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PHARMACOKINETICS AND DISPOSITION

The influence of hepatic impairment on the pharmacokinetics of the dipeptidyl peptidase IV (DPP-4) inhibitor vildagliptin

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Abstract
Objective Vildagliptin is a potent and selective dipeptidyl peptidase-IV (DPP-4) inhibitor that improves glycemic control in patients with type 2 diabetes mellitus by increasing α- and β-cell responsiveness to glucose. This study investigated the pharmacokinetics of vildagliptin in patients with hepatic impairment compared with healthy subjects.
Methods This was an open-label, parallel-group study in patients with mild (n=6), moderate (n=6) or severe (n=4) hepatic impairment and healthy subjects (n=6). All subjects received a single 100-mg oral dose of vildagliptin, and plasma concentrations of vildagliptin and its main pharmacologically inactive metabolite LAY151 were measured up to 36 h post-dose.
Results Exposure to vildagliptin ($AUC_{0-\infty}$ and C_{max}) decreased non-significantly by 20 and 30%, respectively, in patients with mild hepatic impairment [geometric mean ratio (90% CI): $AUC_{0-\infty}$, 0.80 (0.60, 1.06), p=0.192; C_{max}, 0.70 (0.46, 1.05), p=0.149]. Exposure to vildagliptin was also decreased non-significantly in patients with moderate hepatic impairment [−8% for $AUC_{0-\infty}$, geometric mean ratio (90% CI): 0.92 (0.69, 1.23), p=0.630; −23% for C_{max}, geometric mean ratio (90% CI): 0.77 (0.51, 1.17), p=0.293]. In patients with severe hepatic impairment, C_{max} was 6% lower than that in healthy subjects [geometric mean ratio (90% CI): 0.94 (0.59, 1.49), p=0.285], whereas $AUC_{0-\infty}$ was increased by 22% [geometric mean ratio (90% CI): 1.22 (0.89, 1.68), p=0.816). Across the hepatic impairment groups, LAY151 $AUC_{0-\infty}$ and C_{max} were increased by 29–84% and 24–63%, respectively, compared with healthy subjects. The single 100-mg oral dose of vildagliptin was well tolerated by patients with hepatic impairment.
Conclusions There was no significant difference in exposure to vildagliptin in patients with mild, moderate or severe hepatic impairment; therefore, no dose adjustment of vildagliptin is necessary in patients with hepatic impairment.

Keywords Chronic liver disease · Dipeptidyl peptidase-IV inhibitor · Pharmacokinetics · Type 2 diabetes · Vildagliptin

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Introduction

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released from the gastrointestinal tract into the portal vein in response to food intake [1, 11]. GLP-1 and GIP are required for the maintenance of normal glucose tolerance, and they stimulate insulin release in a glucose-dependent

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manner [15, 21]. In healthy subjects, GLP-1 and GIP activity may be responsible for up to 70% of the insulin secreted in response to a meal [17]. In addition, GLP-1 also acts to suppress glucagon release [10]. Patients with type 2 diabetes mellitus show impaired GLP-1 secretion, which may explain, at least in part, the reduced incretin effect seen in these patients [17, 22]. As GLP-1 is rapidly inactivated by the serine peptidase dipeptidyl peptidase IV (DPP-4) [5], a novel therapeutic approach to the treatment of type 2 diabetes is to inhibit DPP-4 activity, and thereby prolong the physiological actions of GLP-1 [6].

Vildagliptin (LAF237) is a potent, selective, orally active DPP-4 inhibitor developed for the treatment of type 2 diabetes mellitus. In a clinical trial in patients with type 2 diabetes, vildagliptin 100 mg once daily for 4 weeks increased post-prandial active GLP-1, reduced glucagon levels and improved glycemic control compared with placebo [3]. A recent study in drug-naive patients with type 2 diabetes has also shown that vildagliptin improves pancreatic β-cell function by increasing the rate of insulin secretion [13]. Moreover, in a long-term study, the addition of vildagliptin 100 mg once daily to metformin therapy significantly improved glycemic control in patients with type 2 diabetes mellitus over the 12 months of treatment [2].

Chronic liver disease can significantly impair the function of hepatic drug-metabolizing enzymes (particularly microsomal oxidases), reduce hepatic blood flow and alter renal function [16, 19, 24]. The main metabolic pathway for vildagliptin in humans is hydrolysis to the inactive metabolite LAY151, which accounts for approximately 69% of total elimination of an oral dose. Although 85% of an oral dose of vildagliptin is ultimately excreted by the kidney, the liver is one of the major sites of vildagliptin metabolism (Novartis, data on file). Liver, kidney and intestinal microsomes are all capable of hydrolyzing vildagliptin to LAY151 in vitro. The aim of this study was to assess the effect of hepatic impairment on the disposition of vildagliptin by evaluating the pharmacokinetics, safety and tolerability of a single 100-mg oral dose of vildagliptin in patients with mild, moderate or severe hepatic impairment compared with healthy subjects with normal liver function.

