SmartPill ®: a new methodology for the study of digestive motility

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" SmartPill ® is a new, single-use capsule allowing the continuous recording of pH, temperature, and pressure in the gastrointestinal tract for up to five days. The data collected by this capsule are transmitted by telemetry to an external, portable recorder. The pH and temperature curves, and the profile of the digestive contractions, can be consulted on screen through the connection of this box to a computer. Tracking of the capsule can be performed by monitoring the variations in pH, with a very rapid transition from acidic pH to a pH greater than 4 when the capsule leaves the stomach, followed by the recording of a clear fall in pH when the capsule crosses the ileocecal valve. This video capsule allows, with a very good tolerance, an ambulatory study of total and segmental transit times (gastric emptying, small bowel transit time, colonic transit time), with results that correlate well with those of the reference methods. Analysis of the propagation of contractions cannot be obtained with the capsule, however it does allow the recognition of gastric hypomotility in gastroparesis patients (gastric emptying > 300 minutes), and the distinction of low colonic motility or, on the contrary, excessive colonic motility (irritable bowel) in constipated patients (colonic transit > 59 hours). This new tool thus offers an exciting new alternative for the direct or indirect (transit time) study of digestive motility."

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Technical aspects

The single-use SmartPill ® capsule is 26.8 mm long, with a diameter of 11.7 mm. It is equipped with pH, pressure, and temperature sensors. The capsule can measure pH changes in the range of pH 0.05 to 9.0, with an accuracy of 0.5 pH units. The pressure sensor is accurate to 5 mm Hg for pressures not exceeding 100 mm Hg. Temperatures can be measured between 25 °C and 49 °C, with an accuracy of 2 °C [1,2].
Data are transmitted from the capsule by telemetry, and are received and stored by a recorder attached to the patient's belt (*figure 1*).

Figure 1. SmartPill ® device: Photographs of the capsule and the recorder.

At the end of the examination, data are downloaded from the recorder to a computer hard drive for reconstruction of pressure, pH, and temperature curves using the MotiliGI Software (SmartPill Corporation) [1, 2].

Examination procedure

In performance validation studies, the subjects fasted overnight and then ingested the capsule immediately after eating a 255-calorie meal containing 2.2% fat, with 50 ml water. No further food intake was permitted until the sixth hour after ingestion of the capsule. Patients were then free to walk and to eat as they wished [2]. A button on the recorder allows events (meals, periods of sleep, elimination of a stool, onset of a symptom, etc.) to be reported, which is useful in the analysis of the graphic representation. The examination, which is carried out as an ambulatory procedure, lasts for a maximum of five days.

The procedure is contraindicated in patients with a history of gastric bezoar and in those with swallowing disturbances, dysphagia, or symptoms suggestive of digestive stenosis. To avoid interference between the capsule and another device, the SmartPill ® cannot be used in patients fitted with electromechanical devices, such as cardiac pacemakers or implanted insulin pumps.

The procedure is not approved by the US-FDA (Food and Drug Administration) for use in children.

Analysis of graphic representation

Ingestion of the capsule results in a rise of the temperature curve. Its arrival in the stomach results in the recording of an acid pH. Subsequently, a substantial increase in pH (at least 2 pH units), above pH 4, marks the arrival of the capsule in the duodenum (*figure 2*) [1].

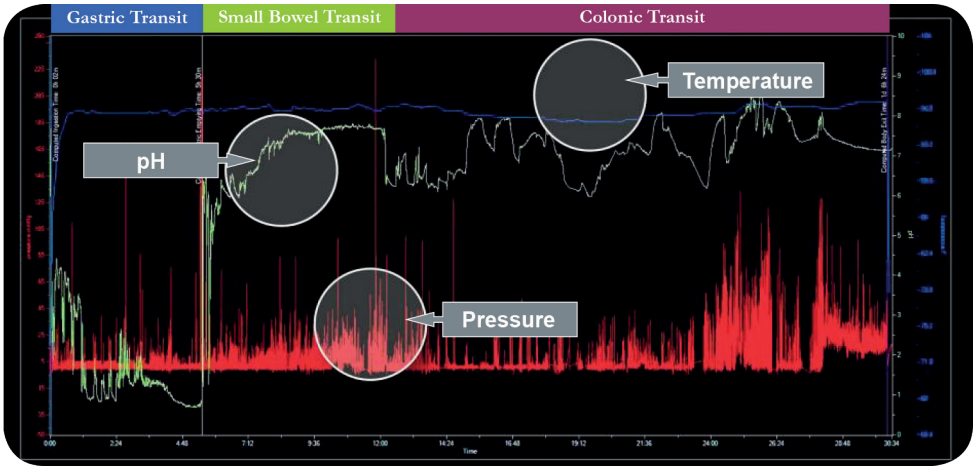

Figure 2. Example of a recording with pH, temperature, and pressure measurement curves. pH variations indicate arrival of the capsule in the stomach, passage through the pylorus and the ileocecal valve.

