EFFECT OF SIMVASTATIN ON THE PHARMACOKINETICS OF SITAGLIPTIN

Michael Cerra, Wen-Lin Luo, Susie (Xiujiang) Li, Catherine Matthews, Edward A O'Neill, John A Wagner, S Aubrey Stoch, Matt S Anderson

Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey, U.S.A.

Corresponding Author: matt.anderson@merck.com

ABSTRACT

Background
Treatment with the combination of sitagliptin (a dipeptidyl peptidase 4 inhibitor which improves glycemic control) and simvastatin (a well characterized lipid-lowering agent) may be considered an appropriate approach to management of type 2 diabetes and its associated increased risk of cardiovascular disease.

Objective
An investigation of the effects of simvastatin on the pharmacokinetics of sitagliptin was conducted.

Methods
Ten healthy men and women were enrolled into an open-label, randomized, 2-period, crossover study. Pharmacokinetics of sitagliptin were measured after a single dose of sitagliptin 100-mg alone, and after a single dose of sitagliptin 100-mg administered on Day 5 of a 7 day course of simvastatin 80-mg once daily.

Results
The geometric mean ratio of (sitagliptin + simvastatin) / sitagliptin and corresponding 90% confidence interval for sitagliptin $AUC_{0-\infty}$ and C_{max} were 1.01 (0.97, 1.05), and 1.12 (1.00, 1.26), respectively.

Conclusions
Simvastatin has no clinically important effect on sitagliptin pharmacokinetics. No dose adjustment for either sitagliptin or simvastatin is recommended when these drugs are coadministered.

Key Words: *Type 2 diabetes; atherosclerosis; dipeptidyl peptidase-4; statin; HMG-CoA reductase; drug interactions*

Patients with type 2 diabetes (T2D) are at risk of vascular complications, including cardiovascular disease,[1-3] and therapy with statins in this population is widely recommended.[4,5] The combination of sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor which improves glycemic control,[6,7] and simvastatin, a well characterized lipid-lowering agent,[8] may be considered an appropriate approach to management of this disease.[4,9] Recently a fixed dose combination of these agents, Juvisync®, was approved for marketing in the United States.[10] Therefore, it is important to evaluate potential drug – drug interaction between these agents. Sitagliptin has no clinically significant effect on the pharmacokinetics of simvastatin.[11] Here we evaluated the effects of simvastatin on the pharmacokinetics of sitagliptin.

METHODS

Study Design

This was a single site, open-label, randomized, 2-period, crossover study to investigate the effect of simvastatin 80-mg at steady state on the single-dose pharmacokinetics of sitagliptin 100-mg. In each subject, sitagliptin pharmacokinetic parameters were measured after a single dose of sitagliptin, and after a single dose of sitagliptin on Day 5 of treatment with simvastatin once daily for 7 days. It has been previously established that plasma levels of simvastatin reach steady-state by Day 5 after multiple dosing at 80 mg/day.[12] There was a minimum 5-day washout between each treatment, after which time plasma concentrations of sitagliptin were below the lower limit of quantification (LLOQ) (1.0 ng/ml). The order in which subjects received these treatments was randomly assigned. Subjects received sitagliptin in the morning with 240 mL of water after an overnight fast, with water restricted one hour prior to and after study drug administration. Simvastatin was administered once daily in the morning and on non-pharmacokinetic sampling days was administered without regard to food.

Study Participants

Subjects were healthy male and female non-smokers with no history of drug or alcohol abuse within 2 years prior to the screening visit, who refrained from strenuous exercise and use of any medications throughout the study.

All subjects provided written informed consent to participate. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory authorities.

Analytical and Pharmacokinetic Techniques

For determination of sitagliptin plasma concentration, a 4 mL blood sample was periodically collected into EDTA Vacutainer tubes and centrifuged at 1700 x g for 10 minutes at 4°C within 30 minutes of collection. Plasma aliquots were transferred to cryotubes and frozen at -20°C within 1 hour of centrifugation. Anapharm Inc. (Quebec, Canada) analyzed plasma sitagliptin concentrations as described.[13] The LLOQ for sitagliptin was 0.99 ng/mL (2.43 nM). The analytical ranges of quantitation were 0.99 to 989.00 ng/mL. The intra-day and inter-day coefficients of variation were less than 7% and 4%, respectively.

