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Liver and biliary

Medical treatment of biliary duct stones: effect of ursodeoxycholic acid administration

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SUMMARY Twenty-eight patients with radiolucent biliary duct stones without cholangitis and jaundice were randomly allocated into two treatment groups receiving ursodeoxycholic acid 12 mg/kg (group A) or placebo (group B) in three daily doses for 24 months. In group A stones disappeared completely in seven patients and partially in one; placebo administration had no effect on stone size and three patients of group B (only one of group A) went to surgery for complications. Ursodeoxycholic acid treatment did not adversely affect liver function tests, and alkaline phosphatase decreased. Abdominal and biliary colics also became less frequent in the first six months of therapy in group A, but not in the placebo group. The bile was supersaturated with cholesterol in both groups, but decreased significantly only in patients receiving ursodeoxycholic acid even though the lithogenic index remained high. Cholesterol saturation of bile does not seem to be the only factor determining the dissolution of biliary duct stones which sometimes contain cholesterol as the main component.

The chemical composition of biliary duct stones has not yet been extensively studied. Calcium bilirubinate is the prevalent component of de novo primary biliary duct stones as consequence of bacterial deconjugation of bilirubin diglucuronide,[1] whereas cholesterol may be the major component of common bile duct stones in patients with gall-bladder or with retained or recurrent choledochal duct stones.[2 3] Treatment with chenodeoxycholic acid for gall-bladder stones has been shown to dissolve common bile duct stones also,[4 5] suggesting that often ductal stones are composed of cholesterol. The low incidence of biliary duct stones when compared with gall-bladder stones is overshadowed by their clinical significance as choledocholithiasis is responsible for much serious morbidity of gall-stone disease. Further retained stones are discovered in around five percent of patients in the first to second year postcholecystectomy, and about 20% of the patients who undergo reoperation for residual stones will develop choledocholithiasis again if the biliary tree is not properly drained.[6] Retained duct stones in patients with T-tube may be dissolved by infusing bile salt solutions or glyceryl-1-monooctanoin directly into the biliary tract *via* the T-tube.[7 8] Furthermore the problem of common bile duct stones is serious in aged patients as they have high surgical risk.[9] In these cases oral treatment with cholelitholytic bile acids (chenodeoxycholic and ursodeoxycholic acid)[5 10–12] should be seriously considered.

As insufficient data are available on the efficacy of chenodeoxycholic and ursodeoxycholic acids to dissolve bile duct stones, and as the influence of hepatic bile saturation is not clearly established, a controlled study was undertaken in order to determine the effects of oral administration of ursodeoxycholic acid to patients with biliary duct stones. This acid was chosen because of its low toxicity on the liver[13] and on the colon.[14]

Methods

PATIENTS AND STUDY DESIGN

Twenty-eight patients with radiolucent biliary duct stones (with or without gall-bladder stones) were studied from the Surgical Department of Modena University, including some outpatients. They gave informed consent to the study and cooperated with us during the trial.

The patients were selected according to the following general criteria: that they were free from

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cholangitis, and jaundice (plasma bilirubin less than 34 μmol/l), and had good radiological opacification of the common biliary duct. The patients were randomly allocated into two treatment groups receiving 12 mg/kg of ursodeoxycholic acid (group A) or 12 mg/kg of lactose (group B) in three daily doses using tablets of identical appearance. The treatment was double masked and was intended to last for 24 months, although some patients developed complications, and some dropped out of the study. Seventeen patients had been operated on (cholecystectomy) one to three years before (Table 1) and at that time the gall-bladder stones had contained mainly cholesterol (>60% by weight). Each patient had a clinical assessment at entry and at two monthly intervals thereafter. After each visit a fasting blood sample was obtained for transaminases, alkaline phosphatase, bilirubin, serum cholesterol, and triglyceride concentrations. The age, sex, and clinical details of the treated patients are listed in Table 1.

