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Postprandial gall-bladder emptying in patients with gall stones

D P MAUDGAL, R M KUPFER, P L ZENTLER-MUNRO, T C NORTHFIELD

Summary and conclusions

Gall-bladder emptying in response to a standard meal was assessed in 34 patients with radiolucent gall stones and 34 matched controls. Percentage gall-bladder emptying, derived from volume measurements made on standardised oral cholecystography, was significantly higher at 15 minutes in the patients than the controls (mean $\pm$ SE of mean $38.0 \pm 3.7\%$ v $28.0 \pm 3.8\%$). This difference was maintained at 30 and 60 minutes.

It is concluded that postprandial gall-bladder emptying is increased in patients with cholesterol gall stones, and that this may be the cause of the small bile-acid pool found in these patients.

Introduction

Patients with cholesterol gall stones have fasting gall-bladder bile that is supersaturated with cholesterol¹ and a reduced bile-acid (BA) pool size.² The cause of this small BA pool is unknown. An inverse relation exists between the size and recycling frequency of the BA pool.³ Thus an increased recycling frequency might cause a small pool by feedback inhibition of the synthesis of BA. Since the gall bladder is the storage organ for the BA pool, its emptying after a meal may determine the recycling frequency and hence the size of the pool.

We therefore tested the hypothesis that postprandial gall-bladder emptying is increased in patients with gall stones by

comparing the response to a standard meal in 34 such patients and 34 controls. To limit the study as far as possible to patients with cholesterol gall stones we included only those with radiolucent stones, since 80% of such stones contain over 70% cholesterol.⁴ We were careful to match the patients and controls in pairs for age, sex, obesity, and race because the prevalence of cholesterol gall stones is related to these factors⁵ and gall-bladder emptying is affected by age and sex.⁷

Patients and methods

We studied 34 patients with radiolucent gall stones in a gall bladder that opacified on oral cholecystography. Patients with calcified gall stones and those whose gall stones occupied over half of the gall-bladder volume were excluded. We also studied 34 control subjects with dyspeptic symptoms and an unequivocally normal cholecystogram. They were matched in pairs with the patients with gall stones for age (within 10 years), height (10 cm), body weight (10 kg), race, and sex. Ten of the pairs were men and 24 women. The mean age of the patients was 52 years and of the controls 53 years; the corresponding mean weights were 72 kg and 68 kg, and the corresponding mean heights 167 cm and 164 cm. Six patients and six controls were over 120% of their ideal body weight. Written informed consent was obtained from all subjects before they entered the study.

We assessed gall-bladder emptying by means of carefully standardised oral cholecystography. The subject was supine, and angulation over the x-ray film was adjusted by means of a wooden wedge to give an angle of 45° . The x-ray tube was adjusted to a distance of 100 cm from the plate. In premenopausal women cholecystography was carried out within 10 days after the onset of the menstrual cycle, thus eliminating differences in emptying during different phases of the menstrual cycle.⁸ X-ray films were taken in the fasting state and 15, 30, and 60 minutes after a standard liquid test meal (Lundh), a pilot study having shown that maximum emptying always occurred within the first hour after the meal. The gall bladder was outlined on tracing paper. Area was measured by means of a grid system, and volume was calculated by the method described and validated by Silva.⁹ Both measurements were made by someone unaware of the diagnosis. Statistical analysis was carried out by using the Wilcoxon signed-rank test for paired samples.

Norman Tanner Gastroenterology Unit, St James's Hospital, and Department of Medicine, St George's Hospital Medical School, London SW17 0RE

D P MAUDGAL, MRCP, senior medical registrar

R M KUPFER, MA, MRCP, research registrar

P L ZENTLER-MUNRO, MA, MRCP, research senior registrar

T C NORTHFIELD, MD, FRCP, consultant physician and senior lecturer

Results

Fasting gall-bladder volume (mean $\pm$ SE of mean) was 78.9 ± 6.2 cm³ in the patients with gall stones and 82.3 ± 6.0 cm³ in the controls (difference not significant; NS). Maximum emptying sometimes occurred before 60 minutes, and was followed by refilling. Cumulative emptying was calculated to take this into account. Figure 1 shows the cumulative emptying expressed as a percentage of the fasting volume. At 15 minutes the decrease in gall-bladder volume

FIG 1—Cumulative gall-bladder emptying (mean $\pm$ SE of mean) in patients with gall stones and controls at 15, 30, and 60 minutes after a standard meal.

