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Effect of prolonged feeding with chenodeoxycholic acid on bile in patients with and without gallstones

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SUMMARY Nineteen patients who received chenodeoxycholic acid 750 mg/day for six months had duodenal bile aspirated before and after treatment. In five patients with hypertriglyceridaemia but no gallstones cholesterol saturation was reversed in every case, the mean cholesterol saturation index (SI $\pm$ standard deviation) changing from 1·38 $\pm$ 0·31 to 0·68 $\pm$ 0·06 ($P < 0·005$). In 14 patients with gallstones there was also an improvement in bile cholesterol content, but this was not sufficient to produce mean unsaturation, saturation index changing from 1·55 $\pm$ 0·52 to 1·13 $\pm$ 0·43 ($P < 0·05$). Only seven of 14 patients with gallstone achieved cholesterol unsaturation. In four patients with hypertriglyceridaemia and gallstones, mean unsaturation was produced and the saturation index changed from 1·70 $\pm$ 0·45 to 0·86 $\pm$ 0·47 ($P < 0·05$). When all nine patients with hypertriglyceridaemia were grouped, the mean saturation index fell from 1·52 $\pm$ 0·40 to 0·76 $\pm$ 0·30 after therapy ($P < 0·001$). In contrast the 10 patients without hypertriglyceridaemia showed no significant fall in saturation index which was 1·50 $\pm$ 0·54 before and 1·24 $\pm$ 0·40 after therapy. The ability of chenodeoxycholic acid feeding to improve bile saturation with cholesterol correlated with the presence of hypertriglyceridaemia whether or not gallstones were present. It did not correlate with gallstone dissolution or body weight.

It is known that bile from most patients with gallstones is characterised by an excessive amount of cholesterol (Isaksson, 1954; Admirand and Small, 1968; Mackay *et al.*, 1972). Cholesterol oversaturation has been observed in subjects without gallstones (Heller and Bouchier, 1973; Holzbach *et al.*, 1973; Northfield and Hofmann, 1973), but less frequently so. As a result of the observation that cholesterol gallstones could be dissolved by feeding chenodeoxycholic acid (Danzinger *et al.*, 1972), it was suggested that fasting bile changes might uniformly be used to predict dissolution of stones (Iser *et al.*, 1975) but this has not been the experience of ourselves or that of others (Northfield *et al.*, 1973; James *et al.*, 1975).

During the clinical monitoring of patients on chenodeoxycholic acid therapy it was observed that serum triglyceride levels were lowered, and as a result chenodeoxycholic acid has been suggested as a useful therapeutic agent in patients with hypertriglyceridaemia (Bell *et al.*, 1973).

The present study was undertaken to ascertain whether there are differences between the response of groups of patients with gallstones, and with hypertriglyceridaemia but without gallstones, to prolonged therapy with chenodeoxycholic acid. There is little information on the effect of chenodeoxycholic acid in subjects without gallstones, and none on prolonged administration.

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Methods

PATIENTS

Gallstones

Fourteen patients with gallstones agreed to take part in the trial of dissolution therapy with chenodeoxycholic acid. All gave informed consent. There were four men and 10 women with an age range of 34 to 86 years. All had functioning gallbladders containing stones shown at cholecystography: one also had common bile duct stones. Before starting treatment the patients attended fasting for the following blood investigations: cholesterol, triglycerides, cellulose acetate lipoprotein electrophoresis, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, bilirubin, albumin, total protein, calcium, phosphate, creatinine, urea, sodium, chloride, potassium, haemoglobin, white cell count, platelets, and blood film. Serum lipid patterns were classified after

two separate determinations at constant weight (Technicon Autoanalyser technique).

After obtaining the blood samples a twin-lumen tube with radiopaque strip was screened into position in the second part of the duodenum. Bile-rich duodenal fluid was aspirated by intermittent suction for up to 20 minutes after cholecystokinin (Boots) 33 Ivy dog units intravenously. A preliminary dosage study indicated that this gave maximum cholecystokinesis while avoiding the frequent and severe reactions produced at higher levels. The most concentrated moiety as judged by inspection was saved for analysis.

