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Gastrointestinal uptake of FDG after *N*-butylscopolamine or omeprazole treatment in the rat

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Objective: Gastrointestinal (GI) uptake of 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) is frequently observed in whole-body positron emission tomography (PET) images. Such physiological uptake may interfere with accurate interpretation. The aim of the present study was to determine whether physiological gastrointestinal FDG uptake can be decreased by means of an antiperistaltic agent, *N*-butylscopolamine, or a gastric secretion inhibitor, omeprazole. ***Methods:*** Sprague-Dawley rats were divided into three groups: omeprazole-treated (n = 6), *N*-butylscopolamine-treated (n = 7), and control group (n = 6). The rats in the omeprazole-treated group were administered omeprazole (1.0 mg/kg) intravenously 45 minutes before FDG injection. The rats in the *N*-butylscopolamine-treated group were administered *N*-butylscopolamine (1.0 mg/kg) intramuscularly 10 minutes before FDG injection. Sixty minutes after FDG injection under overnight fasting state, the gastrointestinal tissues were excised and weighed to determine the radioactivity of ^{18}F using a gamma counter. ***Results:*** The mean values of FDG uptake in the esophagus, stomach, small intestine, cecum and colon of the *N*-butylscopolamine-treated group vs. the omeprazole-treated group were 148% vs. 162%, 109% vs. 113%, 113% vs. 88%, 102% vs. 85%, 105% vs. 70% of the control group, respectively. There were no statistical differences in FDG uptake rate in the esophagus, stomach, or cecum among the three groups. FDG uptake rates in the small intestine and colon of the omeprazole-treated group were significantly lower than those in the control group. ***Conclusion:*** Physiological FDG uptake in the GI tract was not decreased by the administration of *N*-butylscopolamine. Omeprazole was effective in decreasing FDG uptake in the small intestine and colon. Omeprazole has a potential to decrease FDG uptake rate in a limited part of the GI tract.

Key words: FDG, PET, *N*-butylscopolamine, omeprazole, physiological uptake

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) has been recently used in evaluating various types of carcinoma. To make proper interpretations, the normal physiologic distribution should be taken into consideration, since physiologic variants of FDG uptake as well as benign pathologic causes of FDG uptake may mimic true malignant lesions. Along with FDG uptake in various normal organs such as the brain, thyroid gland, skeletal muscles, myocardium, bone marrow, and genitourinary tract, uptake in a normal gastrointestinal (GI) tract is frequently observed in whole-body FDG-PET images.[1–4] The possible causes of FDG uptake in the GI tract are supposed to be active smooth muscles, metabolically active mucosa, swallowed secretions, or microbial flora. Kim et al.[5] in their review of colonic FDG uptake in 314 persons showed that intense colonic uptake with a focal pattern was observed more frequently in the descending colon of patients with constipation. They suggested that colonic contraction in

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Table 1 Biodistribution of FDG in rats (%ID/g/kg)

Tissues	control (n = 6)	omeprazole (n = 6)	omeprazole /control	*N*-butylscopolamine (n = 7)	*N*-butylscopolamine /control
Blood	0.062 ± 0.005	0.051 ± 0.007	0.823	0.069 ± 0.009	1.113
Esophagus	0.079 ± 0.004	0.128 ± 0.058	1.62	0.117 ± 0.039	1.481
Stomach	0.148 ± 0.029	0.167 ± 0.087	1.128	0.161 ± 0.046	1.088
Colon	0.162 ± 0.048	0.114 ± 0.022*	0.704	0.17 ± 0.026	1.049
Cecum	0.046 ± 0.007	0.039 ± 0.006	0.848	0.047 ± 0.004	1.022
Small intestine	0.242 ± 0.022	0.212 ± 0.021*	0.876	0.273 ± 0.035	1.128
Muscle	0.052 ± 0.012	0.04 ± 0.012	0.769	0.039 ± 0.008	0.75
Heart	0.071 ± 0.007	0.081 ± 0.021	1.141	0.085 ± 0.021	1.197
Brain	0.697 ± 0.051	0.614 ± 0.092	0.881	0.694 ± 0.048	0.996
Liver	0.062 ± 0.004	0.055 ± 0.007	0.887	0.076 ± 0.01	1.226

*$p < 0.05$ vs. control value

association with constipation might result in increased muscular activity, which contributes to a high FDG uptake rate. Bowels prepared with an isosmotic solution before the FDG-PET study were reported to reduce artifactual FDG accumulation in the colon.[6] It was also reported that the administration of an antiperistaltic agent, *N*-butylscopolamine, reduced the intestinal FDG uptake rate.[7] However, the cause of intestinal FDG uptake and the factors that influence the level of uptake are unclarified. The purpose of this study was to determine whether the administration of an antiperistaltic agent, *N*-butylscopolamine, or a gastric secretion inhibitor, omeprazole, would suppress physiological FDG uptake in the GI tract.

