Gallbladder Function: Methods for Measuring Filling and Emptying

Rajendra P. Sarva, David P. Shreiner, David Van Thiel, and Nori Yingvorapant

The Nuclear Medicine Service, Veterans Administration Medical Center and the Division of Gastroenterology, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

Cholescintigraphy with [^{99m}Tc]disofenin was used to determine the optimal dose and method of administration of the octapeptide of cholecystokinin, and to determine the kinetics of gallbladder filling and emptying in 22 patients without disease of the liver or gallbladder. The peak filling rate of the gallbladder occurred at 30 min after injection; filling was complete at 1 hr. A 45-min constant intravenous infusion of the octapeptide 20 ng/kg · hr resulted in progressive emptying of the normal gallbladder; the mean ejection fraction at 45 min was 77.2 ± 4.9%. A 1-min injection of 20 ng/kg resulted in a rapid, short-lived emptying; the mean ejection fraction was 52.2 ± 9.3%. Doubling or halving the infusion dose produced no greater response or a smaller response. We conclude that a constant 45-min infusion technique is superior to short injection times, because of more complete emptying, no side effects, and more consistent response.

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The use of ^{99m}Tc-labeled hepatobiliary agents has greatly facilitated the study of gallbladder function. However, several aspects of gallbladder function and the best method for stimulating the gallbladder to contract have not been elucidated adequately. Considerable attention has been paid to the contraction of the gallbladder, while little attention has been given to filling of the gallbladder. Furthermore, various investigators have used different doses and methods of administration of cholecystokinin and its analogs.

In the present study we have attempted to study these aspects of gallbladder function, as well as the kinetics of gallbladder emptying, in patients without gallstones or evidence of hepatic disease. The goals of the present study were to determine an optimal dose and mode of administration of the octapeptide of cholecystokinin (OP-CCK) so that contraction of the gallbladder could be studied in a standardized manner. The count based method of measuring emptying of the gallbladder has been validated by Krishnamurthy et al. (*1*). Normal filling patterns of the gallbladder were also studied.

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For reprints contact: David P. Shreiner, MD, Nuclear Medicine Service, VA Medical Ctr., University Drive C, Pittsburgh, PA 15240.

METHODS

Control subjects

Informed consent was obtained from all subjects for this study.

Control subjects were selected from the GI outpatient clinic of the Oakland VA Medical Center. All patients had normal liver function tests and no evidence of gallstones by oral cholecystography or sonography of the gallbladder. The 22 control subjects studied had the following diagnoses: inactive peptic ulcer (five patients); irritable bowel syndrome or nonspecific abdominal pain (six patients); mild reflux esophagitis (two patients); hypertension (three patients); rectal incontinence (one patient); a history of coronary artery bypass surgery (one patient); a history of colon resection for carcinoma (two patients); chronic obstructive pulmonary disease (one patient); inactive gastric ulcer (one patient). None of the patients with ulcer disease had a vagotomy. All control subjects were male with a mean age of 55.8 yr (range 33–69 yr); a mean body height of 69.9 in. (range 66–72.5 in.); and a mean body weight of 81.7 kg (range 62.1–100.7 kg).

Cholescintigraphy

After an overnight fast, all patients were injected intravenously with 0.5–1.0 mCi of [^{99m}Tc]disofenin. The patient was imaged supine under a gamma camera with

a pinhole collimator for 60 min. (started 60–90 min after injection for emptying study, and immediately after injection for filling study). The collimator was positioned over the right upper quadrant of the abdomen in the area of the gallbladder with a 15° cephalad tilt. This was to allow maximum separation of the gallbladder and bile ducts from subsequent intestinal activity. Octapeptide of cholecystokinin was used as the stimulus for gallbladder contraction. Several subjects were studied more than once with a time interval of at least 48 hr between each study. Subjects received either a 1-min manual injection of 20 ng/kg of OP-CCK over a period of 60 sec, or a constant intravenous infusion administered by an IVAC of either normal saline, 10, 20, or 40 ng/kg·hr of OP-CCK using a fresh vial of drug for each study. Computer images of 1 frame/min were recorded and the data analyzed using a computer. The isotopic activity in a region of interest defined over the gallbladder was calculated for each frame after subtracting the background activity. The time-activity curves were then generated. The curves were normalized to 10^3 counts at time 0. The activity at time intervals of 15, 30, 45, and 60 min were corrected for the physical decay of injected isotope. The percentage of gallbladder emptying was calculated using the following formula:

$$\frac{(\text{Init. cts. GB}) - (\text{Final cts. GB})}{\text{Init. cts. GB}} \times 100,$$

where Init. cts. GB indicates initial counts in gallbladder.