Of the 14 patients with gallstones, six had normal serum lipids, four had pure hypercholesterolaemia (type IIa), two had pure hypertriglyceridaemia (type IV), and two had mixed hypercholesterolaemia and hypertriglyceridaemia (one type IV, one type IIb). Of these 14 patients, one with hypercholesterolaemia was on a low fat diet, and three with hypertriglyceridaemia were on low carbohydrate diets. The others were on no specific diets.

Patients were started and maintained on chenodeoxycholic acid 750 mg/day. Though change in bowel habit was frequent, none developed persistent troublesome diarrhoea. They were followed at monthly intervals for repeat blood tests as above. All patients were reintubated after exactly six months' treatment and a further sample of duodenal juice obtained. Cholecystograms were usually repeated at six-monthly intervals, and all patients were followed up for at least a year.

Hypertriglyceridaemia with or without hypercholesterolaemia

Six consecutive patients with normal cholecystograms in whom dietary therapy had failed to control hypertriglyceridaemia with or without hypercholesterolaemia were referred for treatment with chenodeoxycholic acid, in an attempt to lower their serum triglycerides. All were started on chenodeoxycholic acid 750 mg daily. In one patient diarrhoea necessitated a dose reduction to 500 mg/day and he is not included in the study. The patients were monitored and intubated as above.

These five patients were on a low carbohydrate diet and three of them were also on a low fat diet. Three of these patients had pure hypertriglyceridaemia (type IV) and two mixed hypertriglyceridaemia and hypercholesterolaemia (one type IIb, one type IV). They formed part of a group of 13 patients with hypertriglyceridaemia who received chenodeoxycholic acid 500 to 750 mg daily for six months.

TECHNIQUES

The majority of samples were processed on the day of intubation. With a few samples it was necessary to store by freezing at −20°C. An aliquot of bile was extracted by Folch technique and analysed for phospholipid as detailed elsewhere (Murison *et al.*, 1976).

Analysis for bile acids and cholesterol was conducted differently by a gas-liquid chromatography technique. Cholyl-glycine hydrolase 0·3 ml (Nair *et al.*, 1967) was added to a test tube containing 0·1 ml thoroughly mixed duodenal aspirate, 0·8 ml Sorensen's buffer pH 5·6, and 20 000 dpm ^{3}H glycocholic acid as tracer. The tubes were stoppered immediately and incubated at 37°C for one hour. The incubation was stopped with the addition of 0·1 ml 6N HCl, and extracted thrice with 1 ml ethyl acetate: the mixture was agitated on a Whirlimixer and centrifuged for five minutes at 3000 rpm. The top layers were bulked, dried down by rotary evaporator, and then taken up in 0·5 ml methanol. The method of Klaassen (1971) was then followed.

Diazomethane was prepared freshly daily. N-methyl-N-nitroso-p-toluene sulphonamide (Diazold) 6·4 g was placed in a 250 ml round-bottomed flask immersed in ice and dissolved in 90 ml diethyl ether. To this was carefully added 30 ml ethanol containing 1·2 g potassium hydroxide. The solution was allowed to cool for 10 minutes and then distilled cautiously using minimum heat. The distillate was collected in a tube immersed in ice. This reagent, 0·5 ml, was used to methylate the bile lipid extract, further diazomethane being added dropwise if decolorisation occurred. The solution was dried down under nitrogen and an internal standard of 100 μg stigmasterol added. Trifluoracetic acid (BDH), 0·2 ml, was added and the mixture incubated for one hour at 60°C, and then dried down under nitrogen. Ethyl acetate, 0·1 ml, was added immediately before injection into a GLC column (1% OV 210 on Gas-Chrom Q).

Reference standards of TFA chenodeoxycholic, cholic, deoxycholic, lithocholic, and ursodeoxycholic methyl esters and TFA cholesterol were used to identify and quantify peaks.

Good reproducibility was obtained. For seven pairs of duplicate samples the coefficient of variation for cholesterol was 2·17, and the coefficient between samples $r = 0{\cdot}98$. For the individual bile acids the figures were respectively: lithocholate 8·12, $r = 0{\cdot}94$; deoxycholate 1·56, $r = 0{\cdot}99$; chenodeoxycholate 4·00, $r = 0{\cdot}99$; cholate 1·85, $r = 0{\cdot}99$; and ursodeoxycholate 5·00, $r = 0{\cdot}99$.

