Reproducibility of Gallbladder Emptying Scintigraphic Studies

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This study was designed to investigate the reproducibility of the results obtained from ^{99m}Tc-dimethyliminodiacetic acid (^{99m}Tc-EHIDA) cholescintigraphy, when used as a method of estimating gallbladder emptying. **Methods:** In a random controlled fashion, the reproducibility of scintigraphic gallbladder emptying studies was assessed in 30 subjects, of whom six were normal, four had duodenal ulcers and the remaining 20 had undergone antiulcer gastric surgery. In fasting subjects, who 30 min later drank 250 ml of fresh milk, 2 mCi of ^{99m}Tc-EHIDA was intravenously injected. Liver and gallbladder areas were scanned for 60 sec and then every 5 min for 1 hr. The study was repeated in all subjects within 2–5 wk. From the gallbladder emptying curves, the duration of the lag phase (time from milk ingestion to actual start of emptying), the ejection fraction of emptying (peak to least activity in the gallbladder), the time by which maximal emptying was achieved and the pattern of gallbladder emptying were calculated. **Results:** Two subjects were excluded from the study because their gallbladders did not fill. Lag phase duration was well reproduced in duplicate studies ($r = 0.87$), as was ejection fraction ($r = 0.84$). The time by which maximal emptying was achieved was not sufficiently reproduced. The normal pattern of emptying (exponential function) was reproduced in all controls, subjects with duodenal ulcers and patients after antiulcer surgery that did not involve duodenal exclusion. The abnormal pattern of emptying, characterized by refilling, was reproduced in five of the seven patients with gastric surgery that mainly involved duodenal exclusion. **Conclusion:** Scintigraphy with ^{99m}Tc-EHIDA to assess gallbladder motility is a method with satisfactory reproducibility of both parametric variables and patterns of emptying.

Key Words: gallbladder motility; gallbladder emptying; gastric surgery; vagotomy; gastrectomy; cholescintigraphy

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Cholescintigraphy using ^{99m}Tc-dimethyliminodiacetic acid (^{99m}Tc-EHIDA) as the radiopharmaceutical agent is a well-established method of estimating gallbladder emptying (*1–3*). This method offers several advantages over roentgenographic calculation of the area (*4*) and ultrasonographic calculation of the volume (*5*) changes of the gallbladder. In regard to roentgenography, first, adequate opacification of the gallbladder is a prerequisite, although it is not always achieved; second, the radiation exposure of the subject is significantly higher than in scintigraphy (*6*). Third, equating area changes to actual emptying might not be a realistic hypothesis (*1*). Ultrasonography is a modality devoid of radiation, but as a technique of estimating gallbladder emptying, it relies on the assumption that the volume of the gallbladder can be accurately calculated by a standard mathematic formula and that volume changes correlate with emptying. However, gallbladder changes in the configuration by contraction in turn might change the initially assumed geometric model for the volume calculation, requiring a modification of the mathematic formula in use. Nevertheless, studies are required to test the reliability of ultrasonography against that of scintigraphy in estimating gallbladder emptying.

Studies on the reproducibility of cholescintigraphy in assessing gallbladder emptying are limited. There is one study in which cholescintigraphy was repeated in nine subjects, and the extent and pattern of gallbladder emptying were adequately reproduced (*7*). In the present study, the reproducibility of cholescintigraphy was assessed to estimate gallbladder emptying in a larger series of patients, taking into account a variety of parameters, such as the duration of the lag phase and the extent, duration and pattern of emptying.

PATIENTS AND METHODS

Twenty-eight age-matched and sex-matched, healthy controls and 145 patients underwent a ^{99m}Tc-EHIDA scintigraphy on 263 occasions. Most of the studies were part of a clinical research protocol for the documentation and measurement of enterogastric reflux and estimation of gallbladder emptying before and after antiulcer gastric surgery (*8*). In 30 of the 173 subjects (six controls, four with duodenal ulcers, four after highly selective vagotomy [HSV], eight after truncal vagotomy with pyloroplasty [TVP], one after truncal vagotomy with gastrojejunostomy [TV-GJ], two after Billroth I gastrectomy, three after Billroth II gastrectomy and two after Roux-en-Y antrectomy), the study was performed twice for the assessment of the reproducibility of the results of gallbladder emptying. The 30 subjects were randomly selected, by asking every third individual, in chronologic order

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from each subgroup, to undergo the repeat study. The positive reply rate was approximately 50%. The protocol of the study was approved by the Athens Naval and Veterans Hospital Ethical Committee, and informed consent was given by each subject.