The gallbladder filling phase was studied in 18 of the 22 subjects using a parallel-hole collimator. Similar images of 1 frame/min were obtained beginning with the hepatic phase of the radionuclide. Time-activity curves were generated as above, and the following parameters were examined:

1. Peak filling rate, which is defined as the maximum rate of increase in counts from minute to minute;
2. The time to peak filling rate; and
3. The time to attainment of maximum number of counts over the gallbladder region.

Statistical analysis

The statistical difference between the groups was analyzed using Student's t-test for unpaired values. Not considered significant were p values >0.05.

RESULTS

Gallbladder emptying with a constant 45-min infusion of OP-CCK

A small degree of spontaneous emptying of the gallbladder occurred in response to infusion of normal saline (placebo); percent emptying at 15 min was 6.8 ± 1.2, at 30 min it was 8.9 ± 1.7, and at 45 min it was 12.0 ± 2.0.

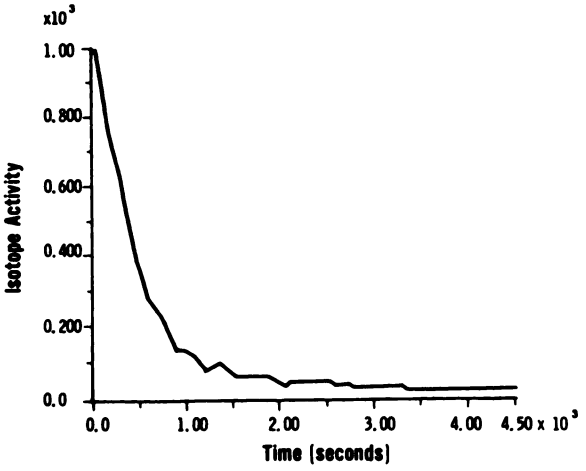

FIGURE 1
Time-activity curve of gallbladder (representative normal subject) showing progressive decline in gallbladder counts (emptying) during constant i.v. infusion of OP-CCK, 20 ng/kg·hr

A constant infusion of OP-CCK 20 ng/kg·hr caused a rapid and progressive emptying of the gallbladder (Fig. 1). All infused doses of OP-CCK caused significantly more emptying when compared to placebo at 15, 30, and 45 min (Fig. 2). A constant infusion of 20 ng/kg·hr produced significantly greater contraction of the gallbladder at all time intervals than did 10 ng/kg·hr ($p < 0.0125$). Increasing the dose to 40 ng/kg·hr did

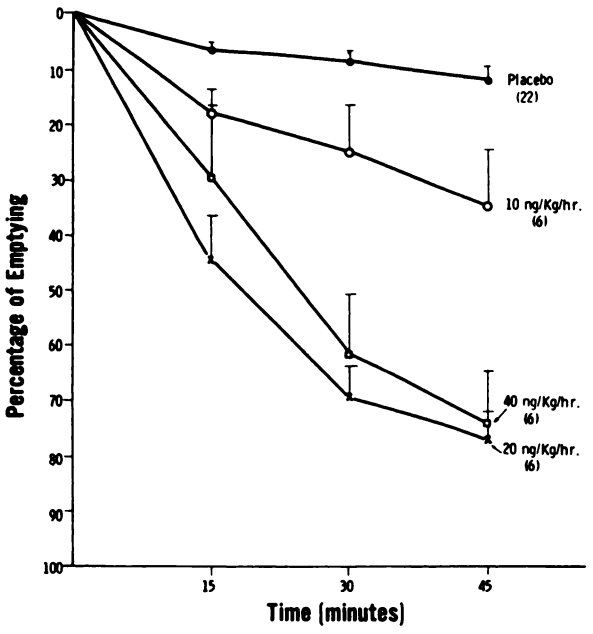

FIGURE 2
Comparison of varying doses of OP-CCK administered by constant intravenous infusion and compared with saline infusion (placebo). Percentage of gallbladder emptying was derived from time-activity curves at 15, 30, and 45 min. Mean ± s.e.m. are shown