The individual bile lipids were expressed in molar concentration as a percentage of the total molar concentration of cholesterol, bile acid, and cholesterol. Bile acids were taken as the sum of the five individual components measured. These were cholic,

deoxycholic, chenodeoxycholic, ursodeoxycholic, and lithocholic acids. No other bile acid was detected in significant amounts.

Results were calculated according to the polynomial formula of Thomas and Hofmann (1973) to derive the saturation index from the data of Admirand and Small (1968) and also the 'lithogenic' index from the data of Holzbach (1973) and Hegardt and Dam (1971). A saturation index of greater than 1 indicates bile definitely oversaturated with cholesterol. A saturation index of less than 1 indicates bile with less cholesterol than usually found. In our laboratory the mean saturation index of 39 patients without gallstones was 1·03. A 'lithogenic' index is derived so that at less than 1 it indicates complete chemical stability of cholesterol solution. The data were also plotted on triangular co-ordinates and the molar ratios of cholesterol to bile acid plus phospholipid calculated. Differences were examined by Student's paired and unpaired *t* tests and Wilcoxon paired and unpaired rank sum tests as appropriate.

Results

BILIARY LIPIDS

There were no significant differences in the biliary lipids of patients with and without gallstones before therapy (Table 1).

There was a significant qualitative difference between the response to chenodeoxycholic acid of 14 patients with gallstones and the five patients without. Only seven of 14 of the patients with gallstone achieved unsaturation of bile even on the criteria of Admirand and Small (1968). All of the patients without gallstones achieved unsaturation of bile by this standard: this was associated with a significant fall in the proportion of cholesterol and a significant rise in that of bile acid. Body weight and dosage were comparable in the two groups.

The patients with gallstones were divided into groups according to their serum lipid pattern. One in four patients with pure hypercholesterolaemia achieved unsaturation, but the mean saturation index for the group was 1·21 ± 0·24 before and 1·24 ± 0·24 after therapy. Of six patients with normal serum lipids three achieved unsaturated bile; the mean saturation index was 1·69 ± 0·64 before and 1·24 ± 0·48 after therapy. The four patients with hypertriglyceridaemia were different. In three unsaturation occurred, and the mean saturation index fell to unsaturated levels (from 1·70 to 0·86, Table 2).

When these four patients with hypertriglyceridaemia and gallstones were compared with the five patients with hypertriglyceridaemia but without gallstones, the values for biliary lipids were similar both before and after treatment (Table 2).

Therefore results for all nine patients with raised serum triglycerides (mean value 3·34 mmol) were pooled and compared with the 10 patients without hypertriglyceridaemia (mean 1·59 mmol). There were seven men in the first group and one man in the second group. The mean weight of the patients with hypertriglyceridaemia was greater, but this did not achieve statistical significance. The absence of effect of chenodeoxycholic acid therapy in the patients without hypertriglyceridaemia could not have resulted from smaller dosage/unit body weight. Of the nine patients with hypertriglyceridaemia, eight achieved unsaturated bile, the mean saturation index falling significantly from 1·52 to 0·76 ($P < 0·001$, Table 3). No such significant change occurred in the other group without hypertriglyceridaemia. There was a correlation between the final saturation index and the pretreatment serum triglyceride level ($r = 0·60$, t 3·09, $P = < 0·01$), though there was no correlation at all between the initial saturation index and this triglyceride level ($r = 0·04$).

In the four patients on a low fat regimen through-

Table 1 *Biliary lipids before and after six months therapy with chenodeoxycholic acid 750 mg/day*

Patients	*Cholesterol*	*Phospholipid*	*Total bile acids*	*Molar ratio*	*Index*		*Mean weight (dose)*
					Saturation	*'Lithogenic'*	
With gallstones (14)							
Before	13·62 ± 4·50	17·29 ± 10·03	69·08 ± 12·93	7·60 ± 2·89	1·55 ± 0·52	2·45 ± 0·88	69·1 kg (55-96 kg)
After	10·54 ± 4·23 (NS)	18·91 ± 8·11 (NS)	70·44 ± 9·63 (NS)	9·68 ± 4·34 (NS)	1·13 ± 0·43 ($P < 0·05$)	1·83 ± 0·72 ($P < 0·025$)	(10·85 mg/kg)
With gallstones (5)							
Before	13·04 ± 3·12	23·12 ± 9·85	63·82 ± 8·28	6·95 ± 1·51	1·38 ± 0·31	1·99 ± 0·17	68 kg (52-74 kg)
After	6·58 ± 0·72 ($P < 0·005$)	18·18 ± 3·32 (NS)	75·23 ± 3·75 ($P < 0·002$)	14·26 ± 1·61 ($P < 0·001$)	0·68 ± 0·00 ($P < 0·005$)	1·13 ± 0·14 ($P < 0·05$)	(11·02 mg/kg)

