NCT Number - NCT02736799

Title of the Study:

Effect of VIBRANT Capsule on Gastric Emptying and Antropyloroduodenal Motility in Healthy Volunteers: A Sham Device Controlled, Single Center Pilot Study

Abstract

Background

The VIBRANT capsule is a novel vibrating device for the treatment of gastrointestinal disorders. The effect of different vibrations on the motor functions of the gastrointestinal tract are unclear. The study will focus on the stomach in healthy volunteers.

Hypothesis

VIBRANT capsule treatment results in acceleration of gastric emptying and stimulation of gastric motility in healthy volunteers.

Aim

To compare the effects of VIBRANT capsule treatment and SHAM capsule treatment on gastric emptying and gastric motility in healthy volunteers.

Methods

We shall perform simultaneous antropyloroduodenal manometry and scintigraphic gastric emptying of solids in 24 healthy volunteers, 6 volunteers per treatment arm with VIBRANT capsule programmed to deliver 0, 1, 3 or 5 vibrations per minute for a period of 4 hours starting 15 minutes after ingestion. This is a pilot study to evaluate potential effects of the VIBRANT capsule on stimulation of gastric motor functions.

Significance

This study will provide new information about the ability of the VIBRANT capsule to impact contractility in the stomach and will determine if specific vibrations patterns result in different contractile activity.

In addition, this study will form the foundation for subsequent application of this method for treatment of motility and functional disorders of the lower stomach, particularly in patients with gastroparesis.

Research Plan

HYPOTHESES AND SPECIFIC AIM

Hypothesis

VIBRANT capsule treatment results in acceleration of gastric emptying and stimulation of gastric motility in healthy volunteers.

Aim

To compare the effects of three different VIBRANT capsule treatment modes (1, 3 and 5 vibrations per minute) and SHAM capsule treatment on gastric emptying and gastric motility in healthy volunteers.

BACKGROUND

The VIBRANT capsule's mechanism of action is still unknown, as well as the effect of different vibration patterns. This study will test for the first time the hypothesis that the VIBRANT capsule effects contractility and analyze the effects of different vibration pattern on stomach contractility.
Furthermore, there is continued unmet need for effective treatments for patients with gastroparesis (1).

RESEARCH DESIGN AND METHODS

Study Design

This is a randomized, double-blind, sham-controlled, parallel-group pilot study. Twenty-four healthy volunteers will be recruited, enrolled, and randomized to one of 4 treatment groups. Subjects meeting all inclusion/exclusion criteria will be randomized to either sham VIBRANT or vibrating VIBRANT capsule at rates of 1, 3 or 5 per minute. The actual studies will be conducted on one day.

Participants

Male and female subjects, aged 18 to 65 years at screening, who meet the following inclusion and exclusion criteria will be eligible for enrollment:

Inclusion criteria

1. Able to provide written informed consent prior to any study procedures, and be willing and able to comply with study procedures
2. No medical problems or chronic diseases, specifically, no type 2 diabetes mellitus

3. Body mass index of 18-35 kg/m^2
4. Female subjects must have negative urine pregnancy tests and must not be lactating prior to receiving study medication and radiation exposure. For females able to bear children, a hormonal (i.e., oral, implantable, or injectable) and single-barrier method, or a double-barrier method of birth control must be used throughout the study. Female subjects unable to bear children must have this documented in the medical record [i.e., tubal ligation, hysterectomy, or post-menopausal (defined as a minimum of one year since the last menstrual period)].

Exclusion criteria

1. Unable or unwilling to provide informed consent or to comply with study procedures
2. Diagnosis of gastrointestinal diseases
3. Structural or metabolic diseases that affect the GI system
4. Unable to avoid the following over-the-counter medications 48 hours prior to the baseline period and throughout the study:

a. Medications that alter GI transit including laxatives, magnesium and aluminum containing antacids, prokinetics, erythromycin

b. Analgesic drugs including NSAIDs and COX-2 inhibitors

NOTE: stable doses of thyroid replacement, estrogen replacement, low-dose aspirin for cardioprotection, and birth control (but with adequate backup contraception as drug-interactions with birth control have not been conducted) are permissible.