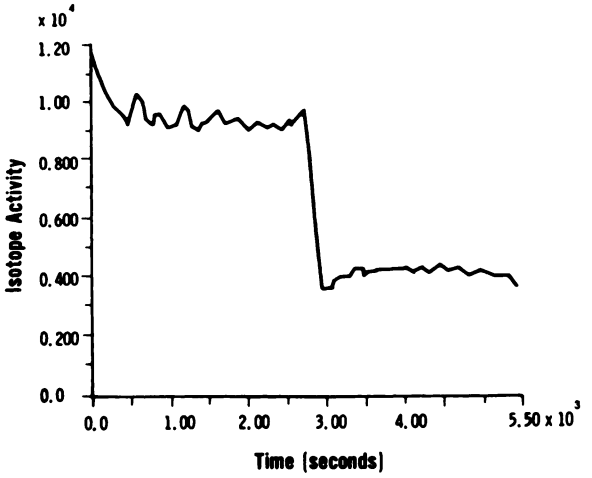

FIGURE 3
Time-activity curve of gallbladder (representative normal subject) showing rapid, but brief, decline in gallbladder counts (emptying) following 1-min injection of OP-CCK, 20 ng/kg

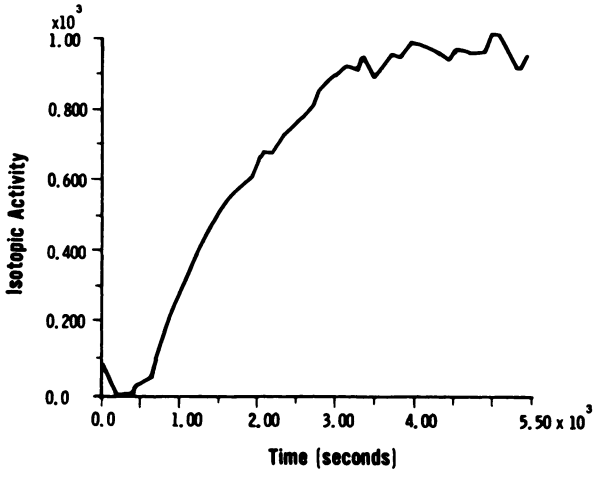

FIGURE 5
Time-activity curve of gallbladder filling phase (representative normal subject) showing rapid filling phase (peak filling rate = maximum slope) and plateau after 1 hr

not result in significantly more emptying than was observed with a dose of 20 ng/kg·hr. The largest dose caused greater contraction than did the 10 ng/kg·hr dose, but was significantly different only at time intervals of 30 min ($p < 0.025$) and 45 min ($p < 0.005$). The largest dose did not differ significantly at any time point from that observed with the intermediate dose of 20 ng/kg·hr.