EVALUATION OF THE EFFICACY

During the trial intravenous cholangiography was carried out initially and at six monthly intervals using identical methods in all patients. The biliary

Table 1 *Clinical data regarding patients taking ursodeoxycholic acid (group A) or placebo (group B)*

				Stone in:		*Treatment:*		
Patients	*Sex**	*Age**	*Weight**	*Bile Duct**	*Gall bladder**	*Months**	*mg/kg/day**	*Outcome†*
GROUP A								
(1) LA	M	39	52	S >1	C 3	12	11·5	Colic
(2) BE	F	66	65	M <1	C 3	24	11·5	Drop out
(3) CA	M	33	60	M <1	A	6	10·0	Drop out
(4) FV	F	69	64	S <1	C 1	6	11·7	++
(5) GF	M	52	65	M <1	A	6	11·5	++
(6) GW	F	44	76	M <1	C 1	12	11·8	++
(7) OR	F	64	61	M >1	C 2	18	12·3	++
(8) RI	M	60	85	M <1	C 2	12	12·3	++
(9) VF	F	70	52	M <1	C 1	18	11·5	++
(10) SM	M	55	67	M <1	C 2	3	13·4	Surgery
(11) TB	F	31	54	M >1	L	24	13·8	+
(12) FA	M	80	74	S >1	L	6	12·1	Drop out
(13) BM	F	42	58	S >1	C 2	6	12·9	Pain
(14) TG	F	17	43	M <1	L	12	10·4	++
MEAN		51·5	62·5				11·9	
±SD		17·9	10·9				1·0	
GROUP B								
(1) MA	M	59	58	M <1	L	12	13·6	Pain
(2) AB	F	69	44	M <1	C 2	12	11·3	Pain
(3) FM	F	51	56	S <1	A	6	11·7	Drop out
(4) MM	F	58	67	M >1	C 3	18	11·5	Drop out
(5) CE	M	36	82	M <1	L	6	10·9	Surgery
(6) PP	M	33	95	M <1	L	12	11·5	Cholangitis
(7) SR	F	40	67	M <1	L	5	11·2	Surgery
(8) MF	M	46	74	S >1	C 2	24	12·1	
(9) BA	F	61	61	M <1	C 1	6	12·3	Pain
(10) RI	M	64	61	M <1	A	8	11·7	Surgery
(11) BA	F	51	64	M >1	C 3	24	12·5	
(12) BC	F	63	50	M <1	C 1	6	12·5	Colic
(13) MI	F	45	57	M <1	C 1	18	12·5	Colic
(14) GO	M	63	74	S>1	C 2	12	12·5	Pain
MEAN		52·7	65·0				11·9	
±SD		11·3	13·1				0·7	

S=solitary, M=multiple (referred to bile duct stones).
C=cholecystectomy, A=no gall stones, L=presence of gall stones, > or <1 means stone size > or <1 cm.
The number in the gall bladder column indicates time-interval since surgery in years.
* not significant at Student's t test and χ^2 test.
† Fisher's exact probability test – p=0·0057.
+ Incomplete dissolution; ++ Complete disappearance.

tract opacified satisfactorily, and in only two cases (one of group A and one of group B) biliary duct opacification was poor and endoscopic retrograde cholangiography was performed to confirm the presence of stones. The initial size of the common bile duct stones was measured and is reported in Table 1. The presence of bile duct stones and their dissolution was accepted when cholangiograms were read by two radiologists who were not aware of the treatment programme. Partial dissolution was established if the apparent diameter of the stone was reduced by at least 25% or if one or more stones had disappeared.

ANALYTICAL METHODS

Hepatic bile samples were aspirated by duodenal intubation after patients had fasted overnight both at the beginning and after four to six months of treatment. Aliquots of the collected biles were immediately diluted 1:9 with isopropyl alcohol and centrifuged; the supernatant was used to determine in duplicate cholesterol,[15] phospholipids,[16] and bile salts.[17] Relative lipid composition is recorded as moles of cholesterol, phospholipids, and bile salts. The cholesterol saturation in bile was calculated evaluating the maximal cholesterol solubility by means of the critical table of Carey[18] assuming a total lipid concentration of 4 g% appropriate to hepatic bile. Biliary bile acid composition was determined by gas-liquid chromatography as previously described.[19] Biliary duct stones obtained at the time of surgery (patient 10 of group A and patients 5, 7 and 10 of group B) were washed with water, weighed after removing excess water and ground in a mortar. After extraction with chloroform: methanol 2:1 (v:v), a portion of the chloroformic phase was used to determine cholesterol content; the values are expressed as percent of weight.

