Gall-bladder sensitivity to cholecystokinin in patients with gall stones

T C NORTHFIELD, R M KUPFER, D P MAUDGAL, P L ZENTLER-MUNRO, S T MELLER, N W GARVIE, R McCREADY

Summary and conclusions

Gall-bladder sensitivity to cholecystokinin (CCK) was determined by dynamic cholecintigraphy in 18 patients with radiolucent gall stones and 18 matched controls during an infusion of CCK in which the rate of infusion was increased. In 10 of the matched pairs the patient was more sensitive than the control, in one the control was more sensitive, and in seven no difference was detected (p=0.012).

It is concluded that patients with cholesterol gall stones have increased gall-bladder sensitivity to CCK, and that this may be important in the pathogenesis of this disease.

Introduction

Altered gall-bladder function may be important in the pathogenesis of cholesterol gall stones. Postprandial gall-bladder emptying is increased in patients with choledocholithiasis compared with matched controls.1 Gall-bladder emptying is initiated by cholecystokinin (CCK), which is released from the duodenal mucosa in response to food. The increased gall-bladder emptying found in patients with gall stones is probably due either to an increase in serum CCK concentrations or to an increase in gall-bladder sensitivity to normal CCK concentrations. We have reported preliminary data obtained by means of a bioassay for CCK, which showed no significant difference in postprandial serum CCK concentrations between patients with gall stones and control subjects.2

The aim of the current study was to compare gall-bladder sensitivity to CCK in patients with gall stones and controls. We used a scintigraphic method to identify the onset of gall-bladder contraction during an infusion of CCK in which the rate of infusion was increased.

Patients and methods

We studied 18 patients, all of whom had radiolucent gall stones in a gall bladder that opacified on oral cholecintigraphy. Eighteen control subjects with dyspeptic symptoms and an unequivocally normal cholecystogram were matched with individual patients for height (within 10 cm), weight (within 10 kg), age (within 10 years), sex, and race. Thirteen of the pairs were women and five men. The mean age of the patients was 53 years and of the controls 54 years; the corresponding mean weights were 73 kg and 67 kg, and the corresponding mean heights 165 and 163 cm. We also studied four additional patients with gall stones, for whom no matched controls were available. All subjects gave written informed consent to the study. Gall-bladder sensitivity to CCK was determined by dynamic cholecintigraphy using 99m technetium-labelled N-(2,6-diethyl-phenylcarbamoylmethyl) iminodiacetate (99m Tc-HIDA). After an overnight fast 10 μCi 99m Tc-HIDA/kg was injected intravenously and the gall-bladder uptake of the radionuclide recorded by using a gamma camera linked to a small computer. Ninety minutes later, when gall-bladder activity had reached a steady state, an intravenous infusion of CCK (Karlofinska) diluted in isotonic saline was started at an initial rate of 0.005 mU (Ivy dog)/kg/min, followed by infusions of 0.01, 0.03, and 0.06 mU/kg/min. Because the half life of CCK is 2.5 minutes each CCK infusion was given for 12 minutes and followed by a six-minute saline infusion before the rate was increased.

Data were stored on magnetic disc for subsequent analysis. A region of interest corresponding to the gall bladder was identified and activity-time curves generated to identify the onset and rate of gall-bladder emptying. Gall-bladder sensitivity to CCK was defined as the threshold infusion rate causing a point of discontinuity on the activity-time curve that resulted in a 10% fall in activity before the infusion at the next rate was started (figure). The rate of gall-bladder

Trazing of gall-bladder radioactivity in one subject, showing gall-bladder contraction in response to a threshold infusion rate of 0.01 mU (Ivy dog) of CCK/kg/min but no response to 0.005 mU/kg/min.
emptying was expressed as percentage fall in gall-bladder activity/min before the next infusion rate. The threshold infusion rate was compared between patients and controls by using McNemar’s test and the sign test, and emptying rates were compared by the Wilcoxon rank sum test.

Cumulative gall-bladder emptying in response to a standard meal was measured radiographically as described and compared in subjects sensitive and insensitive to CCK by using the χ² test.

Results

In only two subjects (controls) was an infusion rate higher than 0-01 μU/IV (dog)/kg/min required to initiate gall-bladder contraction. All other subjects showed gall-bladder contraction at 0-005 or 0-01 μU/kg/min. Fifteen patients were sensitive to CCK (threshold infusion rate <0-005 μU/kg/min) compared with eight controls. Three patients were relatively insensitive to CCK (threshold infusion rate >0-01 μU/kg/min) compared with 10 controls (p<0.05 by McNemar’s test). Nine of the 18 matched pairs were also given an infusion of 0-0015 μU/kg/min: five patients but only one control responded to this rate. Thus when the full range of infusion rates available in each of the 18 matched pairs was considered the patient was more sensitive than the control in 10 of the pairs, the control was more sensitive in one pair, and no difference was detected in seven pairs (p=0.012 by sign test).

Gall-bladder sensitivity to CCK as determined by scintigraphy was related to cumulative emptying in response to food, measured radiographically, in the same 18 matched pairs of subjects plus the four additional patients with gall stones. Of the 25 subjects with a high sensitivity to CCK (threshold infusion rate <0-005 μU/kg/min), 15 had a cumulative gall-bladder emptying of over 50% after a standard meal. Of the 15 subjects who were relatively insensitive to CCK (threshold infusion rate >0-01 μU/kg/min), seven had gall-bladder emptying of over 50%. This trend towards increased gall-bladder emptying in those sensitive to CCK was not significant.

The rate of emptying at the threshold infusion rate (percentage gall-bladder emptying (gall-stones)) determined scintigraphically was 1-7±0.2%/min in 27 sensitive subjects and 2-1±0-2%/min in eight insensitive subjects (NS). We did not compare patients with controls because the design of the study did not permit matching of these two groups with respect to sensitivity.

Four subjects were studied on two occasions and given an infusion at the threshold infusion rate determined on the first occasion. In each case this again caused gall-bladder contraction, which was now followed to completion; the rate of infusion was not increased. Mean gall-bladder emptying was 55%.

Discussion

Patients with cholesterol gall stones showed a clear cut increase in gall-bladder sensitivity to CCK when compared with the matched controls. This increase is probably one of the factors contributing to the increase in postprandial gall-bladder emptying reported in patients with gall stones. The importance of the threshold dose in determining gall-bladder emptying is supported by the finding that when it was given as a single dose to four subjects mean gall-bladder emptying was 55%. Moreover, increased sensitivity to CCK, determined scintigraphically, tended to be associated with increased gall-bladder emptying in response to food, determined radiographically.

The increase in gall-bladder emptying, in turn, probably contributes to the reduced bile-acid (BA) pool size found in patients with cholesterol gall stones. A sudden increase in gall-bladder emptying would be expected to increase BA return to the liver, thus temporarily inhibiting synthesis by a negative feedback mechanism, until a new steady state is reached with a small BA pool circulating more often and a normal rate of synthesis of BA. The rate of BA synthesis is normal in patients with gall stones with a reduced BA pool size, and BA pool size is inversely related to recycling frequency.4 An increase in recycling frequency, produced experimentally by speeding small-intestinal transit in normal subjects, leads to a reduced BA pool size.5 Our findings suggest that increased gall-bladder sensitivity to CCK may increase gall-bladder emptying in response to food; and that these two abnormalities may account for the increased recycling frequency and thus the reduced BA pool size in patients with cholesterol gall stones.

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Requests for reprints should be addressed to Dr T C Northfield, Department of Medicine, St George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE.

References


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