SPECIAL REPORT

Gall stone recurrence and its prevention: the British/Belgian gall stone study group's post-dissolution trial

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Abstract

The British/Belgian Gall Stone Study Group (BBGSG) post-dissolution trial was a prospective, multicentre, randomised, double blind trial of: (i) low dose ursodeoxycholic acid, (ii) placebo, and (iii) a high fibre, low refined carbohydrate diet in the prevention of gall stone recurrence in patients with complete gall stone dissolution. Further aims included establishing the timing and frequency of recurrence and its association with biliary symptoms, a comparison of the sensitivity of ultrasonography *v* oral cholecystectomy in detecting recurrent stones, and a search for risk factors predicting recurrence. Ninety three patients entered the study, and 82 were followed up for up to five years (mean (SEM) 28 (1.5) months) with six monthly ultrasonography and yearly oral cholecystectomy. There were 21 recurrences (26 by oral cholecystectomy or ultrasonography, or both), only two of which were symptomatic, which were detected between 12 and 42 months after trial entry. This corresponded to an actuarial recurrence rate of 33.9 (7.0%) by lifetable analysis at 42 months and subsequently. There were four recurrences in the ursodeoxycholic acid, six in the placebo, and 11 in the diet groups, corresponding to 21.9 (9.9)%, 27.4 (10.1)%, and 45.8 (12.4)% respectively at 42 months by lifetable analysis (NS). Variables including age, obesity, menopausal state, pregnancy, and oestrogen containing drugs were not shown to affect recurrence rate. Men had more frequent recurrence than women (NS). Patients who had had multiple stones experienced more recurrences than did those with single stones (NS). Recurrence did not occur in patients who took non-steroidal anti-inflammatory drugs (NSAIDs) ($p < 0.02$). The stone free interval between stone dissolution and trial entry proved to be important - those stone free $>$ nine months had a recurrence rate of only 12.7 (6.0)% at 42 months compared with 55.4 (12.5)% in those stone free $<$ nine months ($p < 0.01$). There was imbalance between the ursodeoxycholic acid and placebo groups for this factor, and after applying a statistical correction, the adjusted recurrence rate in the ursodeoxycholic acid group was 15% compared with 30% in both placebo and diet groups (NS). These data suggest that after medical dissolution, the risk

of gall stone recurrence is not reduced by a high fibre, low refined carbohydrate diet: it may be lowered, but not abolished, by low dose ursodeoxycholic acid.

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When gall stones have been dissolved and oral bile acid treatment is withdrawn, bile reverts to being supersaturated with cholesterol over one to four weeks¹⁻³ and in some patients, gall stones recur. Initial reports suggested that stones recurred in 30-50% of patients within two to five

TABLE 1 Patient characteristics at trial entry

	No
Total no of patients entering trial	93
Sex	Women 73
	Men 20
Racial group	White 91
	Non-white 2
Ideal body weight	$< 130\%$ 68
	$> 130\%$ 25
Body mass index (wt/ht ²)	< 25 (women)/26 (men) 61
	> 25 (women)/26 (men) 32
Previous gallstone characteristics	Single stone 16
	Multiple stones 77
Previous bile acid treatment	CDCA 62
	UDCA 27
	CDCA + UDCA 4
Post-dissolution maintenance treatment	Yes 16
	No 77
History of previous recurrence	Yes 6
	No 87
Withdrawal/default	Before 6 months 11
	Patients followed up > 6 months 82
Hormonal factors	Women, followed up > 6 months 65
	Premenopausal 20
	Postmenopausal 45
	No replying to questionnaire 55
	Previous pregnancy 45
	Nulliparous 10
	Oestrogen containing drugs 12

Details of patient recruitment into the trial (year of admission and treatment centre)

No of patients	42	12	8	22	5	4
Year	1981	1982	1983	1984	1985	1986

Centres contributing patients to study

Centre	No of patients
Bristol	24
Guy's, London	16
St George's, London	16
Dundee	13
Burnley	10
Brussels	6
Newcastle	3
Birmingham	3
Walsall	2

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years.⁴⁻⁶ These reports, however, were based mainly on small groups of patients studied for short periods of time. Furthermore, there were no prospective trials examining the effects of post-dissolution treatment in preventing recurrence. Therefore, eight British and two Belgian centres pooled their resources to establish the British/Belgian Gall Stone Study Group's (BBGSG) post-dissolution trial.

The principal aim of this prospective, random allocation, double blind, controlled trial was to compare the efficacy of three regimens in patients with confirmed complete gall stone dissolution (CGSD): (i) a high fibre (>30 g per day), low refined carbohydrate (<15 g per day) diet, (ii) low dose (3 mg kg⁻¹ day⁻¹) ursodeoxycholic acid, and (iii) placebo (given double blind with the ursodeoxycholic acid) – in preventing gall stone recurrence over a two, extending to a five, year period. Additional aims included gaining further information about the timing and frequency of recurrence and learning how often this was associated with symptoms. Evidence was sought for factors that might predict gall stone recurrence. The trial also compared the efficacy of oral cholecystography and ultrasonography in the diagnosis/detection of recurrent stones. (These results have been published elsewhere).⁷ In a small number of consenting patients, the study also examined the effect of the three post-dissolution treatment regimens on bile acid and bile lipid secretion, measured by a duodenal marker perfusion technique,^{8,9} before and during post-dissolution treatment.

Patients

DEMOGRAPHIC FACTORS: RISK FACTORS AND PREDICTIVE VARIABLES (TABLE 1)

Ninety three patients fulfilled the entry criteria (see below) and were admitted to the trial. There were 73 women and 20 men, aged between 20 and 85 (median 56) years. With the exception of two women (one Afro-Caribbean and one Pakistani), the remaining 91 were white.

