Calculation of a Gallbladder Ejection Fraction: Advantage of Continuous Sincalide Infusion over the Three-Minute Infusion Method

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The purpose of this study was to investigate alternative methods of infusing sincalide for calculation of a gallbladder ejection fraction (GBEF) during cholescintigraphy (5 mCi ^{99m}Tc-mebrofenin). After gallbladder filling, three methods of infusion were compared in 23 normal volunteers: (1) 0.02 μg/kg as a 3-min infusion, (2) 0.02 μg/kg as a 30-min infusion, and (3) 0.01 μg/kg as a 30-min infusion (14 subjects), all performed on separate days. With the 3-min infusion, the emptying pattern was usually exponential and completed in 15 min. The mean (GBEF) was 52% ± 26% at 20 min and 56% ± 27% at 30 min (range 0%–100%). GBEFs were less than 35% in six subjects and 35%–38% in four. Side effects were noted by 11/23 subjects. With the slow infusions, emptying was linear; no side effects were noted. With 0.02 μg/kg, the mean GBEF was 50% ± 27% at 20 min and 70% ± 22% at 30 min (range 26%–95%). Similar results were seen with 0.01 μg/kg, but the data were more limited. The 30-min infusion had a higher normalcy rate than the 3-min method (91% versus 74%). Females had significantly lower GBEFs than males ($p < 0.05\%$). We conclude that the slow infusion method is preferable; it is more physiological, results in more complete emptying, has no side effects, has less normal variability, and should improve the specificity of this test. The lower mean female GBEF may have pathophysiological significance.

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Calculation of a gallbladder ejection fraction (GBEF) with cholecystokinin (CCK) during cholescintigraphy is an increasingly requested procedure performed in our laboratory. The usual referring diagnosis is acalculous biliary disease or chronic acalculous cholecystitis. These patients have a chronic recurrent pain syndrome suggestive of biliary colic, however, the usual clinical workup is normal. In this setting, cholescintigraphy may demonstrate an abnormality of gallbladder function.

Although a number of preparations of CCK have been investigated and clinically used, sincalide (Kinevac, E. R. Squibb & Sons, Inc., Princeton, NJ), the c-terminal octapeptide, is the only commercially available form in the United States. Various dose rates and methods of infusion have been used, with administered doses ranging from 0.005 μg/kg to 0.04 μg/kg, infused rapidly as a bolus, as a 1–3-min infusion, or as a slower continuous infusion ranging from 15 to 60 min (*1–7*). A commonly recommended and clinically used method of infusion is to give sincalide slowly as a 1–3-min infusion and to calculate a GBEF at the end of 20 min (*8–11*). This method is simple and convenient and avoids the possibility of spasm of the gallbladder neck or cystic duct sometimes seen with infusions of 30 sec and less (*12*). However, side effects (nausea, epigastric pain, and occasional vomiting) are common with this method, occurring in 50%–65% of patients (*13,14*).

Using this 3-min infusion technique for sincalide, an abnormal GBEF has generally been considered to be less than 35% (*8,10–11,15–17*). However, the data on which normal values are based are limited. Few truly normal controls have been studied and the populations studied are often quite biased, e.g., "normal" controls often include symptomatic patients found to have diseases other than cholecystitis and these studies often have a predominance of male subjects in a disease that typically occurs in females. Importantly, there is a surprising discrepancy in the literature as to what constitutes a normal GBEF (*2,4–7,18–19*). The percent gallbladder emptying seems to be very dependent on the administered dose, rate of infusion, and length of infusion.There are also some data suggesting that doses of CCK lower than those commonly used are adequate to induce gallbladder contraction (*1,3,5,20*). Preliminary work in our laboratory using slow constant infusion rates of CCK has been notable for the lack of adverse symptoms in patients referred for suspected biliary pain (*21*). This has been observed by others who have also described more complete gallbladder emptying with slower rates of infusion (*5,7,22*).

The purpose of our study was to compare the 3-min infusion method with a slower infusion method using two different dose rates, to compare their relative effectiveness, incidence of side effects, and to establish normal GBEF

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values for our laboratory using a representative sample of normal male and female subjects.

METHODS

The study population consisted of 23 normal volunteers, 10 males (mean age 27 ± 7 yr, range 20–46) and 13 females (mean age 29 ± 8 yr, range 22–46) (p=ns). All were in good health, had no symptoms suggestive of biliary disease, and were not on any medications, except for four females on birth control pills and one on leuprolide (Lupron), a gonadotropin inhibitor. None of the subjects were obese, had a family history of gallbladder disease, or were of Latin American or Native American descent.

