Standards for non-invasive methods for gastrointestinal motility: Scintigraphy.
A position statement from the Gruppo Italiano di Studio Motilità Apparato Digerente (GISMAD)

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Scintigraphic techniques are well established methods to assess gastrointestinal transit patterns. The main advantages are represented by the possibility to evaluate, in a relatively non-invasive manner, the transit time of specific components of physiological meals as well as of some digestive secretions. These techniques are generally well accepted by the patients and results are largely not operator dependent. Their main limitation is the use of a radioisotope, that prevents repeated applications in all subjects and immediate exclusion of women of childbearing potential. Due to the high costs of these tests and the limited availability of Nuclear Medicine Departments, scintigraphic techniques should be reserved for well-selected patients. A review is made of the technical requirements and indications for scintigraphic tests currently available for clinical purposes (gastric emptying study, oesophageal transit time, evaluation of gastro-oesophageal reflux, intestinal and colonic transit time, evaluation of biliary motility and of duodenogastric reflux).

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Introduction

Scintigraphic techniques are used for the evaluation of gastrointestinal motility, and, more specifically, of the transit through the alimentary tract of ingested meals or digestive secretions. These techniques allow a quantitative evaluation of the transit of individual components of a normal meal (solid-liquid, digestible-indigestible solids, lipid-protein-carbohydrate), are simple and can be applied to any patient, with the only exception of pregnant women, and children. Scintigraphy, unlike ultrasonography, is not, substantially, operator-dependent, and, unlike radiological techniques, it allows evaluation of physiological meals. On the other hand, scintigraphic techniques are performed at specialised centres on account of the necessary precautions in the management of radioisotopes and the high costs of gamma-camera counters.

The most frequent use of scintigraphy in the evaluation of gastrointestinal motility is for the study of gastric and oesophageal transit. Scintigraphic techniques are also used for the evaluation of gastro-oesophageal and duodeno-gastric reflux, biliary motility, and intestinal transit.

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Gastric emptying

Scintigraphic techniques are quite versatile and their use in the study of gastric emptying has favoured the application of a large number of procedures, particularly in the choice of the labelled and unlabelled component of the meal and in the analysis of the results. However, the test must be standardized to avoid the possibility of technical errors [1 2]. Recently, the usefulness of scintigraphy in the evaluation of transit of a meal in the different regions of the stomach has been demonstrated; scintigraphy also allows study of gastric contractile activity. These approaches are currently utilized only for research purposes.

Indications

- symptoms after gastric or oesophageal surgery (gastroparesis, dumping syndrome);
- functional dyspepsia;
- gastro-oesophageal reflux not responding to routine treatment;
- diabetic patients with suspected gastro-intestinal motor abnormalities or with poor metabolic control;
- suspected gastro-intestinal motor abnormalities in patients with systemic (collagenopathies, myopathies, neuropathies, amyloidosis) or endocrinological (hypothyroidism) diseases;
- evaluation of the efficacy of treatment based on drugs modifying gastro-intestinal motility.

Technical requirements

- computerized gamma-camera (operating time: up to 4 hours);
- facilities for correct labelling of the meal;
- specific computer programmes for acquisition of data and analysis of results;
- normal range of values obtained in each centre.

Technical aspects

Liquid acaloric meals (water) are of limited (if any) clinical value, and have a low discriminant power due to the very short emptying time. The evaluation of indigestible solids (fibre, pellets) requires a prolonged observation of the patient, and tends to provide information on the interdigestive motility rather than postprandial motility. Evaluation of a liquid meal with a caloric content of about 500 kcal is sufficient for routine tests [3], although the highest diagnostic yield of scintigraphic techniques is achieved by labelling a specific digestible solid (usually proteins) of a physiological meal, with no loss of isotope from the solid phase to the liquids ingested with the meal or endogenous secretion.

