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ORIGINAL ARTICLE

Impact of rikkunshito, an herbal medicine, on delayed gastric emptying in profoundly handicapped patients

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Abstract
Purpose Rikkunshito is used to treat functional dyspepsia in adults. This study investigated the effects of rikkunshito on delayed gastric emptying in handicapped patients.
Methods A retrospective review was performed in nine profoundly handicapped patients (aged 1–19 years). All were diagnosed with delayed gastric emptying based on their half gastric emptying time ($T_{1/2}$) over 90 min. Gastric emptying was evaluated after the ingestion of liquid meals using the ^{13}C-acetate breath test and the BreathID^{TM} system. Participants were given rikkunshito [0.3 g/(kg day)] with the aim of accelerating gastric emptying. Parameters related to gastric emptying before and during rikkunshito administration were compared using the Wilcoxon signed-rank test. Data were expressed as the median (range).
Results Emesis and hematemesis were relieved with rikkunshito administration in four symptomatic patients. The $T_{1/2}$ and T_{lag} decreased significantly during rikkunshito administration from 115 min (94–167 min) to 107 min (64–66 min; $p = 0.02$), and from 60 min (42–90 min) to 47 min (29–59 min; $p = 0.03$), respectively. The gastric emptying coefficient did not show a significant change [3.1 (2.8–3.8) vs. 3.2 (2.6–4.0), $p = 0.15$)] with rikkunshito treatment.
Conclusion The administration of rikkunshito resulted in symptomatic relief and improved gastric emptying in profoundly handicapped patients with delayed gastric emptying.

Keywords Rikkunshito · Herbal medicine · Gastric emptying · ^{13}C breath test

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Introduction

Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder in the pediatric population. Fundoplication has been the mainstay for the long-term treatment of pediatric GERD, but there are pros and cons regarding its long-term efficacy. Recently, some authors have emphasized that surgery for GERD should be performed after the failure of medical management [1, 2]. The most potent therapeutic option for GERD is proton pump inhibitors (PPIs). PPIs work by reducing gastric acid secretion, but do not reduce the reflux of gastric contents into the esophagus. Current prokinetic drug therapies have not proven to be effective for GERD in children. Therefore, we attempted to control GERD with rikkunshito, an herbal medicine consisting of eight herbs that have been used to treat functional dyspepsia in adults. Our previous study showed that the short-term administration of rikkunshito relieved symptoms and reduced distal esophageal acid exposure through improved esophageal acid clearance in children with GERD [3]. However, evidence demonstrating the physiological effectiveness of this treatment is still limited, as with most herbal medicines [4, 5]. We retrospectively investigated the effects of rikkunshito on gastric emptying in handicapped patients with delayed gastric emptying.

Materials and methods

Patients

A retrospective review was performed using nine patients, ranging in age from 1 to 19 years (median age, 8 years), after first receiving the approval of our institutional review board. Delayed gastric emptying was diagnosed if the patient's half gastric emptying time ($T_{1/2}$) was >90 min; $T_{1/2}$ was determined using the ^{13}C-acetate breath test. All patients had profound neurological impairment, such as cerebral palsy ($n = 5$), chromosomal anomaly ($n = 2$), post-traumatic brain damage ($n = 1$), or lissencephaly ($n = 1$). Eight patients were nourished with gastrostomy and one with a nasogastric tube. The effects of rikkunshito (TJ-43; Tsumura, Tokyo, Japan) were evaluated in five patients after gastrostomy placement for possible future symptoms due to delayed gastric emptying and in four patients with excessive intragastric residue and emesis/hematemesis.

^{13}C-acetate breath test

The ^{13}C-acetate breath test was conducted as part of routine follow-up studies or as required by the patient's clinical condition during hospitalization. Ethical approval for this test was obtained from the departmental committee, and informed consent was obtained from the patient's guardians. The administration of prokinetic agents, H_2-blockers, and PPIs was halted at least 3 days before the initial breath test. Rikkunshito was administered at a dose of 0.3 g/(kg day) via gastrostomy or a nasogastric tube in three divided doses before meals. The second breath test was performed at a median 6 days (4–16 days) after commencing rikkunshito administration. Rikkunshito was given 30 min before measurement at a dose of 0.1 g/kg.

The ^{13}C-acetate breath test measures changes in the $^{13}CO_2/^{12}CO_2$ isotope ratio in the patient's exhaled breath, which result from the absorption and metabolism of a ^{13}C-labeled test meal marker as it exits in the stomach. Specifically, after a baseline collection of the patient's breath, 100 mg of ^{13}C-labeled sodium acetate dissolved in a liquid meal was administered. Liquid formulae given to patients included elemental diet formula ($n = 4$), low residual formula ($n = 4$), and a hypoallergic formula ($n = 1$). The volume of the liquid meal was calculated at 300 ml per 1.73 m^2 of body surface area. Patients were tested for 4 h in the supine position after more than 6 h of fasting.