Routine cholescintigraphy was performed using a large field of view gamma camera with a low-energy all-purpose collimator. After injection of 5 mCi (175 MBq) ^{99m}Tc-mebrofenin (Choletec, E. R. Squibb Diagnostics, Princeton, NJ), a dynamic study was acquired on the computer for 60 min (1 min/frame).

After ensuring that the gallbladder filled, a second acquisition was then set up on the computer for an additional 30 min (30 sec/frame). The gamma camera was placed in the left anterior oblique position in order to better separate the gallbladder from duodenum and common duct (*23*). After two baseline frames, sincalide infusion was begun.

Three methods of sincalide infusion were used. All 23 subjects had a baseline study with sincalide (0.02 μg/kg) infused slowly over 3 min. On another day, all subjects had a second study using the same dose of sincalide (0.02 μg/kg) that was given as a continuous infusion over 30 min. Sincalide was diluted in 15 cc normal saline and administered using a calibrated infusion pump. A third study similar to the second study was performed in 14 subjects (7 M, 7 F), but with half the dose of sincalide (0.01 μg/kg) infused for 30 min. The studies were performed at least 48 hr apart and all three studies were completed within 14 days.

Processing was performed by drawing a region of interest on the computer for both the gallbladder and adjacent liver background; a background-corrected time-activity curve was generated. Two quantitative parameters were calculated: (1) the time until gallbladder emptying began and (2) the GBEF determined at both 20 and 30 min (maximum counts − minimum counts divided by maximum counts, all corrected for background). The results of the three techniques were then compared statistically using the paired Student's t-test.

RESULTS

Cholescintigraphy was completely normal at the end of 1 hr in 21 subjects. Two females with gallbladder filling and common duct visualization at 60 min had no biliary to bowel clearance, but had prompt transit after sincalide infusion.

Using the 3-min infusion method, 11 subjects had mild transient abdominal cramping and/or nausea. No subjects had any symptoms with the two constant infusion methods. With the 3-min infusion technique, the mean time from the start of computer acquisition until the beginning of gallbladder emptying was 3.8 ± 2.6 min (range 0–8 min) and was significantly shorter than the slow infusion methods, 7.8 ± 6.2 min (range 0–20) for the 0.02 μg/kg 30-min infusion ($p < 0.05$) and 6.4 ± 4.2 min (range 0–12 min) for the 0.01 μg/kg 30 min infusion ($p < 0.025$).

With the 3-min infusion method, emptying was usually rapid, exponential in appearance, and completed by 15 min (mean 10.8 ± 6.0 min duration), while with the 30-min infusions, emptying was more gradual, linear and continuous throughout the study (Fig. 1).

There was good correlation between the GBEFs at the two time intervals of 20 and 30 min with all three methods: the 3-min infusion ($r = 0.947$), the 30-min infusions (0.02 μg/kg) ($r = 0.886$) and 0.01 μg/kg ($r = 0.836$). A significant difference between the GBEF results at 20 and 30 min was seen for both slow infusion methods ($p < 0.025$), but not for the 3-min infusion (p = ns).

With the 3-min infusion method, the mean GBEF was 52% ± 26% s.d. at 20 min and 56% ± 27% s.d. at 30 min, with a range of 0%–100% (Tables 1 and 2). Six subjects had GBEFs <35% [five females (34%, 30%, 25%, 18%, 0%) and one male (19%)], and four subjects (three females) had borderline values (35%, 35%, 37%, 38%) (Table 1). Ultrasonography was performed on four of five females with GBEFs less than 35%, and all were normal.

With the continuous infusion method (0.02 μg/kg), the mean GBEF was 50% ± 27% s.d. at 20 min (range 0%–95%) and 70% ± 22% s.d. at 30 min (range 17%–97%) (Table 2). Only two subjects had a clearly low GBEF (17% and 25%); one was borderline (36%). Using the lower dose continuous infusion method (0.01 μg/kg) (14 subjects), the mean GBEF was 44% ± 17% (range 17%–90%) at 20 min and 64% ± 20% (range 26%–95%) at 30 min, which is not statistically different from the 0.02-μg/kg slow infusion dose.

