A Randomized, Open-Label, Crossover Study Evaluating the Effect of Food on the Relative Bioavailability of Linagliptin in Healthy Subjects

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ABSTRACT

Objective: The objective of this study was to determine the relative bioavailability of the dipeptidyl-peptidase-4 (DPP-4) inhibitor linagliptin when administered with and without food, in accordance with regulatory requirements to support dosing recommendations for patients.

Methods: This was a randomized, open-label, crossover study involving 32 healthy white male and female subjects. All subjects received a single dose of 5 mg linagliptin after an overnight fast of at least 10 hours, or immediately after ingestion of a high-fat, high-calorie breakfast. These treatments were separated by a period of 5 weeks. Plasma samples for pharmacokinetic analysis were collected before dosing and at prespecified time points after dosing. The concentration of linagliptin in these samples was analyzed by high-performance liquid chromatography coupled to tandem mass spectrometry. Relative bioavailability was assessed by the total area under the curve between 0 and 72 hours (AUC_{0-72}) and maximum measured plasma concentration (C_{max}) of linagliptin. Tolerability was also assessed.

Results: In 32 subjects (mean age, 34.8 years; weight, 74.3 kg; male, 53%; white race, 100%), intake of a high-fat meal resulted in comparable bioavailability with regard to AUC_{0-72} (geometric mean ratio [GMR] between the fed and fasted group means was 103.5%; 90% CI, 98.1%–109.2%). Individuals' responses to food ranged from a maximum increase in exposure of 38% to a decrease of 32% relative to the fasted state. The concurrent intake of food increased the time to reach maximum plasma concentration (T_{max}) by approximately 2 hours and reduced C_{max} by about 15% (GMR 84.7%; 90% CI, 75.9%–94.6%). Since adequate drug exposure for inhibition of DPP-4 was still given for the entire 24-hour dosing interval, this result was considered to be of no clinical relevance. Linagliptin was well tolerated during the study.

Conclusions: Intake of a high-fat meal reduced the rate of linagliptin absorption but had no influence on the extent of absorption; this finding suggests that food has no relevant influence on the efficacy of linagliptin. (*Clin Ther.* 2011;33:1096–1103)

Key words: bioavailability, DPP-4 inhibitor, food, linagliptin, pharmacokinetics, type 2 diabetes.

INTRODUCTION

Linagliptin is a structurally novel dipeptidyl-peptidase-4 (DPP-4) inhibitor currently in late-stage development for the treatment of type 2 diabetes,[1,2] with high selectivity for DPP-4 relative to other dipeptidyl-peptidases.[1] In an extensive multinational program of Phase III studies, linagliptin was well tolerated and improved glycemic control in patients with type 2 diabetes as monotherapy or in combination with other antihyperglycemic agents.[3–9]

Linagliptin has nonlinear pharmacokinetics owing to the high-affinity binding of linagliptin to DPP-4 in plasma and tissues.[10,11] The high affinity of linagliptin for DPP-4 is also responsible for the long terminal half-life ($t_{½}$) of the drug, at >130 hours.[10,12] However, these binding sites are present at low concentrations (5–6 nM in human plasma) and are therefore readily saturated at human therapeutic dose levels.[13–16] Once the

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DPP-4 binding sites have been saturated, the unbound linagliptin is eliminated quickly ($t_{½}$ of 11.1 h).[16] This leads to an accumulation $t_{½}$ of linagliptin of approximately 11 hours, minimal accumulation of the drug, and a less-than-proportional increase in drug exposure with increasing doses.[12,17] Linagliptin has a predominantly nonrenal route of excretion; >90% of an oral dose is excreted unchanged, primarily in feces.[18] Metabolism of the drug has been reported to be minimal, with pharmacologically inactive metabolites.[18]

The present study investigated whether exposure to linagliptin would be affected by food intake, in accordance with regulatory requirements to support dosing recommendations for patients with type 2 diabetes. Depending on the characteristics of the drug, food may either increase or decrease the drug's exposure, or it may have no effect at all.[19] Because linagliptin is characterized by high aqueous solubility at physiologic pH values (pH 7.4, >5 g/L),[20] it was not expected that food would increase or accelerate absorption, but effects associated with a food-related delay in gastric emptying could not be ruled out. Therefore, the objective of this study was to investigate the effects of food on the pharmacokinetics of single doses of linagliptin in healthy male and female subjects.

SUBJECTS AND METHODS

Study Participants

Subjects were recruited from the pool of volunteers at the Human Pharmacology Center, Department of Clinical Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany, depending on their availability. Participants were compensated according to inconvenience, discomfort, and loss of time, as approved by the Independent Ethics Committee. The study aimed to recruit 32 healthy male and female subjects aged 18 to 50 years with a body mass index of 18.5 to 29.9 kg/m^2. Subjects were in good general health according to routine medical history, physical examination, vital signs (blood pressure and pulse rate), and laboratory data (clinical chemistry, hematology, urinalysis, drug screening, and serology for hepatitis B and C, and HIV). Female subjects were required to use appropriate birth control measures until 2 months after completion of the study.

All subjects gave written informed consent. The study was conducted in compliance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki (1996 version) and in accordance with applicable regulatory requirements. Approval was obtained from the local Independent Ethics Committee (Ethik-Kommission bei der Landesärztekammer Baden-Württemberg, Stuttgart, Germany) and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany). On-site monitoring was performed by the Clinical Research Organization, CenTrial GmbH, Tübingen, Germany.

Study Design

This was a single-center, open-label, 2-way crossover study conducted in healthy male and female subjects. Following a 21-day screening period and baseline evaluation, subjects were randomized in a 1:1 ratio to 1 of 2 study period sequences: fed–fasted or fasted–fed. In the "fed" study period, subjects received a single oral dose of 5 mg linagliptin following a high-fat, high-calorie breakfast (test treatment). In the "fasted" study period, dosing occurred after an overnight fast of at least 10 hours (reference treatment). The randomization list was generated using a validated pseudo-random number generator and a supplied seed number so that the allocation of medication numbers would be both reproducible and not predictable. In each case, linagliptin was administered between 8 AM and 9 AM with 240 mL of water. Subjects randomized to receive linagliptin in the fed state took the drug immediately after consuming a standard US Food and Drug Administration high-fat breakfast of approximately 945 Kcal.[21] This consisted of 2 eggs (120 g), 2 strips of bacon (30 g), 2 slices of toast (60 g), butter (30 g), hash brown potatoes (120 g), and whole milk (240 mL). Subjects in both treatment arms were required to fast for a further 4 hours after administration of the drug.

A period of 5 weeks separated the treatments when no medication was taken. The subjects then crossed over to the alternate treatment regimen. The crossover design removes intersubject variability of the treatment comparisons, since each subject served as his or her own control. End-of-study medical evaluations were performed within 7 to 14 days after the final treatment with linagliptin. Subjects admitted to the study center were not permitted to smoke or consume any food or drink other than that provided by the staff, and had to avoid excessive physical activity.