Dipeptidyl Peptidase-IV Inhibitors: Pharmacological Profile and Clinical Use

John R. White, Jr., PA, PharmD

A decade and a half ago, the choice of an oral antihyperglycemic agent for any particular patient was in some ways a debate of nuance. Sulfonylureas (SUs) were the only class available, and providers were left to sift though pharmacokinetic, small efficacy, and sometimes significant side effect differences among the various choices within this class. The situation today demands a more robust evaluation of multiple categories of medications with different mechanisms of action. Providers must consider the possible choices of an SU, a biguanide, an α-glucosidase inhibitor, a meglitinide, a thiazolidinedione (TZD), a bile acid resin (BAR), or a dipeptidyl peptidase-IV (DPP-IV) inhibitor. In addition, several injectable compounds are available for the treatment of hyperglycemia. This article provides an overview of the function of the endogenous DPP-IV enzyme system and the pharmacology and clinical use of DPP-IV inhibitors.

Incretin Hormones and DPP-IV

Any discussion of DPP-IV and its inhibitors would be incomplete without mention of the endogenous incretin hormones glucagon-like peptide-1(GLP 1) and glucose-dependent insulinotopic hormone (GIP). These hormones are released from the L and K cells of the gastrointestinal tract, respectively, when those cells are stimulated by intraluminal glucose.[1] Both GLP-1 and GIP cause a glucose-dependent increase in insulin secretion. GLP-1 also contributes to glucose homeostasis through its effects on insulin biosynthesis and its inhibition of glucagon release.[2]

Because GLP-1 stimulates insulin secretion only under hyperglycemic conditions, there is minimal risk of hypoglycemia, making this molecule and its congeners likely candidates for use as antihyperglycemic agents. GLP-1 is also associated with increased satiety, possibly because it reduces the rate of gastric emptying. People with type 2 diabetes have reduced circulating levels of GLP-1 but retain their ability to respond to this hormone. Thus, it is possible to improve glycemic control through administration of exogenous GLP-1.

Unfortunately, under normal physiological conditions, GLP-1 and GIP are rapidly degraded by the enzyme system DPP-IV and therefore are not themselves viable as pharmacological agents. The creation of molecules that circumvent or reduce the rate degradation by DPP-IV while maintaining the agonist effects of GLP-1 has been pursued aggressively. One GLP-1 analog (exenatide) is available in the United States, and another (liraglutide) is in phase III trials.

In addition to GLP-1 analogs, molecules that inhibit the activity of DPP-IV and thereby prolong the activity of endogenous GLP-1 are of great interest. Because GLP-1 analogs are proteinacious in structure, they will most likely all require administration via injection, as exenatide does already. In contrast, DPP-IV inhibitors may be smaller molecules that can be absorbed intact from the gastrointestinal tract, making their oral administration possible. One DPP-IV agent (sitagliptin) is available; the Food and Drug Administration (FDA) approval of another (vildagliptin) is probably imminent; and several others (saxagliptin, alogliptin, and denagliptin) are in development. DPP-IV inhibitors are an important addition to the list of pharmacological options for the treatment of hyperglycemia.

IN BRIEF

Sitagliptin is the first agent in a new category of medications, the dipeptidyl peptidase-IV (DPP-IV) inhibitors. It was recently approved in the United States for the management of hyperglycemia in patients with type 2 diabetes; vildagliptin, a second agent in this class, is likely to join it on the U.S. market soon. These compounds accentuate the activity of endogenously produced antihyperglyemic incretin hormones and are generally well tolerated. This article provides an overview of the pharmacology and clinical use of the DPP-IV inhibitors.

Effects of DPP-IV Inhibitors

Based on the effects of the DPP-IV enzyme system, inhibition presumably would result in increased serum levels of GLP-1, leading to a net antihyperglycemic effect. This effect has been demonstrated in both animal and human models. Animal trials evaluating the impact of DPP-IV inhibition have demonstrated improvement in glucose tolerance, enhancement of insulin secretion, and even delay in the onset of overt diabetes

in Zucker diabetic fatty rats.[3] Further animal studies have suggested that inhibition of DPP-IV improves insulin sensitivity and may reverse glucose toxicity.[4] It has been suggested that DPP-IV inhibition and its resultant preservation of endogenous GLP-1 activity may lead to β-cell preservation via augmentation of GLP-1's antiapopotic effects.

Although DPP-IV inhibition has been associated with an enhancement of β-cell survival and neogenesis in streptozotocin-treated diabetic rats,[4] this effect has not yet been demonstrated in humans. This exciting possibility undoubtedly will be evaluated in humans as a potential agent or class of agents for the prevention of type 2 diabetes.