Gastric emptying was evaluated via a continuous breath test in real time using the BreathID^{TM} system (Oridion BreathID Ltd., Jerusalem, Israel). Patients were connected to the device via a cannula, which was attached to the nose for seven patients or via a tracheostomy for two patients. The test meal was processed and emptied by the stomach and, after absorption and metabolism, ^{13}C was produced and exhaled in the breath as CO_2. The device continuously measured the ratio of ^{13}C and ^{12}C in exhaled CO_2 using molecular correlation spectroscopy, which absorbs radiation emitted by the radioisotope [6]. The BreathID^{TM} device measures the ratio of C isotopes, which is normalized for patient weight, height and ^{13}C substrate and dose, and provides a percentage dose recovery and cumulative percentage dose recovery. The excretion of $^{13}CO_2$ in the breath was mathematically analyzed using two non-linear regression equations to find the best fitting curve through the measured data points with the affiliated computer software (Oridion Research Software^{TM}). The data from the breath test were used to calculate three common parameters for gastric emptying, using formulas based on the analysis described by Ghoos et al. [7]. (1) The half emptying time ($T_{1/2}$) is the time required for half of the gastric contents to be emptied. In this study, delayed gastric emptying was defined as a $T_{1/2}$ value >90 min [7–9]. (2) The lag time (T_{lag}) is the time corresponding to the point of inflection of the curve after mathematical integration (i.e., the time of maximal $^{13}CO_2$ excretion based on the fitted curve). (3) Finally, the gastric emptying coefficient (GEC) is an index of the global gastric emptying rate.

Data analysis

The values of the three gastric emptying parameters were expressed as medians (range). These parameters before and during the administration of rikkunshito were compared statistically using the Wilcoxon signed-rank test. Statistical significance was accepted at $p < 0.05$.

Results

Clinical findings

Of the four symptomatic patients, emesis or hematemesis was relieved in all individuals during rikkunshito administration. Therefore, rikkunshito was given continuously after the breath test in those patients. Five postoperative patients without observable symptoms did not show significant clinical changes during rikkunshito administration. No adverse effects were noted.

^{13}C-acetate breath test (Fig. 1)

The breath test was completed successfully in all patients. During rikkunshito administration, $T_{1/2}$ decreased significantly from 115 min (94–167 min) to 107 min (64–166 min; $p = 0.02$). T_{lag} also decreased significantly from

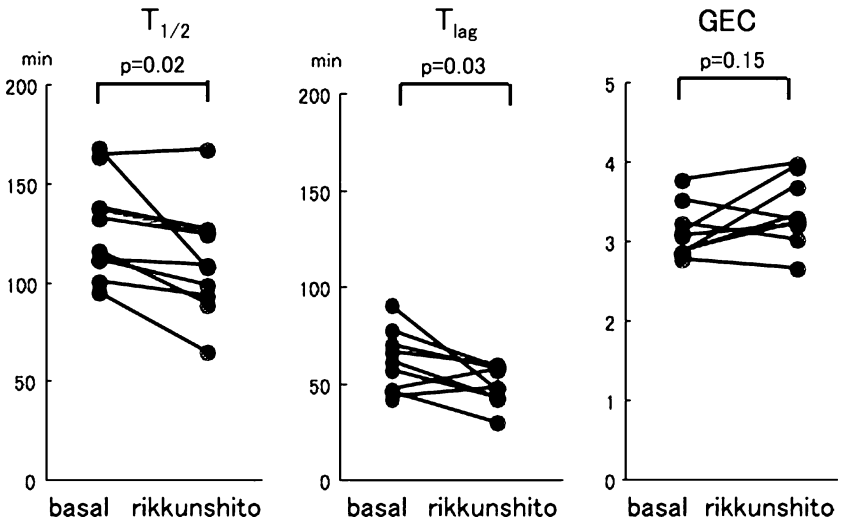

Fig. 1 Effects of rikkunshito on $T_{1/2}$, T_{lag}, and the gastric emptying coefficient (GEC). Data are shown as data points for each subject before (basal) and during rikkunshito administration

60 min (42–90 min) to 47 min (29–59 min; $p = 0.03$). GEC did not show a significant change [3.1 (2.8–3.8) vs. 3.2 (2.6–4.0); $p = 0.15$]. In the four symptomatic patients, $T_{1/2}$ decreased in all participants, whereas T_{lag} and GEC decreased in only three individuals.

