EFFECT OF MODERATE HEPATIC INSUFFICIENCY ON THE PHARMACOKINETICS OF SITAGLIPTIN

Elizabeth M Migoya[1], Catherine H Stevens[1], Arthur J Bergman[1], Wen-lin Luo[1], Kenneth C Lasseter[2], Stacy C Dilzer[2], Michael J Davies[1], John A Wagner[1], Gary A Herman[1]

[1]Merck Research Laboratories, Rahway, NJ; [2]Clinical Pharmacology of Miami, Inc., Miami, FL

Corresponding Author: *gary_herman@merck.com*

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ABSTRACT

Background
Sitagliptin is a highly selective dipeptidyl peptidase-4 inhibitor for the treatment of patients with type 2 diabetes. Sitagliptin is primarily excreted by renal elimination as unchanged drug, with only a small percentage (~16%) undergoing hepatic metabolism.

Objectives
The primary purpose of this study was to evaluate the influence of moderate hepatic insufficiency on the pharmacokinetics of sitagliptin.

Methods
In an open-label study, a single 100-mg oral dose of sitagliptin was administered to 10 male or female patients with moderate hepatic insufficiency (Child-Pugh's scores ranged from 7 to 9) and 10 healthy control subjects matched to each patient for race, gender, age (± 5 yrs) and body mass index (BMI kg/m^2 $\pm 5\%$). After administration of each dose, blood and urine samples were collected to assess sitagliptin pharmacokinetics.

Results
The mean $AUC_{0-\infty}$ and C_{max} for sitagliptin were numerically, but not significantly ($p > 0.050$), higher in patients with moderate hepatic insufficiency compared with healthy matched control subjects by 21% and 13%, respectively. These slight differences were also not considered to be clinically meaningful. Moderate hepatic insufficiency had no statistically significant effect on the T_{max}, apparent terminal $t_{1/2}$, fraction of the oral dose excreted into urine ($f_{e,0-\infty}$) and renal clearance (Cl_R) ($p > 0.100$) of sitagliptin. Sitagliptin was generally well tolerated by both patients and subjects; all adverse experiences were transient and rated as mild in intensity.

Conclusions
Moderate hepatic insufficiency has no clinically meaningful effect on the pharmacokinetics of sitagliptin.

Key Words: *Dipeptidyl peptidase-IV; MK-0431; incretins; antihyperglycemic therapy; www.clinicaltrials.gov - NCT00696826*

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Non-alcoholic fatty liver disease (NAFLD) is a relatively common co-morbidity in patients with type 2 diabetes[1] and is a leading cause of chronic liver disease.[2] It is also known that for patients with type 2 diabetes, the risk of developing cirrhosis or hepatocellular carcinoma is doubled.[3] Furthermore, the risk of dying from liver cirrhosis was doubled in a cohort of patients with type 2 diabetes relative to the general population in the Verona Diabetes Study.[4] Considering the increasing prevalence of type 2 diabetes worldwide[5] and the association between

diabetes and NAFLD, the prevalence of cirrhosis and hepatic failure will likely increase, presenting a particularly challenging problem for patients with type 2 diabetes.

Antihyperglycemic agents that are extensively metabolized may be contraindicated in patients with hepatic insufficiency.[6] Sitagliptin, a highly-selective dipeptidyl peptidase-4 (DPP-4) inhibitor represents a new class of oral antihyperglycemic agents.[7] Sitagliptin is primarily excreted by renal elimination as unchanged drug, with only a small percentage (~16%) undergoing hepatic metabolism.[8] Considering the high prevalence of chronic liver disease in patients with type 2 diabetes, the objective of this study was to evaluate the influence of moderate hepatic insufficiency on the pharmacokinetics and tolerability after administration of a single 100-mg dose of sitagliptin.