Differences examined by Student's paired *t* test.
Lipid results expressed as molar percentage of total lipids (±SD)

$$\text{Molar ratio} = \frac{\text{Total bile acids (M)} + \text{phospholipid (M)}}{\text{Cholesterol (M)}}$$

Table 2 *Biliary lipids before and after six months' therapy with chenodeoxycholic acid 750 mg/day (mol %): patients with hypertriglyceridaemia, with and without gallstones*

Patients	*Cholesterol*	*Phospholipid*	*Total bile acids*	*Molar ratio*	*Index*	
					Saturation	*'Lithogenic'*
Before						
With gallstones (4)	16·42 ± 4·10	18·58 ± 6·18	64·99 ± 7·03	5·37 ± 1·57	1·70 ± 0·45	2·61 ± 1·09
Without gallstones (5)	13·40 ± 3·12	23·12 ± 9·85	63·82 ± 8·28	6·95 ± 1·51	1·38 ± 0·31	1·99 ± 0·17
After						
With gallstones (4)	8·35 ± 5·07	17·84 ± 5·98	73·80 ± 9·46	13·49 ± 5·58	0·86 ± 0·47	1·41 ± 0·65
Without gallstones (5)	6·58 ± 0·72	18·18 ± 3·32	75·23 ± 3·75	14·26 ± 1·61	0·68 ± 0·00	1·13 ± 0·14

Differences examined by Student's unpaired *t* test.

Table 3 *Biliary lipids before and after six months' therapy with chenodeoxycholic acid 750 mg/day (mol %)*

Patients	*Cholesterol*	*Phospholipid*	*Total bile acids*	*Molar ratio*	*Index*		*Mean weight (dose)*
					Saturation	*'Lithogenic'*	
With hypertriglyceridaemia (9)							
Before	14·54 ± 3·79	21·10 ± 8·28	64·34 ± 7·29	6·25 ± 1·66	1·52 ± 0·40	2·26 ± 0·96	71·7 kg (55-90 kg)
After	7·36 ± 3·29 (P < 0·001)	18·33 ± 4·35 (NS)	76·60 ± 6·38 (P < 0·01)	13·99 ± 3·62 (P < 0·001)	0·76 ± 0·30 (P < 0·001)	1·25 ± 0·44 (P < 0·001)	(10·46 mg/kg)
Without hypertriglyceridaemia (10)							
Before	12·50 ± 4·33	16·78 ± 11·47	70·71 ± 14·67	8·49 ± 2·85	1·50 ± 0·54	2·38 ± 0·84	66·2 kg (55-96 kg)
After	11·42 ± 3·78 (NS)	19·34 ± 9·07 (NS)	69·10 ± 9·84 (NS)	8·16 ± 2·79 (NS)	1·24 ± 0·40 (NS)	2·00 ± 0·70 (NS)	(11·32 mg/kg)

Differences examined by Student's paired *t* test.

out the study, a pronounced improvement occurred in the bile of each (SI 1·49 → 0·99, 1·35 → 0·77, 1·22 → 0·63, 1·36 → 0·60).

SERUM LIPIDS

Cholesterol levels did not change, nor did normal triglyceride levels. In 13 patients with hypertriglyceridaemia treated with chenodeoxycholic acid 750 mg/day (12) or 500 mg/day (one), the serum triglycerides fell from 3·56 ± 0·99 to 3·03 ± 0·83 mmol (P < 0·05) over six months.

INDIVIDUAL BILE ACIDS

In every case there was an increase in chenodeoxycholic acid and its metabolites after therapy, and a decrease in cholic acid and its metabolite (Table 4). Not all bile contained detectable amounts of ursodeoxycholic acid even after therapy. In nine patients it appeared for the first time after treatment with cheodeoxycholic acid, but in three it was not detected in either sample.

There was significantly more lithocholic acid in the bile of gallstone patients after therapy (6·61 ± 4·42 compared with 3·41 ± 1·33 mol/dl, P < 0·02) but no other differences before or after therapy.