Typically the test meal includes, besides the labelled component, other unlabelled nutrients in order to achieve a caloric value of at least 200 kcal (necessary for complete activation of digestive functions), although a total caloric intake of 300 kcal would be advisable. Early studies proposed a cumbersome in vivo labelling procedure of chicken liver, but, more recently, it has been demonstrated that also the in vitro labelling is equally accurate [4]. The in vitro technique consists in multiple micro-injections of Tc-sulphur colloid on small cubes of liver, which are subsequently cut, in order to be incorporated into ground beef to form a hamburger [4]. The Tc-albumin labelling of the proteins of egg white has been demonstrated to be an excellent alternative to labelled liver. The simultaneous labelling of the solid and liquid components of the meal with different isotopes is also used in some laboratories, but results may be affected by possible interference [4], and double labelling must be carefully validated in each setting before being used for clinical purposes.

Methods

The test should be carefully described to the patients before the ingestion of the meal, to avoid any possible stress, that could affect the results. The patients should fast overnight for at least 4 hours after a light breakfast depending on the test meal adopted. Any drug likely to interfere with the test should be interrupted for at least 48 hours. The meal should be ingested within a standardized time (usually ten minutes).

At the end of meal ingestion (usually considered time 0), the first image of the gastric area is acquired by a computerized gamma-camera. Each acquisition consists of a 1-minute anterior image (obtained with the abdomen close to the collimator of the gamma-camera) immediately followed by 1-minute posterior image (with the back close to the collimator). These acquisitions are repeated at 10-15 minute intervals, for a total time that must be longer than the mean half-time of the control group. Shorter intervals in the first 30 minutes of the tests allow a better evaluation of the initial phase of emptying. Between acquisitions, the patients should remain seated, without smoking. It is usually possible to examine more than one patient simultaneously.

Any image acquired is made up by a consistent number of pixels representing the presence of the isotope in the region observed. After meal ingestion, the operator can identify the gastric region in the monitor, differentiating the gastric activity from the activity emerging from the intestine. For every image, the radioactivity emerging from the gastric region is calculated, and the geometric mean of anterior and posterior images of any acquisition is corrected for depth attenuation in or-

der to create an activity-time curve describing the intragastric radioactivity during the test.
This geometric mean is a simple correction to avoid possible errors due to the progressive distribution of intragastric contents towards the anterior abdomen wall, because acquisitions by anterior images alone could lead to an under-estimation of emptying rate. In the event of a single (anterior or posterior) image, it is necessary to acquire a lateral view for later corrections [1]. Other possible sources of error, common to nuclear medicine techniques (radio-isotope decay, scatter, etc.), must also be taken into consideration [1].

Data analysis
Several parameters can be obtained from the activity-time curve, the most common of which, in the study of solid meals, are gastric emptying half times ($T^1/_2$) and intragastric residual radioactivity at 60 and 120 minutes after meal ingestion. The evaluation of residual radioactivity should be prolonged to 240 minutes if meals with a high caloric or fibre content are used. Due to the biphasic nature of the gastric emptying curve of digestible solids, characterized by an initial phase of plateau (lag phase), it is necessary to calculate the half-time by the following bi-exponential function [5]:

$$f = 2^{-(t/t^1/_2)^{\beta}}$$

where $t^1/_2$ is the half-time and β the shape of the curve ($\beta>1$ when a plateau initial phase exists). The initial phase of such a gastric emptying curve, during which emptying is absent or negligible, is followed by a linear phase, during which emptying rates are relatively constant. The slope (k) of the linear phase represents the rate of gastric emptying, while the initial plateau phase (usually called "lag phase") is of uncertain significance [3]. It may represent the time for intragastric distribution of the meal from the gastric fundus to the antrum, or the time needed to evoke an efficacious grinding of the digestible solids [2]. The length of the lag phase (e.g. the time from the end of meal ingestion and the start of the linear phase) can also be calculated as the time required to observe the first appearance of the isotope in the duodenum. A mixed visual and mathematical method for the estimation of the lag time from the gastric emptying curve consists in the determination of the time from the start of the test to the intercept between the rectilinear portion of the curve with the tangent to the peak of the curve [6,7]. The latter is simple and easily standardized, since it is only minimally operator-dependent. Expressing the rates of gastric emptying by the slope of the post-lag phase provides a comprehensive parameter as compared both to residual activities at different times and half-time values derived from rather artificious mathematical formula.
Another important aspect to be taken into consideration when starting the technique in a new Centre is the need of a control group of at least 20 subjects [1]. This control group should include both males and females in order to identify sex-specific normal values. In fact, sex differences have been reported in some studies in healthy and diseased subjects [1,6]. The influence of age is debatable, but this factor would not appear to exert an important effect on gastric emptying. In contrast, when body weight is well outside the normal range, gastric emptying rate may be modified [1,7]