METHODS

Patients

Ten patients with moderate hepatic insufficiency (Child-Pugh classification scores of 7 to 9[9]; Table 1) were recruited for this study. At least two patients each having a score of 7, 8, and 9 on the Child-Pugh's scale were included in the study. Patients were to be between the ages of 18 and 75 years, inclusive, with a body mass index (BMI) of ≤40 kg/m². Patients had to have a diagnosis of chronic (>6 months) and stable hepatic insufficiency with features of cirrhosis, regardless of the etiology. Patients were excluded if they had acute episodes of illness related to deterioration in hepatic function within 2 months of the screening visit. Each patient had a healthy control subject that was matched for gender, race, age (±5 years), and BMI (±5%). For patients with hepatic insufficiency, certain prescription medications used to treat manifestations of hepatic disease (e.g., diuretics, lactulose, etc.) were allowed to be taken during the study; but the patient was to be on a stable dose and regimen of each medication for at least 1 month prior to study drug administration. Allowed medications were held on Day 1 unless medically necessary, in which case thiazide and other diuretics (including hydrochlorothiazide, chlorthalidone, amiloride, triamterene, and spironolactone) were permitted to be administered 4 to 6 hours postdose. Healthy matched control subjects were restricted from use of all prescription and non-prescription medications from 14 days prior to and after study drug administration. Because sitagliptin is primarily excreted by renal elimination, all participants had to have normal renal function with a creatinine clearance of >80 mL/min, either estimated by serum creatinine values using the Cockcroft-Gault equation or measured directly with a 24-hour urine collection.

All participants provided written informed consent to participate. The study was approved by the Southern Institutional Review Board (Miami, FL) and was performed in accordance with the Declaration of Helsinki.

TABLE 1 Child-Pugh's classification of the severity of liver disease

	Points Score for Increasing Abnormality		
	1	2	3
Encephalopathy[†]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Albumin (g/L)	>35	28 to 35	<28
Prothrombin time (seconds over control)	<4	4 to 6	>6
Bilirubin (mg/100 mL)—only for PBC[§]	<4	4 to 10	>10
Bilirubin (mg/100 mL)—not PBC[‡§]	<2	2 to 3	>3
[†] Portal-system encephalopathy is Staged 0 to 4.			
[‡] PBC=Primary Biliary Cirrhosis.			
[§] Select only one level depending upon the type of cirrhosis.			

Study Design

In an open-label Phase I study, a single 100-mg dose of sitagliptin was administered after an overnight fast and blood samples for determination of plasma sitagliptin concentrations were collected over a 96-hour period (predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72 and 96 hours postdose). Urine collections for determination of urinary sitagliptin concentrations were obtained over a 24-hour period (predose and 0-4, 4-8, 8-12 and 12-24 hours postdose).

Pharmacokinetic Analysis

Sitagliptin concentrations were measured in plasma and urine samples by mass spectrometry detection following specialized high-performance liquid chromatography with an internal standard.[10] Calculations for pharmacokinetic parameters were completed according to established methods.[11]

Safety

Safety and tolerability were assessed from adverse experiences and measurement of vital signs, 12-lead electrocardiograms, and laboratory safety parameters. Adverse experiences were evaluated as to their intensity, seriousness, and potential relationship to study drug.

Statistical Analysis

The pharmacokinetic parameters for sitagliptin were compared between groups using an ANCOVA model, which contained the following factors as covariates: patient group, age, gender, and BMI. A log transformation was applied to the area under the sitagliptin plasma concentration curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), maximal concentration (C_{max}), and renal clearance (Cl_R) data. Data transformations were applied to the pharmacokinetic parameters (rank for time to C_{max} [T_{max}], reciprocal of apparent $t_{1/2}$). Back-transformed summary statistics and inferential results were reported. Based on the relatively wide therapeutic index for sitagliptin[12], an increase in plasma sitagliptin exposure (i.e., $AUC_{0-\infty}$) of less than 2-fold was considered not to be clinically meaningful. Therefore, if the 90% confidence interval (CI) for the geometric mean ratio (GMR; moderate hepatic insufficiency/control subjects) for $AUC_{0-\infty}$ of sitagliptin fell within the pre-specified bounds (0.5, 2.0), the change was

considered not to be clinically meaningful. $AUC_{0-\infty}$ was considered the most relevant pharmacokinetic parameter since it represents the plasma AUC over the recommended dosing interval (i.e., 24 hours) at steady state and is appropriate for a chronically administered drug.