MATERIALS AND METHODS

Animal Studies

The experimental protocol was fully approved by the Laboratory Animal Care and Use Committee of Hokkaido University. All studies were conducted in a manner that minimizes pain and distress in the animals. Sprague-Dawley rats weighing between 250–350 g were used. They were maintained with a supply of water and diet except for overnight fasting prior to FDG injection. The rats were divided into three groups subjected to various treatments for bowel preparation:

1. Omeprazole-treated group (n = 6),
2. *N*-butylscopolamine-treated group (n = 7),
3. Control (n = 6).

The rats in the omeprazole-treated group were administered omeprazole (1.0 mg/kg) intravenously via the tail vein 45 minutes before FDG injection. The rats in the *N*-butylscopolamine-treated group received an intramuscular (i.m.) injection of *N*-butylscopolamine (1.0 mg/kg) into the left calf 10 min before FDG injection. The rats in the control group received an i.m. injection of saline (1.0 m*l*/kg) 10 min before FDG injection. The rats were anesthetized with ether and were injected with 5.55–7.4 GBq (150–200 μCi) of FDG. Sixty minutes after FDG injection, the animals were sacrificed and tissues were quickly excised from the esophagus, stomach, small intestine, cecum and colon and then weighed. The wall and intraluminal contents were not separated. Non-GI tissues were collected from the blood, brain, heart, muscles and liver. Plasma glucose level was measured at the times of FDG injection and sacrifice. The pH of stomach contents was measured using a test paper. The radioactivity of ^{18}F was determined using a gamma counter with a window width of 511 keV ± 10%. FDG uptake in the tissues was expressed as the percentage activity of injected dose per gram of tissue normalized to the animal weight (%ID/g/kg).

Statistical Analysis

In this text, all data are shown as mean ± SD. Statistical analysis was performed using the unpaired Student-t test. A two-tailed value of $p < 0.05$ was considered significant.

RESULTS

The weights of rats in the omoprazole-treated group (312 ± 8 g) and the *N*-butylscopolamine-treated group (305 ± 12 g) were similar to those in the control group (304 ± 10 g). pHs of stomach contents in the omeprazole-treated group (6.0 ± 1.1) and *N*-butylscopolamine-treated group (3.9 ± 1.3) were significantly higher than those in the control group (3.0 ± 0.9) ($p < 0.05$). The plasma glucose levels in the omeprazole-treated group were significantly higher than those in the control group before FDG injection (92.7 ± 5.4 mg/d*l* vs. 77.0 ± 11.6 mg/d*l*) ($p < 0.05$) and one hour after FDG injection (100.8 ± 6.7 mg/d*l* vs. 87.5 ± 10.1 mg/d*l*) ($p < 0.05$). The plasma glucose level in the *N*-butylscopolamine-treated group was significantly higher than that in the control group one hour after FDG injection (107.0 ± 14.9 mg/d*l* vs. 87.5 ± 10.1 mg/d*l*) ($p < 0.05$).

Table1 summarizes the biodistribution of FDG in rats. The mean values of FDG uptake in the *N*-butylscopolamine-treated group were 148% (0.117 ± 0.039 vs. 0.079 ± 0.004) in the esophagus, 109% (0.161 ± 0.046 vs. 0.148

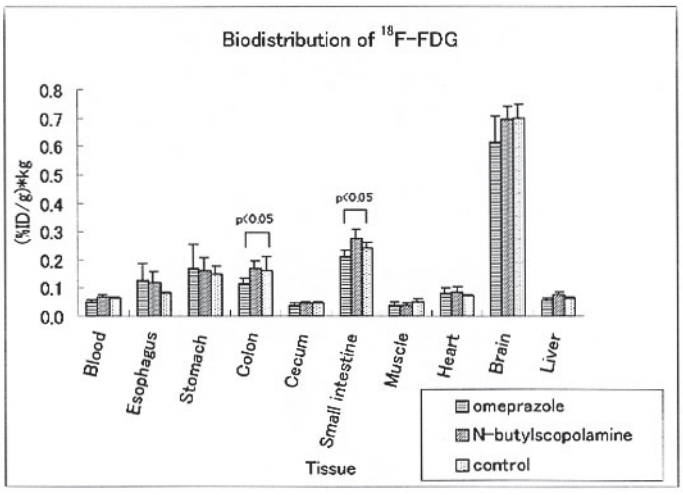

Fig. 1 The tissue distributions of FDG in the three study groups.