DPP-IV inhibitors probably exert most, if not all, of their pharmacological effects in humans by inhibiting the degradation of GLP-1. Through this function, they cause some of the same effects of GLP-1, including stimulation of insulin secretion, inhibition of glucagon secretion, and enhancement of β-cell mass.[1] Conversely, they seem to have only a marginal slowing effect on the rate of gastric emptying and no obvious effect on satiety or weight loss.[1] Table 1 compares the action of endogenous GLP-1 with that of DPP-IV inhibitors.

Table 1. Effects of Endogenous GLP-I Versus DPP-IV Inhibition

Feature of Type 2 Diabetes	Action of Endogenous GLP-1	Mimicked by DPP-IV Inhibitors?
Impaired insulin secretion	Glucose-dependent stimulation of insulin	Yes
Hyperglucagonemia	Suppression of glucagon secretion	Yes
Reduced pancreatic β-cell mass	Increased synthesis of proinsulin	Yes
Abnormally high rate of β-cell apoptosis	Inhibition of β-cell apoptosis	Probably
Gastric emptying accelerated, decelerated, or normal	Deceleration of gastric emptying	Marginally
Hypercaloric energy intake/obesity	Suppression of appetite/ induction of satiety Weight loss	Not obvious No

Adapted from Ref. 1

Sitagliptin

In October 2006, sitagliptin became the first DPP-IV inhibitor to gain FDA approval for the treatment of type 2 diabetes. Sitagliptin tablets are commercially available as 100-mg (beige), 50-mg (light beige), and 25-mg (pink) tablets.[5] Sitagliptin is also available in a combination product with metformin in doses of 50 mg sitagliptin/500 mg metformin and 50 mg sitagliptin/1,000 mg metformin.

The usual recommended dose of sitagliptin is 100 mg per day. However, the agent is available in three strengths to allow for lower dosing in patients with moderate to severe renal impairment. The sitagliptin-metformin combination should be taken twice daily with meals and titrated slowly to minimize potential gastrointestinal side effects associated with metformin.

Clinical trials

Clinical trials have demonstrated that sitagliptin is safe and efficacious for the management of hyperglycemia in type 2 diabetes. One phase III trial demonstrated that sitagliptin administered in 100-mg and 200-mg daily doses reduced hemoglobin A_{1c} (A1C) levels by 0.79 and 0.94%, respectively, at 24 weeks. These differences were statistically significant when compared to placebo ($P < 0.001$).[6] Patients with A1C levels > 9.0% showed greater reductions in A1C. Improvements in fasting plasma glucose and postprandial glucose levels were also reported in those treated with sitagliptin.

In another report, daily doses of 100 mg sitagliptin were associated with statistically significant ($P < 0.001$) 0.65% reductions in A1C in patients with an initial mean A1C of 8%.[7]

Sitagliptin also has been evaluated in combination with other antihyperglycemic medications. In one trial, 701 patients with a mean baseline A1C of 8% (range: 7–10%) who were previously treated with metformin continued therapy with metformin and were randomized to receive either 100 mg sitagliptin or placebo daily for 24 weeks.[8] Patients in the placebo group experienced no changes in A1C, whereas those treated with sitagliptin plus metformin realized a 0.65% reduction in A1C at 24 weeks. In the combination therapy group, 47% of the patients concluded the trial with A1C levels < 7%, and 17% reached an A1C of < 6.5%. Only 18% of patients in the placebo group reached an A1C level < 7%, and only 5% reached an A1C < 6.5%. Similar results have been published from other clinical trials evaluating the efficacy of combination metformin and sitagliptin therapy.[9,10]

One study evauated 353 patients previously treated with pioglitazone.[11] Patients received either 100 mg sitagliptin or placebo daily in addition to 30 or 45 mg/day pioglitazone for 24 weeks. Mean baseline A1C values reported in this trial were 8% (range: 7–10%) at the completion of a short run-in period pioglitazone. A mean reduction in A1C of 0.7% was reported in patients treated with combination therapy, compared

to no significant change in A1C in the placebo group.

In summary, evidence suggests that sitagliptin is an efficacious antihyperglycemic agent when used as monotherapy or in combination with metformin or pioglitazone for the treatment of type 2 diabetes. In addition to favorable changes in A1C, clinical trials of sitagliptin have shown improvement in fasting and postprandial glucose levels.

Side effects, contraindications, and precautions

Patients treated with sitagliptin monotherapy or combination sitagliptin-metformin or sitagliptin-pioglitzone therapy had an incidence of adverse events and rates of discontinuation of therapy similar to those of control subjects. Three side effects have been reported to occur with more frequency in sitagliptin-treated patients than in control subjects: nasopharyngitis (5.2% in the sitagliptin group vs. 3.3% in the placebo group), upper respiratory tract infection (6.3% in the sitagliptin-pioglitazone group vs. 3.4% in the pioglitazone-only group), and headache (5.1% in the sitagliptin-pioglitazone group vs. 3.9% in the pioglitazone-only group).

