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Dose-Response Relationship of Bile Flow to Cholecystokinin Stimulation as Measured by Duodenal Drainage

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A study was done to evaluate the dose-response of cholecystokinin administered intravenously to normal patients and to patients with diseased gallbladders. The volumes of bile and bilirubin units were measured in duodenal aspirates. A dosage of cholecystokinin between 12.5 and 25 Ivy dog units differentiated the several categories studied. Lower doses of cholecystokinin resulted in no change in the volume of bile, but significantly reduced the output of bilirubin units.

In work reported earlier by us on the use of cholecystokinin, 70 Ivy dog units were given intravenously as the stimulating dose. No important toxic reactions were observed in approximately 500 patients to whom this dose was administered. A transient sensation of facial heat sometimes accompanied by flushing was commonly experienced and occasionally, a generalized sensation of warmth occurred. However, more serious reactions, such as urticaria or hypotension, were not noted.

Subsequent observations indicated that such side effects which did occur were markedly decreased when reduced doses of cholecystokinin were injected slowly. It was also noted that an adequate flow of bile for diagnostic biliary drainage could be secured by using smaller doses. The present study was undertaken, therefore, to evaluate the dose-response relationship of bile flow as measured in duodenal drainage following the intravenous injection of small doses of cholecystokinin.

**Methods**

A total of 217 patients was studied comprising four separate groups: group 1, normal controls (81 subjects); group 2, patients with cholelithiasis whose gallbladder visualized by oral cholangiography (42 patients); group 3, patients with cholelithiasis whose gallbladder failed to visualize (51 patients); and group 4, patients who previously had undergone surgical removal of the gallbladder (43 patients). A double lumen tube was introduced in the duodenum and placed under fluoroscopic observation so that the proximal lumen drained the antrum of the stomach and the distal lumen drained the duodenum in the area of the ampulla of Vater. Continuous gastric and duodenal aspi-
ration was accomplished by pump suction at a fixed pressure. After a 10-minute basal period, cholecystokinin was given intravenously and was followed by collection of duodenal specimens at intervals of 10 minutes for one hour.

The cholecystokinin used was supplied in dry form* containing 75 Ivy dog units. An Ivy unit is that amount of cholecystokinin which, dissolved in normal saline solution, produces in an anesthetized 15 Kg dog a rise in intragallbladder pressure of one cm of bile within three minutes after intravenous injection. Each 3 mg (75 Ivy dog units) was known to contain other gastrointestinal hormones, including 40 clinical units of secretin and 100 Crick-Harper-Raper units of pancreozymin. Jorpes has described how closely cholecystokinin and pancreozymin accompany each other during steps of purification. Cholecystokinin and pancreozymin are assumed to be the same homogeneous peptide of 33 amino acid units.

Cholecystokinin was given intravenously in doses of 25, 18.5, 12.5, and 7.5 units to each of the four groups of subjects (Table I). Since maximum contraction of the gallbladder in response to cholecystokinin has been found to occur within 20 minutes, the duodenal aspirates collected within the first 20 minutes after cholecystokinin administration were measured for volume and bilirubin content. The latter was expressed as “output of bilirubin units”, a comparative value described by Burton et al as the volume of the sample in milliliters multiplied by the icterus index of the specimen determined by Meulengracht’s method.12

The aspirated duodenal contents were centrifuged and the sediment examined under the microscope for cholesterol crystals, calcium bilirubinate pigment, microspheroliths, and parasites. As noted previously, cholecystokinin stimulation provides a sediment free of the confusing materials found after such cholecystogogues as olive oil and magnesium sulfate.

The several study groups were compared using the Krushal Wallis One Way Analysis of Variance. The hypothesis tested by this method is that all values come from the same overall population. The data was evaluated at the 5% level of significance. Results are expressed as P, the probability that all values come from the same population. If P is greater than 0.05, there would be no reason to reject the assumption that all values come from the same population. If P equals or is less than 0.05, the hypothesis that the values come from the same population is interpreted as without support. Using median as the central value, the lower and upper limits were expressed as the 10th and 90th percentiles, respectively. When there were fewer than nine patients in a group, however, the next larger percentile was used.