The pharmacokinetic (PK) parameters were calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (*e.g.*, three or more non-zero plasma concentrations). All area under the curve (AUC) parameters was estimated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-last} and Ct/λ, where Ct was the last measurable concentration, and the apparent terminal rate constant (λ) was estimated from a semi-log plot of the plasma concentration-versus-time curve. The apparent terminal half life ($t_{½}$) was calculated as $\ln 2/\lambda$. The maximum plasma concentration (C_{max}) and time at which C_{max} was reached (T_{max}) were obtained by inspection of the concentration-time data. Plasma sitagliptin concentration values below the assay limit of quantitation were replaced with zero.

Statistical Analysis

The effect of multiple dose administration of simvastatin for 7 days on single dose sitagliptin pharmacokinetic parameters $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} was analyzed using a linear mixed-effect model appropriate for a 2-period crossover design. The linear mixed-effect model included sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. Natural log transformation was used on the $AUC_{0-\infty}$, AUC_{0-last}, and C_{max}. Back-transformed summary statistics and inferential results were calculated.

It was prespecified that if the 90% CIs of the geometric mean ratios (GMR) ([simvastatin + sitagliptin]/sitagliptin) for the sitagliptin $AUC_{0-\infty}$ and C_{max} were contained within the interval [0.50, 2.00], it would be concluded that the sitagliptin pharmacokinetics were not clinically meaningfully altered by coadministration with simvastatin. Bounds of [0.50, 2.00] were prespecified to define clinically meaningful changes in the sitagliptin $AUC_{0-\infty}$ and C_{max} because both the efficacy and safety of sitagliptin 200 mg and 50 mg doses once daily are similar to that observed with the approved clinical dose of 100-mg once daily.[14] Furthermore, a sample size

of N=10 provided this study a 99.9% probability of observing the 90% CI for the GMR ([sitagliptin + simvastatin]/sitagliptin) for sitagliptin $AUC_{0-\infty}$ or C_{max} to be contained within [0.50, 2.00] if the true GMR is 1.00.

Safety Assessment

Safety and tolerability were assessed by tabulating adverse experiences. All adverse events (AEs) were rated by the study site investigators for intensity and relationship to study drug.

RESULTS

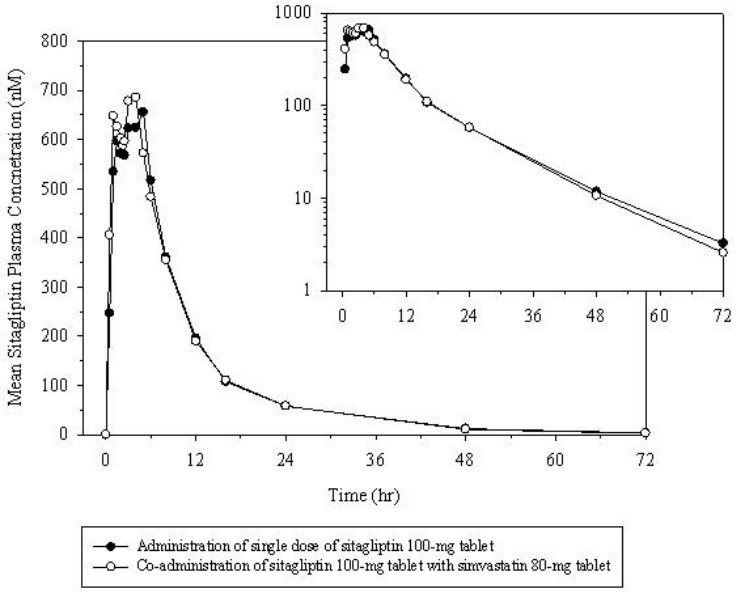
Subjects

The study population consisted of 5 healthy male subjects (age 21 - 30 years) and 5 healthy female subjects (age 20 – 52 years) with a mean weight of 76.2 kg (range, 57.6-92.9 kg) and a mean age of 28.4 years (range, 20-52 years). Seven subjects were Caucasian (3 males and 4 females) and three were black (2 males and 1 female). All subjects completed both treatments. All doses were administered at the clinical site and witnessed by clinical staff. No compliance issues were noted and all doses were administered per protocol.