Body weight/obesity – Table I gives the results for initial body weight, expressed both as a percentage of ideal body weight (%IBW) and as the body mass index (BMI:wt/h²). Based on an arbitrary definition of obesity as >130%IBW, 25 patients were obese and 68 non-obese. Similarly if obesity is defined, again arbitrarily, as a BMI of >25 in women and >26 in men, there were 32 obese (a number which includes all 25 with %IBW values >130) and 61 non-obese. Large changes in body weight (increases or decreases equal to or >10% of starting weight) were also considered as a possible risk factor. Such changes were seen in 12 patients (six of whom gained and six of whom lost equal to or >10% of their pre-trial weight).

Previous bile acid treatment and gall stone characteristics – Most (n=62) of the patients had previously taken chenodeoxycholic acid for dissolution of their original or 'primary' gall stones but 27 had taken ursodeoxycholic acid and four had taken a combination of chenodeoxycholic acid and ursodeoxycholic acid. After complete gall stone dissolution, most (n=77) of

the patients had taken no post-dissolution treatment but 16 had been given maintenance treatment with half the full dissolution doses of either chenodeoxycholic acid or ursodeoxycholic acid. Six patients who had had gall stone recurrence in the past, followed by successful re-dissolution, were included in the trial. Before primary gall stone dissolution, 16 patients had had solitary stones: the remaining 77 had had multiple stones.

Stone free interval – The median stone free interval between gall stone dissolution and trial entry was nine (range 1 to 80) months. The stone free interval was greater, however, in patients whose primary gall stones had been dissolved with chenodeoxycholic acid (median 14: range 1–80 months) than in those who had been treated with ursodeoxycholic acid (median 4: 1–24).

Menopausal state, pregnancy, and oestrogen containing drugs – Because of the possible influence of menopausal state, pregnancy and oestrogen containing drugs,¹⁰⁻¹² details about these factors were sought by questionnaire in the 65 women who were followed up for more than six months. Of these, 20 were pre-menopausal and 45 post-menopausal. Forty five of the 55 women (82%) who replied to the questionnaire had had one or more pregnancies before dissolution treatment began. Ten women (18%) were nulliparous. Four became pregnant after their primary gall stones had dissolved but before trial entry. Only 12 patients had taken oestrogen containing preparations. Ten had taken an oral contraceptive (oestrogen content unspecified) for periods ranging from four months to 13 years. Although nine patients had taken oral contraceptives before gall stone dissolution, only one did so afterwards. Two further patients had taken oestrogen containing hormone replacement treatment (again dose not known) for menopausal symptoms, before and during the trial.

Non-steroidal anti-inflammatory drug ingestion – The influence of non-steroidal anti-inflammatory drugs (NSAIDs) was also examined retrospectively: these results have been published in full elsewhere.¹³

ADMISSION CRITERIA

Patients with complete gall stone dissolution, confirmed by two oral cholecystectographies three months apart during continued oral bile acid treatment, were eligible for inclusion into the study. To ensure that those who had not had recent oral cholecystography or ultrasonography studies were still gall stone free, these investigations were repeated not more than six weeks before trial entry. Although a normal ultrasonography was not one of the original admission criteria, it became one in 1982–83. In fact, all but four patients had a pre-trial ultrasonogram that invariably showed no gall bladder stones.

Women at risk of becoming pregnant were accepted only if they undertook to use effective contraceptive measures. Despite this undertaking, two patients became pregnant during the trial. As both were in the diet group, they continued in the study and subsequently had normal babies.

RANDOMISATION/STRATIFICATION

Patients who fulfilled the inclusion criteria were randomised, from a central office, to one of the three groups (see above) with stratification and secondary 'biased randomisation' for obesity and the stone free interval, as follows:

Obesity – Obesity is a risk factor for primary gall stone formation^{14–16} and, therefore, possibly also for the development of recurrent stones. Furthermore, the results of most studies suggest that obese individuals respond less well to oral bile acid treatment than the non-obese.^{17–19} For these reasons, the patients were stratified (as described above) into obese (arbitrarily >130%IBW) and non-obese (<130%IBW) subgroups, using Metropolitan Life Insurance tables. This ensured that after randomisation, there were about equal numbers of obese patients in the three treatment groups (diet, n=5; ursodeoxycholic acid, n=8; placebo, n=9).

Stone free interval – Earlier reports suggested that if gall stones were going to recur, most would do so within two years of stopping bile acid treatment or not at all.^{4–6} Therefore, we reasoned that patients who had been stone free for two years or more might represent a 'protected' subgroup at low risk for recurrence. For this reason, the patients were also stratified according to stone free intervals of >, or <, two years and biased randomisation performed as described above.

FOLLOW UP PROTOCOL

The patients were seen every three months at their local hospital jointly by their own physician and the trial coordinator. At each visit, symptoms and side effects were noted and blood was taken for haematological and biochemical screening tests. Ultrasonography was performed six monthly and oral cholecystectomy yearly. If biliary pain developed, however, before these investigations were due, they were performed early.

Study design

CRITERIA FOR DIAGNOSING GALL STONE RECURRENCE

The trial was planned in 1979/1980, began in 1981, and ran until 1987. When it was designed, oral cholecystography was the method of choice for the diagnosis of gall stones. At that time, ultrasonography was less developed than it is today and was not available in all 10 treatment centres. (Over the intervening years, technical advances and improved operator expertise have now made ultrasonography the imaging technique of choice for gall stone detection).^{20–21} Therefore, the main trial criterion for diagnosing gall stone recurrence was oral cholecystography unless the patient was, or became, sensitive to the oral contrast media (n=7) or refused cholecystography (n=4) in which case the diagnosis was based on two successive ultrasonography scans, not more than four weeks apart. With the exception of these 11 patients, when

ultrasonography suggested gall stone recurrence it was always accompanied by an oral cholecystogram. In the event of a discrepancy between the two techniques, decisions about the presence or absence of recurrent stones were based on oral cholecystography rather than on ultrasonography. In the results section, however, the outcome is shown based on both imaging techniques.

RATIONALE FOR THE CHOICE OF POST-DISSOLUTION TREATMENT

In 1980, studies of gall stone pathogenesis (primary and recurrent) were directed mainly at biliary cholesterol supersaturation²² and this was the reason for the choice of the two post-dissolution treatments.

