Early Effect of Single-dose Sitagliptin Administration on Gastric Emptying: Crossover Study Using the $^{13}$C Breath Test


1Gastroenterology Division, Yokohama City University Hospital, Yokohama, Japan; 2Department of Medical Education, Yokohama City University School of Medicine, Yokohama, Japan; 3Marketing Department, Kyowa Hakko Kirin Co., Ltd, Tokyo, Japan; and 4Office of Postgraduate Medical Education, Yokohama City University Hospital, Yokohama, Japan

Background/Aims
The gastrointestinal motility effects of endogenous incretin hormones enhanced by dipeptidyl peptidase-IV (DPP-IV) inhibitors have not yet been sufficiently investigated. The aim of this study was to determine whether single pre-prandial sitagliptin, the DPP-IV inhibitor, administration might have an effect on the rate of liquid gastric emptying using the $^{13}$C-acetic acid breath test.

Methods
Ten healthy male volunteers participated in this randomized, two-way crossover study. The subjects fasted for overnight and were randomly assigned to receive 50 mg sitagliptin 2 hours before ingestion of the liquid test meal (200 kcal per 200 mL, containing 100 mg $^{13}$C-acetate) or the test meal alone. Under both conditions, breath samples were collected for 150 minutes following the meal. Liquid gastric emptying was estimated by the values of the following parameters: the time required for 50% emptying of the labeled meal ($T_{1/2}$), the analag to the scintigraphy lag time for 10% emptying of the labeled meal ($T_{lag}$), the gastric emptying coefficient and the regression-estimated constants ($\beta$ and $\kappa$), calculated by using the $^{13}$CO$_2$ breath excretion curve using the conventional formulae. The parameters between the 2 test conditions were compared statistically.

Results
No significant differences in the calculated parameters, including $T_{1/2}$, $T_{lag}$, gastric emptying coefficient or $\beta$ and $\kappa$, were observed between the 2 test conditions.

Conclusions
The present study revealed that single-dose sitagliptin intake had no significant influence on the rate of liquid gastric emptying in asymptomatic volunteers.

(J Neurogastroenterol Motil 2013;19:227-232)

Key Words
Breath tests; Gastric emptying; Sitagliptin

Received: November 6, 2012 Revised: February 21, 2013 Accepted: March 3, 2013

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Correspondence: Masahiko Inamori, MD, PhD Gastroenterology Division, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan Tel: +81-45-787-2640, Fax: +81-45-784-3546, E-mail: inamorim@med.yokohama-cu.ac.jp

Financial support: None.

Conflicts of interest: None.

Author contributions: TN analyzed, collected the clinical data and wrote the manuscript, with contributions from MI, YS, HI, EY, HO, ES and TH were responsible for the design of the study and collected the clinical data. TN, KH, HE CN and MI performed the statistical analyses. TK, HT, KF, MY, AG, AK, NK, EG, SM, AN and MI analyzed the clinical data and participated in the design and coordination of the study. All authors read and approved the final manuscript.
Introduction

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are peptides secreted from the intestine into the circulation in response to food ingestion, and they help manage glycemic control by regulating insulin and glucagon release, slowing gastric emptying, and reducing caloric intake.1-4 Physiologically, the clinical utility of native GLP-1 and GIP is limited because they are rapidly degraded and inactivated by the enzyme dipeptidyl peptidase-IV (DPP-IV).5,6

Inhibition of this enzyme leads to an increase in circulating endogenous GLP-1 and GIP levels. Therefore, DPP-IV inhibitors are a novel therapeutic strategy for type 2 diabetes. Since the release of sitagliptin in 2006, numerous studies have documented the advantages of DPP-IV inhibitors in the management of type 2 diabetes mellitus.7-10 However, the effect of DPP-IV inhibitor-induced enhancement of endogenous incretin hormones on gastrointestinal motility has not yet been sufficiently investigated.11,12 In the present study, the pharmacological effects of pre-prandial single-dose sitagliptin administration on the rate of liquid gastric emptying were examined in healthy volunteers using a $^{13}$C-acetic acid breath test.

Materials and Methods

Subjects

The subjects were 10 asymptomatic male volunteers (median age 34 years, range 27-50 years). The height and weight of the subjects were as follows: median height, 169 cm; height range, 162-181 cm; median weight, 64.5 kg; and weight range, 60-92 kg. None of the subjects were habitual drinkers. All were non-smokers and none had a history of gastrointestinal disease or abdominal surgery. None of the subjects was on any routine medication at the time of the study.

The study (Clinical trial registry number: UMIN 000006213) was conducted in accordance with the Declaration of Helsinki. Prior to study initiation, written informed consent was obtained from all participants. The study protocol using the $^{13}$C-acetic acid breath test was approved by the Ethics Committee of Yokohama City University School of Medicine.

$^{13}$C-acetic Acid Breath Test

Ten subjects participated in this randomized, two-way crossover study (Fig. 1). After overnight fasting (at least 8 hours), the subjects received 50 mg sitagliptin orally 2 hours before ingestion of the test meal (sitagliptin condition) or the test meal alone (control condition) in a random sequence. The 2 test conditions were separated by a washout period of at least 7 days.

The test meal was a 200 kcal per 200 mL liquid meal (Racol with milk flavor, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) containing 100 mg of $^{13}$C-acetic acid (Cambridge Isotope Laboratories, Inc., USA), and the subjects were requested to consume the meal within 5 minutes.

Gastric emptying was measured using the $^{13}$C-acetic acid breath test while the subjects were seated. Breath samples were collected in air bags at baseline (before test meal) and at 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135 and 150 minutes after completion of the test meal ingestion. The $^{13}$CO$_2$/^{12}$CO$_2$ ratio in collected breath samples was determined as the difference above baseline using non-dispersive infrared spectrophotometry (POCone, Otsuka Electronics Co., Ltd., Osaka, Japan).

Data Analysis

In accordance with the method reported by Ghoos et al.,13 the percentage of $^{13}$CO$_2$ recovery in expired breaths per hour (percent dose per hour) against time was fitted to the formula $y(t) = a e^{-b t}$ by non-linear regression analysis, where $y$ is the percentage of $^{13}$C excretion in breath per hour, $t$ is time in hours, and $a$, $b$, and $c$ are constants. The time-course of cumulative $^{13}$CO$_2$ recovery in expired breaths can be fitted to another formula, $z(t) = \int_{0}^{t} y(t') dt'$.