STATISTICAL ANALYSIS

The significance of differences of the variables between groups was tested by the Student's t test and by the χ^2 test. The litholytic effect and changes from the pretreatment values during urso and placebo administration periods were evaluated by the χ^2 test and split-plot analysis of variance, respectively.[20]

Results

STONE DISSOLUTION

The effect of treatment with ursodeoxycholic acid and with placebo is listed in Table 1. In group A the stones completely disappeared in seven subjects and partially in one (57·1%), while the stone number and size remained unchanged in patients taking placebo. The difference is statistically significant ($p<0·003$). In group B three patients underwent surgery for complications (obstructive jaundice patients 5 and 7, and recurrent biliary colics patient 10); in group A one patient (SM) was operated for obstructive jaundice after three months of treatment. Ursodeoxycholic acid administration did not adversely affect liver function tests: on the contrary, alkaline phosphatase decreased significantly ($p<0·01$) in group A patients as did plasma triglyceride concentrations ($p<0·05$) (Table 2). Abdominal pain and biliary colic, while not statistically different at the beginning of the therapy, became less frequent ($p<0·001$ and $p<0·05$ respectively) in group A compared with group B (see Table 2).

EFFECT ON BILE

The relative composition of hepatic bile before and after four to six months of treatment is tabulated in Table 3 where the lithogenic index values are also reported. The lithogenic index was very high in hepatic bile of both groups and decreased significantly only in group A receiving ursodeoxycholic acid ($p<0·0017$), whereas no changes were observed in placebo group. The values were not corrected for the biliary content of ursodeoxycholic acid. The variations of bile acids of hepatic bile during ursodeoxycholic acid feeding are tabulated in Table

Table 2 *Plasma lipids, liver function tests and symptoms before and during ursodeoxycholic acid (group A) or placebo (group B) treatment*

Clinical data and symptoms	*Group*	*Before*	*During*
Total bilirubin (nv <17 μmol/l)	A	20·0±3·7	14·6±0·8
	B	17·3±2·7	18·7±1·8
Alkaline phosphatase (nv <200 mU/ml)	A	170·3±19·5	118·9±6·3*
	B	158·6±18·9	161·3±13·1
ASAT (nv <25 mU/ml)	A	17·7±3·4	11·4±1·8‡
	B	16·6±3·2	20·4±3·8
Triglyceride (nv <1·71 mmol/l)	A	1·2±0·05	1·0±0·03‡
	B	1·2±0·05	1·2±0·05
Cholesterol (nv <5·7 mmol/l)	A	5·5±0·2	5·5±0·2
	B	4·9±0·2	5·0±0·2
Abdominal discomfort	A	10/14	1/14
	B	11/14	10/14†
Biliary colic	A	4/14	0/14
	B	5/14	5/14§

ASAT=aspartic serum amino-transferase; A=UDCA group; B=placebo group.
Values are expressed as mean±SE (biochemical data).
* $p<0·01$ ‡ $p<0·05$ } paired Student's t test (between before and during).
§ $p<0·05$ † $p<0.001$ } between group A and B (Fisher exact probability test).

3: in the basal condition the bile acid composition is very close in the two groups; the percentage of ursodeoxycholic acid increased greatly in group A (from 1·2 to 53·7%). No changes were observed when placebo was administered (group B). The content of cholesterol in analysed stones was very high in patients 10 of group A and 5 and 7 of group B (78, 62 and 88% respectively), whereas it was low in patient 10 of group B (10% of total weight).

Discussion

The results of this trial show that ursodeoxycholic acid administration was effective in dissolving biliary duct stones. Dissolution has been obtained also with chenodeoxycholic acid administration.[4 5 21–23] Kutz *et al*[24] and Stiehl *et al*[25] reported the disappearance of intrahepatic radiolucent stones in subjects with Caroli's syndrome treated with chenic acid. Lirussi *et al*[12] recently reported dissolution of intrahepatic stones with prolonged ursodeoxycholic acid administration. These studies were not controlled, however, and they do not provide data about the safety of treatment. In our experience ursodeoxycholic acid is effective in dissolving biliary duct stones in patients who had had cholecystectomy or with gall bladder *in situ*. The group receiving the placebo showed a high incidence of complications which required surgery (21% against 7% of group receiving ursodeoxycholic acid). The finding that ursodeoxycholic acid administration may dissolve stones located in the biliary tract, reducing the painful symptoms such as abdominal discomfort and the biliary colics, and decreasing plasma alkaline phosphatase concentrations offers an important addition to the more traditional treatments (endoscopic papillotomy and the direct removal of stones) for choledocholithiasis in patients with high surgical risk.