Choice of bile acid – Ursodeoxycholic acid was chosen in preference to chenodeoxycholic acid because it is virtually free from side effects.

Choice of ursodeoxycholic acid dose – As full dose (10 mg kg⁻¹ day⁻¹) ursodeoxycholic acid dissolves cholesterol gall stones, we reasoned that continued full dose treatment should prevent gall stone recurrence indefinitely – unless the patient developed 'acquired tolerance' to the oral bile acid treatment.^{23–24} Longterm full dose ursodeoxycholic acid treatment, however, is expensive and we reasoned that by giving one third of the full therapeutic dose, the cost of maintenance treatment would be acceptable. Further, low dose ursodeoxycholic acid frequently desaturates bile in gall stone patients.²⁵ Moreover, it has been suggested that only a short period of desaturation – perhaps as little as 30 minutes during a 24 hour period – may be all that is necessary to prevent cholesterol crystal nucleation from bile.²⁶

Timing of ursodeoxycholic acid dose – The low dose ursodeoxycholic acid was given as a single bedtime dose because of the reported superiority of this timing of administration for reducing biliary cholesterol supersaturation.²⁷ It is also likely to improve patient compliance in taking the daily quota of bile acid.

The choice of diet – Two dietary factors – supplementing the diet with wheat bran^{28–29} and reducing the intake of refined carbohydrates³⁰ – reduce cholesterol saturation of bile in subjects with supersaturated bile. It is not known if the combination of these dietary factors has an additive effect. None the less, by combining the two measures we hoped to maximise our chances of identifying a dietary method of preventing gall stone recurrence. This would be the least expensive and most acceptable form of longterm prophylaxis against gall stone recurrence.

TREATMENT AND COMPLIANCE

Tablets

Ursodeoxycholic acid (Roussel Uclaf, Paris) was dispensed as 100 mg plain, white, scored tablets: the placebo tablets were identical in appearance. Compliance in taking the prescribed tablets was assessed by history, and by counting residual tablets when the prescriptions were renewed.

TABLE II Batch analysis of Prewett's bran

	Lab 1	Lab 2
Water holding capacity	4.74 g/g	4.99 (0.26) g/g
Moisture content	10.4%	13.1%
Lignin	3.6 g%	Ash content 3.8%
Fibre	49.7 g%	Non-starch polysaccharides (NSP) 8.38%
Magnesium	0.46 g%	Cellulose 34.78%
Zinc	92 mg/kg	Non-cellulose 43.16%
Iron	228 mg/kg	Total NSP
Phosphorus	1.09 g%	Particle size
Sodium	225 mg/kg	>1400 µm 47.0%
Potassium	1.42 g%	1000–1400 28.2%
Calcium	120 mg%	500–1000 19.4%
Salt	80 mg%	<500 5.2%

Diet

In all three groups, dietary assessments were made before starting treatment and again at each follow up visit. These assessments were performed by a senior dietitian in each centre whose work was supervised by a central coordinating dietitian. The patients were asked to keep a record of all foods they had eaten during a typical midweek day and during a typical weekend day, once every three month period. In addition, the dietitians completed a standardised questionnaire for each patient at every follow up visit. This recorded the pattern of the meals, and the amount and frequency of certain food types, consumed. From this, scores for sugar (1 point = 5 g sugar) and fibre (1 point = 1 g fibre) intake were derived.

Patients randomised to the tablet groups were advised to continue their pre-trial diets – unless they had already been taking a high fibre diet – in which case they were encouraged to reduce their fibre intake during the trial. Those in the diet group were asked both to reduce their intake of refined carbohydrates and to increase their dietary fibre by substituting high for low fibre products and by taking supplements of standardised wheat bran (three or four $\times 7.5$ g sachets of Prewett's coarse wheat bran). In addition, the patients in the diet group were given dietary advice, printed information sheets, and suggested recipes for high fibre, low refined carbohydrate meals.

Table II shows the results of analysing the standardised wheat bran in two separate laboratories. To avoid variation in bran composition over the period of the study, a large supply, adequate for the whole study, was stored centrally and distributed to the patients as necessary.

ETHICAL CONSIDERATIONS

In each of the participating hospitals, Ethical Committee permission was obtained for the study and all patients gave their informed consent.

STATISTICAL METHODS

Recurrence rates were calculated by lifetable analysis (LTA) and compared by the log rank test.³¹ Cochran, Mantel Haenzel statistics were used to test the association between variables (SAS package on an IBM computer). The direct standardisation method³² was used to correct for inadvertent imbalance of risk factors between the three treatment groups (see below).

Results

DEFAULT/WITHDRAWALS

Eleven patients, three men and eight women, aged 31–70 (median 62) years, withdrew from the study before their first, on trial ultrasonography examination at six months. Of these, one 66 year old man died from a myocardial infarction and three further patients stopped because of ill health or frailty, or both, unrelated to gall stone disease or trial treatment. Two patients withdrew because they claimed intolerance to the trial tablets. One complained of diarrhoea and the other of abdominal discomfort and bloating. Subsequently, when the code was broken, both were found to have been taking ursodeoxycholic acid. Two further patients could not tolerate the high fibre diet and the remaining three defaulted for no apparent reason.

This subgroup of 11 defaulters was comparable with the remaining group of 82 patients in terms of age, sex, body weight, and distribution among the three treatment groups. The 82 patients who contributed to analysis were distributed among the three treatment groups as follows: ursodeoxycholic acid, $n=23$; placebo, $n=28$; and diet, $n=31$.

SIDE EFFECTS

In the 82 patients followed up for more than six months, all three post-dissolution regimens were well tolerated. None of the 82 reported diarrhoea or other side effects. With few exceptions (see below), all the haematological and biochemical values were normal at the start of the study and remained so throughout. At trial entry, however, there were mild abnormalities of fasting serum lipids in 12 patients. Thus in four the serum cholesterol ranged from 8.9 to 9.7 mmol/l (normal <8.5); in five the serum triglyceride concentrations were raised at 2.4–3.6 mmol/l (normal <2.2) while in three there was mixed hyperlipidaemia. In these and the remaining 70 patients, the serum lipids remained unchanged throughout the study. There was no hypertransaminasaemia either before or during the trial. One patient, who had radiological evidence of Paget's disease of bone, had consistently raised serum alkaline phosphatase concentrations (600–905 U/l; $n<300$).