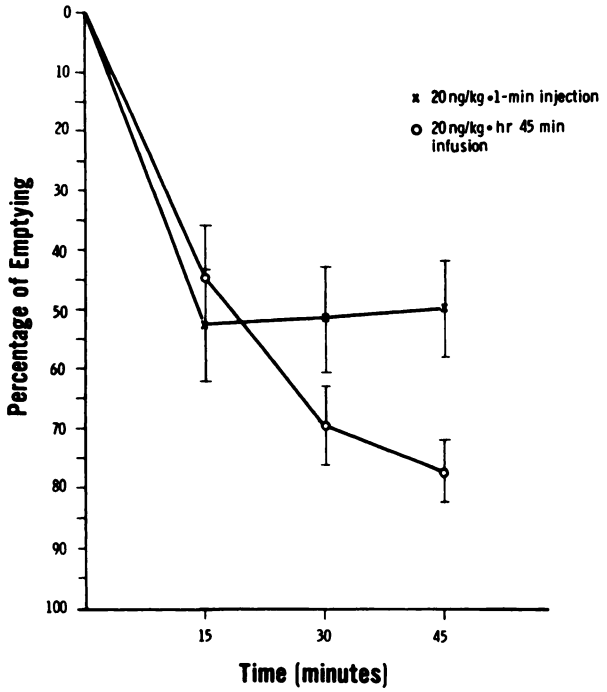

FIGURE 4
Comparison of gallbladder emptying induced by 1-min injection and 45-min constant infusion of OP-CCK. Mean ± s.e.m. are shown. Gallbladder emptying ceases shortly after 1-min injection, whereas emptying is more progressive and complete with constant infusion technic

Comparison of 1-min injection with a 45-min constant infusion of OP-CCK

A 1-min injection of OP-CCK produced a more rapid but less complete emptying of the gallbladder (Fig. 3), as compared to a 45-min infusion (Fig. 1). The mean percentage emptying of the gallbladder with a 1-min injection of 20 ng/kg was 52.2 ± 9.3% at 15 min, and changed little at 30 min (51.5 ± 8.9%) and at 45 min (50.0 ± 7.9%). In contrast, a 45-min or longer constant infusion of 20 ng/kg·hr of OP-CCK produced continuous emptying of the gallbladder up to 45 min ($p < 0.025$) (Fig. 4). Little or no further emptying occurred after 45 min.

Furthermore, a 1-min injection of OP-CCK caused a much more variable contraction of the gallbladder (range of ejection fractions = 11.8–92.4%); while a constant infusion of OP-CCK resulted in a more consistent and complete emptying of the gallbladder (range of ejection fractions = 65.4–96.4%). Three subjects were tested on different days by both the 1-min and 45-min constant infusion techniques. The maximum percentage emptying with the 1-min technique was 12.3%, 57.5%, and 54.6% for these subjects; for the 45-min constant infusion technique the comparable values were 75.4%, 63.5%, and 96.4%, respectively.

Gallbladder filling

Twenty-six studies of gallbladder filling were performed on 18 of the 22 control subjects. Figure 5 shows a representative curve of gallbladder filling. The maximum slope of the ascending curve corresponds to the calculated peak filling rate. The mean peak filling rate

TABLE 1
Review of Cholescintigraphic Studies of Gallbladder Emptying in Normal Subjects

Source	Stimulus*	Route	Duration of infusion	Dose	Mean % ejection fraction†
Krishnamurthy et al. (*4*)	OP-CCK	i.v.	3 min	10–40 ng/kg	59 ± 4 (±s.e.m.)
Krishnamurthy et al. (*5*)	OP-CCK	i.v.	3 min	20 ng/kg	34 ± 24 (±s.d.)
Lalyre et al. (*6*)	OP-CCK	i.v.	1 min	20 ng/kg	26.5 ± 8.2 (±s.e.m.)
	OP-CCK	i.m.	—	100 ng/kg	47.3 ± 8.2 (±s.e.m.)
	OP-CCK	i.m.	—	400 ng/kg	54.4 ± 7.2 (±s.e.m.)
Shafer et al. (*7*)	CCK	i.v.	5 min	75 Ivy Units	53.6 ± 41.9 (±s.d.)
	Lipomul	p.o.	—	30 ml	31.7 ± 10.9 (±s.d.)
Bobba et al. (*8*)	Fatty meal	p.o.	—	8 oz/70 kg	64.4 ± 6.7 (±s.e.m.)
Mesgarzadeh et al. (*9*)	OP-CCK	i.v.	3 min	20 ng/kg	35 ± 17 (±s.d.)
	OP-CCK	i.v.	3 min	40 ng/kg	43 ± 26 (±s.d.)
Sarva et al.	OP-CCK	i.v.	1 min	20 ng/kg	52.2 ± 9.3 (±s.e.m.)
	OP-CCK	i.v.	45 min	20 ng/kg·hr	77.2 ± 4.9 (±s.e.m.)