Methods

Study design

This was an open-label, single-dose, parallel-group study conducted at a single study center. Following a 21-day screening period, eligible subjects underwent baseline evaluation (Day −1) and received a single 100-mg oral dose of vildagliptin on Day 1. Blood samples were taken at regular intervals after dosing for the measurement of plasma drug levels. End-of-study evaluations were performed immediately after the last blood sample (36 h post-dose). Selection of the 100-mg dose of vildagliptin was based on the highest expected clinical dose. Treatment compliance was assured by the administration of vildagliptin under supervision of study center personnel and confirmed by the presence of vildagliptin in the plasma and urine.

All subjects were admitted to the study center at least 14 h prior to vildagliptin administration, and they were discharged following completion of the end-of-study evaluation. Vildagliptin was administered as a single tablet with 240 mL of water between 7:00 and 8:30 A.M. following an overnight fast of at least 10 h. All subjects continued fasting for another 2 h after dosing, and unless performing a study assessment, subjects were required to rest quietly for a further 4 h.

The primary objective of this study was to assess the single-dose pharmacokinetics of vildagliptin 100 mg in patients with stable chronic liver disease compared with healthy subjects with normal liver function. A secondary objective was to assess the safety and tolerability of vildagliptin in patients with impaired hepatic function.

Study population

The study recruited men or women (ages: 18–60 years) of body weight ≥55 kg with a body mass index (BMI) of 22–40 kg/m^2, resting pulse rate of 60–100 beats per minute and platelet count ≥50×10^9/L at screening and baseline. Female subjects had to be surgically sterile, postmenopausal, or use a double-barrier method of contraception.

A total of 22 subjects were recruited, comprising healthy control subjects (n=6) and patients with mild (n=6), moderate (n=6) or severe (n=4) hepatic impairment. The diagnosis of cirrhosis was based on medical history and the presence of physical signs (liver firmness to palpitation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy or gynecomastia). The Child-Pugh clinical assessment score was used to evaluate the degree of hepatic impairment based on guidance for clinical trials in patients with impaired hepatic function from the United States Food and Drug Administration [7]. Mild, moderate and severe hepatic impairment were defined by Child−Pugh assessment scores of 5–6, 7–9 or 10–12, respectively (Table 1) [18].

Apart from hepatic impairment, all participants were in good health, as determined by medical history, physical examination, vital signs, electrocardiogram (ECG) and laboratory tests at screening. Blood pressure (BP) inclusion criteria for healthy volunteers were a systolic BP (SBP) of 90–160 mmHg and a diastolic BP (DBP) of 60–100 mmHg. For patients with hepatic impairment, inclusion criteria were an SBP of 90–180 mmHg and a DBP of 60–115 mmHg.

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Table 1 Child-Pugh classification scores for patients with mild, moderate or severe hepatic disease

	Mild hepatic impairment (n=6)	Moderate hepatic impairment (n=6)	Severe hepatic impairment (n=4)
Overall	6	7–8	10–12
Encephalopathy	1–2	2	2
Ascites	1–2	2	1–3
Bilirubin	1	1–2	1–3
Albumin	1	1–2	2–3
Prothrombin time	1	1	1–3

Data are shown as minimum-maximum values for overall score and each component score

Exclusion criteria for healthy volunteers included subjects who had used any prescription medication within 1 month prior to dosing or over-the-counter medications or vitamins within 14 days prior to dosing. Additional exclusion criteria for patients with hepatic impairment included: symptoms or history of Stage II (or worse) degree of encephalopathy within 6 months of study entry; clinical evidence of severe ascites; history of surgical portosystemic shunt; prothrombin time >18 s; any evidence of progressive liver disease within the previous 4 weeks, as indicated by changes in hepatic transaminases, alkaline phosphatase and γ-glutamyltransferase, or a ≥50% worsening of serum bilirubin or prothrombin time. Patients with hepatic impairment were also excluded if, in the opinion of the study investigator, the degree of encephalopathy impaired the ability to provide written informed consent.

Study participants were not permitted to engage in strenuous physical exercise for 7 days before dosing or to take alcohol for 72 h before dosing until after the study completion evaluation. Intake of xanthine-containing foods or beverages was discontinued 48 h before dosing and not permitted while participants were admitted to the study center.