COMPLIANCE WITH DIET

Figure 1 shows the results for the fibre (A) and sugar (B) scores.

The mean pre-trial fibre scores (approximately 20 points) were almost identical in all three groups. (These scores may be somewhat higher than normal as, before joining the study, some patients had already been encouraged to take a high fibre intake.) During the trial, the mean fibre score in the diet group rose to 33.6 and over the three years for which reliable results are available, compliance in taking the high fibre diets seemed good with very little 'drift' in mean values that ranged from a minimum of mean (SEM) 31.0 (3.7 points) at 36 months to a maximum of 35.5 (2.2) at 12 months. In the two

Figure 1: Dietary intake of fibre (A) and sugar (B) at the point of entry into the trial (time zero) and over the subsequent 36 months (means (SEMs)). For derivation of the fibre and sugar 'scores', see text. UDCA= ursodeoxycholic acid.

tablet groups, the mean fibre scores both dropped slightly at six months – to 17.9 (2.2) in the ursodeoxycholic acid treated, and to 16.5 (1.3) in the placebo treated groups – probably because, for the purposes of the trial, the patients were encouraged to avoid high fibre foods. Thereafter, however, the fibre scores remained relatively constant.

At the point of entry into the study, the mean sugar scores were comparable in the ursodeoxycholic acid (8.4 (1.3) points) and diet (8.6 (1.1)) groups but, largely because three obese individuals in the placebo group consistently took large amounts of refined carbohydrates, the mean score in this group was 13.6 (1.9). During the trial, the sugar scores remained constant in both tablet groups but, as intended, the scores in the diet group fell by an average of 40–48%. In all three groups, however, the mean values remained constant throughout the study – again implying good compliance in controlling sugar, as well as fibre, intake.

COMPLIANCE WITH TABLETS

This was judged by patient history and counting residual tablets (the placebo and ursodeoxycholic acid were given double blind) when the prescriptions were renewed and compliance in taking the prescribed tablets was excellent. A small number of patients admitted to missing the capsules on single days but only one patient admitted to stopping treatment for several weeks. He had previously claimed 100% compliance in taking his tablets over three to four years. When the code was broken, it was found that he had been taking placebo rather than ursodeoxycholic acid. None the less, his results were censored from the trial analysis at the point of his last 'on treatment' oral cholecystectomy/ultrasonography.

RECURRENCE

The overall gall stone recurrence rates, independent of treatment, are considered in three ways based on different diagnostic techniques: (i) according to the trial criteria (mainly oral cholecystography – see above); (ii) ultrasonography alone; and (iii) either method.

Trial criteria – Twenty one patients developed gall stone recurrence. These were all detected between 12 and 42 months after trial entry corresponding, by LTA, to 0% at six months, 8.9 (3.2)% at 12 months, 14.3 (4.0)% at 18 months, 22.9 (4.9)% at 24 months, 29.2 (5.7)% at 36 months, and 33.9 (7.0)% at 42 and subsequent months (Fig 2).

Ultrasound alone – A total of 24 recurrences was recognised by ultrasonography corresponding to actuarial rates of 8.5 (3.1)% at six months, 14.9 (3.9)% at 12 months, 20.5 (4.6)% at 18 months, 23.4 (4.9)% at 24 months, 34.4 (6.2)% at 36 months, and 39.1 (7.2)% at 42 months, and thereafter (Fig 2).

Either method – If recurrence is defined as stone detection by either imaging technique, the total number was 26 which corresponds, by LTA, to 8.5 (3.1)% at six months, 17.4 (4.2)% at 12 months, 22.8 (4.7)% at 18 months, 25.7 (5.0)% at 24 months, 36.4 (6.2)% at 36 months, and 41.0 (7.2)% at 42 and subsequent months.

Comparative sensitivity of different imaging techniques in detecting gall stone recurrence – Ultrasound detected gall stone recurrence earlier and more frequently than did either the trial criteria or oral cholecystography alone (Fig 3). Thus, at six months, no recurrences were detected by oral cholecystography, but five were apparent by ultrasonography. All five were confirmed subsequently by oral cholecystography and repeat ultrasonography. By one year, 12 recur-

Trial criteria								
No at risk	82	79	68	60	39	32	15	10
Recurrences	0	7	4	6	2	1	1	0

Ultrasound								
No at risk	82	72	61	54	38	31	14	8
Recurrences	7	5	4	2	2	3	1	0

Figure 2: Actuarial or lifetable analysis (LTA) rates of gall stone recurrence, studied as a function of time over 48 months, when diagnosed by the original trial criteria (mainly oral cholecystography: see text) or by ultrasound (US). Results are means (SEMs): pooled data independent of trial treatments. The number (no) of patients 'at risk' and the number of recurrences are shown for each time period (below).

Figure 3: Lifetable analysis (LTA) showing the cumulative percentage of patients developing gall stone recurrence over four years as detected by ultrasound (US) or by oral cholecystectomy (OCG). Results are means (SEMs) while the number of patients at risk and the actual number of recurrences are shown for each time period (below).

recurrences had been diagnosed by ultrasonography but only seven had been detected by oral cholecystectomy. In five of these seven, the stones were also found by ultrasonography but in two, recurrences were identified by oral cholecystectomy, which had not been detected by echography. In 16 patients who had had both imaging techniques, gall stone recurrence was identified simultaneously in only five. In the remaining 11, the recurrence was detected 6 to 18 months earlier by ultrasonography, than by oral cholecystectomy.

Frequency of symptomatic gall stone recurrence – Of the 21 patients who developed gall stone recurrence by the original criteria, only two had complained of biliary colic during the study. In the remainder, the recurrent stones were silent or asymptomatic. The same finding applies to

the 26 patients whose gall stone recurrence was detected by either imaging technique.