Discussion

Acid suppressors and prokinetic agents have been used in the medical treatment of GERD. Although acid suppression therapy eliminates acid-related reflux symptoms, it does not prevent the reflux of intragastric contents into the esophagus. Prokinetic agents are thought to reduce the reflux of intragastric contents by improving the contractility of the esophageal body and/or accelerating gastric emptying. However, the efficacy of prokinetic agents for GERD has been demonstrated only for cisapride [10], which is not widely used because of possible adverse cardiac effects. Therefore, we examined the effectiveness of rikkunshito in the medical treatment of pediatric GERD in a previous study [3]. Rikkunshito is an herbal formulation used in Kampo medicine. In Japan, it is well known as an effective treatment for functional dyspepsia and anorexia in adults [4]. The powder extract of rikkunshito is a mixture of Atractylodis Lanceae Rhizoma, Ginseng Radix, Pinelliae Tuber, Hoelen, Zizyphi Fructus, Aurantii Nobilis Percarpium, Glycyrrhizae Radix, and Zingiberis Rhizoma. However, data on the effectiveness of rikkunshito for human gastrointestinal motor disorders in the English literature are limited [4, 5]. Although this study was performed on a small cohort, our data suggest that rikkunshito effectively improved esophageal acid clearance in children with GERD [3]. The mechanism underlying improved esophageal clearance capacity after rikkunshito treatment has not been clarified. Rikkunshito may decrease esophageal acid exposure by augmenting esophageal contractions. However, we did not detect significant changes in the amplitude of distal esophageal contractions or esophageal sphincter tone after the administration of rikkunshito (unpublished data).

Tatsuta et al. [4] used the acetaminophen absorption method to demonstrate that rikkunshito significantly accelerated gastric emptying in adult patients with chronic idiopathic dyspepsia. Kido et al. [11] identified hesperidin and L-arginine as two of the active ingredients contributing to the ability of rikkunshito to facilitate gastric emptying in rats. Recently, Takahashi et al. [12] used the dual scintigraphic technique to show that rikkunshito improved gastric emptying of solid meals from the remnant stomach after a pylorus-preserving gastrectomy, but did not accelerate gastric emptying of liquid meals in adult patients who had undergone the same procedure [12]. In the current study, the ^{13}C breath test showed significant changes in $T_{1/2}$ and T_{lag}, but not in GEC, after the administration of rikkunshito in handicapped patients with delayed gastric emptying. Although these three parameters reflect different aspects of gastric emptying capacity, $T_{1/2}$ is the most popular parameter to measure gastric emptying. Therefore, we assumed that rikkunshito has a significant impact on delayed gastric emptying, although changes in the GEC did not reach significance ($p = 0.15$). Although the subjects and methodology used in previous studies were diverse, rikkunshito appears to have an effect on delayed gastric emptying. If the intragastric residue is reduced by rikkunshito administration, a subsequent reduction in the reflux volume may reduce esophageal acid exposure. However, Carmagnola et al. [13] reported a negative relationship between changes in gastric emptying and reflux variables after administering cisapride, which improves esophageal acid clearance and gastric emptying. Therefore, further studies are necessary to clarify effects of

rikkunshito on esophageal acid clearance and gastric emptying.

We used the ^{13}C-acetate breath test to measure gastric emptying in handicapped patients in this study. Scintigraphy has been considered the gold standard for measuring gastric emptying, but this technique is associated with radiation exposure to patients and personnel. Recently, breath tests using a substrate (i.e., acetate or octanoic acid) labeled with the stable isotope ^{13}C, a naturally occurring nonradioactive isotope, have been used as an alternative technique to measure gastric emptying in children; this test is advantageous in that it is easy, noninvasive, and nonradioactive [14]. Patients ingest the ^{13}C-labeled acetate, which passes through the stomach and is absorbed in the duodenum and proximal jejunum. The ^{13}C-labeled acetic acid is then metabolized in the liver and excreted from the lungs as $^{13}CO_2$. This phenomenon makes it possible to measure gastric emptying in a noninvasive manner [15]. The BreathID^{TM} system used in this study collects continuous breath samples and can serve as a real-time analysis at the point of patient care. Therefore, this system is especially suitable for studies in profoundly handicapped patients. However, the threshold to diagnose delayed gastric emptying using this system has not been established. In this study, patients with a $T_{1/2}$ >90 min were recruited retrospectively. Lysy et al. [9] reported that the normal $T_{1/2}$ for adults after ingesting mixed meals was in the range of 50–94 min, based on previous work performed by Ghoos et al. [7]. Gatti et al. [8] reported that the $T_{1/2}$ for milk was 74 ± 12 min in healthy children [8]. Based on these data measured using the ^{13}C breath test, the upper threshold of $T_{1/2}$ was set at 90 min in this study.

In conclusion, the administration of rikkunshito provided symptomatic relief and improved gastric emptying in profoundly handicapped patients with delayed gastric emptying. This finding suggests that rikkunshito provides clinical benefits to patients with functional gastrointestinal disorders.

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