5. History of recent surgery (within 60 days of screening)
6. Acute or chronic illness or history of illness which, in the opinion of the investigator, could pose a threat or harm to the subject or obscure interpretation of laboratory test results or interpretation of study data, such as frequent angina, Class III or IV congestive heart failure, moderate impairment of renal or hepatic function, poorly controlled diabetes, etc.
7. Any clinically significant abnormalities on physical examination or laboratory abnormalities identified in the medical record, as determined by the investigator
8. Acute GI illness within 48 hours of initiation of the baseline period
9. Females who are pregnant or breastfeeding
10. History of excessive alcohol use or substance abuse
11. Participation in an investigational study within the 30 days prior to dosing in the present study
12. Any other reason, which in the opinion of the investigator, would confound proper interpretation of the study

Gastric Motility Studies

Participants will come to the Clinical Research Unit on the 7th floor of the Charlton Building at Mayo Clinic. They will arrive fasting, at a predetermined scheduled appointment time. A urine pregnancy test will be performed, when applicable, within 48 hours of the start of the test.

Following an overnight fast, subjects will undergo introduction of the multilumen manometric catheter into the proximal small intestine with sensors across the antroduodenal junction. Trained technologist (DB) and staff physician (MC) will perform the manometry tube placement in accordance with standard practice over the past 25 years. A 4-meter Teflon® (green) guidewire and manometry tube will be placed transnasally and advanced into the duodenum with the distal end of the manometry tube within the distal duodenum or proximal jejunum. The position of the manometry tube will be verified using fluoroscopy to ensure that the 12 manometric sensors that are 1 cm apart are located across the antropyloroduodenal junction. Following placement of the manometry tube a 30 minute baseline motility assessment will be performed followed by the first of two VIBRANT OR SHAM VIBRANT CAPSULES will be administered as randomly assigned. Motility assessment will be performed for an additional 25-30 minutes before the digestion of the standardized breakfast test meal. A single spot image will be obtained to document the location of the capsule prior to the meal.

Approximately thirty minutes following ingestion of the capsule, subjects will ingest a standardized breakfast meal (320kcal egg, toast, milk) containing ^{99m}Tc. Anterior and posterior gamma camera images will be obtained immediately following ingestion of the meal and every 15 minutes until 240 minutes. In addition, every 30 minutes one hundred millimeter Visual analog scales (VAS) will be recorded to assess levels of nausea, fullness, gas, and abdominal pain. Subjects will be seated in a semi-recumbant position (~45 degrees) for recording of motility and obtaining anterior scintigraphy images, simultaneously. Following the 90 minute scan the subject will ingest a second active VIBRANT or sham capsule. Subsequent scans will continue at scheduled intervals until 240 minutes after the test meal ingestion in order to complete the assessment of gastric emptying. At the conclusion, the subject will be escorted to the fluoroscopy room for a spot image to document the location of both capsules. Following the spot image, the multilumen manometric catheter will be removed and the subjects will be dismissed. The total duration of the study is ~6 hours. Subjects will leave the study center at the end of the study.

Transit Data Analysis

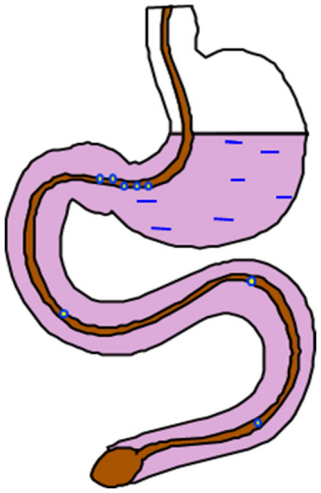
A variable region of interest program is used to quantitate the counts in stomach. These counts will be corrected for isotope decay, and tissue attenuation.

Data will be analyzed as in previous studies using geometric mean of counts in stomach.

Gastric Motility

See Appendix Radiation Exposure for assessment of radiation exposure levels from fluoroscopy.