Using the mean ± 2 s.d.s as a normal range, only the

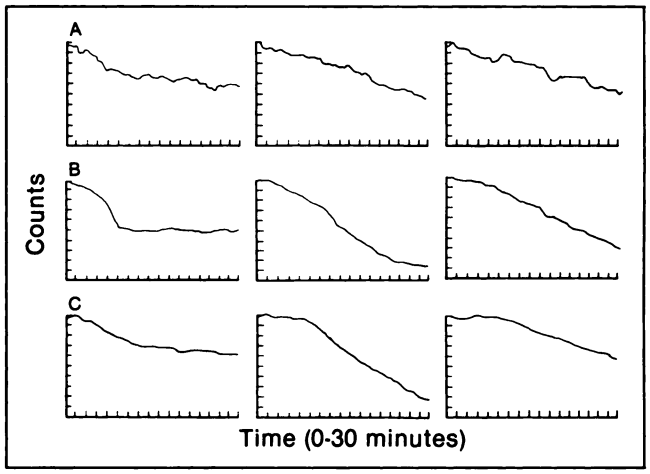

FIGURE 1. Gallbladder emptying curves from three representative normal subjects who received all three doses of sincalide [left: 3 min infusion (0.02 μg/kg), middle: 30-min infusion (0.02 μg/kg), right: 30-min infusion (0.01 μg/kg)]. From top to bottom, these time activity-curves are from Subjects 9, 12, and 8 listed in Table 1. Note the rapid, usually exponential emptying pattern with the 3-min infusions, which is completed by 15 min. With the 30-min infusions, emptying is more gradual, linear, continuous, and more complete. The two slow infusion dose rates produce similar results.

TABLE 1
Gallbladder Ejection Fractions for All Normal Subjects Using Different Rates of Sincalide Infusion

Subject no.	Sex	% GBEF Sincalide 3-min infusion at 20 min 0.02 μg/kg	30-min infusion at 30 min 0.02 μg/kg	0.01 μg/kg
1	F	0	17	
2	F	18	25	52
3	M	19	65	75
4	F	25	55	
5	F	30	36	
6	F	34	85	
7	M	35	61	62
8	F	35	81	43
9	F	37	55	51
10	F	38	54	26
11	F	52	79	80
12	M	54	85	73
13	M	55	74	75
14	F	61	69	43
15	F	67	87	87
16	M	68	84	
17	F	68	89	
18	M	75	97	95
19	F	78	86	
20	M	80	95	
21	F	80	91	
22	M	89	57	57
23	M	100	81	78
Mean ± s.d.		52% ± 26%	70% ± 22%	64% ± 20%

0.02 μg/kg and 0.01 μg/kg continuous infusions at 30 min gave clinically useful normal ranges, with abnormal being <26% and <24%, respectively. One subject was particularly interesting and puzzling; she had no response to the 3-min infusion, a very delayed poor response to the slow 0.02-μg/kg infusion, but a good response with a double dose (0.04 μg/kg) slow infusion of sincalide (Fig. 2). Exclusion of the data for this one subject would raise the abnormal range with the 0.02-μg/kg slow infusion to <31%.

In an attempt to determine the specificity or false-positive rate of the GBEF for diagnosing chronic acalculous cholecystitis, a "normalcy rate" (*24*) was calculated. This was defined as the number of normal subjects in this study with GBEF in the normal range as defined by two

TABLE 2
Mean and Range for Gallbladder Ejection Fraction in 23 Normals

GBEF	Method of Sincalide Infusion 3 min 0.02 μg/kg	30 min 0.02 μg/kg	30 min 0.01 μg/kg
20 min (range)	0%–100%	0%–95%	17%–90%
(mean% ± 1 s.d.)	52 ± 26	50 ± 27	44 ± 17
30 min (range)	0%–100%	17%–97%	26%–95%
(mean% ± 1 s.d.)	56 ± 27	70 ± 22	64 ± 20

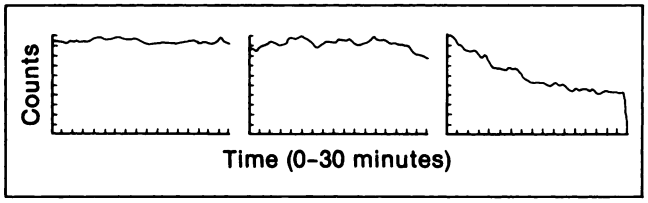

FIGURE 2. Exceptional response to sincalide in one normal volunteer. Left: No response to a 3-min infusion (0.02 μg/kg) of sincalide. Middle: A very delayed and poor response (17%) with the 0.02 μg/kg 30-min infusion. Right: The infusion rate was doubled to 0.04 μg/kg, resulting in 52% emptying over the next 30 min. The reason for this apparent reduced sensitivity to sincalide is not known.

recent large clinical studies where normal was defined as ≥35% (*25*) and ≥40% (*26*) by dividing that number by the total number of normals in this study. With the 3-min infusion, the normalcy rate was 74% and 55%, respectively, with the 30-min infusion (0.02 μg/kg), 91% and 87%.