Recurrence in the three treatment groups (Fig 4) – Of the 21 recurrences diagnosed according to the trial criteria, there were four in the ursodeoxycholic acid treated, six in the placebo, and 11 in the diet groups. In those taking ursodeoxycholic acid, this corresponds, by LTA, to 0% at 6 and 12 months, 4.8 (4.6)% at 18 months, 14.8 (7.9)% at 24 months, and 21.9 (9.9)% at 36 and subsequent months. (There were no recurrences after three years in the ursodeoxycholic acid treated patients.) In the placebo group, the recurrence rates were 15.4 (7.1)% at 12 and 18 months, 20.1 (8.1)% at 24 months, and 27.4 (10.1)% at 36 months and thereafter. In those taking the diet, they were 9.7 (5.3)% at 12 months, 19.4 (7.1)% at 18 months, 29.9 (8.4)% at 24 months, 34.9 (9.2)% at 36 months, and 45.8 (12.4)% at 42 and subsequent months. These rates were not significantly affected by subdivision of the diet group into those who achieved a high fibre score from mainly non-bran sources ($n=7$) and those who were compliant in taking bran supplements (31.4 (18.6)% *v* 49.4 (13.9)% respectively by LTA at 42 months: NS). Thus, despite a two-fold difference between mean values in the ursodeoxycholic acid treated and diet groups at 42 months, when the recurrence rates are considered independent of the stone free interval (see below), there were no significant differences between the results in the three groups. If recurrence is considered to have developed when diagnosed by either oral cholecystectomy or ultrasonography ($n=26$), then the rate at 42 and subsequent months by LTA is 25.7 (10.4)% in the ursodeoxycholic acid treated, 26.2 (9.8)% in the placebo and 60.2 (12.0)% in the diet, groups (diet *v* placebo; $p<0.05$).

RISK FACTORS AND PREDICTIVE VARIABLES (TABLE III)

Age

Gall stone recurrence was equally common in all age groups.

Sex

There was a non-significant trend towards a higher gall stone recurrence rate in men than in women: 46.4 (13.3)% *v* 29.4 (7.8)% respectively by LTA at 42 months.

Type of dissolution treatment

Patients who had initially been given chenodeoxycholic acid as dissolution treatment had a significantly lower recurrence rate than those who had been treated, originally, with ursodeoxycholic acid (17.8 (5.8)% at 42 months by LTA compared with 67.1 (16.4)%; $p<0.05$). This apparent difference, however, was compounded by the stone free interval between gall stone dissolution and trial entry, which was 6.78 (1.46) months (range 1–24) in the ursodeoxycholic acid treated *v* 21.0 (2.6) months (range 1–80) in the chenodeoxycholic acid treated patients ($p<0.001$).

Figure 4: Lifetable analysis (LTA) showing the percentage of patients developing gall stone recurrence as a function of time in the three treatment groups (see legend to Figs 2 and 3). Note that the symbols are different from those used in Figure 1.

Patients who joined the study between 1981 and 1985 tended to have been treated with ursodeoxycholic acid as it had become widely available at that time and was considered to be the oral bile acid treatment of choice for gall stone dissolution. Furthermore, they were recruited into the trial immediately after their gall stone dissolution had been confirmed – rather than months or years later. As patients who have been stone free for >nine months constitute a low risk group for recurrence (see below), the apparently lower recurrence rate in the chenodeoxycholic acid treated patients may be an artefact.

Only four patients were given a combination of ursodeoxycholic acid plus chenodeoxycholic acid: this group was too small for statistical scrutiny.

Previous history of gall stone recurrence

Of the six patients who had previously had gall stone recurrence, five (83%) developed a further recurrence during the trial compared with 16 recurrences in the 76 patients who had not previously had recurrent stones (21%). By the χ^2 test, this difference is statistically significant ($p < 0.05$). This comparison, however, does not take into account the duration of follow up, and the number of patients who had previously had recurrence is too small to permit valid conclusions

from a multivariate analysis. None the less, the results suggest that a history of previous recurrence does indeed predict a high risk for subsequent recurrence.

Previous stone number

Before their initial gall stone dissolution treatment, 15 of 82 patients followed up for more than six months had had solitary stones, compared with 67 who had had multiple stones. There were only two recurrences in the solitary stone group compared with 19 in the multiple stone group – equivalent to LTA recurrence rates of 14.8 (9.7)% and 41.7 (9.3)% at 42 months respectively. As the number of patients who originally had had solitary stones was small, the difference does not reach statistical significance and this was also true when the analysis was based on the 26 patients who had recurrence diagnosed by oral cholecystography or ultrasound, or both (14.5 (9.5)% for those who had had single stones and 46.4 (8.1)% for those with multiple stones: NS).

Patients who originally had multiple 'primary' gall stones always had multiple recurrent gall stones while those who initially had solitary stones invariably had solitary recurrent stones.

Obesity

The overall recurrence rate was similar in non-obese (<130%IBW) and obese (>130%IBW) patients: 33.5 (8.6)% v 35.3 (12.3)% by LTA at 42 months respectively.

With regard to the possibility that large changes in body weight (equal to or >10% of initial weight) might represent a risk factor, only one case of gall stone recurrence was detected in those who lost >10% of starting weight and none was seen in those who gained weight.

Effect of pregnancy and oestrogen based treatment

There was no significant difference in actuarial recurrence rates at 42 and subsequent months, for pre-menopausal (24.6 (10.9)% and post-menopausal (35.9 (13.1)% women (Table III). Moreover, there was no correlation between recurrence rates and the number of either past or recent pregnancies. Forty five patients had previously been pregnant and in this subgroup, there were 11 recurrences compared with only one in the 10 patients who were nulliparous – corresponding to LTA rates of 31.2 (9.0)% and 20.0 (17.9)% respectively at 42 months (NS). Of the 10 patients who had taken oral contraceptives, only one developed gall stone recurrence but neither of the two patients taking hormone replacement treatment developed recurrent stones.

