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Gallstone Dissolution with Ursodeoxycholic Acid in Patients with Chronic Active Hepatitis and Two Years Follow-Up

A Pilot Study

U. LEUSCHNER, MD, M. LEUSCHNER, J. SIERATZKI, MD, W. KURTZ, MD, and K. HÜBNER, MD

Chemical dissolution of cholesterol gallstones using ursodeoxycholic acid (UDCA) in six patients with histologically confirmed HB_sAg-negative chronic active hepatitis was started after a minimum of one year of therapy with steroids, azathioprine, or chloroquine and a treatment-free period of 8–15 months. The treatment with UDCA lasted 3–20 months with a daily dose of 8–11 mg/kg. Four patients served as controls. A decrease in transaminases ($P < 0.05$) occurred in all patients during the UDCA therapy. After completion of the treatment, the figures rose again, but did not return to the initial value. The stones dissolved in five patients. A second liver biopsy was carried out in two patients after UDCA therapy, and this showed no detectable deterioration. Four patients refused biopsy because the laboratory parameters had improved under UDCA. A stone recurred in one patient six months after the end of therapy; the others have remained free of stones for up to 24 months.

The dissolution of cholesterol stones in the gallbladder using chenodeoxycholic acid (CDCA) or its 7β-epimer ursodeoxycholic acid (UDCA) has been carried out successfully and without serious side effects since 1972 and 1975, respectively (1–3). Hepatic disorders are regarded as an absolute contraindication, but chemical treatment can nevertheless become necessary for symptomatic gall stones when the patient refuses surgery or its associated risks appear too great.

Among the 126 patients with cholecystolithiasis, whom we have treated with CDCA ($N = 45$) and UDCA ($N = 81$) from 1973 to 1981, it was not uncommon to find a decrease, and occasionally even a normalization, of the raised values for transaminases (4). This observation, together with the finding that UDCA, in contrast to CDCA, does not lead to increases in transaminases or diarrhea, encouraged us to use UDCA to treat six patients with histologically confirmed chronic active hepatitis (CAH) and cholelithiasis. This had been preceded by several years of therapy for CAH using steroids, chloroquine, or azathioprine and a treatment-free period. All patients refused cholecystectomy.

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From the Center of Internal Medicine, Department of Gastroenterology, and Center of Pathology of the Johann Wolfgang Goethe-University, Frankfurt/Main, West Germany.

Address for reprint requests: Prof. Dr. U. Leuschner, Center of Internal Medicine, Department of Gastroenterology, University Hospital, Theodor Stern Kai 7, 6000 Frankfurt/Main 70, West Germany.

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MATERIALS AND METHODS

Patients and Therapy. The six patients, three women and three men from 42 to 64 years of age, had CAH and cholecystolithiasis for at least one year. The diagnosis of CAH had been confirmed by the course of the disease and by biochemical, laparoscopic, and histological investigation. All six had repeated attacks of biliary colic, some of which were severe. They refused surgery because of the existing liver damage.

The gallstones had been diagnosed by using ultrasound (Vidoson 635 ST, Siemens; linear-array-scan equipment, 2.2 MHz, multiformat camera) and radiography. For the latter, a plain x-ray of the gallbladder was taken to exclude radiopaque concrements, and then Endomirabil® (Byk Gulden, GmbH, FRG) or Biliscopin® (Schering AG, FRG) was administered intravenously over 10–20 min. Thereafter, standing and supine radiographs were prepared under standard conditions. All patients had radiographically functioning gallbladder and bile ducts free of stones. We presumed that in those patients with biliary colic, stones had passed. Litholysis was assessed by ultrasonography. The result of the treatment was confirmed by ultrasound and cholangiography.

GOT, GPT, and γ-GT, GLDH, bilirubin, protein electrophoresis, and levels of iron in the serum were measured at six-week intervals at least one year before the UDCA therapy, and these were checked monthly or every three months during and for at least one year after treatment. Virological (HB_sAg, anti-HB_s, anti-HB_eAg) and immunological investigations (antinuclear factors, antibodies against smooth muscle fibers, antimitochondrial antibodies) were carried out at intervals of six months. According to the investigations of Poupon et al (5), radioimmunological measurements of serum cholylglycine have been used as sensitive indicators of liver damage before, four and eight weeks after start of UDCA treatment, and four weeks after end of therapy (RIA, Abbott).

In five of the six patients, at least one laparoscopy with liver biopsy had been carried out before starting UDCA therapy to confirm the diagnosis. Patient 4 could not be examined due to the existence of hemophilia A. Repeat laparoscopy and biopsy were carried out on patients 3 and 6 after completion of the UDCA treatment. Again, patient 4 could not be examined. The other three patients, all of whom felt well and had been continuously informed of their laboratory parameters, refused further investigations.

Patients 3, 4, and 5 had been treated with prednisolone (10–20 mg daily), chloroquine (0.25–0.50 g/daily), or azathioprine (100–150 mg daily) because of a marked inflammatory activity of their disease. After no further improvement was appreciated, the drugs were discontinued 8, 12, and 15 months, respectively, before the start of UDCA therapy. In this period no deterioration or improvement occurred prior to the start of litholysis.

