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Original article

Effect of GLP-1 receptor agonist on gastrointestinal tract motility and residue rates as evaluated by capsule endoscopy

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ABSTRACT

Aim. – This study evaluated the effects of a glucagon-like peptide-1 receptor agonist on gastrointestinal (GI) tract motility and residue rates by examining GI transit time and lumen using capsule endoscopy.
Material and methods. – GI motility and lumen were assessed by capsule endoscopy before and after liraglutide administration in 14 patients with type 2 diabetes mellitus (T2DM).
Results. – Gastric transit time in the group with diabetic neuropathy (DN) was 1:12:36 ± 1:04:30 h before liraglutide administration and 0:48:40 ± 0:32:52 h after administration (nonsignificant difference, $P = 0.19$). Gastric transit time in the non-DN group was 1:01:30 ± 0:52:59 h before administration and 2:33:29 ± 1:37:24 h after administration (significant increase, $P = 0.03$). Duodenal and small intestine transit time in the DN group was 4:10:34 ± 0:25:54 h before and 6:38:42 ± 3:52:42 h after administration (not significant, $P = 0.09$) and, in the non-DN group, 3:51:03 ± 0:53:47 h before and 6:45:31 ± 2:41:36 h after administration (significant increase, $P = 0.03$). The GI residue rate in the DN group was 32.1 ± 24% before administration and 90.0 ± 9.1% after administration (significant increase, $P < 0.001$), and increased in all patients; in the non-DN group, it was 32.1 ± 35.3% before and 78.3 ± 23.9% after administration (significant increase, $P < 0.001$), and also increased in all patients.
Conclusion. – Liraglutide causes delayed gastric emptying and inhibits duodenal and small intestine motility. However, these GI movement-inhibiting effects may be decreased or absent in patients with DN-associated dysautonomia.

Introduction

Incretins are hormones secreted into the gastrointestinal tract upon food ingestion. They promote insulin secretion by acting on pancreatic β cells in a blood-glucose-dependent manner. Two incretins, glucose-dependent insulinotropic polypeptide and glucagon-like peptide (GLP)-1, have been identified [1,2]. GLP-1 receptor agonists (GLP-1RAs) can reduce blood glucose levels and have been reported to have several extrapancreatic effects [3].

GLP-1 suppresses gastric emptying by inhibiting peristalsis of the stomach while increasing tonic contraction of the pyloric region [4,5]. The dye dilution method using phenol red and the acetaminophen method [6,7] have both been used in studies to evaluate gastrointestinal motility. While inhibition of gastric emptying can be achieved with these methods, the evaluation of motor function in each intestinal region is difficult.

In the present study, the long-acting GLP-1RA liraglutide, which has a half-life in blood of 13 h [8], was administered to inpatients at the Dokkyo Medical University Nikko Medical Center (Tochigi, Japan). Capsule endoscopy was performed before and after liraglutide administration to investigate its influence on gastric emptying and motility of each gastrointestinal region. Also, the amount of gastrointestinal residue before and after liraglutide administration was compared, using the Boston Bowel Preparation Scale [9], a 10-point scale used in colonoscopy.

In addition to evaluation of all our inpatients, findings were further analyzed in those with and without diabetic neuropathy (DN). In this way, differences in the effects of liraglutide on gastrointestinal motility and residue rates due to DN were also investigated.

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Methods

Participants

The study protocol was approved by the Institutional Review Board of the Dokkyo Medical University Nikko Medical Center (ID: 26016) and all procedures followed were in accordance with the standards of the ethics committee for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained from all patients for study inclusion.

The study cohort comprised 15 patients with type 2 diabetes mellitus (T2DM), aged $\geq$ 30 years or $<$ 80 years, who had not undergone treatment with either dipeptidyl peptidase (DPP)-4 inhibitors or GLP-1RAs after being admitted for diabetes treatment.

Exclusion criteria were patients who had:

- type 1 diabetes mellitus (T1DM);
- T2DM dependent on insulin due to a reduced ability to secrete insulin;
- a history of arrhythmia and its treatment;
- marked dysautonomia associated with DN, according to diagnostic criteria established by the Diabetic Neuropathy Study Group [10];
- a history of acute/chronic pancreatitis, ileus or surgery of the abdominal region;
- a contraindication to capsule endoscopy (those with small bowel stenosis, pregnant patients and any patients deemed unsuitable for clinical study by the investigators).