Non-steroidal anti-inflammatory drugs (NSAIDs)

None of the patients who regularly took aspirin and other NSAIDs experienced gall stone recurrence, compared with 20 recurrences in the 63 patients who did not ($p < 0.02$; Fisher's exact test).²⁶ The only patient who had previously had gall stone recurrence, but who did not experi-

TABLE III Gall stone recurrence among subgroups

	No of recurrences	Cumulative recurrence rate by LTA at 42 months (mean (SEM))	Statistical analysis
Overall recurrence			
Detection by: Trial criteria	21	33.9 (7.0)%	
US alone	24	39.1 (7.2)%	
Either method	26	41.0 (7.2)%	
Symptomatic recurrence			
Yes	2		
No	19		
Recurrence in treatment subgroups			
Detection by: Trial criteria			
UDCA	4	21.9 (9.9)%	} NS
Placebo	6	27.4 (10.1)%	
Diet	11	45.8 (12.4)%	
Detection by: US or OCG			
UDCA	5	25.7 (10.4)%	} NS
Placebo	6	26.2 (9.8)%	
Diet	15	60.2 (12.0)%	
Sex			
Men	7	46.4 (13.3)%	} NS
Women	14	29.4 (7.8)%	
Age			
<50	4	28.8 (12.3)%	} NS
>50	17	38.4 (10.8)%	
<median age 56	10	36.0 (9.9)%	} NS
>median age 56	11	28.2 (7.5)%	
Type of dissolution treatment			
Chenodeoxycholic acid	9	17.8 (5.8)%	} p<0.05
Ursodeoxycholic acid	9	67.1 (16.4)%	
Ursodeoxycholic acid + chenodeoxycholic acid	3		
Previous gall stone recurrence			
Yes	5	83%	} p<0.05
No	16	21%	
Previous stone number			
Single	2	14.8 (9.7)%	} NS
Multiple	19	41.7 (9.3)%	
Obesity			
Non-obese (<130%IBW)	15	33.5 (8.6)%	} NS
Obese (>130%IBW)	6	35.3 (12.3)%	
Wt gain/loss >10% (n=12)	1		
Hormonal factors			
Premenopausal women	4	24.6 (10.9)%	} NS
Postmenopausal women	10	35.9 (13.1)%	
Previous pregnancy	11	31.2 (9.0)%	} NS
Nulliparous (n=10)	1	20.0 (17.9)%	
Oral contraceptive takers (n=10)	1		
Hormone replacement treatment (n=2)	0		

Figure 5: Influence of the before trial stone free interval on the cumulative recurrence rate (pooled results independent of trial treatment). Results are means (SEMs) for patients shown to be stone free for > or < the median of nine months.

ence a further recurrence, had taken NSAIDs regularly.

Stone free interval (Fig 5)

In those who, at the point of entry into the trial, had already been stone free for > the nine month median, there was a significantly lower recurrence rate (12.7 (6.0)% at 42 months by LTA) than in those who had been stone free for <nine months (55.4 (12.5)%; $p<0.01$).

Despite the study design and our attempts to stratify for the stone free interval (based on > or <2 years), there was an imbalance between the three treatment groups on either side of the median (nine months). Although the distribution of patients who were stone free for > or <nine months was about equal in the diet group (43% >nine months and 57% <nine months), it was appreciably different in the two tablet groups. At trial entry, 19 of 28 patients (68%) in the placebo group had already been stone free for equal to or >nine months – compared with only eight of 23 (35%) in the ursodeoxycholic acid group. As the stone free interval proved to be one of the most important predictive factors for gall stone recurrence, this imbalance introduced a potential bias towards a greater recurrence rate in the ursodeoxycholic acid group, than in the placebo group. After correcting for this imbalance by the direct standardisation method,³⁴ the recurrence rate in the ursodeoxycholic acid treated patients (15%) was only half that seen in the other two groups (30%) although this difference still failed to reach statistical significance.

Discussion

PATHOGENESIS OF RECURRENT GALL BLADDER STONES

Before primary gall stones form, there must be at least a triple^{33,34} defect: (i) the secretion of bile that is supersaturated with cholesterol, (ii) a nucleation defect due to an excess of promoters

or a deficiency of inhibitors of crystallisation, or both, and (iii) stasis within the gall bladder secondary to impaired gall bladder motor function.

The same triple defect probably contributes to the formation of recurrent gall bladder stones. Thus, recurrence of supersaturated bile is almost invariable after withdrawing oral bile acid treatment. The defect in gall bladder contractile function also persists after gall stone clearance by oral bile acids alone,^{35,36} or by extracorporeal shock wave lithotripsy plus adjuvant bile acids.³⁷ It is not known, however, if the nucleation defect also persists after the stones have been removed. Conventionally, cholesterol crystal nucleation times are measured in gall bladder bile obtained by needle aspiration at the time of surgery: they cannot be measured reliably in bile rich duodenal fluid.³⁸ As access to the gall bladder is rarely possible after gall stone clearance, it seemed that, until recently, they could not be studied in patients with complete gall stone dissolution. Swobodnik and colleagues,³⁹ however, showed that percutaneous ‘skinny’ needle puncture of the gall bladder can be performed safely for diagnostic aspiration of gall bladder bile. We have recently applied this technique⁴⁰ to studies of post-dissolution patients and have found that abnormally rapid nucleation of cholesterol microcrystals is present in some, but not all, patients.⁴¹

Importance of cholesterol crystal nucleation

Several indirect lines of evidence suggest that nucleation may be more important than biliary cholesterol supersaturation in the pathogenesis of recurrent gall bladder stones.

Firstly, as shown by the present results and those of Villanova *et al*,⁴² gall stones recur two to three times more frequently in patients who originally had multiple stones than in those who, before dissolution treatment, had solitary stones. This suggests that in patients who form multiple stones, there is a more severe nucleation defect than in those who form single stones. Indeed, Groen *et al*⁴³ showed recently that the nucleation time is shorter in patients with multiple gall bladder stones than in those with solitary stones.