* OP-CCK: octapeptide of cholecystokinin; CCK = cholecystokinin.
† s.e.m. = standard error of mean; s.d. = standard deviation.

was 0.928 ± 0.061 in these control subjects. The mean time to the peak filling rate was 29.8 ± 2.2 min. The mean time to attainment of maximum number of counts (maximum gallbladder filling) within the gallbladder was 63.1 ± 3.4 min.

DISCUSSION

These investigations demonstrate that a 45-min constant infusion of OP-CCK at a dose of 20 ng/kg·hr produced a more consistent and complete emptying of the gallbladder than did a similar dose given as a 1-min injection. The observed differences in the fractional emptying of the gallbladder are probably related to the pharmacokinetics of OP-CCK. OP-CCK is ten times more potent than cholecystokinin on a molar basis (*2*). The kinetics and metabolism of OP-CCK have not been well-defined. Spellman et al. stated that the half-life for exogenous cholecystokinin was probably 2.5 min (*3*). Octapeptide of cholecystokinin also probably has a short half-life, which would explain the more rapid but less complete emptying of the gallbladder in response to the 1-min injections. It should be noted that none of the subjects that received a 45-min constant infusion of OP-CCK had any side effects, while nine of the 11 subjects who received a 1-min injection experienced some minor side effect, e.g., transient abdominal cramps, nausea, or dizziness. The lack of side effects observed with the 45-min constant infusion technique should be added to the other advantages of the infusion technique which include a more consistent response than the 1-min injection.

The data also demonstrate that a 45-min constant infusion of 20 ng/kg·hr of OP-CCK produced a greater contraction of the gallbladder than either placebo or the 10 ng/kg·hr dose. The higher dose of 40 ng/kg·hr did not produce a significantly greater contraction of the gallbladder than did the 20 ng/kg·hr dose.

Table 1 shows our results with a 1-min injection of OP-CCK are similar to those of Krishnamurthy and others (*4–9*). An infusion given over a period of 1–5 min produces a rapid, but short-lived, inconsistent, and less complete emptying of the gallbladder. It also is associated with unpleasant side effects, particularly at larger doses. Intramuscular OP-CCK may produce greater emptying than it does when given as a 1–5 min i.v. injection, but its use is still associated with occasional side effects (*6*). Our results with the 45-min infusion technique using 20 ng/kg·hr (Table 1, Sarva et al.) demonstrate the highest mean ejection fraction and the lowest variability, when compared with the other reported techniques.

Our data confirm the work of Spellman et al. (*3*) in that a constant infusion of OP-CCK over 30–60 min produces a progressive and consistent contraction of the gallbladder. We have shown also that the most complete and consistent response can be obtained using a constant i.v. infusion of OP-CCK 20 ng/kg·hr over a 45 min period. Furthermore, no side effects have been observed with the use of this constant infusion technique, even when a supramaximal dose of 40 ng/kg·hr has been used.

Our work also shows that there may be slight spontaneous emptying of the gallbladder, even in the fasting state. Others have made similar observations and have reported fluctuations in plasma motilin levels to occur with changes in the size of the gallbladder (*10*). Such partial emptying may be due to interdigestive myoelectrical activity of the gallbladder produced in response to motilin.

Our studies of the filling phase of the normal gallbladder indicate that maximal filling occurs about 1 hr

after injection of the radiopharmaceutical. The peak filling rate can be calculated from the slope of the time-activity curve; the time to achieve the peak filling rate was about 30 min. These parameters of gallbladder filling may be useful in studies of the abnormal gallbladder.

In conclusion we have shown that a 45-min infusion of OP-CCK at a rate of 20 ng/kg·hr produces a more complete contraction of the gallbladder than any dose administered over a shorter period. Furthermore, no patient experienced side effects with this method of administration, and larger doses were unnecessary. Since evaluation of the filling phase of the gallbladder can be done as part of the examination of gallbladder contraction, it seems reasonable to measure filling rate and time during future studies of the gallbladder in various diseases, to evaluate the diagnostic usefulness of this parameter of gallbladder function.

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