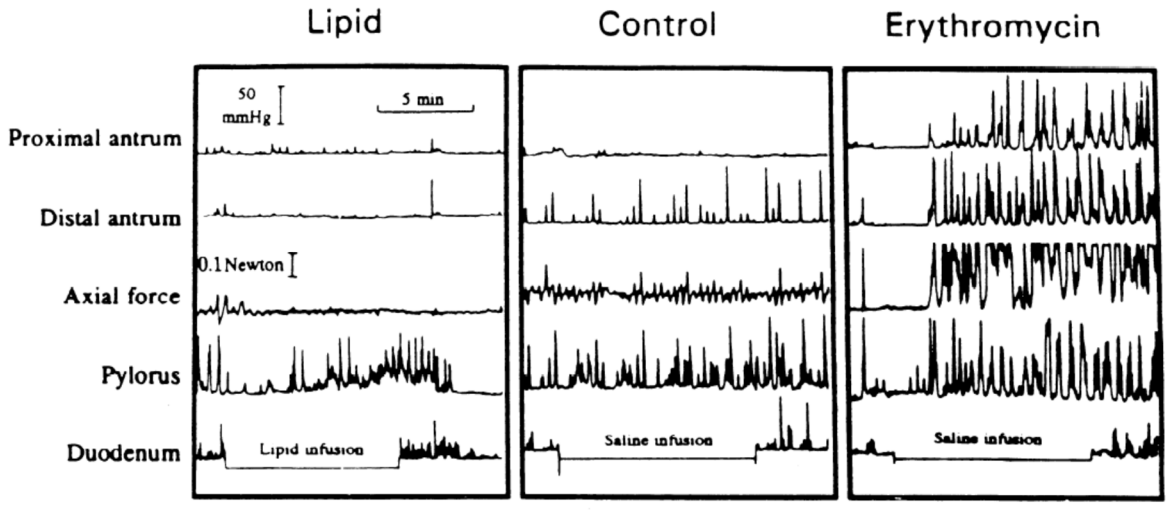
Figure 1. Multi-lumen manometric assembly in the upper gastrointestinal tract to measure distal antral motility in postprandial period



Each of the channels of the multi-lumen manometric tube will be perfused with distilled water via a pneumohydraulic pump (perfusion rate 0.15mL/min, perfusion pressure 14psi) and attached to a strain gauge transducer (model PX-MK099, Edwards Lifesciences, Irvine, CA.). One side opening has been made in each channel of the multi-lumen tube, and the positions of these openings will be fluoroscopically placed across the antroduodenal region; thus, the tip of the tube will lie within approximately 10cm of the ligament of Treitz. Gastrointestinal pressure activity will be recorded in each subject for 1 hour while fasted. Then, each individual will ingest a 320-calorie mixed solid-liquid meal consisting of 2 eggs, bran bread toast, and 240mL of skim milk.

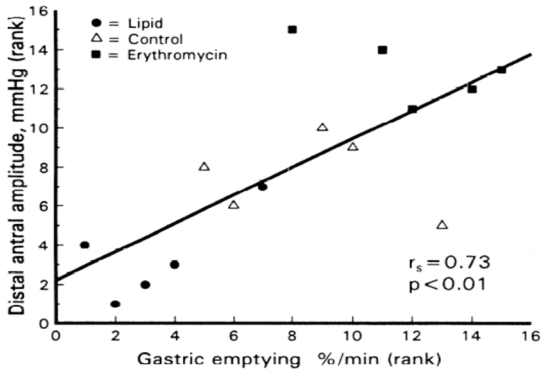
Pressure activity will be recorded for 5 hours (2) while participants are seated at a 45 degree angle.

Figure 2 shows an example of the inhibition of postprandial antral motility and forces with lipid and stimulation by erythromycin (3).



Antral pressure activity determines the rate of gastric emptying of solids.

Figure 3 shows a correlation between distal antral contraction amplitude and rate of gastric emptying (3).



Analysis of Manometric Recordings

Phasic pressure activity in the distal antrum recorded on the manometric tracing will be quantified manually. The most distal antral site will be identified as a site recording up to three waves per minute which are (a) just proximal (1 cm) to a site recording duodenal-type waves or (b) just proximal to a site exhibiting a mixture of antral-type and duodenal-type waves associated with baseline elevation (pyloric-type activity). For each sequential 15-minute period and for the entire 2-hour postcibal period, a motility index (MI) will be calculated using the formula: MI = loge (sum of amplitude x number of contractions + 1). The average 15-minute antral motility index will be then calculated; previous studies have shown that the cumulated slope of antral motility indices is linear (4).