No correlation was found between age and GBEF. There was no statistical difference in GBEFs between subjects >30 yr of age (17 subjects) and those less than 30 yr of age (6 subjects) with either the 3-min or 30-min infusions. However, there was a statistically significant difference in the mean GBEF between men and women ($p < 0.05$) (Fig. 3). No significant difference in the GBEF was found between women who were and were not on birth control pills.

DISCUSSION

The infusion of sincalide, 0.02 μg/kg, over 1–3 min is not physiological. In response to the normal endogenous production and release of CCK by the duodenal mucosa, serum CCK rises over 15–30 min and plateaus as a steady-state is achieved (*27,28*). Gallbladder contraction is threshold-dependent, emptying correlates with the level of serum CCK (*1,3,23,29–31*), and maximum contraction occurs 40–60 min after ingestion of a fatty meal (*27,32–33*). As food exits the duodenum, the serum CCK level slowly declines towards baseline. In contrast, when 0.02 μg/kg sincalide is intravenously infused over 1–3 min, serum CCK peaks rapidly at a supraphysiological level and then promptly returns to baseline with a serum half-life of 2.5 min (*34*). The nonphysiological pharmacodynamics and supraphysiological dose may be reasons for the high incidence of side effects and the more variable and less complete emptying.

Reproduction of the patient's symptoms with CCK has been felt by some to be of diagnostic importance (*35–37*), however, CCK has physiological effects other than causing gallbladder contraction and sphincter of Oddi relaxation, e.g., CCK decreases gastroesophageal sphincter tone, inhibits gastric emptying, increases small and large bowel motility, etc. (*38*). CCK is thought to be an important aggravating factor in the symptoms associated with the

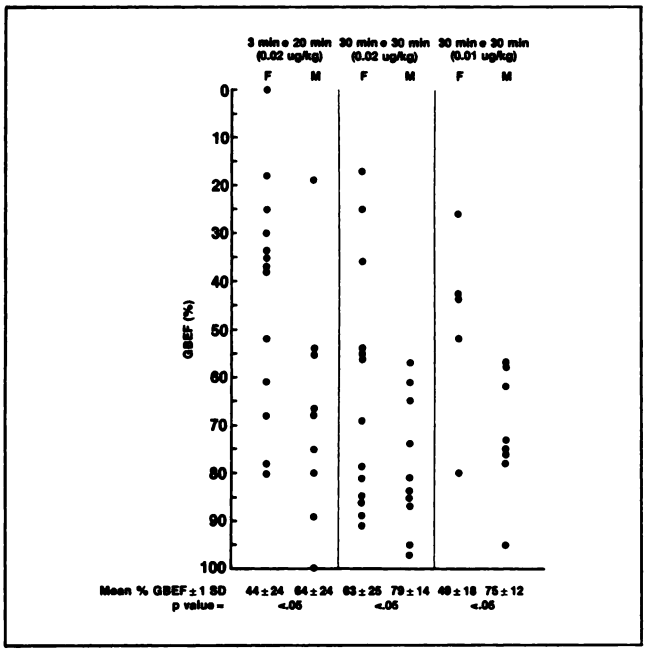

FIGURE 3. Gallbladder ejection fractions for men versus women using three different methods of infusion. (Left) 3-min infusion (0.02 μg/kg), (Middle) 30-min infusion (0.02 μg/kg), and (Right) 30-min infusion (0.01 μg/kg). The very different distribution of GBEFs for men versus women is obvious for all three techniques. The means and p values are noted at the bottom.

irritable bowel syndrome, a common malady with symptoms often similar to biliary colic (*39*). Adverse symptoms occur not only in symptomatic patients with and without biliary disease, but also in normal subjects (*3,18,28,40*). Although severe pain is uncommon in normals, abdominal cramping and nausea are frequent. In our study, 11/23 subjects had symptoms using the 3-min infusion method, but not with the slower infusions. Since sincalide-induced symptoms are neither specific nor diagnostically useful, a method that could produce gallbladder contraction without side effects would be preferable.