Method

After a 12-hr fast, 2 mCi of ^{99m}Tc-EHIDA was injected intravenously into all subjects, at approximately 9:30 a.m. Smoking was not allowed for the last 12 hr nor were prokinetic drugs for the last 2 days prior to the study. Thirty minutes later, when most of the radiopharmaceutical agent had been accumulated in the hepatobiliary region, a scan of the whole abdominal field was obtained for 60 sec (time 0). Thereafter, all subjects drank 250 ml of fresh milk, and a series of 60-sec scans of the abdominal field as obtained every 5 min for 1 hr using a Scintiview II Siemens Gamma Camera (Siemens Gammasonics, Inc., Erlangen, Germany) linked to a computer with disk-recording facilities. The subjects stood during imaging and sat between scanning sessions. The interval between the two studies for each subject ranged from 2–5 wk. The elapsed time from gastric surgery to the first study was more than 6 mo. Hence, no change or improvement in gallbladder motility was expected during the interval between the two studies.

To analyze the data retrospectively, radioactivity was mapped over the hepatobiliary region, and over the gallbladder in particular, at all time points, using a light pen. Corrections of counts were made for both isotopic decay and blood background levels. Gallbladder radioactivity in each view was expressed as a percentage of its initial value (at time 0) and plotted against time to yield the gallbladder emptying curve.

Data Analysis

From the initial scanning, the gallbladder partitioning of the radiopharmaceutical agent over both the hepatobiliary region (HP_0) and the whole abdominal field (AP_0) at time 0 was calculated and expressed as a percentage. The variables calculated from the gallbladder emptying curves were: (1) the duration of the lag phase, i.e., the time elapsed from milk consumption to the first detection of radioactivity in the small bowel; (2) the ejection fraction of emptying, which was expressed as the percent reduction from peak to least activity during the 60 min of the study; (3) the time point at which maximal emptying was achieved and (4) the morphology of the curve, which was defined as the pattern of gallbladder emptying.

Unless otherwise stated, the values are expressed as mean ± s.d. Simple regression analysis and paired Student's t-test were used to estimate the reproducibility of each variable. Any p value less than 0.05 was considered to be statistically significant.

RESULTS

The AP_0 and HP_0 indices obtained from the first study were 44 ± 4% (range 38%–53%) and 55 ± 9% (range 42%–67%), respectively. In the repeat study, there were two subjects who showed either spontaneous evacuation of the gallbladder before milk consumption or whose gallbladder did not fill with radiolabeled bile, causing a substantial amount of the tracer to be found in the small intestine. These two cases were excluded from further consideration. The AP_0 and HP_0 indices in these two excluded patients were less than 17% (16% and 13%) and 26% (25% and 23%), respectively. The AP_0 and HP_0 indices obtained from the second study were 42 ± 8% (range 28%–52%) and 56 ± 10% (range 43%–70%), respectively, and did not differ significantly from those obtained from the first study. However, no correlation of paired values of either AP_0 or HP_0 was found between the two studies. In other words, in the first study, if a subject had an AP_0 or HP_0 index at the highest limit of the range of values, the respective index in the second study might be found either toward the lowest or the highest limit of the range.

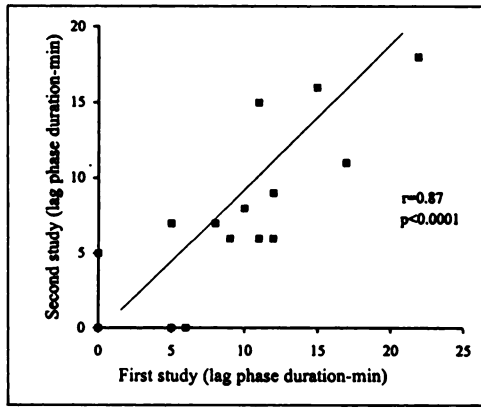

FIGURE 1. Reproducibility of the lag phase duration of gallbladder emptying in repeat studies. In 13 of the 28 subjects, the lag phase duration was 0 min in both studies. This is depicted by a single dot.