Secondly, the results of three studies suggest that aspirin or other NSAIDs, or both may prevent both primary and recurrent gall stone formation – apparently by inhibiting gall bladder mucosal prostaglandin synthesis, mucus glycoprotein production,⁴⁴ and nucleation.⁴⁵ Thus in prairie dogs fed a lithogenic diet, aspirin inhibits mucus glycoprotein secretion by the gall bladder, cholesterol microcrystal formation, and the development of gall stones that would otherwise have occurred.⁴⁶ Similarly, in obese patients undergoing weight reduction, Broomfield and colleagues⁴⁷ found that in a dose of 1300 mg/day, aspirin inhibited (albeit to a non-significant extent) the development of microcrystals, microstones, and gall stones – which developed with high frequency in untreated patients. In the present trial, longterm (>six months) NSAID ingestion seemed to prevent gall stone recurrence.

Our emphasis on biliary cholesterol saturation

in the pathogenesis of recurrent stones, therefore, may have been incorrect. In retrospect, our attempts to prevent recurrence should, perhaps, have been directed at identifying and manipulating (by increasing the amounts of inhibitors or decreasing the amounts of promoters) nucleating factors that induce crystal, and thereby gall stone, formation from supersaturated bile.

STUDY DESIGN

The choice of ursodeoxycholic acid dose

In doses as low as 3 mg kg⁻¹ day⁻¹, oral ursodeoxycholic acid significantly lowers biliary cholesterol secretion and saturation.^{25 48 49} Initially, we postulated that any protective effect of ursodeoxycholic acid against gall stone recurrence would be mediated through changes in biliary cholesterol saturation. The results of recent studies suggest, however, that ursodeoxycholic acid, but not chenodeoxycholic acid, also inhibits the nucleation of cholesterol microcrystals from supersaturated bile.^{50 51} This may explain why low dose chenodeoxycholic acid does not prevent gall stone recurrence⁵² while the results of this and other^{42 53} studies suggest that low dose ursodeoxycholic acid may do so.

Duration of follow up

After the present study was designed, longterm studies using actuarial analysis were published,^{7 42 53–55} which showed that a longer follow up period than two years was required to establish reliable recurrence data. For this reason, and also to ensure that adequate numbers of patients had been recruited, the present trial was extended from two, to a maximum of five, years. In the event, we never saw gall stone recurrence beyond 3.5 years with the result that there was a plateau in the actuarial recurrence rate after this time. Similar observations have been made by others^{42 54 55} although in the different studies, the time of onset of the plateau has varied from three to seven years. In all such studies, however (including this trial), the number of patients at risk diminishes appreciably with time so that the confidence of the prediction that there really is a plateau, also diminishes with time.

The stone free interval

The present and other^{42 52 54 55} results suggest that there is a linear increase in cumulative recurrence rates with time (about 10–15% per annum) until the plateau is reached. If so, how can we reconcile this with the finding that patients stone free for >nine months before joining the study, represent a 'protected' subgroup at low risk for recurrence?

One possibility is that some patients thought to be stone free may, in reality, have had residual debris despite our use of the best available techniques (ultrasonography + oral cholecystectomy) to 'confirm' complete gall stone dissolution. (Neither imaging technique is sensitive in detecting individual gall bladder stones measuring <2 mm.^{56 57}) By contrast, those still

stone free nine months or more after dissolution treatment has stopped are genuinely likely to have had complete gall stone dissolution. The only way to prove this would be to subject the patients with apparent complete gall stone dissolution to surgery when the contents of the gall bladder could be examined directly. This is not possible for obvious ethical reasons.

EFFECT OF POST-DISSOLUTION TREATMENT ON GALL STONE RECURRENCE

As the results in Figure 5 show, before correcting for the imbalance in the distribution of low risk patients (stone free >nine months) between the three groups, there was no significant difference in the actuarial recurrence rates between the ursodeoxycholic acid and diet groups – despite a twofold difference in mean values. The absence of a significant difference in LTA recurrence rates, however, may represent a type II error due to inadequate numbers towards the end of the study, rather than to a lack of effect.

Effect of the high fibre, low refined carbohydrate diet

Despite reservations about comparatively small numbers of patients, we can say that by the trial criteria, the diet did not prevent or reduce gall stone recurrence – whether or not an adjustment is made for the stone free interval. Indeed, when the diagnosis of recurrence was based on either oral cholecystography or ultrasonography, the only significant difference between the three groups was a higher rate of recurrence in the diet treated patients than in the other two groups.

Why increases in dietary fibre^{28 29} or decreases in refined carbohydrate intake³⁰ should reduce cholesterol supersaturation of bile in control subjects, but should fail to prevent recurrence in our gall stone patients, is unknown. One possible explanation relates to the differing effects of different types of dietary fibre on bile lipid composition. In this study, the fibre score was based on the total fibre intake, and not just on fibre derived from the standardised wheat bran. All the evidence that high 'fibre' intake reduces biliary cholesterol saturation is based on studies using wheat bran. Legume seeds, however, which are high fibre foods may actually increase biliary cholesterol saturation and probably predispose to gall stone formation.⁵⁸

Effect of low dose bile acids

In this study, low dose bedtime ursodeoxycholic acid did not significantly reduce gall stone recurrence rates diagnosed either by the original criteria or by the use of either imaging technique (oral cholecystography or ultrasonography). Even when the recurrence rates were adjusted, the 15% rate in the ursodeoxycholic acid treated patients was not significantly different from the 30% rate in the other two groups. Again, this lack of statistical significance may represent a type II error.

Chenodeoxycholic acid – In the United States National Co-operative Gallstone Study (NCGS),⁴⁹ there was no significant difference in recurrence rates between placebo treated

patients (5 of 27 or 28.5%) and those given 375 mg chenodexychoic acid/day (5 of 26 or 23.9%). The dose of chenodexychoic acid used, however, was low (again about one third of the full gall stone dissolution dose) and the follow up comparatively short (three years). By contrast, in a preliminary report from Valencia, Perez-Aguilar and colleagues⁵³ found only three recurrences in 12 post-dissolution patients (25%) given 250 mg chenodexychoic acid/day, compared with six recurrences in 10 patients (60%) given no treatment.