Power

At the design stage, if the true $AUC_{0-\infty}$ adjusted geometric means following the administration of sitagliptin 100-mg for both the patients with moderate hepatic insufficiency and their matched control group are the same, then a sample size of 10 moderate insufficiency patients and 10 matched healthy control subjects provide this study with at least 99% probability of observing the 90% CI for the geometric mean ratio (GMR) to be contained within (0.50, 2.00). If the true GMR is within the interval of 0.59 to 1.69, this study has at least an 80% probability of observing the 90% CI within (0.50, 2.00).

RESULTS

Patient Characteristics

For the patients with moderate hepatic insufficiency, there were 5 men and 5 women with a mean age of 55 years (range: 48 to 71 years) and a mean BMI of 27 kg/m.[2] Three patients had type 2 diabetes and were being treated with insulin. In the healthy matched control subjects, there were 5 men and 5 women with a mean age of 56 years (range: 50 to 71 years) and a mean BMI of 27 kg/m.[2]

Pharmacokinetics

Mean plasma sitagliptin concentration over time is shown for both groups in Figure 1. The pharmacokinetic parameters after administration of a single 100-mg dose of sitagliptin are presented in Table 2. The mean $AUC_{0-\infty}$ and C_{max} for sitagliptin were numerically, but not significantly, higher in patients with moderate hepatic insufficiency compared with healthy matched control subjects by 21% and 13%, respectively (Table 2). Furthermore, as stated in the study protocol, the 90% CI of the GMR (patients with moderate hepatic insufficiency/control subjects) for the $AUC_{0-\infty}$ of sitagliptin was contained within the pre-specified comparability bounds of (0.50, 2.00), indicating

that this parameter was not altered in a clinically meaningful manner by moderate hepatic insufficiency. Moderate hepatic insufficiency also had no significant effect on T_{max}, apparent terminal $t_{1/2}$, $f_{e0-\infty}$, and Cl_R for sitagliptin (Table 2).

FIG. 1 Mean plasma sitagliptin concentrations over time after administration of a single 100-mg dose of sitagliptin to patients with hepatic insufficiency and healthy matched control subjects.
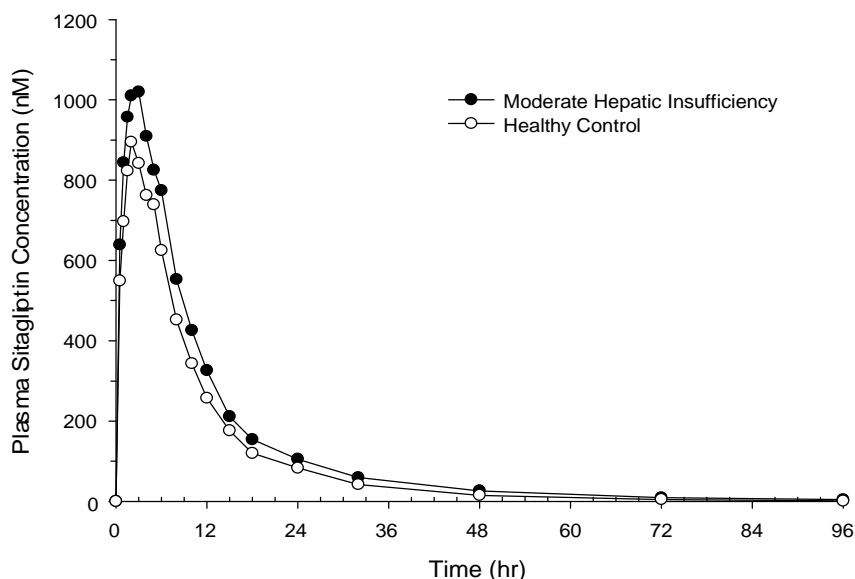

TABLE 2 Summary statistics for sitagliptin pharmacokinetic parameters after administration of single 100-mg doses of sitagliptin in patients with moderate hepatic insufficiency and healthy matched control subjects.