This increase in pH, although less pronounced, is observed in patients receiving antisecretory treatment with proton pump inhibitors [3]. Taking proton pump inhibitors before the examination is, however, advised against. Considering its size, the capsule only crosses the pylorus during the return of the first antral phase III, a substantial time after the meal [4], passage of the pylorus occurring when 97% of the volume of the meal has been evacuated from the stomach [4]. The sharp and prolonged fall in pH, of at least 1 unit for at least 10 minutes, reflects the passage of the ileocecal valve by the capsule, if this pH fall occurs at least 30 minutes after passage of the pylorus [1, 5]. Subsequently, a sudden drop in temperature (from 37 °C to ambient temperature) or loss of signal reflects the elimination of the capsule.

Analysis of the plot is firstly visual, to determine the times of the different steps in the progression of the capsule. A pressure analysis software program allows the calculation of the frequency of contractions

at various levels of the gastrointestinal tract, the area under the curve for endoluminal pressure, and a motility index, defined as:

Ln (sum of amplitudes x number of contractions + 1) [2].

Indications and results

The capsule provides information on both total and segmental transit times (*table 1*).

Table 1. Cut-off values for the interpretation of segmental transit times using the SmartPill ® capsule.

	Acceleration	Delay
Gastric emptying	< 2.5 hours rapid transit diarrhea)	> 5 hours (gastroparesis)
Small bowel transit time	< 2.5 hours (rapid transit diarrhea)	> 6 hours
Colonic transit time	< 5 hours (rapid transit diarrhea)	> 59 hours (constipation)

It also permits quantification of the amplitude and frequency of digestive contractions.

Studying different digestive transit times

Studying gastric emptying to investigate gastroparesis

One of the two main indications of this capsule is the diagnosis of gastroparesis, which is defined as an objective slowing of gastric emptying in the absence of any mechanical obstacle.
The reference method for studying gastric emptying is scintigraphy, which measures, with a gamma camera, the decrease in radioactivity in

the stomach area after ingestion of a doubly labeled meal (technetium 99 for the solid phase of the meal, indium 111 for the liquid phase). Measurement of emptying for at least four hours after the meal is recommended. The parameters calculated are the retention of isotopes at the second, and most importantly at the fourth hour. International standards base the diagnosis of gastroparesis on the demonstration of a gastric retention of the isotope greater than 60% at two hours and 10% at four hours after a meal of 255 calories containing only 2% fat and 2% fiber [6]. An alternative to scintigraphy is a breath test for octanoic acid labeled with a stable, nonradioactive isotope of carbon, 13C. This test, validated by several groups, allows the measurement of the T50 for gastric emptying of solids, with an accuracy comparable to scintigraphy [7]. These two tests both have shortcomings (*table 2*) and are available only in expert centers.

The validity of the capsule for the evaluation of gastric emptying has been the subject of several studies. Comparative studies showed that the parameter best correlated with the gastric emptying time measured with the capsule was the amount of isotope remaining in the stomach at four hours during a scintigraphic emptying study ($r = 0.73$). If this retention of isotope at four hours is taken as a reference, the sensitivity and specificity of the data provided by the capsule for the diagnosis of gastroparesis are 87% and 92%, respectively [8, 9]. A lower level of correlation is obtained for isotope retention at two hours ($r = 0.63$). The American and European Societies of Neurogastroenterology and Motility have concluded that an elimination time of the capsule from the stomach of less than five hours should be considered as normal [1], and that a gastric emptying time greater than 300 minutes supports a diagnosis of gastroparesis, with a sensitivity of 65% and a specificity of 87%. This value of 300 minutes has led to the overdiagnosis of gastroparesis in only 13% of controls. However, the diagnosis of gastroparesis is more common with the capsule than with scintigraphy (65% *versus* 44%). This is because scintigraphy measures only the evacuation of the isotopically labeled meal, whereas the capsule calculates the time between ingestion of the meal and its propulsion into the duodenum during the return of the first antral phase III. This return may be a little delayed compared to the complete evacuation of the two phases of the meal.

The capsule could also be used to demonstrate an acceleration of gastric emptying. However, the threshold value below which a diagno-

sis of accelerated gastric emptying can be made is not currently clearly established [1, 2].
A final point to highlight is that the capsule is able to detect accelerated emptying under the effect of drugs.

Table 2. Advantages and disadvantages of different gastric emptying study techniques according to the American and European Neurogastroenterology and Motility Societies [2].