There was no significant difference in the proportions of bile acids between patients with and without hypertriglyceridaemia.

DISSOLUTION

The gallstones of three patients completely dissolved, as evidenced by two consecutive normal oral cholescystograms. One of these achieved bile unsaturation (SI 1·63 → 0·71, cholesterol 11·90 → 7·18 mol%). However, two became more saturated after therapy (SI 1·20 → 1·46 and 1·27 → 1·47, cholesterol 11·77 → 14·79 mol% and 12·07 → 13·43 mol%).

Discussion

The purpose of the present study was to compare the response of biliary lipids of patients with and without gallstones to chenodeoxycholic acid therapy. It

Table 4 *Individual bile acids as percentage of total bile acids (mol%)*

	Cholate	*Deoxycholate*	*Chenodeoxycholate*	*Lithocholate*	*Ursodeoxycholate*
All gallstones (14)					
Before	29·73 ± 11·82	29·45 ± 21·32	39·90 ± 13·43	3·01 ± 1·62	2·87 ± 5·59
After	7·56 ± 7·89	7·82 ± 9·75	74·40 ± 16·89	6·61 ± 4·42	3·18 ± 2·62
	(P < 0·001)	(P < 0·005)	(P < 0·001)	(P < 0·01)	(NS)
Hypertriglyceridaemia + no stones (5)					
Before	23·65 ± 8·48	27·51 ± 5·54	45·17 ± 12·59	2·09 ± 0·94	1·55 ± 2·31
After	5·10 ± 3·73	6·31 ± 5·61	82·41 ± 9·87	3·41 ± 1·33	2·75 ± 1·37
	(P < 0·01)	(P < 0·01)	(P < 0·01)	(NS)	(NS)

Differences examined by Wilcoxon's paired rank sum test.

Table 5 *Initial bile acid composition of nine patients with and 10 without hypertriglyceridaemia (mol% total bile acid)*

	Cholate	*Deoxycholate*	*Chenodeoxycholate*	*Lithocholate*	*Ursodeoxycholate*
Hypertriglyceridaemia (9)	22·40 ± 6·49	29·57 ± 9·07	42·25 ± 11·52	2·55 ± 1·47	3·21 ± 3·52
All others (10)	33·29 ± 12·20	20·06 ± 16·16	39·01 ± 14·97	2·96 ± 1·60	1·90 ± 6·02

No significant differences by Wilcoxon's unpaired rank sum test.

was observed that important differences in response to treatment occurred, which related more to the serum lipid pattern than to the presence of gallstones.

It is established that fasting gallbladder and hepatic bile in Western countries is frequently oversaturated with cholesterol (Heller and Bouchier, 1973; Holzbach *et al.*, 1973; Northfield and Hofmann, 1973). In addition, diurnal rhythms of hepatic bile composition are of crucial importance in determining lithogenicity (Smallwood *et al.*, 1972; Metzger *et al.*, 1973).

It is not necessarily significant that the five patients without gallstones and with hypertriglyceridaemia had oversaturated bile. Our experience is that serum lipid patterns do not correlate with biliary lipid composition, though obesity (Freeman *et al.*, 1975) and treatment of lipid disorders may well do so (Grundy *et al.*, 1972; Einarsson *et al.*, 1973; Grundy, 1975).

In response to therapy the bile of patients with gallstones did not achieve mean unsaturation, whereas in patients without gallstones mean unsaturation was produced. When all patients with hypertriglyceridaemia were examined as a group, they showed a uniformly good response to feeding with chenodeoxycholic acid, and this was not related to the presence of gallstones or to the effectiveness of dissolution treatment. This accords with previous work performed elsewhere (James *et al.*, 1975), but others suggest that biliary lipid analysis is helpful in prediction of dissolution (Iser *et al.*, 1975).

No patients were taking clofibrate, nicotinic acid, or oral contraceptives during the period of study. There were no significant weight changes on therapy. Though four patients were on a low fat regimen throughout the study, this did not prevent a distinct improvement in bile in all of them. There was no significant difference in the dosage of patients with or without gallstones (10·85 compared with 11·02 mg/kg), nor in the dosage of patients with or without hypertriglyceridaemia (10·46 compared with 11·32 mg/kg). The dose of chenodeoxycholic acid used (750 mg/day) has been found sufficient to induce changes consistently in bile by others (Mok *et al.*, 1974), and there is no reason to suppose that higher doses would have produced a qualitatively different answer.