Statistical Analysis

The primary endpoints for analysis will be:

a. Gastroduodenal manometry (GDM) measurement of first hour postprandial distal antral motility index.
b. Gastric emptying of solids:$T_{1/2}$ and lag time in minutes

The secondary endpoints will be:

a. Gastric emptying at 1h
b. Gastric emptying at 2h
c. First 0.5h postprandial distal antral motility index
d. Abdominal Symptom assessments-VAS

The effects of the VIBRANT CAPSULE treatment on the primary and secondary response measures will be assessed using an analysis of covariance (ANCOVA) with suitable transformation for skewness in the distributions of measured parameters (e.g., ANCOVA on

ranks, if necessary). The covariates considered for inclusion in the analyses will be age, gender, and body mass index.

Administrative look

Administrative look will be done when 12 subjects completed the study.
The objective of the administrative look is to assist in future development of the medical device

The process:

1. The study site of Mayo who continue to enroll and assess the HV subjects in the study continue to be blinded, thus no treatment assignment is revealed nor any potential bias may be associated with the process.
2. Sponsor Staff especially the clinical team who communicate with the study site staff will continue to be blinded.
3. The sponsor decision making responsible person, will receive the data of the 1st 12 subjects (3 /arm : shame, 1,3 and 5 vibrating modes) will be blinded to subject numbers and get the data per treatment arm with No Subjects Identification
4. Since this analysis is for administrative purposes and No changes to the Clinical Trial Protocol will be made as a result of looking at the data, the P Value remain Unadjusted (does not change)
5. Descriptive Rather than Inferential analysis.

Sample Size Assessment

Table 1 below summarizes data for the primary response measures and uses the (relative) variation (CV%) to estimate the effect size detectable with 80% power based on a two-sample t-test (i.e., assuming the variation values are known) at a two-sided alpha level of 0.05. The effect size is the difference in group means as a percentage of the overall mean for each response and assumes 6 subjects per group. The ANCOVA should provide 80% power to detect similar (pairwise) differences using a pooled estimate of variation across all three groups and potentially even smaller effect sizes by adjusting for important covariates. The data from the scintigraphic transit studies are unpublished, but are based on the same methods proposed for this study.

Sample size assessment is based on the results of primary endpoints in our laboratory [data show mean ± SD). The standard deviation used for the sample size calculations was calculated from the observed number of distal antral activity in healthy volunteers in the absence of any treatment: 11.5±0.6 (SD) (2,4,5).

Table 1. Primary Response Measures

Response	Mean	SD	Effect size detectable, n=4 per group, absolute (%)
Postprandial distal antral MI*	11.5	0.6	1.184 (10.3% change)
Gastric emptying T1/2 (min)	121.7	29.6	58.4 min (48% change)

*Based on data from previous studies (2,4-6).
Effect size is the difference between means as a percentage of listed mean index between the two treatment groups (shown in table with 80% power, α =0.05). Estimated effect sizes are based on a paired t-test with expected difference in mean of 1.6 motility index units in distal antral activity or 13.6% change in the antral motility index in ACTIVE compared to SHAM (2,4,5). It is to be noted that this is on a logarithmic scale and, therefore, an 10% change constitutes a clinically relevant difference.

Clinical or Biological Relevance of Change in Antral Motility Index

The magnitudes of the changes detectable are clinically relevant or have been observed in prior studies using pharmacological agents such as cisapride and erythromycin.

Effect of Cisapride on Antral Motility Index

Cisapride resulted in a significant increase in the gastric emptying of solids ($p < 0.05$) compared with placebo, and cisapride also tended to increase the postprandial antral motility (7). The difference in the 2-hour antral motility index (median values) was 0.75 units.

Table 2. Postprandial Antral Motility Index at 2 Hours (median)

Gastroparesis group (N)	2-h postprandial median antral motility index
Cisapride (6)	13.38
Placebo (6)	12.63

There was no effect of placebo on gastric emptying in contrast to the effect of cisapride, and these effects on the antral motility index were associated with significant changes in gastric emptying (particularly of solids).