With regard to the changes of bile lipid composition, our data confirm previous reports that ursodeoxycholic acid decreases biliary cholesterol (from 13·0 to 8·4% in group A) inducing a striking increase in the proportion of ursodeoxycholic acid in the biliary bile acid pool;[26] this result indicates compliance on the part of the patients (in fact the range of ursodeoxycholic acid percentage in bile was from 45·0 to 57·8). Using cholesterol saturation values appropriate to the total lipid concentration of bile coming into contact with choledochal stones (g 4%),[27] all studied patients had supersaturated bile; this finding is frequent in both normal individuals[28] and in patients with gall stones.[27] Our data support other reports indicating that patients with common bile duct stones have supersaturated bile with cholesterol years after cholecystectomy[2 29] and that cholesterol is the main component of some duct stones.[2 3 30]

Ursodeoxycholic acid administration did not desaturate bile: lithogenic index was 1·36±0·28 during therapy. Even though the calculation of saturation index on samples of low total bile acid concentration may give quite misleading results[31]: this raises the question: how did the common bile duct stone disappear? They could migrate into duodenum when bile flow rises and the sphincter of Oddi relaxes; ursodeoxycholic acid can greatly increase bile flow,[32] and consequently its administration

Table 3 *Lipid composition, lithogenic index and bile acid composition of bile of patients with common bile duct stones taking ursodeoxycholic acid (group A) or placebo (group B)*

	Group A								Group B							
	Before				After				Before				After			
	C	PL	BS	LI	C	PL	BS	LI	C	PL	BS	LI	C	PL	BS	LI
	(mol%)				(mol%)				(mol%)				(mol%)			
Mean	13·0	20·4	66·4	2·11	8·4	22·1	69·3	1·36*	14·0	20·8	65·0	2·26	13·9	20·7	65·1	2·25
±SD	2·27	2·36	4·10	0·46	1·67	2·10	2·71	0·28	2·95	2·81	4·38	0·44	1·75	2·16	3·04	0·27
		LCA	DCA	CDCA	UDCA	CA				LCA	DCA	CDCA	UDCA	CA		
Before		0·8	25·9	34·8	1·2	37·2		mean		0·9	20·2	34·7	1·0	43·1		
		0·4	9·1	4·7	0·2	5·2		±SD		0·5	3·3	7·6	0·2	4·5		
After		1·6	10·3	22·3	53·7*	12·0		mean		1·0	22·6	30·2	1·3	44·8		
		0·6	3·7	5·1	3·8	2·0		±SD		0·4	2·6	4·8	0·2	5·9		

C=cholesterol; PL=phospholipids; BS=bile salts; LI=lithogenic index.
LCA=lithocholic acid; DCA=deoxycholic acid; CDCA=chenodeoxycholic acid; UDCA=ursodeoxycholic acid; CA=cholic acid. The values of bile acids are expressed as mean (percentage of total bile acids) ±SD.
* $p<0·001$ between before and after treatment.

could induce the disappearance of bile duct stones through their expulsion into the duodenum. We did not collect stools during the treatment to validate this hypothesis. The radiological findings (patients 6, 7, 8, 9 and 11 of group A) show the sequential reduction of stone size; the same evidence was obtained by Sue *et al*[23] giving chenodeoxycholic acid for choledocholithiasis.

Our patients showed reduction of cholesterol saturation of bile, but not desaturation. Therefore the mechanism by which ursodeoxycholic acid dissolves cholesterol rich stones is complex. *In vitro* a mesomorphic liquid crystalline phase is formed during cholesterol monohydrate incubation with physiological micellar solution of ursodeoxycholic acid-conjugates plus lecithin,[33] which disperses a large amount of cholesterol.[34] The non-micellar (mesomorphic) solubilisation of cholesterol suggests (if operative *in vivo*) an explanation for the observed dissolution of bile duct stones in spite of the persistent supersaturation of bile.

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