	Scintigraphy	*Breathtest*	*SmartPill ®*
Validation	+++	+++	+++
Standardization	++	+++	+++
Stable quantitative results	+++	+++	+++
Availability	+	+	++
Ease of implementation	+	++	++
Patient discomfort	++	++	+
Tolerance	+++	+++	+++
Irradiation	+	-	-
Cost	++	+	++

Studying small intestinal transit time

An evaluation of small bowel transit time can be considered in patients suffering from unexplained and refractory nausea, vomiting, or bloating, or to investigate an endoluminal bacterial overgrowth.
The main method of analysis is the breath test, usually after the ingestion of 10 g lactulose. This test is based on the detection of a peak of hydrogen and/or methane of at least 5–10 ppm in the exhaled air after ingestion of the sugar. This peak is the manifestation of lactulose transformation by colonic bacteria. It thus reflects the arrival of sugar in the cecum after oral intake. This breath test has been criticized for three main reasons:

a) its result encompasses gastric emptying time and transit time in the small intestine;
b) the interpretation of the hydrogen peak can be awkward, as it can be an indication of sugar metabolism by small intestinal rather than colonic bacteria (endoluminal bacterial overgrowth), thus leading to an overdiagnosis of accelerated small bowel transit;
c) lactulose modifies transit time.

The other technique is scintigraphy, which is not widely implemented, and which encompasses gastric emptying and small bowel transit time. With the SmartPill ®, small bowel transit time is defined as the time interval between the arrival of the capsule in the duodenum (reflected by the sudden appearance of a pH close to neutral) and its entry into the cecum (extended fall in pH, of at least 1 pH unit, after a period of at least 30 minutes following the gastric exit of the capsule). The normal transit time is on average 4.6 hours, ranging from 4.0 to 5.9 hours in control subjects [1, 2, 10].

Studying colonic transit time

The benefit of measuring colonic transit in patients with diarrhea, and especially in those with constipation, is the interpretation of symptoms and possible adaptation of treatment. The two current main study methods are the measurement of radio-opaque marker colonic transit time (which can be performed by various methods) and colonic scintigraphy, which is only available in a few centers throughout the world, primarily for use in pharmacological research.
Using SmartPill ®, the colonic transit time is defined as the time between the arrival of the capsule in the cecum and its expulsion

through the anus.
Comparisons of capsule performance have mostly been carried out in relation to colonic transit times established with markers. The study by Rao et al. [11] showed that the capsule identified decelerations of transit and differentiated constipated subjects from a control population. There is a good correlation between the transit times determined by the number of radio-opaque markers eliminated and those calculated using the capsule. The correlation coefficients between the two calculation techniques at day 2 and day 5 were 0.74 and 0.69, respectively, in constipated subjects, and 0.70 and 0.40 in control subjects. At day 2, the sensitivity of the capsule as compared with transit time for the diagnosis of constipation was 0.73, with a specificity 0.95. At day 5, the sensitivity and specificity were 71% and 95%, respectively [11, 12]. In addition, the reproducibility of the results of the calculation of colonic transit times using the capsule may support its use in evaluation of the effectiveness of new treatments. However, this indication has not yet been validated.

Studying digestive contractions

This application of the capsule has been less well evaluated. As well as stationary recordings, the capsule also provides the possibility of recording in ambulatory conditions. However, in such conditions, motion artifacts may occur. In addition, the capsule has only one sensor. It cannot, therefore, provide any information regarding the propagated nature of the contractions registered. Explorations in gastroparetic patients have identified those in whom the slowdown in gastric emptying is associated with a significant decrease in the frequency and amplitude of antral contractions. In constipated patients with a transit time greater than 59 hours, exploration by capsule has led to the identification of two subgroups: constipated patients in whom colonic contractions are reduced, and those in whom these contractions were, on the contrary, increased in comparison with a control population, which directs the diagnosis towards that of irritable bowel syndrome with constipation. This potential diagnostic value of the capsule requires confirmation.

Technical failures and tolerance

Only 0.6% of patients were unable to swallow the capsule. Genuine technical failures (absence or interruption of recording before elimina-

tion of the capsule, impossibility to transfer capsule data to computer) were identified in only 36 of 495 cases [2]. The difficulties were mainly problems of interpretation: in approximately 5% of patients, this was due to the impossibility to determine with certainty the successive stages of capsule progression using the pH measurement data. The failure rate for the calculation of colonic transit time was calculated as 3%. Published findings all show agreement that the procedure is generally very well tolerated.

Conclusions

The SmartPill ® capsule is a new and interesting alternative for exploration, in ambulatory conditions, of the phenotype of patients with different functional digestive disorders. In particular, it represents a real alternative to the tests that are currently available to study the total transit time, and for the calculation of segmental transit times, particularly gastric and colonic transit times. It has been approved by the US FDA for these two latter indications

Conflicts of interest

Philippe Ducrotté is a member of the scientific advisory board of Given Imaging Covidien GI Solutions.

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