dosages of 50 mg once or twice daily [15,16]. Vildagliptin has recently been studied in patients with moderate to severe renal

Table Similarities and differences between the DPP-4-inhibitors sitagliptin, vildagliptin, linagliptin and saxagliptin. Modified from [15]

	sitagliptin	vildagliptin	linagliptin	saxagliptin
chemical structure				
substrate binding	non-covalent	covalent	non-covalent	covalent
duration of substrate binding	very short	~ 55min	short	> 30min
administration therapeutic dose	peroral, OD 100 mg	peroral, BID 2 × 50 mg	peroral, OD 5 mg	peroral, OD 5 mg
renal clearance (%)	70	31	NA	5
dose reduction with renal impairment	yes	no	no	yes
excreted in faeces (%)	13	4	22	>90
clinical effects	HbA_{1c} lowering, improving post-prandial glucose improved GLP-1 action glucagon suppression, suppression of endogenous glucose production			
additional advantages		reduced mean amplitude of glucose excursions (MAGE) improved insulin sensitivity	improved insulin sensitivity	

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dysfunction [18,19]. In these studies, vildagliptin at dosages of 50 mg once daily has been shown to be safe and effective in patients with renal impairment [18] including patients on hemodialysis [19]. Similar to sitagliptin, it is excreted predominantly in the urine [15]. Metabolism occurs at the level of the kidney and not through the CYP3A4 system, thus vildagliptin does not affect this enzymatic system [16]. Coadministration of metformin and vildagliptin in patients with T2D resulted in small and clinically insignificant effects on the pharmacokinetics of each drug; however, neither drug should require a dose adjustment in the presence of the other [16]. Significant drug interactions with vildagliptin have not been seen in studies with glyburide, pioglitazone, ramipril, amlodipine, valsartan, simvastatin, digoxin, or warfarin [16]. Drug metabolism does not appear to be affected by gender, body mass index or ethnic background [15,16]. In contrast to sitagliptin and vildagliptin, saxagliptin is metabolized via CYP 3A4/A5 [15]. For linagliptin renal excretion of the unchanged drug was below 1% after administration of 5 mg of the DPP-4-inhibitor [15]. 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 renal impairment is not necessary for linagliptin [15]. Whether these differences in the profile of the currently available four DPP-4-inhibitors translates into clinically relevant differences concerning the efficacy and safety profile in patients with T2D remains to be determined. In the clinical practice, the most obvious difference is that vildagliptin dose should be splitted in two administrations per day (2 × 50 mg), whereas other gliptins are prescribed once a day (sitagliptin 100 mg/day, saxagliptin 5 mg/day, linagliptin 5mg/day). The efficacy of the different DPP-4-inhibitors is difficult to compare, since data were obtained in individual randomized clinical trials. However, it has been recently suggested that improvement in HbA_{1c} is more pronounced at a given baseline HbA_{1c} with vildagliptin compared to all other DPP-4-inhibitors [20].

Direct comparison between sitagliptin and vildagliptin

Since sitagliptin (as a competitive antagonists of DPP-4) and vildagliptin, which acts as substrate for DPP-4 have distinct pharmacokinetics, differences in clinically relevant parameters of glycemic control have been suggested [15,16]. Therefore, efficacy of sitagliptin 100 mg once daily was compared to vildagliptin 50 mg twice daily on daily blood glucose fluctuations in patients with T2D in a recent study including a total 38 individuals [21]. Patients with T2D have been included into the study when glycemia was inadequetaly controlled by metformin. Glucose metabolism was characterized by 48 hours continuous subcutaneous glucose monitoring (CSGM) over 3 months [21]. Although sitagliptin and vildagliptin were indistinguishable effective in improving fasting, post prandial and mean plasma glucose concentrations, the mean amplitude of glycemic excursions (MAGE) was significantly higher in the sitagliptin compared to the vildagliptin group [21]. The differences in improving MAGE may be due to significantly more pronounced increase in GLP-1 activity during interprandial period in vildagliptin compared to sitagliptin treated patients [21]. In addition, meal related glucagon secretion was more suppressed in subjects receiving vildagliptin compared to those receiving sitagliptin [21]. The difference between sitagliptin and vildagliptin in improving diurnal glucose variability may be clinically important, since there is increasing evidence that glycemic disorders such as rapid glucose fluctuations over a daily period might play an important role in the development of metabolic and cardiovascular complications [21,22]. Glycemic variability has been associated with mortality in critically ill patients [22]. It has been shown in a large survey of more than 4,000 individuals requiring intensive care, that higher daily glucose variations are associated with increased mortality, even after adjustment for severity of illness [22]. The effects of higher glucose excursions were independent of T2D [22]. From such studies, it can be concluded that minimizing mean amplitude of glycemic excursions may have significant beneficial impact on outcomes of T2D patients.

Summary and conclusions

There is an unmet need for effective and safe innovative treatment strategies to improve the management of patients with type 2 diabetes. New compounds have been developed for improving glucose-induced insulin secretion and glucose control, without the elevated risk of inducing hypoglycaemia or weight gain. Dipeptidylpeptidase-4 (DPP-4) inhibitors are new oral glucose-lowering agents, which may be used as monotherapy or in combination with other antidiabetic compounds. Sitagliptin, vildaglipin, saxagliptin and linagliptin are approved in many countries, either as single agents or in fixed-dose combined formulations with metformin. In general DPP-4-inhibitors are effective in improving hyperglycemia, are well tolerated without inducing hypoglycaemia or weight gain. Among DPP-4-inhibitors there are important differences, including half-life, systemic exposure, bioavailability, protein binding, metabolism, presence of active metabolites and excretion routes. Such differences may explain differences in efficacy and the safety profile of different DPP-4-inhibitors.

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