The study protocol was approved by the relevant local ethical review board. This study was conducted in accordance with the Guidelines for Good Clinical Practice and adhered to the ethical principles of the Declaration of Helsinki. All subjects provided written informed consent.

Pharmacokinetic measurements

Blood samples were taken by either direct venipuncture or by an indwelling cannula inserted in a forearm vein, at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 24 and 36 h after vildagliptin administration. Blood samples were collected into sodium or lithium heparin tubes and stored at −70°C prior to analysis. Plasma samples were split equally for analysis of vildagliptin and LAY151. Urine samples were collected during the following time periods: pre-dose (overnight), 0–12, 12–24 and 24–36 h post-dose; urine collected during each time period was pooled, and a 5-mL aliquot was frozen.

Plasma and urinary concentrations of vildagliptin and plasma concentrations of LAY151 were determined by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) methods. All sample extractions were performed on 10-mg Oasis HLB 96-well plates (Waters, Milford, Mass.) using an Automated Liquid Handling System model Multi probe II Plus HT EX. For the measurement of vildagliptin in plasma or urine, samples and internal standards were diluted in 4 mmol/L ammonium acetate (urine samples were also mixed with water). Samples were transferred to the extraction plates and successively washed with methanol:2% ammonium hydroxide (5:95, v/v), methanol:2% ammonium hydroxide (20:80, v/v) and water, and then eluted twice with methanol:0.1% trifluoroacetic acid (TFA; 80:20, v/v). Samples were evaporated to a final volume of approximately 50 μL and then diluted with methanol:0.5% ammonium hydroxide (15:85, v/v). For the measurement of LAY151 in plasma, samples and internal standards were mixed with 4 mmol/L ammonium acetate. Samples were transferred to the extraction plates, successively washed with 0.1% TFA and 0.01% TFA and then eluted twice with methanol:0.5% ammonium acetate (80:20, v/v).

The samples were analyzed by high-performance liquid chromatography (HPLC) using an XTerra MS C18 5 μm (150×2.1 mm) column (Waters) at 30°C with isocratic elution using 40% mobile phase A [10 m*M* ammonium acetate-methanol (95:5, v/v), pH 8] and 60% mobile phase B [acetonitrile-methanol (10/90, v/v)] at a flow rate of 0.2 mL/min. Detection was performed by MS/MS using an API3000 (Applied Biosystems, Foster City, Calif.) or Quantum Discovery (Thermo Finnigan, San José, Calif.) mass spectrometer. The general conditions used were: positive ion mode with turbo ion spray or electro spray ionization. The masses for vildagliptin were precursor ion *m/z* 304 and product ion *m/z* 154; the masses for LAY151 were precursor *m/z* 323 and product *m/z* 173. For vildagliptin, the lower limit of quantification (LOQ) was 2 ng/mL in 0.2 mL of plasma and 5 ng/mL in 0.1 mL of urine. The internal standard for vildagliptin was (2S)-1-[[(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)amino]acetyl]-2-pyrrolidine-*2,3,4,5*-^{13}C-^{15}N-carbonitrile-*cyano*-^{13}C (Novartis Pharmaceuticals Corp, N.J.). Within-study assay validation showed an assay precision (co-efficient of variation) of 3.1–6.0% (bias of −4.2 to 3.5%) for plasma samples (nominal concentrations of 5.25, 400 and 900 ng/mL), and a precision of 6.5–7.4% (bias of −5.5 to 1.3%) for urine samples (nominal concentrations of 15, 2000 and 4000 ng/mL). For LAY151, the LOQ was 2 ng/mL in 0.2 mL of plasma. The internal standard was [D_7] LAY151 (Novartis Pharma AG, Basel, Switzerland), and within-study assay

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validation showed a precision of 2.5–3.6% and a bias of −2.4 to 5.9% (nominal concentrations of 5.01, 5.03, 406, 412, 902 and 915 ng/mL). A single laboratory assayed all plasma and urine samples. Within-study assay validation was performed by an analysis of quality control samples.

Safety and tolerability assessments

Safety and tolerability assessments included the monitoring and recording of all adverse events (AEs), concomitant medications and significant non-drug therapies. Assessment of standard blood chemistries, hematological profile, urinalysis, physical examination, ECG and vital signs were performed at screening, baseline and at the end of the study.