Pharmacokinetics

The sitagliptin plasma concentration-time profiles are shown in Figure 1. The model-based summary statistics for the pharmacokinetic parameters of sitagliptin are shown in Table 1. The geometric mean ratio (GMR, [sitagliptin + simvastatin]/sitagliptin) and corresponding 90% confidence interval (CI) was 1.01 (0.97, 1.05) for $AUC_{0-\infty}$, and 1.12 (1.00, 1.26) for C_{max}. Thus, the 90% CIs of the GMR for $AUC_{0-\infty}$ and C_{max} for sitagliptin were within the study's prespecified bounds of (0.50, 2.00). The apparent terminal $t_{½}$ of a single sitagliptin dose were 10.4 and 11.5 hours with or without coadministration of simvastatin, respectively.

FIG. 1 Mean plasma concentrations of sitagliptin following a single oral dose of sitagliptin 100 mg with or without multiple oral doses of simvastatin 80 mg (n=10)
(Insert: Semi-log Scale)



J Popul Ther Clin Pharmacol Vol 19(3): e356-e360; October 9, 2012

TABLE 1 Summary statistics for the pharmacokinetic parameters of sitagliptin following a single oral dose of sitagliptin 100 mg with or without multiple oral doses of simvastatin 80 mg (N=10)

Parameter	Sitagliptin +Simvastatin GM (95% CI)	Sitagliptin GM (95% CI)	GMR (90% CI)
$AUC_{0-\infty}$ (nM•hr)	7302 (6426, 8297)	7217 (6351, 8201)	1.01 (0.97, 1.05)
AUC_{0-last} (nM•hr)	7222 (6346, 8219)	7134 (6269, 8119)	1.01 (0.97, 1.05)
C_{max} (nM)	913 (787, 1059)	816 (704, 946)	1.12 (1.00, 1.26)
T_{max} (hr)	2.5 (0.5, 5.0)	2.0 (0.5, 5.0)	
Apparent terminal $t_{1/2}$ (hr)	10.4 (1.6)	11.5 (1.2)	

For T_{max} the median (min, max) and for apparent terminal $t_{½}$ the harmonic mean with jack-knife standard deviation are shown.
Abbreviations: GM, back-transformed geometric least-squares mean from mixed effect model performed on natural log-transformed values; GMR, geometric least square mean ratio for (sitagliptin + simvastatin) / sitagliptin; CI, confidence interval.

Safety and Tolerability

Both treatment regimens were generally well tolerated, and there were no discontinuations due to AEs. Four subjects reported a total of 5 AEs and each was reported once. One AE (psoriasis during sitagliptin + simvastatin treatment) was considered by the investigator to be possibly related to study drug. The subject had no previous history of psoriasis. All AEs were transient and considered by the investigator to be mild or moderate in intensity.

DISCUSSION

A priori, there is no metabolic reason to expect that sitagliptin and simvastatin would exhibit a significant pharmacokinetic interaction. Sitagliptin is primarily cleared by renal filtration without significant metabolism;[15] whereas, simvastatin is largely cleared by oxidation mediated by CYP3A.[16] Sitagliptin is neither an inhibitor nor inducer of CYP3A4.[11,17] In a previous study, multiple doses of sitagliptin did not alter the plasma pharmacokinetics of simvastatin.[11] However, the effects of simvastatin on the pharmacokinetics of sitagliptin had not previously been characterized. In this study, multiple doses of simvastatin had no clinically meaningful effect on the single dose pharmacokinetics of sitagliptin.

For this study, multiple doses of 80 mg simvastatin were chosen to maximize the potential to quantify a pharmacokinetic interaction. A single 100-mg dose of sitagliptin was considered sufficient to assess the effects of simvastatin on the pharmacokinetics of sitagliptin because sitagliptin plasma $AUC_{0-\infty}$ increases in a dose-proportional manner and C_{max} increases only modestly greater than dose-proportionally across the 25-mg to 400-mg dose range.[18]

The results of the current study, together with the previous analysis of the effect of steady state dosing of sitagliptin on the pharmacokinetics of single dose simvastatin,[11] indicate that relative to individual drug administration, neither sitagliptin nor simvastatin plasma pharmacokinetics are altered when these drugs are coadministered. As the plasma pharmacokinetics of each drug when administered, as a single dose is predictive of steady state pharmacokinetics, no clinically significant pharmacokinetic interaction between these drugs is anticipated in clinical therapy.

In conclusion, steady-state simvastatin does not affect the pharmacokinetics of a single dose of sitagliptin and both drugs were generally well tolerated. Therefore, no dose adjustment for either

drug is recommended when they are coadministered.

Acknowledgements

The authors wish to thank the study participants and study staff whose involvement made this work possible. All authors are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Whitehouse Station, NJ, U.S.A.

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