Study design

This single-center, observational study was performed with 15 inpatients who had T2DM. Neurological examination was performed in all patients upon hospital admission by a diabetologist certified by the Japan Diabetes Society and the presence or absence of DN was determined. Patients with a coefficient of variation of $<$ 2.0% for the R–R interval on electrocardiography (ECG) at rest who fulfilled two or more of the following three conditions were designated the DN group:

- paraesthesia and allodynia in the bilateral tips of the toes or soles of the feet;
- reduced or absent bilateral Achilles tendon reflexes;
- reduced ($<$ 10 s) vibratory sensation on the lateral medial malleoli as evaluated by a tuning fork (C-128 Hz).

After hospital admission, all antihyperglycaemic medications from the outpatients' clinic were withdrawn in all cases and temporary basal–bolus therapy was initiated to correct hyperglycaemia. For all patients, the bolus insulin dose was 16.8 ± 4.1 units, basal insulin was 8.0 ± 2.5 units and the duration of insulin treatment was 10.8 ± 3.6 days. In the DN group, the bolus insulin dose was 16.9 ± 5.0 units, basal insulin was 8.9 ± 2.8 units and the duration of insulin treatment was 12.7 ± 3.8 days while, in the group without DN, the bolus insulin dose was 15.1 ± 2.8 units, basal insulin was 7.1 ± 1.8 units and the duration of insulin treatment was 8.9 ± 2.0 days. No significant differences were noted between groups in insulin amounts used or duration of insulin treatment (Table S1; see supplementary materials associated with this article online).

After treatment initiation, blood levels of C-peptide were measured and the C-peptide immunoreactivity (CPR) index calculated when fasting blood glucose had decreased to $\leq$ 150 mg/dL and its level 2 h after consumption of a meal had decreased to 200 mg/dL [11,12], to ensure that conditions were non-insulin-dependent. Liraglutide was then administered to all patients, along with the concomitant administration of glimepiride (1.0 mg/day). Metformin was not given concomitantly throughout the study period because it can exert adverse effects on the digestive system that, in turn, may influence gastrointestinal motility [13].

Titration of liraglutide was initiated at 0.3 mg at 0800 h before breakfast. This dose was increased by 0.3 mg each week to a final dose of 0.9 mg (the maximum dose approved in Japan).

In addition, blood glucose was determined before each meal, using a self-monitoring blood glucose device (OneTouch Ultra®; Johnson & Johnson, New Brunswick, NJ, USA). Metabolic factors [body mass index (BMI), systolic blood pressure, diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)] were also measured before liraglutide administration and when the dose reached 0.9 mg.

The gastrointestinal motility test, using a capsule endoscope (PillCam® SB 2 and PillCam® Recorder DR3 Simulator; Covidien Japan, Tokyo, Japan), was performed before liraglutide treatment and 1 week after the dose reached 0.9 mg. According to the dosing schedule, eating and drinking were prohibited after 2100 h on the day before the capsule endoscopy. On the day of the examination, liraglutide was injected subcutaneously at 0800 h, followed by ingestion of the capsule endoscope. Drinking water was allowed 2 h after the capsule endoscope was swallowed and a normal meal was ingested from 1200 h onwards.

Based on the results of capsule endoscopy, the following time points were recorded: 'gastric transit initiation time' was when the gastric mucosa was visible; 'gastric transit completion time' and 'duodenal–small bowel transit initiation time' was when the duodenal bulb was visible; and 'duodenal–small bowel transit completion time' was when the caecum was reached.

The capsule endoscopy results were analyzed by a physician in the gastroenterology department of our institution using RAPID® for PillCam® software at a RAPID workstation (Covidien Japan). For the gastrointestinal residue rates, the proportions of 'poor' and 'unsatisfactory' cases in the duodenum and small intestine were calculated, using the Boston Bowel Preparation Scale [9].

Statistical analysis

All data were analyzed with SPSS v23 software (IBM Corp., Armonk, NY, USA). The results are presented as means ± standard deviation (SD). To compare the two groups, the paired t test or Mann–Whitney U test for continuous variables was performed. $P < 0.05$ (two-tailed) was considered statistically significant.

Results

The present study initially included 15 patients with T2DM. However, the capsule endoscope did not reach the large intestine within the observation period in one patient, who was therefore excluded. Thus, the study was completed with 14 patients (Fig. S1; see supplementary materials associated with this article online) (Table 1).

Fasting blood glucose and metabolic conditions

Fasting blood glucose was measured three times a day at: 0800 h (breakfast), 1200 h (lunch) and 1800 h (dinner). For all patients, the level of fasting blood glucose before liraglutide administration was 116.6 ± 22.3 mg/dL at 0800 h and decreased to 100.3 ± 12.8 mg/dL after administration, showing significant improvement ($P = 0.03$). The level at 1200 h improved from 105.9 ± 23.2 to 95.9 ± 11.2 mg/dL ($P = 0.17$) and, at 1800 h, from

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