Limitations
- Due to radiation exposure, the test must not be used in pregnant women, and its use should be limited in children;
- the absorbed radiation dose depends on the type and dose of isotope, but is small when ^{99m}Tc is used [8].

Oesophageal transit time

The scintigraphic study of oesophageal transit of endoluminal contents represents a subsidiary test in the evaluation of oesophageal motility when compared to manometry. It is useful when a non-invasive and physiological test is required or when manometry is not feasible. The sensitivity of scintigraphy in the detection of oesophageal motor disease is 75-80% compared to manometry, with a positive predictive value of 73-100% and a negative predictive value of ≥94% [9].

Indications
- Suspected oesophageal motor disorders, idiopathic or secondary to systemic (e.g.. scleroderma) or metabolic (diabetes) diseases;
- evaluation of oesophageal transit in children;
- post-surgery follow-up;
- patients with gastro-oesophageal reflux disease which does not respond to routine treatment;
- non-cardiac non-respiratory chest symptoms;
- evaluation of the efficacy of treatment based on drugs acting on oesophageal motility.

Technical requirements
- Computerized gamma-camera (occupation time: 15 min);
- specific computer programmes for acquisition of data and analysis of results;
- normal range values obtained in each centre in an appropriate control group.

Technical aspects
The test is simple, since a liquid meal is generally used (250-300 μCi of ^{99m}Tc-sulphur-colloid stirred in 20 ml water). Alternatively, ^{81Kr}glucose, which presents a low

radiation burden, may be used. A solid meal could improve the diagnostic yield of the test[9], but its use increases the frequency of false positive results.

Methods

The test is not time-consuming, but it should however be preceded by some training of the patient with a non-radioactive meal[9]. The patient drinks the liquid meal in a single swallow. No swallowing is allowed for the next 30 seconds, then further dry deglutition is requested every 30 seconds for a 2-minute period. The entire test is performed with the patient lying under the collimator of the gamma-camera, in order to obtain a complete recording (1 frame/0.3 seconds) of the study. The patient generally lies supine, since major interference due to gravity would influence the results obtained while standing. The image of the gamma-camera must include the entire oesophageal tract, from the cricoid to gastric fundus, and it is usually divided into three regions of interest (upper, medium and distal oesophagus).

Data analysis

Images are digitalized to obtain an activity-time curve of radioactivity in each of the three regions of interest. The total transit time is usually calculated as the period between the first appearance of the marker in the proximal oesophagus and the time needed to obtain 90% radioactivity clearance from the oesophageal area. The residual 10% of the marker in the distal oesophagus is ignored in order to avoid any potential overlap with the marker contained in the gastric fundus. Besides total and segmental transit times, a clearance rate at time t is usually obtained, with the following formula:

$$C=(E_{max}-E_t)/E_{max} * 100\%$$

where E_{max} is the maximal oesophageal radioactivity and E_t is the radioactivity at time t.