Parameter	Moderate Hepatic Insufficiency Patients N = 10	Healthy Matched Control Subjects N = 10	GMR (90% CI) (Moderate Hepatic Insufficiency Patients/Healthy Matched Control Subjects)	p-value
$AUC_{0-\infty}$ ($\mu M \cdot hr$)*	11.5 ± 4.9	9.5 ± 2.2	1.21 (1.01, 1.46)	0.089
C_{max} (nM)*	1186 ± 682	1046 ± 286	1.13 (0.91, 1.42)	0.341
T_{max} (hr)[†]	1.8 ± 1.1	1.5 ± 1.3	--	0.726
Apparent $t_{1/2}$ (hr)[‖]	14.4 ± 3.9	13.9 ± 2.0	--	0.691
$f_{e,0-\infty}$[§]	0.689 ± 0.084	0.681 ± 0.075	0.01 (-0.05, 0.07)	0.788
Cl_R (mL/min)*	243 ± 98	292 ± 84	0.83 (0.68, 1.02)	0.128
*Data are expressed as least-squares (LS) mean ± standard deviation (SD) and geometric mean ratio (GMR) of LS means (90% confidence intervals [CI]); [†]Median values ± SD for median; [‖]Harmonic LS mean ± SD; [§]Arithmetic LS mean ± SD and difference between arithmetic LS means (90% CI) $AUC_{0-\infty}$ = Area under the plasma level vs. time curve from time zero extrapolated to infinity from the last measured time point; C_{max} = highest concentration observed; $f_{e,0-\infty}$ = fraction of dose excreted unchanged in urine extrapolated to infinity; Cl_R = renal clearance; T_{max} = time from dosing to C_{max}; -- not calculated				

Safety and Tolerability

Sitagliptin was generally well tolerated in this study. No serious adverse experiences were reported, no subject discontinued due to an adverse experience, no laboratory adverse experiences were reported, and no meaningful changes were observed in laboratory parameters, including alanine aminotransferase and aspartate aminotransferase. There were a total of 4 patients for whom clinical adverse experiences were reported (one in patients with hepatic insufficiency and 3 in healthy control subjects): these 4 patients reported headaches, which were mild and resolved without treatment. No adverse experiences of hypoglycemia were reported.

DISCUSSION

In this study, the influence of moderate hepatic insufficiency (Child-Pugh classification scores 7 to 9) on pharmacokinetics for sitagliptin was assessed. As anticipated, since sitagliptin is excreted primarily by renal elimination, with metabolism playing a minor role[8], there were no significant alterations in the pharmacokinetics of sitagliptin in patients with moderate hepatic insufficiency. Compared with healthy-matched control subjects, the $AUC_{0-\infty}$ and C_{max} for sitagliptin were numerically higher by up to 21% in the patients with moderate hepatic insufficiency; however, these differences were not statistically significant and not considered to be clinically meaningful considering the wide therapeutic index associated with sitagliptin. Furthermore, based on these results, it is reasonable to conclude that the pharmacokinetics of sitagliptin would not be meaningfully altered in patients with mild hepatic insufficiency (i.e., Child-Pugh classification scores 4 to 6).

This small single-dose study, performed early in the development of sitagliptin, was not intended to be a safety study. Nevertheless, single 100-mg doses of sitagliptin were well tolerated with no meaningful changes observed in liver function tests or any other laboratory or safety parameters assessed in this study. In subsequent clinical trials in patients with type 2 diabetes, more adequately powered to assess safety and tolerability, clinical doses of sitagliptin have been well tolerated relative to placebo or an active comparator.[13] In summary, moderate hepatic insufficiency had no clinically meaningful effect on the pharmacokinetics of sitagliptin. Combined with the safety experience of sitagliptin in patients with type 2 diabetes[13], no dosage adjustments are recommended for patients with mild to moderate hepatic insufficiency.

Acknowledgements

Conflicts of Interest

EMM, CHS, AJB, WL, MJD, JAW, and GAH are employed by Merck & Co., Inc., the manufacturer of sitagliptin and may hold stocks or stock options in the company.

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