Concerning lag phase duration, no significant differences were found between the two studies ($t = 1.11$, $p = 0.28$). In addition, there was a highly positive correlation of corresponding values of lag phase duration between the two studies. The correlation coefficient for paired data points was 0.87 ($p < 0.0001$) (Fig. 1). In 13 subjects, no lag phase was found in either study. The duration of lag phase was less than 10 min for four subjects and more than 10 min for another five patients in both studies. For three subjects, the duration of lag phase was zero in one study and less than 10 min in the other. Finally, three subjects had a duration of lag phase less than 10 min in one and more than 10 min in the other study. No correlation was found between lag phase and either AP_0 or HP_0 indices.

The ejection fraction of gallbladder emptying ranged from 51%–89% in the first study (74 ± 12%) and did not differ significantly ($t = 0.03$, $p = 0.49$) from the respective parameter obtained from the second study (range 44%–89%, mean 74 ± 13%). A highly significant positive correlation of corresponding values was found between the two studies ($r = 0.84$, $p < 0.0001$) (Fig. 2). However, although the mean time point at which maximal gallbladder emptying was achieved after milk ingestion did not differ significantly between the two studies (45 ± 9 min versus 43 ± 10 min), no correlation of paired values was found.

Two distinct patterns of gallbladder emptying were observed: (1) type I pattern, which was characterized by a lack of lag phase or less commonly a rather short lag phase; less continuous filling, if present, for a few minutes after the milk ingestion; and subsequent emptying of the gallbladder, either fast and more complete or slower and less complete; and (2) type II pattern of emptying, which was characterized by a rather long lag phase, almost always present and significant gallbladder continuous filling after milk ingestion and subsequent emptying of approximately one-half of the gallbladder content, which was followed by refilling almost at the initial level of time point 0 and by new emptying. Maximal gallbladder emptying in the type II pattern was achieved at the bottom of either the first or the second emptying slope. More rarely, the gallbladder did not empty at all after refilling (Fig. 3).

Twenty-three subjects presented with a type I pattern of gallbladder emptying in the first study. They were either subjects who had not undergone operations or patients who had predominantly undergone antiulcer surgery without duodenal exclusion. The remaining five patients—all but two after duodenal exclusion—exhibited a type II pattern of gallbladder emptying. In the second study, the pattern was reproduced in all but two cases. In detail, from the first to the second study, one patient after TV-GJ shifted from type I to type II and one patient after Billroth II gastrectomy shifted from type II to type I pattern of emptying (Table 1).

The common correlation coefficient for paired data points extracted from the emptying curves of all subjects was 0.91 ($p < 0.0001$). The least deviation of values from the identity line was observed for those obtained from approximately the lower third of the emptying curve (15%–40% of the initial gallbladder activity). Paired data points extracted from the emptying curves of subjects who either exhibited a type II pattern or shifted pattern between studies showed the greatest deviation from the identity line (Fig. 4).

DISCUSSION

In the present study, milk was given instead of the intravenous administration of cholecystokinin to induce gallbladder emptying because the former is considered to be a physiologic cholagogue stimulus. When estimating gallbladder emptying, most authors give the cholagogue standard meal after the radioactivity within the gallbladder area

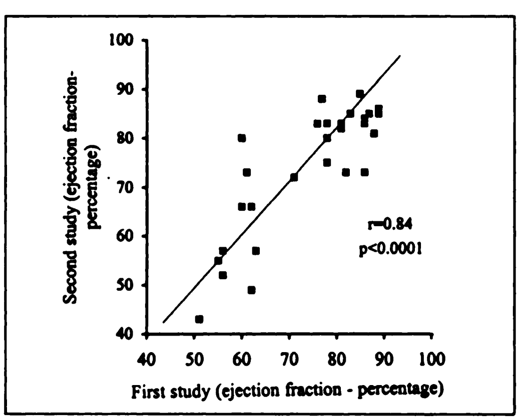

FIGURE 2. Scatterplot depicting the paired values of ejection fraction from duplicate studies.

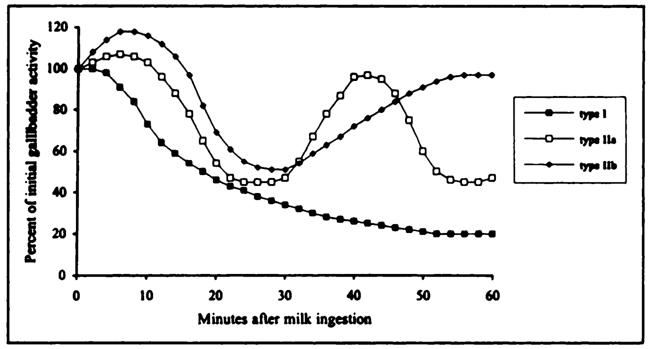

FIGURE 3. Type I (closed squares) gallbladder emptying pattern, exhibited by normal subjects; patients with duodenal ulcer and patients after HSV, Billroth I gastrectomy and most of those with TVP. A minority of patients after TVP and most of the patients who underwent antiulcer surgery including duodenal exclusion exhibit a type IIa (open squares) (two pairs of emptying and refilling sequential events) or a type IIb (closed diamonds) (initial emptying followed by slow refilling with no further emptying) pattern of emptying.