FIG 2—Cumulative gall-bladder emptying (mean $\pm$ SE of mean) at 60 minutes in patients with gall stones and controls, showing individual data points.

was $38.0 \pm 3.7\%$ in the patients and $28.0 \pm 3.8\%$ in the controls ($p < 0.05$); at 30 minutes it was $52.5 \pm 2.8\%$ in the patients compared with $44.2 \pm 3.0\%$ in the controls (NS); and at 60 minutes $59.3 \pm 3.2\%$ in the patients compared with $48.5 \pm 2.7\%$ in the controls ($p < 0.01$). Figure 2 shows the individual data points for cumulative emptying at 60 minutes. When assessed by the alternative method based on area 60-minute cumulative emptying was $45.7 \pm 2.8\%$ in the patients and $32.7 \pm 2.4\%$ in the controls ($p < 0.01$). In the patients the results at 60 minutes increased by 5.0% when the area occupied by the gall stones was subtracted from the area measurement and by 2.5% when the volume occupied by the stones was subtracted from the volume measurement.

In seven normal subjects gall-bladder emptying was measured on two separate occasions six weeks apart. The mean difference between the two measurements was 4.0% when based on area and 8.0% when based on volume. There was a good correlation between the measurements of gall-bladder emptying based on area and those based on volume in 67 patients and controls ($r = 0.93$; $p < 0.001$). Measurement of gall-bladder emptying was repeated in four patients after their gall stones had been completely dissolved and chenice acid treatment stopped. Mean gall-bladder emptying by volume in these four subjects was $50.7 \pm 6.0\%$ before dissolution and $58.0 \pm 2.7\%$ after complete dissolution.

Discussion

The results of this study confirm our hypothesis that gall-bladder emptying in response to food is greater in patients with cholesterol gall stones than in matched controls. This difference was fully established at 15 minutes and was maintained at 30 and 60 minutes. It was found with both methods of measurement. The results of repeat studies after complete dissolution make it unlikely that this difference is a secondary effect due to the presence of gall stones.

Our findings contrast with the report of van der Linden¹⁰ that patients with decreased gall-bladder emptying are more prone to develop gall stones in later life. Most of his subjects who subsequently developed gall stones were women, whereas most who did not, and thus acted as controls, were men. There was no matching for other factors such as weight and age. The women were not studied at a fixed point in the menstrual cycle; gall-bladder emptying is decreased in the second half of the cycle.⁸ We studied all our premenopausal subjects, both patients and controls, during the first 10 days of the menstrual cycle.

Increased gall-bladder emptying probably contributes to the decreased BA pool size reported in patients with gall stones. Gall-bladder emptying in our patients exceeded that in controls by a third at 15 minutes and by a fifth at 60 minutes, but values overlapped considerably at both times. This overlap would have been only slightly reduced if we had subtracted the volume occupied by the gall stones from our emptying measurements. By contrast, Vlahcevic *et al* reported little overlap in BA pool size.² Their subjects were all male, and subsequent studies have shown greater overlap in pool size between female patients and controls.¹¹ Our study included six patients and six controls more than 120% above ideal body weight. Obesity is associated with increased biliary cholesterol secretion,¹² which is probably more important than changes in BA pool size in causing super-saturated bile in these patients.

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

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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 cholescintigraphy 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 cholesterol gall stones 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 cholecystography. 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 cholescintigraphy using ^{99m}Tc-labelled *N*-(2,6-diethyl-phenylcarbamoylmethyl) iminodiacetate (^{99m}Tc-HIDA). After an overnight fast 10 μ Ci ^{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 (Karolinska) 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

Tracing 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.

Norman Tanner Gastroenterology Unit, St James's Hospital, and Department of Medicine, St George's Hospital Medical School, London SW17 0RE

T C NORTHFIELD, MD, FRCP, consultant physician and senior lecturer
R M KUPFER, MA, MRCP, research registrar
D P MAUDGAL, MRCP, senior medical registrar
P L ZENTLER-MUNRO, MA, MRCP, research senior registrar

Department of Nuclear Medicine, Royal Marsden Hospital, Sutton
S T MELLER, MRCP, senior registrar
N W GARVIE, MRCP, senior registrar
R MCCREADY, MSC, FRCP, consultant