Ursodeoxycholic acid – In a large but uncontrolled study from Bologna, Villanova *et al*⁴² reported recurrence rates in 86 patients who had had 96 episodes of gall stone dissolution (in 10, recurrent stones were dissolved with a further course of oral bile acid treatment). On 36 occasions, the patients were treated with 300 mg ursodeoxycholic acid/day, which resulted in a recurrence rate of 32 (18)% by LTA at seven and subsequent years, compared with 69 (12.4)% on the 60 occasions when no post-dissolution treatment was given ($p < 0.01$). This protective effect of ursodeoxycholic acid was confined to patients aged 50 or less. Although we could not confirm this finding statistically, none of the small number of our patients aged less than 50 ($n = 18$) who was treated with ursodeoxycholic acid, developed recurrence. In the present study, the dose of ursodeoxycholic acid varied with body weight. Eighteen of 23 ursodeoxycholic acid treated patients took only 200 mg/day while two took 250 mg and only three took 300 mg/day. There were no obvious differences in recurrence rates as a function of ursodeoxycholic acid dose but with only five patients taking > 200 mg/day, the number is too small to draw valid conclusions. Given that it was impossible to predict the response to the three post-dissolution treatment regimens, some degree of imbalance between the groups was almost inevitable. Indeed, in prospective random allocation trials, this happens frequently and the application of an adjustment or correction factor is common. Having done so, we found a twofold difference in the recurrence rates between the ursodeoxycholic acid treated and placebo treated patients and although this was not statistically significant, these data, when coupled with the results of the Italian and Spanish studies^{42,53} suggest that ursodeoxycholic acid reduces and probably delays, but does not prevent, gall stone recurrence.

Symptomatic v asymptomatic recurrence

Only two of the patients with gall stone recurrence in this study had symptoms of biliary colic: in the remainder, the recurrent stones were silent or asymptomatic. This shows that the presence of symptoms is unreliable as a predictor of recurrence. In a preliminary report,^{58,59} however, Tint *et al* noted that 75% of their patients who developed gall stone recurrence after dissolution of their primary stones by oral bile acid treatment, had symptoms. Furthermore, in 58 patients rendered stone free with extra corporeal shock wave lithotripsy and adjuvant bile acids, Sackmann *et al*⁶⁰ found that 100% of their

patients with recurrent stones had symptoms.

The difference in the frequency of symptomatic recurrence may be explained by an evolving policy of management when considering gall stone patients for non-surgical treatment. In the past, many patients were accepted for bile acid treatment without specific, gall stone related symptoms. Since extra corporeal shock wave lithotripsy was introduced in 1985, however, the consensus has changed and most investigators now recommend active treatment only if patients have specific symptoms attributable to their gall stone disease.^{61,62}

Frequency of gall stone recurrence

In this study, the highest figure for gall stone recurrence is 26 (diagnosed by either oral cholecystography or ultrasonography) of 82 patients followed up for at least six months (60 of whom were followed up for not less than two years) giving a crude recurrence rate of 31.7% which corresponds, by LTA, to a cumulative actuarial rate of 41.0 (7.2)% at 3.5 and subsequent years. These overall results may be distorted, however, by the influence of post-dissolution treatment. Therefore, they may not be representative of recurrence rates in untreated individuals.

Although gall stone recurrence rates of 30–40% are substantial, they are, none the less, considerably less than those reported in many other studies.^{42,48,54,55} One reason for these variable results may relate to the differing degrees of stringency applied to the diagnosis and confirmation of complete gall stone dissolution.

The present studies are important not only for gall stone recurrence after oral dissolution treatment but also for recurrence in any situation where the gall bladder remains *in situ* but the stones have been removed by percutaneous cholecystolithotomy, instillation of contact solvents such as methyl ter-butyl ether and, to a lesser extent because of patient selection, by extra corporeal shock wave lithotripsy with or without adjuvant bile acids. Based on these findings, and on those by Villanova *et al*⁴² showing that: (i) patients with multiple primary stones tend to develop multiple recurrent stones while those who originally had solitary stones tend to develop single stone recurrence; and (ii) the recurrence rate in those who initially had solitary stones is only one third of that in patients who originally had multiple stones, we can predict that since patients selected for extra corporeal shock wave lithotripsy mainly have solitary stones, the recurrence rate after lithotripsy should be lower than that reported here. Data for gall stone recurrence after extra corporeal shock wave lithotripsy are only now starting to emerge but the initial results showing 11–15% gall stone recurrence rates one to two years after lithotripsy certainly confirm this prediction.⁶²

The present studies are important not only for recurrent stone disease but also because a knowledge of gall stone recurrence is likely to provide valuable clues about the pathogenesis and treatment of primary gall stone disease. In the future, the emphasis on studies of recurrence should,

perhaps, be directed not at subjects who develop recurrent stones but at the significant percentage of patients who do not and who, given the best currently available information, may never do so.

The assumption that once a gall stone inducing risk factor is present it will persist, may not always apply. Thus, the primary stones may have developed in women during the childbearing period of life as a result of the cyclic production of hormones, pregnancy or the ingestion of oestrogen containing oral contraceptive drugs, or both.¹⁰⁻¹² Transfer of these subjects from premenopausal to postmenopausal 'status' should, theoretically, reduce the risk of developing recurrent stones. Conversely, the prescription of hormone replacement treatment as prophylaxis against postmenopausal osteoporosis, could diminish this potential benefit. In this study, there were too few patients who became menopausal during the study for valid analyses. More longterm studies would be necessary to answer this point. Furthermore, patients who were obese, or actively losing weight at the time when the primary gall stones developed might, on achieving ideal body weight, no longer suffer this risk factor. Again there are too few patients who fall into the category of significant changes in body weight to permit valid conclusions but given the limited information, this did not seem to influence these results.

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