All patients were informed of possible side effects of the UDCA treatment and of the risks of surgery and provided their written consent. Four patients with mild CAH received 9–11 mg/kg of UDCA daily, and two patients with more severe inflammatory activity received 8 mg/kg. The duration of treatment was three to five months for two patients and 14–20 months for four patients. No prophylaxis against recurrence after dissolution of the stones was given.

The transaminase values before, during, and after the UDCA treatment were examined for statistically significant differences using the paired *t* test. For this purpose, the mean value of the enzyme activity measured in the particular period was calculated for each patient. Four other patients with comparable inflammatory activity and gallstones were not given UDCA and served as controls.

RESULTS

Before UDCA Treatment. The enzyme activities in the serum before UDCA therapy varied to a marked extent (Table 1, Figure 1). For patient 3 the γ-GT was between 40 and 50 units/liter for a relatively long period, but then suddenly rose to 183 units/liter shortly before the start of UDCA treatment.

Hepatitis B antigen was not detected in any patient. Two patients were found to have antibodies against hepatitis B-Ag. Antimitochondrial, antinuclear antibodies, and smooth muscle antibodies were not detected in any patient. The data of the four untreated patients are given in Table 2.

The mean values of cholylglycine before and after UDCA therapy do not differ significantly. After four weeks of treatment, serum cholylglycine levels dropped in three and rose in three patients. After eight weeks, however, the levels decreased in comparison to the four-week values in three patients (Table 3). There was no change in the four untreated patients.

The findings of laparoscopy before UDCA-treatment are summarized in Table 4. The histology showed that the lobular structure was still intact in all five patients with markedly enlarged periportal fields infiltrated with lymphocytes and histiocytes, piecemeal necroses, and proliferation of the Kupffer cells. The inflammatory process was of relatively low activity in patients 1, 2, and 5 and of relatively high activity in patients 3 and 6 (Figure 2). Morphological findings of the untreated patients are shown in Table 5.

During UDCA Treatment. The gallstones of five patients had dissolved after treatment lasting 5–20 months. Patient 2 wanted to discontinue treatment after three months, no decrease in the size of a 2-cm stone yet being detectable (Table 6). Table 7 gives the stone data of the four untreated patients. The follow-up has been performed by ultrasound only.

TABLE 1. LABORATORY FINDINGS SIX MONTHS BEFORE UDCA TREATMENT, DURING 18 MONTHS UDCA TREATMENT, AND DURING 12 MONTHS FOLLOW-UP AFTER UDCA TREATMENT*

	Patient					
	1	*2*	*3*	*4*	*5*	*6*
Age/Sex	51/M	50/M	64/M	42/F	58/F	61/F
Anti-HB_s	0	0	0	+	0	+
Rheumatoid factor	+	0	0	0	+	+
Elevated IgG	0	0	+	+	+	+
Transaminases before UDCA						
GOT (range)	55–78	25–37	48–410	45–55	20–35	40–200
GOT (average)	66	28	142	48	31	84
GPT (range)	117–211	44–60	66–440	38–60	30–49	22–340
GPT (average)	160	50	200	52	44	86
GT (range)	16–78	15–20	40–183	10–15	20–25	
GT (average)	42	19	80	12	21	
Transaminases during UDCA						
GOT (range)	13–70	15–42	41–103	25–45	17–26	14–38
GOT (average)	32	27	52	31	22	27
GPT (range)	19–139	30–64	98–130	30–57	26–36	16–20
GPT (average)	63	47	113	42	31	19
GT (range)	8–78	10–20	137–187	9–11	11–20	6–8
GT (average)	34	15	162	10	13	7
Transaminases after UDCA						
GOT (range)		25–42	62–68	32–67	17–34	12–30
GOT (average)		31	64	55		20
GPT (range)	25–65	45–60	50–145	36–101		14–36
GPT (average)		50	114	76		26
GT (range)	12–55	14–15	281–657		16–28	7–21
GT (average)		15	392			13

*Normal values (M/F): GOT 18/25, GPT 23/19, GT 28/18 units/liter.