There has been some dispute as to the exact criteria for definition of the hyperlipidaemias. Serum lipids do not have a normal distribution in the population, nor is there a bimodal distribution with clear separation, and therefore separation of 'normal' and 'raised' levels is necessarily arbitrary (Fredrickson, 1975). The same cut-off level for serum triglycerides, 2·48 mmol, was used for both sexes and this accords with current thought (Tabaqchali *et al.*, 1974; Fredrickson, 1975). The mean triglyceride level in the group under study with hypertriglyceridaemia was clearly well in excess of this upper limit. Men were over-represented among patients with hypertriglyceridaemia, and this is to be expected in the community.

There are no consistently reported differences in the bile of patients with various patterns of hyper-

lipidaemia or with normal serum lipids. Obesity is often associated with raised serum triglycerides, and in extreme cases is linked with excessive production of cholesterol (Miettinen, 1971) and uniform cholesterol oversaturation of bile (13·0 ± 0·7 mol/dl) compared with controls (6·6 ± 0·5 mol/dl) (Freeman *et al.*, 1975). As serum triglycerides parallel total body production of cholesterol (Sodhi and Kudchodkar, 1973), whereas serum cholesterol levels do not (Miettinen, 1971; Sodhi and Kudchodkar, 1973), a logical connection may be seen between enhanced synthesis and enhanced excretion by the main pathway. Differences in weight were not observed between our patients with or without hypertriglyceridaemia, so this was not a factor.

Studies by others into the bile acid metabolism of patients with hyperlipidaemia have shown that the major differences in bile acid metabolism are the increased synthesis and pool of cholic acid and total bile acids in hypertriglyceridaemia (type IV, Fredrickson *et al.*, 1967) and a decreased synthesis and pool of cholic acid and total bile acids (50%) in hypercholesterolaemia (type IIa, Beaumont *et al.*, 1970) (Einarsson and Hellstrom, 1972; Einarsson *et al.*, 1974).

It is likely, but not yet proven, that this relates to differences in the activity of the rate-limiting liver enzymes responsible for cholesterol and bile acid synthesis in the liver. Both β-hydroxymethylglutaryl-coenzyme A reductase and cholesterol 7 α-hydroxylase might be expected to be more active in hypertriglyceridaemia, as both body synthesis of cholesterol and of bile acids is increased. It could be that there is a greater potential for inhibition of HMGCoA reductase, and hence cholesterol output in bile, in hypertriglyceridaemia. Conversely, liver cholesterol synthesis and HMGCoA reductase activity may possibly below in hypercholesterolaemia (Einarsson and Hellström, 1972), which would limit the scope for effective inhibition.

It seems that biliary lipid response to bile acid feeding is determined by factors which also influence systemic lipid metabolism. This may account for some of the observed failures of response to dissolution therapy.

The bile acid patterns showed only one striking finding before therapy—a smaller proportion of cholic acid in the bile of patients with hypertriglyceridaemia (22·40 ± 6·49%) than in the others (33·29 ± 12·20%)—and this just failed to achieve statistical significance. Patients with gallstones were not found to be significantly different from patients without gallstones in this study.

In response to feeding with chenodeoxycholic acid the expected increase occurred in the proportion of biliary chenodeoxycholic acid and its metabolites, and decrease in cholic and deoxycholic acid occurred. This did not correlate with changes in the cholesterol saturation of bile nor was it a prerequisite of dissolution.

In gallstone disease about one-third of the lithocholic acid is sulphated and this increases to three-quarters after chenodeoxycholic acid therapy (Stiehl *et al.*, 1975). Our GLC technique measured only unsulphated lithocholic acid, so changes in bile lithocholate levels may be of even greater magnitude than documented here (Table 4). The proportion of lithocholate sulphated after chenodeoxycholic acid feeding would be unlikely to depend on the presence of gallstone or on serum lipid patterns.

We conclude that there is a relationship between systemic triglyceride metabolism and biliary lipids, which governs response to chenodeoxycholic therapy. This does not depend on the presence of gallstones, which is itself not a predictor of response. These findings are of prime importance in the monitoring of bile in the management of gallstone dissolution therapy.

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