This rate is usually calculated after a certain number (8-40) of dry swallows performed at 15-second intervals after bolus swallows (namely after 2-10 minutes). Since some swallows are not completely propagated also in healthy subjects (up to 20%), the procedure may need to be repeated 4-6 times[10]. A more complex analysis of data is provided by the so-called "condensed image", that allows visualization of the complete study in only one image. The scintigraphic study of oesophageal transit can be carried out also in non-cooperating unweaned babies. They are usually placed in a semi-recumbent position lying with their back against the collimator of the gamma camera.

In healthy subjects, the oesophageal transit time is usually less than 15 seconds, but a centre-specific control group should be evaluated to minimize the technical differences caused by the preparation of the meal or by the position of the patient during the test. The presence of a hiatus hernia should be made known to the operator to obtain a correct region of interest of the distal oesophagus.

Limitations

- The test is not indicated in pregnant women, and its use should be limited in children;
- the total body radiation burden is lower than that of a conventional radiological evaluation[9].

Gastro-oesophageal reflux

Scintigraphic techniques, like any other technique recording for a short period of time, is considered to be of inferior diagnostic value, compared to 24-hour pH-metry in the evaluation of the gastro-oesophageal reflux[11]. However, it has surprisingly been demonstrated that scintigraphy can detect reflux episodes not recorded by pHmetry[12]. From a practical point of view, scintigraphic techniques are used primarily in children in order to avoid more invasive techniques, and, moreover, they have a higher sensitivity for reflux than radiology and a good specificity compared to pHmetry[13]. In adults scintigraphy plays a complementary role to pHmetry, and may be used in difficult cases[14].

In adults, a liquid meal (300 ml of acidified orange juice = 150 ml of orange juice + 150 ml of HCl 0.1 N) labelled with 0.3-1 mCi of ^{99m}Tc-sulphur colloid[9] is generally used, while in children this same marker is usually stirred into milk or a nutritional formula[15].

In adults, the scintigraphic images are obtained with the patients lying supine under the gamma-camera collimator. An inflatable device, able to increase the abdominal pressure, is usually employed to provoke reflux. The pressure of the device is increased from 0 to 100 mm Hg in 20 mm Hg steps. At each pressure step, 30-second frames are usually obtained and the following index of reflux (IR) is calculated:

$$IR=(E_t-E_b)G_0*100\%$$

where E_t is the radio-activity at time t, E_b is the basal oesophageal radioactivity and G_0 is the intra-gastric basal radioactivity[9]. A mean reflux of 4% is generally considered the upper limit of the normal range. At the 4th hour, an image of the pulmonary region is obtained to localize the presence of marker in the lungs. Evaluation of the images is based on the selection of the oesophageal region to obtain a time-space curve in which the episodes of reflux are visible as peaks. The height of the peaks represents the quantity of reflux, while the length of the base of the peak represents the duration of the reflux. This technique allows simultaneous evaluation of gastric emptying of liquids.

Intestinal transit time

This technique presents certain advantages compared to the breath test, since it allows evaluation of segmental transit, is not influenced by small bond bacterial overgrowth, and allows the use of physiological meals rather than non-absorbable sugars that could interfere with the results [16]. The test is likewise performed in the gastric emptying study, with regular acquisitions for up to ten hours. Image acquisition and data analysis are also similar to those of other scintigraphic transit tests, but require particular attention as far as concerns identification of the gastric, intestinal and colonic regions in order to avoid any overlap of the regions. These anatomical overlaps are corrected by specific filling-emptying curves for the stomach, the small bowel and the colon, respectively, followed by a mathematical subtraction generating a new curve that describes the intestinal transit time [16].

Since the fragments of the ingested food pass through the gut at different individual rates, the results of this test should be expressed as mean transit time. The most accurate index for the expression of the results is a complex deconvolution technique, that allows a spectrum of different transit times to be recorded [17]. Usually, mean transit time is obtained by subtracting gastric emptying $T^1/_2$ from colonic filling $T^1/_2$, or by calculating the time between the start of gastric emptying and the start of colonic filling.

The scintigraphic technique is not a routine test, but may often be used for the evaluation of complex cases such as patients with pseudo-obstruction or to discriminate, by the simultaneous use of the breath test, between diarrhoea due to accelerated transit or to bacterial overgrowth.