The sitagliptin package insert reports that a slight increase in white blood cell count (~ 200 cells/µl) was observed in patients treated witih sitagliptin compared to those receiving placebo. This small increase primarily results from an increase in the number of neutrophils. This observation was deemed clinically insignificant by investigators.[5]

The reported incidence of hypoglycemia in subjects receiving sitagliptin is similar to that in control subjects (1.2 vs. 0.9%). Additionally, the occurrence of hypoglycemia with sitagliptin treatment is not enhanced by the addition of metformin or pioglitazone.[5,12,13]

Sitagliptin is a pregnancy risk Category B agent and should only be used during pregnancy if deemed necessary. Caution is also advised in women who are nursing. It is currently unknown whether sitagliptin is secreted in human breast milk, and the effects on nursing babies are also unknown.

Safety and efficacy in patients < 18 years of age have not been studied, but nothing thus far suggests that problems would result from using the agent in younger patients with type 2 diabetes.

Sitagliptin is contraindicated in patients with type 1 diabetes and is not intended for use in the treatment of diabetic ketoacidosis.[5] Patients with moderate renal insufficiency receiving 50 mg/day sitagliptin had a slightly greater increase in serum creatinine (0.05 mg/dl) than matched control subjects with the same degree of renal impairment receiving placebo.[14]

Pharmacokinetics and drug interactions

Sitagliptin is an interesting compound from a pharmacokinetic standpoint, in part because it is an enzyme inhibitor. Its inhibition of DPP-IV results in prolonged incretin activity, which in turn results in enhanced glucose-dependent insulin release.[15] Dipeptidyl peptidase encompasses a large family of enzymes. Full-scale inhibition of an enzyme system such as this could cause myriad deleterious effects, and, because of this, the selectivity of an inhibitor is of prime importance. Sitagliptin exhibits a > 2,600-fold higher affinity for DPP-IV than for structurally related DPP-VIII and DPP-IX enzymes.[16] Sitagliptin has not been associated with toxicity as a result of inhibition of these related enzyme systems.[17]

Sitagliptin is rapidly absorbed (peak concentration at 1–4 hours) after oral administration and has a high oral bioavailability (F = 0.87). Clinical trials to date have reported no correlation between changes in the pharmacokinetic parameters of sitagliptin and age, sex, race, or BMI. The average volume of distribution (Vd) at steady state is 198 l after a single dose of sitagliptin. Sitagliptin is moderately bound to plasma proteins (bound fraction = 38%).[5]

Sitagliptin is primarily excreted in an unchanged form in the urine (79%) via active tubular secretion. The terminal t1/2 of sitagliptin was 12.4 hours after a single 100-mg dose in healthy volunteers.[5] A relatively small fraction of sitagliptin undergoes hepatic metabolism primarily via cytochromes P450 3A4 and 2C8.[18] However, when sitagliptin pharmacokinetics were studied in patients with moderate hepatic impairment (Child-Pugh score 7–9), significant differences in pharmacokinetic parameters were not found.[19]

Because of limited hepatic metabolism of sitagliptin by cytochrome P450 enzymes 3A4 and 2C8, it is not considered likely that any clinically relevant interactions exist with other drugs that use the cytochrome P450 system or p-glycoprotein transport system. This statement is supported by the fact that no clinically important pharmacokinetic interactions requiring dosage adjustment were identified during clinical trials.[5]

Because sitagliptin is primarily eliminated unchanged via renal excretion, dosage adjustments are required for patients with moderate to severe renal impairment. A dose of 50 mg/day is recommended in patients with a creatinine clearance (CrCl) ≥ 30 to < 50 ml/min. A dose of 25 mg/day is recommended for patients with a CrCl < 30 ml/min or in patients with end-stage renal disease requiring dialysis.[5]

Dosage and indications

Sitagliptin is available commercially in 25-mg, 50-mg, and 100-mg tablets. It is indicated for mono- or combination therapeutic management of hyperglycemia in patients with type 2 diabetes. In patients with normal renal function, it is dosed at 100 mg daily; in patients with CrCl ≥ 30 to < 50 ml/min, the dose is 50 mg/day; and in patients with CrCl < 30 ml/min, the dose is 25 mg daily. It can be taken with or without food.

Vildagliptin

FDA approval for vildagliptin, a second DPP-IV inhibitor, is being sought. The FDA has asked the manufacturer to provide additional safety data for review before approval.

