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The Effect of Sex and Age on Small Intestinal Transit Times in Humans

Monika Fischer [1], Hala M. Fadda [2,*]

[1] Indiana University Division of Gastroenterology and Hepatology, Indianapolis, Indiana 46202
[2] Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Butler University, Indianapolis, Indiana 46208

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ABSTRACT

This study utilizes a novel approach of small bowel video capsule endoscopy for investigating the influence of sex and age on small intestinal transit times (SITT) in humans. A total of 81 outpatients undergoing investigations with the small bowel video capsule endoscope (SB-VCE) and meeting inclusion criteria were included in this study. Following an overnight fast, patients swallowed the SB-VCE with a glass of water. SITT were calculated from the first duodenal image to the first cecal image. This study showed that the SB-VCE provides accurate and reliable measurements of SITT under real-life conditions. A large inter-individual variability in SITT was observed, with times ranging from 50 to 460 min. This variability can have implications on drug absorption and bioavailability. The median SITT were 219 min for females and 191 min for males. Although SITT were 28 min longer in females than males, this difference was not found to be statistically significant ($p = 0.66$). No correlation was found between age and SITT (Pearson correlation coefficient 0.19). Therefore, any drug bioavailability differences of modified release dosage preparations that are observed between adult patient groups of different age or sex are unlikely to be attributable to SITT.

Introduction

Several studies have explored gastric transit times of dosage forms and the influence of sex, food intake, and posture on gastric residence times.[1-4] Few studies have explored the effect of physiological variables on small intestinal transit times (SITT). We have previously shown that the timing of food intake can accelerate small intestinal transit[5]; there is a paucity of evidence, however, on other factors that influence SITT in humans, particularly with respect to age and sex. Moreover, the evidence has been conflicting with some studies showing SITT to be affected by age and sex, whereas other investigations showing no differences. It is important to understand the variability, if any, of SITT between different patient populations. By virtue of its large surface area, the small intestine is considered the major site of not only nutrient, but also drug absorption, and therefore plays an important role in drug bioavailability. The rate and extent of drug absorption from the small intestine can be impacted by the transit time of the drug (dosage form) as transit times will determine how long a compound will be in contact with its absorptive site.[6] This is particularly important for modified release preparations or drugs with poor solubility in gastrointestinal (GI) luminal fluids. SITT variations between different patient groups, for example, different sex or age, may help explain some of the drug disposition differences seen in different populations.[7,8] SITT also directly impacts the duration of exposure of dosage forms to the different pH conditions of the gut. Mesalamine, the first line treatment for ulcerative colitis, is available as enteric coated preparations with a high pH-dissolution threshold (e.g., Asacol® HD and Lialda®). In some patients, only partial disintegration of these tablets and their passing through the gut intact has been reported.[9-11] We have shown that the disintegration of these systems is not only dependent on the pH of the ileum, but also the time the dosage form spends there.[12] This illustrates that SITT can impact the performance, and ultimately the efficacy of these medicines.

In this current study, we utilize the novel approach of small bowel video capsule endoscopy, to explore the influence of sex and age on SITT of large, dense, non-disintegrating capsules in humans. To our knowledge, this is the largest study that explores the influence of sex and age on the small intestinal transit of single, non-disintegrating units administered to fasting individuals. The small bowel video capsule endoscope (SB-VCE) is a wireless video capsule that allows visualization of the entire small intestine for the investigation of pathologies, including obscure GI bleeding, celiac disease, and polyps.[13,14] The capsule passes through the GI tract and

* *Correspondence to:* Hala M. Fadda (Telephone: +317-940-8574; Fax: +317-940-3046).
E-mail address: hfadda@butler.edu (H.M. Fadda).

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is excreted with a bowel movement. It is composed of a light source, lens, camera, battery (≥8 h battery life) and a wireless transmitter. The camera has a 156° angle of view and it captures 2 images per second. The images are transmitted via a sensor belt to a digital recorder carried by the patient. The data are fed to a computer and can be viewed as an uninterrupted video.[15] From the video generated, the time at which the SB-VCE enters and leaves the small intestine can be determined. We have recently shown that the SB-VCE provides a reliable and discriminative tool for exploration of SITT in different inflammatory bowel disease patient groups and we have correlated transit times to disease activity.[16] The SB-VCE (Pillcam SB2) is 26 mm in length and 11 mm in diameter. It is of similar size to some types of modified release tablets and capsules and can thus provide a good reflection of the time modified release drug preparations spend in the small intestine.

Methods

Recruitment Criteria

A retrospective review was performed on ambulatory patients who underwent investigations with the SB-VCE at Indiana University Hospital between January 2013 and February 2014. Patients with normal SB-VCE reports were included in the study. The following exclusion criteria were applied: (i) patients who had previously undergone any GI surgery (e.g., gastric bypass), (ii) patients with systemic medical conditions that can affect the GI tract, (iii) patients where endoscopy shows evidence of GI pathology, (iv) patients with incomplete SB-VCE investigations whereby the VCE did not reach the cecum by the end of the study, (v) patients requiring endoscopic placement of the capsule into the small intestine, and (vi) patients where there was residual food in the stomach or debris in the intestine. These exclusion criteria are similar to those adopted by Fich et al.[17] This study was approved by the Institutional Review Board of Indiana University Medical School.