± 0.029) in the stomach, 113% (0.273 ± 0.035 vs. 0.242 ± 0.022) in the small intestine, 102% (0.047 ± 0.004 vs. 0.046 ± 0.007) in the cecum, and 105% (0.170 ± 0.026 vs. 0.162 ± 0.048) in the colon as compared with those in the control group. There were no significant differences in the FDG uptake rate between the control group and the *N*-butylscopolamine-treated group in any part of the gastrointestinal tract. The mean values of FDG uptake in the omeprazole-treated group were 162% (0.128 ± 0.058 vs. 0.079 ± 0.004) in the esophagus, 113% (0.167 ± 0.087 vs. 0.148 ± 0.029) in the stomach, 88% (0.212 ± 0.021 vs. 0.242 ± 0.022) in the small intestine, 85% (0.039 ± 0.006 vs. 0.046 ± 0.007) in the cecum and 70% (0.114 ± 0.002 vs. 0.162 ± 0.048) in the colon as compared with those in the control group. In the omeprazole-treated group, the FDG uptake rates were significantly lower than those in the control group in the small intestine ($p < 0.05$) and colon ($p < 0.05$) (Fig. 1). There were no statistically significant differences in FDG uptake rate in non-GI tissues among the three groups.

DISCUSSION

Rapid advances in morphological imaging have improved the diagnostic value of ultrasonography, CT, and MRI in the study of gastrointestinal tumors.[8] While FDG-PET has been recognized as a powerful clinical tool for evaluating malignant tumors, physiological FDG accumulations in many organs[1,4] may interfere with accurate diagnosis and localization of the lesions. In the analysis of FDG uptake in GI tract, the stomach wall may show moderate FDG accumulation. It is not known whether FDG uptake occurs in the smooth muscle or other layers of the gastric mucosa. Similarly, FDG activity may be detected in the small intestine and more commonly in the large intestine. This is usually of relatively low grade that would not be misinterpreted as a malignancy.[9]

There have been a number of attempts to decrease physiological FDG uptake rate in the GI tract to improve diagnostic accuracy in detecting malignant lesions. Atropine produces a prolonged inhibitory effect on bowel motility, which is characterized by a decrease in tone, amplitude and frequency of peristaltic contractions. Atropine was expected to decrease FDG uptake rate. However, there were no significant differences in FDG uptake rate when the baseline study was compared with postmedication images in clinical use.[10] Glucagon has been widely used to inhibit intestinal motility in contrast to radiography of the GI tract.[11–13] However, hyperglycemia caused by glucagon could impair tumor targeting by FDG.

Compared with glucagon, *N*-butylscopolamine has the advantages of a longer antispasmodic action and a lower risk of hyperglycemia. The antiperistaltic agent *N*-butylscopolamine has been used in clinical studies. The rate of bowel FDG uptake that interfered with scan interpretation decreases in the *N*-butylscopolamine-treated group. The administration of *N*-butylscopolamine decreases the intestinal FDG uptake rate and may facilitate the accurate interpretation of clinical abdominal FDG-PET studies.[7] However, the present study showed that *N*-butylscopolamine did not decrease the FDG uptake rate in any part of the GI tract. The changes in the pH of stomach contents indicate that the agent was effective in suppressing peristalsis throughout the study. Although we did not use different doses for precise assessment of the effect of *N*-butylscopolamine on FDG uptake in the GI tract, the current study suggests that the dose of *N*-butylscopolamine suppressing peristalsis was not sufficient to decrease FDG uptake rate in the GI tract. Another possible explanation is that the suppression effect on peristalsis was too transient to decrease the FDG uptake rate in the GI tract. We measured radioactivities in both the intraluminal contents and the bowel wall. A separate analysis of these radioactivities, might clarify the effects of *N*-butylscopolamine

on FDG uptake. On the other hand, *in vivo* FDG-PET images represent total FDG uptake in the intestinal wall and intraluminal contents. Therefore, our results indicate that the use of *N*-butylscopolamine was not effective to decrease the FDG uptake rate in the GI tract with the current dose.

The major finding of our study is that FDG uptake rates were significantly decreased by omeprazole in the small intestine and colon, but not in the stomach. Omeprazole suppresses gastric secretion by inhibiting Na^+K^+ATPase in the gastric mucosa without inhibiting peristalsis.[14] It also inhibits the activities of the mucosal enzymes, such as Na^+K^+ATPase and Ca^{2+} ATPase in the rat jejunum.[15] The inhibition of Na^+K^+ATPase activity may cause malabsorption of glucose as well as Na. As a result, FDG uptake in the small intestine may be altered. In addition, omeprazole causes diarrhea[16,17] and may change the population of microflora in the gut. Such actions may change colonic FDG accumulation. However, the precise mechanisms by which the FDG uptake rate in some parts of the GI tract is decreased by omeprazole remain unknown. Further studies are required to determine factors that influence FDG uptake rate in the normal bowel in a clinical setting.

CONCLUSION

Physiological FDG uptake rate in the GI tract was not decreased by the administration of an antiperistaltic agent, *N*-butylscopolamine. On the other hand, a gastric secretion inhibitor, omeprazole, was effective in decreasing the FDG uptake rate in the small intestine and colon. Thus, omeprazole has the potential to decrease FDG uptake in a limited part of the GI tract.

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