Clinical trials

Vildagliptin has been evaluated for the management of hyperglycemia in type 2 diabetes as monotherapy and in combination with metformin, pioglitazone, or insulin and has demonstrated ability to improve glycemic control in type 2 diabetes.[20–22] Patients treated with 100 mg/day vildagliptin for 24 weeks showed mean reductions in A1C of 1.1% from a mean baseline A1C of 8.7% in 1,301 subjects *(P* < 0.01 vs. baseline values).[23]

The addition of vildagliptin to metformin therapy resulted in improved glycemic control compared to metformin plus placebo.[24] After ~ 1 year of combination vildagliptin-metformin therapy, 41.7% of subjects achieved a A1C level of 7% (from a baseline level of 7.6–7.8%). Conversely, only 10.7% of patients on metformin plus placebo reached an A1C < 7%.

Vildagliptin has also been shown to be effective when used with pioglitazone.[25] Patients treated with either 50 mg/day vildagliptin plus 15 mg/day pioglitazone or 100 mg/day vildagliptin plus 30 mg/day pioglitazone for 24 weeks achieved greater improvements in A1C values from baseline compared to subjects receiving 30 mg/day pioglitazone as monotherapy. Mean A1C changes from baseline were −1.7, −1.9, and −1.4%, respectively *(P* < 0.05).

Another trial evaluated 256 patients whose diabetes was inadequately controlled on insulin therapy. This study demonstrated that the addition of vildagliptin resulted in improvement in glycemic control endpoints for these patients.[26] Patients receiving 50 mg vildagliptin twice daily in addition to their insulin therapy experienced a statistically significant reduction in A1C of 0.5% versus a reduction of 0.2% in the placebo-plus-insulin group *(P* = 0.022) after 24 weeks of therapy.

In summary, studies have suggested that vildagliptin is useful in the management of hyperglycemia in patients with type 2 diabetes as a monotherapeutic agent and when used in conjunction with metformin, pioglitazone, or insulin.

Side effects, contraindications, and precautions

Vildagliptin was generally well tolerated in phase III trials. One case of significant peripheral edema was reported and attributed to the study drug in clinical trials of vildagliptin. In this case, peripheral edema was reported in a patient treated with vildagliptin plus metformin in a 40-week extension of the vildagliptin-plus-metformin combination therapy study.[24]

Withdrawal rates from clinical trials because of adverse events were low in monotherapeutic and combination therapy studies (3.2–7.8% and 1.4%, respectively), and no deaths resulted in either study.[24,27]

The most common adverse events reported with vildagliptin were mild and included nasopharyngitis, headache, and dizziness. Vildagliptin has been associated with very few episodes of hypoglycemia when used as monotherapy or in combination with other antihyperglycemic medications. No significant laboratory abnormalities have been observed during or resulting from trials involving vildagliptin.[28]

Pharmacokinetics and drug interactions

As has been observed with sitagliptin, the pharmacokinetic parameters of vildagliptin appear unaffected by age, sex, and BMI.[29] Vildagliptin is rapidly absorbed with maximal concentrations being reached within 1–2 hours after an oral dose of the drug.[30] The oral bioavailability of vildagliptin appears to be similar to sitagliptin (F = 0.85). The reported volume of distribution at steady state is a mean of 70.5 l.[29]

Vildagliptin is hydrolyzed to a pharmacologically inactive metabolite. Excretion of this metabolite is carried out mainly through the urine (85%), with 15% excreted within the feces. The mean terminal t1/2 of vildagliptin has been reported to be between 1.68 and 2.54 hours.[31] The disparity between the long duration of action of vildagliptin and the short plasma half-life is thought to be the result of the slow-binding inhibition kinetics seen with this agent.[32]

Vildagliptin does not appear to induce or inhibit the cytochrome P450 enzyme system.[30] The t1/2 was not affected by the presence of hepatic impairment when studied.[33] Additional clinical trials are underway to evaluate the potential effects of renal impairment on the pharmacokinetic disposition and clinical activity of vildagliptin.

Drug interaction data for vildagliptin are limited. However, clinically significant drug interactions have not been reported in clinical trials involving the coadministration of pioglitazone,[34] metformin,[35] or glyburide.[31]

Dosage and indications

Because of the pending FDA review of vildagliptin, the adult daily dosage for which the manufacturer will receive approval is not known, although one could assume that the dose in an adult with normal renal function will probably be 100 mg/day.

Summary

One DPP-IV inhibitor is available for use in the United States, and the approval of a second agent is imminent. DPP-IV inhibitors offer a safe and efficacious method for modestly reducing hyperglycemia alone or in combination with other agents in patients with type 2 diabetes without causing weight gain, significant hypoglycemia, or other major side effects. These agents can be taken orally and are given in a single daily dose. They represent a significant

additional option in ongoing efforts to control hyperglycemia in patients with type 2 diabetes.

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John R. White, Jr., PA, PharmD, is a professor of pharmacotherapy at the Washington State University College of Pharmacy in Spokane.