Video Capsule Endoscopy and Determination of Transit Times

The day before the procedure all patients were instructed to have a light breakfast followed by clear liquids until 7 pm and sips of water until midnight. No purgative agent was used. The administration of the SB-VCE with respect to the timing of food intake and type of food was standardized. Solid food was withheld for 24 h before the procedure to ensure there was no residual food or debris in stomach and small intestine so that they are entirely clear to allow for optimal viewing conditions and identification of any GI pathologies. Patients swallowed the SB-VCE (Pillcam SB2; Given Imaging Ltd., Yokneam, Israel) with a glass of water in the morning. The patients were allowed to drink fluids after 2 h and to consume a light meal after 4 h consisting of either of the following food choices: scrambled eggs, chicken broth–based soups, applesauce, plain yoghurt, or Jell-O. No prokinetic agents were administered. Patients were allowed to resume their daily activities after swallowing the capsule. SITT were calculated, in minutes, from the first duodenal image of the SB-VCE to the first cecal image. Figure 1 illustrates snapshot images of different regions of the GI tract from the same patient obtained from the SB-VCE recording.

Data Analysis

Non-parametric statistical analysis was conducted using Wilcoxon rank sum tests. Origin Pro 9.1 software (Origin-Lab Corporation, Northampton, MA) was employed.

Results are expressed as medians and 25th and 75th percentiles. A significance level of 0.05 was used in all testing. Correlation analysis was performed using the Pearson rank correlation coefficient.

Results

A total of 81 patients who underwent small bowel video capsule endoscopy and met study criteria were included in the study. The median age for all the patients recruited was 53 years (range 17–89). Of those patients 53 were female and 28 were male. The median age of the female patients was 50 years (range: 17–87 years) and the median age of the male patients was 59 years (range 18–89 years).

The median SITT of all patients (male and female) was 208 min (132–287 min, 25th and 75th percentiles). The median SITT for females was 219 min (154–275 min, 25th and 75th percentiles). The median SITT for males was 191 min (124–298 min, 25th and 75th percentiles). Although SITT were found to be 28 min longer in females compared with males, this difference was not found to be statistically significant ($p = 0.66$) (Fig. 2). No correlation was found between age and SITT (Fig. 3). Pearson correlation coefficient was 0.19. Multiple linear regression analysis to deconvolute the effect of age and sex on SITT was performed. No statistically significant association between sex and SITT ($p = 0.95$) or age and SITT was found ($p = 0.086$). The R^2 value was 0.038.

Discussion

Small intestinal transit times (SITT) are important for drug absorption. Reductions in drug bioavailability have been observed when transit times through the small intestine are accelerated.[18,19] The median SITT of all the patients included in this study was 208 min, this is in accordance with other studies using different types of dosage forms.[5,20] Davis et al.[21] conducted a meta-analysis analyzing the transit times of solutions, pellets and single-unit systems from 201 investigations. The mean transit time for the different dosage forms, irrespective of their type, was 3–4 h. Even large capsules reaching 25 × 9 mm in size had similar average transit times. This supports that the SB-VCE provides accurate and reliable measurements of SITT as well as a good reflection of the GI transit of non-disintegrating, modified release dosage forms.

This study also illustrates the large inter-individual variability of SITT. SITT were found to range from 50 to 460 min. The large inter-subject variability in small intestinal transit is neglected as SITT are generally thought to be consistent, and average times of 3–4 h are almost always reported. The variability in SITT can have implications on drug bioavailability. Digenis et al.[22] observed a 50% reduction in the bioavailability of enteric coated erythromycin pellets on fast transit of the dosage form through the small intestine. SITT ranging from 0.5 to 9.5 h have been reported by Davis et al.[21] and Coupe et al.[23] This variability in transit times is not surprising considering the extremely variable activity of the migrating motor complex (MMC), both within and between individuals.[24] The MMC is a cyclic motor pattern that occurs in the stomach and small intestine in the fasted state and is interrupted by food intake. Each cycle is of 90–120 min duration and comprises four phases, phase I is a quiescent phase with no motor activity, phase II is characterized by irregular motor activity, phase III comprises continuous, high amplitude contractions and finally phase IV has decreasing contractions as the cycle transitions back to phase I.[25] The variability in the MMC, both within and between individuals, has specifically been observed in the duration of the MMC cycle, phase II contractile activity and propagation velocity of phase III.[24] It is the phase III contractions of the MMC that are primarily responsible for the movement of large, non-digestible solids along the GI tract.[26,27]