has reached a plateau, usually at 45 to 60 min after the injection of the ^{99m}Tc-EHIDA (*1–3,9*). However, by this time, labeled bile is usually exhausted, and further filling of the gallbladder with unlabeled bile, if present, cannot be assessed. In this case, consecutive emptying and filling events can be incorrectly interpreted as continuous emptying (*7*). Therefore, when milk is given 30 min after the injection of the ^{99m}Tc-EHIDA in this and other studies (7), there is still labeled bile to fill the gallbladder, and further gallbladder filling events can be assessed.

It is conceivable that less radioactivity is partitioned over the gallbladder area at 30 min rather than at 45 or 60 min after the injection. It might be argued, however, that, by 30 min, radioactivity over the gallbladder area might not offer satisfactory visualization for the assessment of gallbladder emptying or that gallbladder complete filling with labeled bile might occur at 45 or even 60 min after the injection. However, although different iminodiacetic acid analogs have different hepatic clearance rates, the appearance time of radioactivity over the gallbladder area does not differ significantly between these analogs and is approximately 15 min for the EHIDA (*10*). By 30 min, approximately one half of the radioactivity of the hepatobiliary region is found over the gallbladder, offering adequate visualization (7). Furthermore, the extent of partitioning of radioactivity over the gallbladder, if greater than a certain level (AP_0 > 25%), does not seem to affect the parameters that characterize gallbladder emptying (7).

Although partitioning of radioactivity over the gallbladder is not a reproducible parameter in statistical terms, the mean values of the indices that express this parameter (AP_0 and HP_0) did not differ significantly between the two studies. Furthermore, these indices, if found within the normal range, do not seem to affect the actual pattern and the extent of gallbladder emptying in this and other studies (7).

Spontaneous emptying of the gallbladder before the administration of the cholagogue meal or even in the absence

TABLE 1
Gallbladder Emptying Characteristics Reproduced in Two Studies

Patient group	No.	First study Type I	First study Type II	Second study Type I	Second study Type II
Controls	6	6	—	6	—
DU	3	3	—	3	—
HSV	4	4	—	4	—
TVP	7	5	2	5	2
TV-GJ	1	1(1)	—	—	1(1)
Billroth I gastrectomy	2	2	—	2	—
Billroth II gastrectomy	3	1	2(1)	2(1)	1
Roux-en-Y gastrectomy	2	1	1	1	1
Total	28	23	5	24	4

DU = duodenal ulcer; HSV = highly selective vagotomy; TVP = truncal vagotomy with pyloroplasty; TV-GJ = truncal vagotomy with gastrojejunostomy. Numbers in parentheses are patients who had shifted emptying patterns between studies.

of substantial filling of the gallbladder with radiolabeled bile can be occasionally observed both in normal subjects and in patients who have undergone antiulcer surgery (*2,7*). This phenomenon is the result of gallbladder contraction, initiated at the late phase II of the migrating motor complex, which might randomly occur either before the ingestion of the meal or even just before the injection of the radiopharmaceutical agent (*11*). Taking into account that the migrating motor complex occurs during the fasting state approximately every 100 min, to wait for more than 30 min after the radiopharmaceutical agent injection increases the possibility of a new complex occurring and spontaneously emptying the gallbladder before the milk ingestion. Conceivably, in the case of spontaneous gallbladder emptying, most of the radioactivity is detected in the small intestine because a reciprocal relationship exists between the gallbladder and intestine, concerning the appearance time of radioactivity (*10*).

The parameters of importance, as determined by the gallbladder emptying curves, are the delay in the onset of emptying (defined as the lag phase), the ejection fraction of emptying and the pattern of emptying (*2,3,7*). The duration of emptying, as expressed by the time by which the maximal emptying is achieved, varies extensively, as shown by others (*7*) and by the findings of the present study. In addition, taking into account that this variable is not a reproducible one and does not actually affect the extent of emptying, it can be speculated that calculating the duration of emptying is a parameter of minor importance in estimating gallbladder emptying.