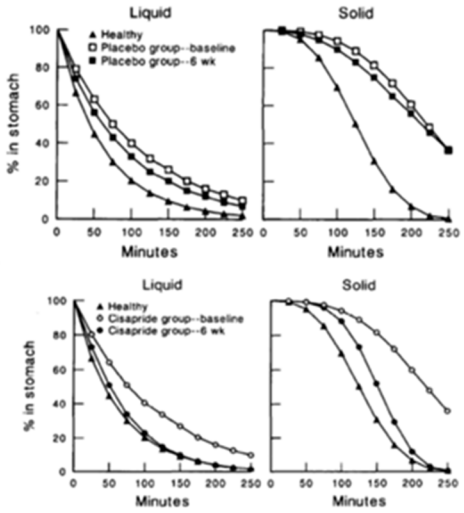
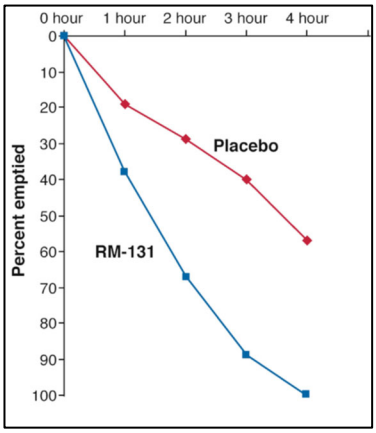


Figure 4 (upper panel) shows median gastric emptying plots for placebo treatment (baseline and 6 weeks) in subjects with gastroparesis and chronic intestinal pseudo-obstruction, and healthy controls. The lower panel shows similar data for the subjects receiving placebo, with baseline and 6-week data presented. Note that cisapride accelerates gastric emptying.



Effect on Gastric Emptying

A 48% change in gastric emptying $T_{1/2}$ is in the clinical range that can be expected to be relevant, as shown in studies using gastric emptying scintigraphy in patients with diabetes and upper GI symptoms (8). For example, the ghrelin agonist RM-131 has such an effect (54%) on gastric emptying $T_{1/2}$

	Placebo	RM-131
GE $t_{1/2}$ solid, *min*	75.7 (66.4–188.6)	58.2 (40.4–86.6)

Figure 5 shows an example of gastric emptying profile from a parate occasions with patient with type I diabetes treated on se placebo and RM-131 (relamorelin)

Therefore, the effect size demonstrable in the prioposed study would be clinically relevant, justifying the proposed design and sample size in each of the three treatment groups.

Strengths and Limitations

The major strengths of this study include the ability to noninvasively measure gastric emptying, as well as the resources available in the Clinical Research Unit on Charlton 7. Therefore, completion of this study is highly feasible. We have a well-established track record using these techniques in patients with diverse lower gastrointestinal functional disorders in previous studies. We have sufficient power to detect clinically relevant differences between the treatment groups. Variability in body size and weight are accounted for by inclusion as covariates in the ANCOVA analysis of transit parameters.

Feasibility and Time Frame

This study involves one noninvasive gastric transit study with simultaneous antropyloroduodenal manometry measurement in healthy volunteers. The study is feasible. Based on past experience, recruitment of study subjects should be uncomplicated.

Anticipated Results and Significance

We anticipate that VIBRANT capsule (compared to SHAM) will impact stomach contractility. and
will accelerate gastric emptying. This study will form the foundation for subsequent application of this method for treatment of motility and functional disorders of the gastrointestinal tract, particularly in subjects with gastroparesis.

HUMAN SUBJECTS SAFETY

Recruitment and Consenting of Participants and Gender/Minority Mix

Twenty-four healthy participants will be recruited from the local community by public advertisement as part of the main study protocol.

Subjects will be recruited by public advertisement:
Healthy volunteers, aged 18-65 years, are needed for a study to evaluate the effect of an experimental therapy, VIBRANT capsule, on movement of the stomach. This study requires taking study capsule administered orally once, and noninvasive gastric emptying and tube measured gastric motility on one occasion. Remuneration offered. For more information, call Amy Boldingh at 538-6599 or send email to boldingh.amy@mayo.edu

Informed consent will be obtained by the principal investigator or study coordinator following both a review of the written consent form and a conversation outlining the risks, benefits, and goals of the investigation. Documentation will be recorded with signatures of the study participant and the individual obtaining consent (on the standard informed consent document). This study cohort will reflect the population of Olmsted County, Minnesota with 90% Caucasian, 5% Asian and 5% other. Previous experience would suggest an age range of volunteers from 18-65 years, with a mean age of approximately 45 years. No subpopulations or special classes of subjects are involved in this trial.
There are no known ethnic or gender differences in the effects of VIBRANT CAPSULE. Hence, we anticipate the results of our study will be generalizable.