Pharmacokinetic analyses

The following pharmacokinetic parameters were calculated for vildagliptin using plasma concentration data: C_{max} (maximum plasma concentration), t_{max} (time to reach C_{max})), $AUC_{0–36\ h}$ (area under the plasma concentration–time curve for time period 0–36 h), $AUC_{0–\infty}$ (area under the plasma concentration-time curve extrapolated from time 0 to infinity), $t_{1/2}$ (elimination half-life associated with the terminal rate constant), CL/F (total clearance of drug from plasma, corrected for bioavailability F), V_z/F (apparent volume of distribution, corrected for bioavailability F) and CL_R (renal clearance of drug from plasma). The total amount of vildagliptin excreted into urine was also measured. CL_R was calculated using both plasma and urine data over the 36-h assessment period. The following pharmacokinetic parameters were calculated for LAY151 using plasma concentration data: C_{max}, t_{max}, $AUC_{0–t}$, $AUC_{0–\infty}$ and $t_{1/2}$. Pharmacokinetic parameters were obtained according to the non-compartmental methods using WINNONLIN PRO (ver. 4.0; Pharsight Corp., Mountain View, Calif.).

Statistical analyses

The sample size was determined mainly on the basis of the sensitivity of statistical testing to detect a clinically meaningful change in drug exposure between patients with hepatic impairment and healthy volunteers, and with reference to the sample sizes commonly used in pharmacokinetic studies in patients with hepatic impairment. Assuming an inter-subject co-efficient of variation (CV) of 0.25, a sample size of six in each of the three hepatic impairment patient subgroups and in the healthy subject group would ensure an 80% power to detect a 45% difference in pharmacokinetic parameter values between the healthy and hepatic-impaired groups, based on a two-sample, two-sided *t*-test at a 95% significance level. Previous vildagliptin pharmacokinetic studies in patients with type 2 diabetes mellitus showed that inter-subject CV ranged from 0.25 to 0.29 for AUC and C_{max}, respectively. Statistical comparisons of pharmacokinetic parameters between the hepatic impairment groups and the healthy subjects group were performed for log-transformed $AUC_{0–\infty}$, $AUC_{0–36\ h}$ and C_{max} of vildagliptin using an analysis of variance (ANOVA) model. The source of variation included in the ANOVA model was hepatic group. Geometric mean ratios and corresponding 90% confidence intervals (CI) for each hepatic impairment group versus the healthy subjects group were calculated. Statistical comparisons of pharmacokinetic parameters were performed using the PROC MIXED SAS procedure (SAS Institute, Cary, N. C.).

Results

Patient characteristics

A total of 22 subjects were enrolled and completed the study (i.e. received vildagliptin and completed all post-dosing evaluations). Although the study originally planned to recruit six subjects in each group; only four subjects were enrolled in the severe hepatic impairment group due to the difficulty of recruiting these patients. Several patients were recruited with minor protocol deviations; one subject had a BMI (18.5 kg/m^2) below the lower limit defined in the inclusion criteria; six participants were older than the maximum specified age of 60 years; one subject had a platelet count that was below that stated in the inclusion criteria. However, none of the deviations were considered significant by the investigator, and these subjects were allowed to participate in this study.

Patients with hepatic impairment and healthy subjects showed similar baseline and demographic characteristics (Table 2), except that mean age was lower in the healthy subjects group (37.8 years) than in the hepatic impairment subgroups (54.8–56.5 years). The majority of patients with hepatic impairment had a medical history of alcoholism, which was not an active condition at the time of the study, or had existing medical conditions related to hepatic impairment (Table 2). Prothrombin time was increased in patients with mild, moderate or severe hepatic impairment compared with healthy subjects and was the longest in the severe hepatic impairment group. Total bilirubin was also markedly higher in patients with severe hepatic impairment than in patients in the other groups. Overall, ten (62.5%) patients with hepatic impairment were receiving medication for the treatment of hepatic disease or associated illnesses; the most common co-medication was spironolactone. There were no significant past or present medical conditions in the healthy volunteers group, and none of the healthy subjects were taking medications prior to enrolment.

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Table 2 Baseline and demographic characteristics