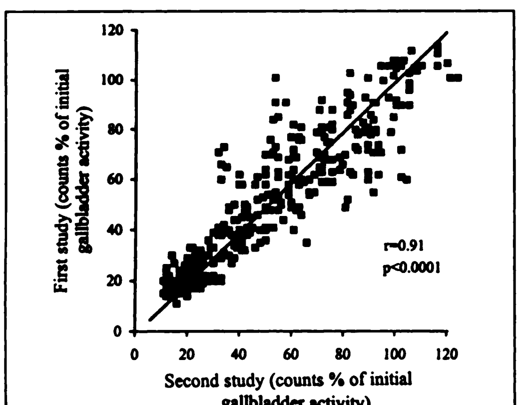

FIGURE 4. Reproducibility of gallbladder emptying in repeat studies. Scatterdots represent paired values of gallbladder remaining activity (percent of the initial value) at all time points of scanning.

The onset of gallbladder emptying after a meal occurs before the stomach begins to empty its contents into the duodenum (*2*). This fact, in addition to the presence of cholinergic receptors on the gallbladder's musculature (*1*), signifies that preduodenal, most likely vagally mediated mechanisms regulate the onset of gallbladder emptying (*2,12*). Consequently, any delay in the onset could be interpreted as a disturbance of the cephalic phase of gallbladder emptying, for example, as occurs after truncal vagotomy (*1,2,13,14*). Therefore, the calculation of the lag phase duration is significantly important in assessing gallbladder emptying, especially in postgastric surgical patients who are prone to develop symptoms resulting from gallbladder dysmotility (*9,13–16*). As shown by the results of the present study, when milk ingestion and ^{99m}Tc-EHIDA scintigraphy is applied to estimate gallbladder emptying, this parameter is sufficiently reproduced, adding to the reliability of the method.

The most essential variable that expresses the extent of gallbladder emptying is the ejection fraction, which is calculated from the emptying curve and defined as the percent reduction from peak to least activity (*3,7,12*). In addition to the duration of the lag phase, the ejection fraction is a sufficiently reproducible parameter of gallbladder emptying. This could be of significant clinical importance because a variety of conditions, including antiulcer gastric surgery (*1,2*) and diabetes mellitus (*17*), might lead to symptomatic gallbladder dysmotility, which can be expressed in a reduced extent of emptying.

The normal pattern of gallbladder emptying is that, which is described by a double-exponential function, characterized by a first phase with rapid emptying and a second one with a slower emptying that usually terminates to a plateau. In addition, a lag phase of small duration might occasionally precede emptying. The authors defined this normal pattern of emptying as type I. Baxter et al. (*2*) subdivide this pattern into two subgroups, according to the rate of emptying. The first one is characterized by a faster and more complete emptying than the other one. The minority of patients after TVP (*2*) and about one-half of the patients after gastrectomy with Billroth II or Roux-en-Y gastrojejunostomy (unpublished data of the authors) exhibit a different pattern of gallbladder emptying, defined as type II. This is characterized by a rather long lag phase and a subsequent emptying event, which is followed by either a refilling or a refilling and a new emptying event. The type II pattern of emptying might be the result of (1) gallbladder and sphincter of Oddi discoordination because of vagotomy (*2*), (2) disturbed gastric emptying because of vagotomy or Roux-en-Y diversion (*18–20*) and (3) exclusion of the duodenum after Billroth II or Roux-en-Y gastrectomy. The last two possibilities seem to be the most likely ones.

The pattern of gallbladder emptying is fully reproduced in normal subjects and patients who undergo HSV or TVP. After antiulcer operations that involve duodenal exclusion, the pattern of gallbladder emptying is consistent in most but not all patients. Although the number of the patients who exhibited a type II pattern of emptying was small and conclusions cannot be drawn with certainty, the change in pattern of gallbladder emptying might not be a weakness of the method itself but might reflect an inconsistent pattern of gastric emptying.

In conclusion, cholescintigraphy using ^{99m}Tc-EHIDA as the radiopharmaceutical agent and milk ingestion as the cholagogue stimulus is a well-established method for estimating gallbladder emptying. The reproducibility of the method is high, both as to the patterns and the parametric variables of gallbladder emptying, namely the duration of the lag phase and the ejection fraction.

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