Research Materials

Facilities and equipment are available for these studies in the GI Physiology Core Laboratory of the Clinical Research Unit on Charlton 7. All data retrieved during the study will be used specifically for research purposes.

Potential Risks and Protection in Substudy

The study involves the use of radiation that is within limits permissible for healthy volunteers. The PI has >28 years' experience with these methods. The study device safety to date in healthy volunteers has been excellent.

Definitions of adverse event and serious adverse events are included in the main study.

Radiation exposure is within permissible limits for human volunteer studies. All female participants who are still menstruating and have not been surgically sterilized will have a negative pregnancy test within 48 hours of the study.
The table shows the radiation organ dose exposure per radiopharmaceutical dosing for the gastric emptying tests.

Radiopharmaceutical	Act	Body	Gonads	Breast	Red marrow	Lung	Thyroid	Bone	ULI	Colon	Stom	Blad	Liv	Esoph	Other mCi
	-ach	-der	-er	-agus											
^{99m}Tc, s.c.	1.0	20	90			20			420	300	130	20	10	220	

(mrad= radiation absorbed dose to organs)
H_e or the radiation effective dose to the body summarizes the risk to the whole body as the individual doses to each of the organs; effective dose is used to compare risks among various types of x-ray and radionuclide studies: ^{99m}Tc-SC, 1.0 mCi, He90 mrem (mrem = radiation equivalent dose)

Radiation Exposure from Fluoroscopy

Average time, <1minute; no more than 2 minutes will ever be used.

DOSIMETRY CALCULATIONS

	ESE (mR)	Lung	Bone Marrow	Thyroid	Remainder† Tissue	Testes	Breasts	Ovaries	Uterus (Fetus)	Other	
Abdominal Fluoroscopy* (2 min @ 1 R/min)	2000	7	77	--	85	6	--	104	93		
TOTAL:	2,000	7	77	0	85	6	0	104	93	0	Total H(E)
x W(t)		0.12	0.12	0.03	0.30	0.25	0.15	0.25			37 M
H(E):		1	9	0	26	2	0	26	0	0	62 F

Table 42 - HHS Publication (FDA) 89-8031 (Rosenstein)
* GCRC mobile C-arm

† Trunk for radiographic/fluoroscopic. Average of all relevant remainder organs for CT.

All imaging will be undertaken by trained technicians in the laboratory with 30 years' aggregate experience using scintigraphic techniques.

BENEFITS

There are no benefits for participants in this study. Participants may choose not to participate.

STUDY REPORT AND PUBLICATION POLICY

After conclusion of the study, the investigator will analyze the data and write a report for publication. The study sponsor will have the opportunity to review the study data according to the conditions stipulated in the contract developed by Mayo Clinic Legal Department. Publication rights are specifically identified in the contract.

BUDGET (attached)

Budget Justification

PERSONNEL

Dr. M. Camilleri, will be responsible for the clinical conduct of the study and overseeing the coordinators and technologists.
Research fellows will work under the direction of the site Principal Investigator, Dr. M. Camilleri.
Technologists: Trained technologists (Duane Burton, Deborah Rhoten, and Michael Ryks) will be involved in the synthesis of radioisotopic materials in the "hot lab" in the CRU in Charlton 7. They will also conduct the acquisition of images. The physiologic testing of this study requires 1 day of participation per subject; there will be 12 participants. The technologists will be responsible for the analysis of scintigraphy imaging. They will place all data in an EXCEL spreadsheet for further analysis.
Coordinators: Clinical research coordinators will be responsible for recruiting and scheduling examination of participants and maintenance of study records (case report forms and symptom recordings). These coordinators will notify the PI of any adverse events, maintain records and documentation for IRB, and work with study monitors.
Data analyst: A biostatistician from the Mayo Clinic Department of Biomedical Statistics requires data analyst support for randomization schedule, "clean up" and final analysis of study data in this study. This will be accomplished by one of the analysts assigned to his area in the Department of Biostatistics.

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