Characteristic	Healthy subjects (n=6)	Patients with hepatic impairment		
		Mild (n=6)	Moderate (n=6)	Severe (n=4)
Age (years)	37.8±10.9	56.0±5.8	56.5±6.6	54.8±14.7
Range	19–53	49–64	48–63	44–76
Weight (kg)	70.3±9.4	79.2±16.2	80.5±17.8	72.8±20.3
Height (cm)	165±7	168±9	171±13	163±14
Gender, n (%)				
Male	3 (50)	3 (50)	5 (83)	2 (50)
Female	3 (50)	3 (50)	1 (17)	2 (50)
Ethnicity, n (%)				
Caucasian	0	4 (66.7)	1 (16.7)	1 (25)
Black	0	1 (16.7)	4 (66.7)	1 (25)
Other[a]	6 (100)	1 (16.7)	1 (16.7)	2 (50)
Etiology of hepatic disease, n (%)				
Alcohol-induced liver cirrhosis	0	6 (100)	6 (100)	3 (75)
Hepatitis C	0	3 (50)	3 (50)	4 (100)
Clinical manifestations of hepatic disease				
Encephalopathy, n (%)	0	5 (83.3)	6 (100)	4 (100)
Ascites, n (%)	0	4 (66.7)	4 (66.7)	4 (100)
Peripheral edema, n (%)	0	2 (33.3)	1 (16.7)	1 (25)
Albumin (g/dL)	4.4±0.1	4.3±0.2	3.8±0.5	3.0±0.6
Total bilirubin (mg/dL)	0.9±0.3	0.7±0.3	1.0±0.5	2.4±0.9
Prothrombin time[b] (s)	11.8±0.4	12.1±0.8	12.2±1.1	16.1±2.6
Creatinine clearance[c] (mL/min/1.73m^2)	81.6±7.0	78.2±13.4	69.1±7.9	91.1±33.5

Data are presented as mean±SD unless otherwise stated
[a] 'Other' ethnic category includes ethnically Hispanic subjects of either Caucasian or black heritage
[b] Prothrombin time was measured at screening
[c] Calculated using the formula [(140–age in years) × weight in kg]/(serum creatinine × 72)

Pharmacokinetics of vildagliptin in patients with mild, moderate or severe hepatic impairment

The plasma concentration-time profiles for vildagliptin are illustrated in Fig. 1. The pharmacokinetic parameters for both vildagliptin and LAY151 are summarized in Table 3. Exposure to vildagliptin (AUC and C_{max}) in patients with mild or moderate hepatic impairment was lower than in healthy subjects following the administration of a single 100-mg oral dose. In patients with mild hepatic impairment, vildagliptin $AUC_{0-\infty}$ and C_{max} were reduced by 20% and 30, respectively, compared with healthy subjects [geometric mean ratio (90% CI): $AUC_{0-\infty}$, 0.80 (0.60, 1.06); C_{max}, 0.70 (0.46, 1.05)]. The reductions in $AUC_{0-\infty}$ and C_{max} were not statistically significant compared with healthy subjects (p=0.192 and p=0.149, respectively). Vildagliptin $AUC_{0-\infty}$ was reduced by 8% and C_{max} by 23% in patients with moderate hepatic impairment compared with healthy subjects [mean ratio (90% CI): $AUC_{0-\infty}$, 0.92 (0.69, 1.23); C_{max}, 0.77 (0.51, 1.17)]; however, these differences were not statistically significant ($AUC_{0-\infty}$, p=0.630 and C_{max}, p=0.293 vs. healthy subjects). Plasma concentrations of vildagliptin following the administration of a single 100-mg oral dose were higher in patients with severe hepatic impairment than in healthy subjects

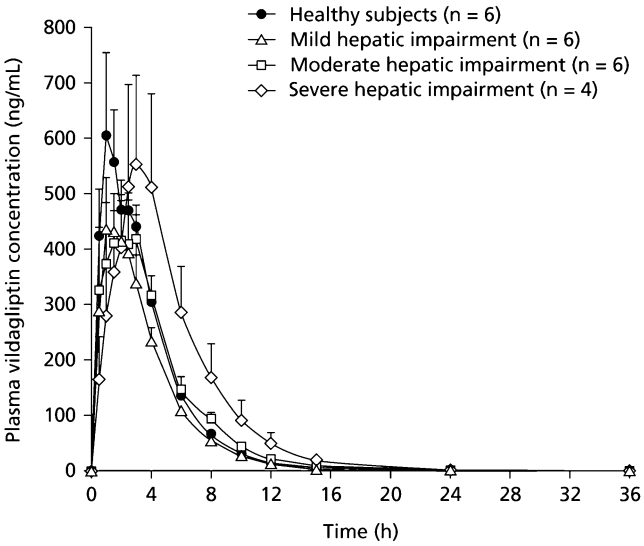

Fig. 1 Plasma concentration–time profiles of vildagliptin in healthy subjects and patients with mild, moderate or severe hepatic impairment. Plasma concentrations of vildagliptin are shown after the administration of a single 100-mg oral dose to healthy subjects (n=6) and patients with mild (n=6), moderate (n=6) or severe (n=4) hepatic impairment. Data are presented as mean±SEM

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