Results

The volume and content of bilirubin units of the duodenal aspirates obtained

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*Vitrum—Stockholm
from the group of normal subjects after varying amount of cholecystokinin are shown in Table II. The differences between the volume and bilirubin content of the duodenal aspirates were not statistically significant, regardless of the stimulating dose of cholecystokinin used. The suggestion is obtained, however, that the values tend to be lower with the smaller doses.

The volume differences among the several study groups are shown in Table III. These differences were not found to be statistically significant, regardless of the dose of cholecystokinin used for stimulation. In all categories the evaluation of volume resulted in a $P$ value greater than 0.05.

The differences in the "output of bilirubin units" among the diagnostic categories when 18.5, 12.5 and 7.5 units of cholecystokinin were used to stimulate secretion was statistically significant (Table IV). However, the $P$ value of 0.39 indicated no statistical significance when 25 units of cholecystokinin was given.

**Discussion**

Cholecystokinin induces relaxation...
of the sphincter of Oddi and decrease in tonus of the lower common bile duct as well as evacuation of the gallbladder. The fact that essentially equal 20-minute volumes were obtained in the normal subjects and in the postcholecystectomy patients we studied suggests that the gallbladder contributes little to the total volume of the duodenal aspirate at these doses of cholecystokinin. On the other hand, subtraction of the median bilirubin content (Table IV) of the postcholecystectomy group from the normal control group yields a value of about 3000 bilirubin units, regardless of the dose of cholecystokinin used. Results of this method for calculating bilirubin units indicate that the gallbladder is contributing at least this amount to the duodenal aspirate. In support of these concepts, Edholm found that the average amount evacuated from the gallbladder was only 15 ml or 45% of the initial volume (average 33 ml) when 70 units of cholecystokinin were used. An even smaller amount might be anticipated from the doses used in this study, especially since an intravenous injection of 25 Ivy dog units in a normal person produces an average of only 40% emptying of the gallbladder.

Other possible influences that could affect the volume of duodenal aspirate are the flow of bile from the liver itself and the flow of pancreatic juice. Although Adlercreutz et al concluded that cholecystokinin is not capable of stimulating bile secretion from the liver, Torsoli and associates provided data indicating that cholecystokinin has a choleretic effect. The studies of Jonsson et al with secretin in dog preparations have suggested a choleretic effect of purified secretin. This choleretic action might increase bile flow in patients with nonfunctioning gallbladders or in patients whose gallbladder has been removed. The secretin present in the cholecystokinin preparation would certainly be expected to stimulate the flow of pancreatic juice.

Another variable is the possibility of endogenous cholecystokinin in the
blood of the patients tested. Caroli et al have described a cholecystokinin inhibitor which is present normally and in slight quantities even in cholecystectomized patients. Apparently, normal subjects and those with diseased gallbladders differ in their degree of responsiveness to cholecystokinin. Thus, stimulation of a degree sufficient to cause evacuation of the gallbladder in normal persons may be ineffective in patients with poorly functioning gallbladders. With respect to cholecystokinin, the dose that seems to accomplish this differentiation is greater than 12.5 but less than 25 Ivy dog units. The fact that the gallbladder response to 25 Ivy dog units was not significantly different in the various diagnostic categories we studied suggests that large doses of cholecystokinin stimulate diseased as well as normal gallbladders.

Summary
A study was made to test the dose-response relationship of bile flow to intravenously administered cholecystokinin as measured by duodenal drainage. Cholecystokinin was given for this purpose in doses of 25, 18.5, 12.5 and 7.5 Ivy dog units.

Normal persons exhibited no significantly different response in 20-minute volumes and 20-minute bilirubin concentrations of their duodenal aspirates with each of the doses used. There was a suggestion, however, that smaller doses, especially 7.5 units, gave lower values.

In patients with functioning gallbladders containing stones, or non-functioning gallbladders and in cholecystectomized patients, lowering the cholecystokinin dosage resulted in no significant change in the 20-minute volume flow of bile. The output of bilirubin units in the duodenal aspirates, however, was lowered significantly by decreasing doses of cholecystokinin in the range from 18.5 to 7.5 units.

The median output of bilirubin was approximately 3000 units less than the normal median at any dosage of cholecystokinin tested in the postcholecystectomized patients.

The dosage of cholecystokinin which served to differentiate the bile flow response to cholecystokinin in the several diagnostic categories was greater than 12.5 but less than 25 Ivy dog units.

REFERENCES
Priest, Gluckmann, Berk and Rinaldo