Colonic transit time

The most serious technical problem encountered in the radioisotope evaluation of colonic transit time is dispersion of the labelled ingested along the gastrointestinal tract. This problem can be overcome by ingesting the marker through a oro-colonic tube [18] or by releasing it through ano-caecal tube positioned during colonoscopy [19]. A major improvement in the evaluation of colonic transit time has been achieved using Amberlite pellets. Amberlite is a resin which can be labelled with ^{111}In and separated into small pellets [20]. The pellets can be included in methacrylate capsules, which are non-soluble at intragastric acid pH, but rapidly dissolve at higher pH, to provide the discharge of the pellets in the distal gut, to obtain an accurate evaluation of the total and segmental colonic transit [21]. Results similar to those obtained with the pellets have recently been reported with activated charcoal in a methacrylated-coated capsule [22]. The possibility to monitor the intra-colic discharge of an enteric-coated drug is one important application of this technique, that, at present, is not used for routine clinical purposes.

Biliary motility

The scintigraphic evaluation by ^{99}Tc-HIDA can be performed in basal conditions and during a slow infusion of cholecystokinin (20 ng/kg), in order to evaluate gallbladder contractility. Scintigraphic techniques can be useful for the evaluation of biliary transit in post-cholecystectomy patients, but are of limited value when the choledochus is enlarged. On the contrary, chole-scintigraphy is not suitable for the evaluation of biliary-motility in patients in whom the gallbladder is still functioning as a bile reservoir [23]. This technique can evaluate only one motor cycle of the biliary tract and does not provide valuable information concerning the volume and content of the gallbladder, nor about filling. Biliary scintigraphy is relatively expensive and gallbladder motor function is assessed more appropriately by ultrasonography.

Duodeno-gastric reflux

With scintigraphic techniques it is possible to evaluate duodeno-gastric reflux by visualization and quantitation of markers secreted by the liver selectively linked to bile components. The marker that is most used is ^{99}Tc-HIDA. It reaches a peak gallbladder concentration within 30 minutes after iv bolus infusion (2 mCi). Patients can be studied in basal conditions, after hormonal stimuli (CCK, caerulein) or after physiological meals. By labelling the meal with an isotope with a gamma-camera window different from that of the ^{99}Tc (e.g. ^{111}In), it is possible to simultaneously evaluate gastric emptying and duodeno-gastric reflux rates, that can be expressed as the rate between the intra-gastric radioactivity and the residual radioactivity in the biliary tract [24]. This technique does not allow prolonged evaluation of duodeno-gastric reflux. An isotope with a long half-life (^{75}Se-HCAT) provides information over a longer period [25], and it has been demonstrated to be useful as a bile acid malabsorption test [26]. The high costs and prolonged use of the gamma-camera required by this technique represent the main limitations of its use in routine clinical practice. Other clinical limitations are represented by the possibility of obtaining only a semi-quantitative evaluation of the reflux, and possible errors due to the overlapping of intestinal loops [27].

Conclusions

Scintigraphic techniques provide a useful tool in the study of gastrointestinal motility allowing direct evaluation of the passage of specific gut contents through the alimentary tract. So far, the following parameters have been demonstrated to be measurable by means of scintigraphic techniques with important clinical implications: oesophageal transit time, gastro-oesophageal reflux, gastric emptying, duodeno-gastric reflux, intestinal transit times, biliary motility. Scintigraphic studies represent the gold standard for the study of gastric emptying when solid meals need to be evaluated. Scintigraphic techniques allow a quantitative description of the fate of individual components of physiologic meals as well as of digestive secretions. They are simple and substantially operator independent. However, they require expensive organization of a Nuclear Medicine Department and involve exposure to gamma rays from the isotopes thus preventing their use in females of childbearing potential as well as in children. Other non-invasive techniques should, therefore, be preferred, if available.

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