Gallbladder emptying was more complete with slow infusions compared to the 3-min infusion method. The degree of emptying is dependent on several independent factors: the dose, dose rate, and length of infusion. Although the total dose administered (0.02 μg/kg) was similar for the 3-min and 30-min infusions, the dose rate and length of infusion were not, i.e., 6.6 ng/kg/min for 3 min versus 0.67 ng/kg/min for 30 min. Better emptying resulted with a ten-fold decrease in the dose rate given for 10 times as long. The purpose of our study was not to repeat or expand on previous pharmacokinetic studies or to determine the optimum dose rate and length of infusion, but rather to compare clinically used methods.

Another advantage of the continuous infusion method is less variation in normal values. Our study found a very wide normal range for GBEFs using a 3-min infusion (0%–100%!) (mean 52% ± 26% s.d.) (Tables 1 and 2). Establishing normal values is clinically useless. The continuous infusion method also had considerable variability, but to a lesser degree: 17%–97% (mean 70% ± 22% s.d.). Abnormal (mean ±2 s.d.) would be <26%. When males and females are evaluated separately, the results are quite different. We demonstrated a statistically significant difference between the GBEFs of males and females ($p < 0.05$) (Fig. 3). An abnormal GBEF would be <51% (mean ±2 s.d.) for males, but <13% for females. Although some previous studies have found no gender difference (*1,6*), one study (*22*) found more rapid emptying for males than females (p = ns). Previous studies have been limited by the small number of subjects. Our study may indicate that stasis plays a role in a female's increased risk of gallbladder disease. Alternatively, we may be detecting preclinical disease in a subgroup of predisposed women.

The demonstration of a functional abnormality in gallbladder contraction, as defined by a low GBEF during cholescintigraphy, is increasingly being used to confirm the biliary origin of a recurrent pain syndrome that goes by various names, including acalculous biliary disease, gallbladder spasm, cystic duct syndrome, or chronic acalculous cholecystitis. These diagnoses are difficult to confirm by the usual laboratory and radiological tests. Although the symptoms are strongly suggestive of biliary colic, oral cholecystography, ultrasonography, and routine cholescintigraphy, are usually normal. Several reports have found CCK-stimulated cholescintigraphy a useful clinical test (*10–11,15–16,41*), however, there is some contrary evidence (*18,42*) and resulting controversy (*43*). Two recently published large series confirm the test's high sensitivity (92%–94%) for predicting chronic cholecystitis pathologically and a good clinical response to cholecystectomy (*25,26*). Interestingly, one study used a 3-min infusion (*25*) and the other a slow infusion of sincalide (*26*).

However, these studies did not investigate its specificity. This is difficult to do since patients with negative tests, i.e., normal GBEFs, do not usually go on to surgery. In the clinical setting where this study has been used to date, specificity may not be a problem. Usually these patients have had recurrent symptoms over a long period of time and have been well worked up to rule out other causes for their pain. This preselected population has a high likelihood of disease and a positive test is likely to be a true-positive. The results can be used by physicians to confirm their clinical diagnosis and proceed with cholecystectomy. However, as this test becomes more generally accepted and used, patients might be referred with symptoms of shorter duration and less thorough evaluation. In that scenario, the specificity of this test becomes of more concern. With the 3-min infusion, 6/23 of our normal subjects had GBEFs <35% (a value considered abnormal by numerous investigators) and 4 others were borderline (35%–38%). A recent publication noted even more variation amongst normal volunteers with 16/25 having GBEFs <35% using the 3-min method (*25*). However, with the continuous infusion method, only two of our subjects had

a clearly low GBEF (17, 25%), and one was borderline (36%). We have attempted to look at the question of specificity by calculating a "normalcy rate" (*24*). By defining an abnormal GBEF as ≥35% (*39*) or ≥40% (*26*), the normalcy rate in our study was 74% and 57%, respectively, for the 3-min infusion, but 91% and 87%, respectively, for the 30-min infusion. This suggests that fewer false-positives would result using the slower infusion method.

In summary, our results show a definite advantage for administering sincalide as a 30-min infusion compared to the commonly used 1–3-min infusion method. In addition to being more physiological, the slow infusion method had no side effects, resulted in better emptying, had less intersubject variability, and would likely result in less false-positives when used clinically to diagnose acalculous biliary disease. We have also found that females have significantly lower mean GBEFs than males.

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