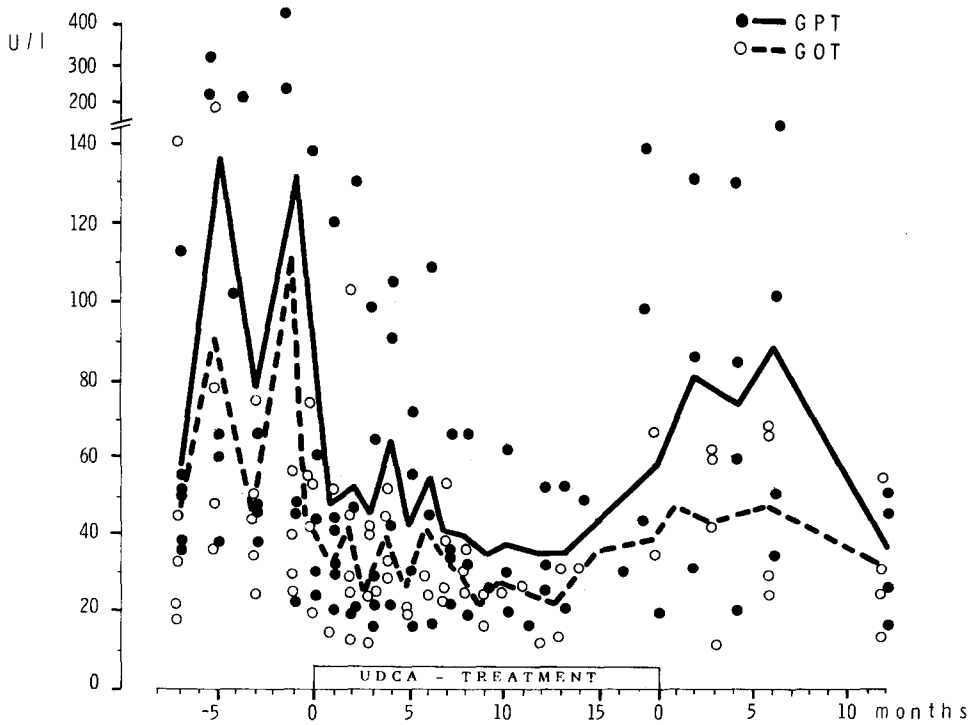

Fig 1. Serum enzyme activity of glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT). Individual and mean values before and during UDCA treatment and in the follow-up period.

TABLE 2. LABORATORY FINDINGS OF FOUR PATIENTS WITH CAH AND GALLSTONES BUT WITHOUT UDCA OR ANY OTHER TREATMENT

	Patient			
	7	*8*	*9*	*10*
Age/Sex	44/F	55/F	51/M	52/F
Anti-HB_s	+	0	0	0
Rheumatoid factor	0	0	0	0
Elevated IgG	+	+	+	+
GOT (range)	35–95	80–165	45–65	15–65
GOT (average)	40	145	55	22
GPT (range)	55–80	75–175	35–65	18–47
GPT (average)	48	150	55	33
GT (range)	24–75	60–120	30–85	28–60
GT (average)	45	65	35	30

*The table represents data from the beginning of the study until the end. Normal values (M/F): GOT 18/25, GPT 23/19, γ-GT 28/18 units/liter.

TABLE 3. SERUM CHOLYLGLYCINE LEVELS (μmol/liter) IN SIX CAH PATIENTS UNDER UDCA THERAPY

Patient	*Before therapy*	*After 4 weeks*	*After 8 weeks*	*4 weeks after end of therapy*
1	5.00	5.33	3.37	5.00
2	1.94	7.14	4.38	2.15
3	2.01	0.70		1.95
4	1.43	0.44	0.27	0.84
5	1.32	0.45		0.95
6	2.03	4.41		2.63
Mean	2.29	3.08	2.67	2.25
SD	1.36	2.93	2.14	1.52

No deterioration in the general well-being or the laboratory parameters occurred in any patient. The values for transaminases decreased throughout the first year of UDCA treatment and were statistically significant ($P < 0.05$). GPT and GOT rose again slightly in the second year of treatment, but they remained markedly below the maximum values measured before treatment in all patients (Table 1).

Follow-Up After Treatment. No deterioration in the course of the disease occurred even after ending treatment with UDCA. The transaminases rose markedly after completing UDCA therapy, but they decreased again to the same extent after about six months. In the first year after UDCA therapy, the average GOT was 43 and GPT was 66 units/liter, the differences from the figures for the enzymes before and during UDCA therapy are not, however, significant (Table 1). In patient three, the γ-GT rose to 657 units/liter in the first six months after discontinuation of UDCA, but then decreased again to 281 units/liter. All the other laboratory values remained unchanged. Cholylglycine values did not change in two follow-up investigations.

The follow-up biopsies in patients 3 and 6 showed a decrease in inflammatory activity (Table 4), and in

TABLE 4. MORPHOLOGIC FINDINGS IN PATIENTS WITH CAH BEFORE AND AFTER UDCA TREATMENT*

	Patient					
	1	*2*	*3*	*4*	*5*	*6*
Laparoscopy						
Red spotted color	+	+	+ (+)		0	+ (+)
Faded lobular limitation	+	+	+ (+)		+	+ (0)
Subcapsular vessels	+	+	+ (+)		+	+ (+)
Capsular fibrosis	0	0	+ (0)		++	+ (++)
Flat cicatrices	0	0	0 (+)		0	+ (0)
Pathology						
Piecemeal necrosis	+	++	+ (+)		+	++ (0)
Portal infiltration	++	++	+++ (++)		+	++ (+)
Cellular and nuclear polymorphism	0	++	++ (+)		+	++ (0)
Parenchymal degeneration	0	0	0 (+)		+	++ (+)
Kupffer cell proliferation	++	+	+ (+)		+	++ (+)

*Examination after UDCA treatment in parentheses. Patient 3 and patient 6, five and eight months, respectively, after UDCA treatment. + = visible; ++ = marked; +++ = excessive.

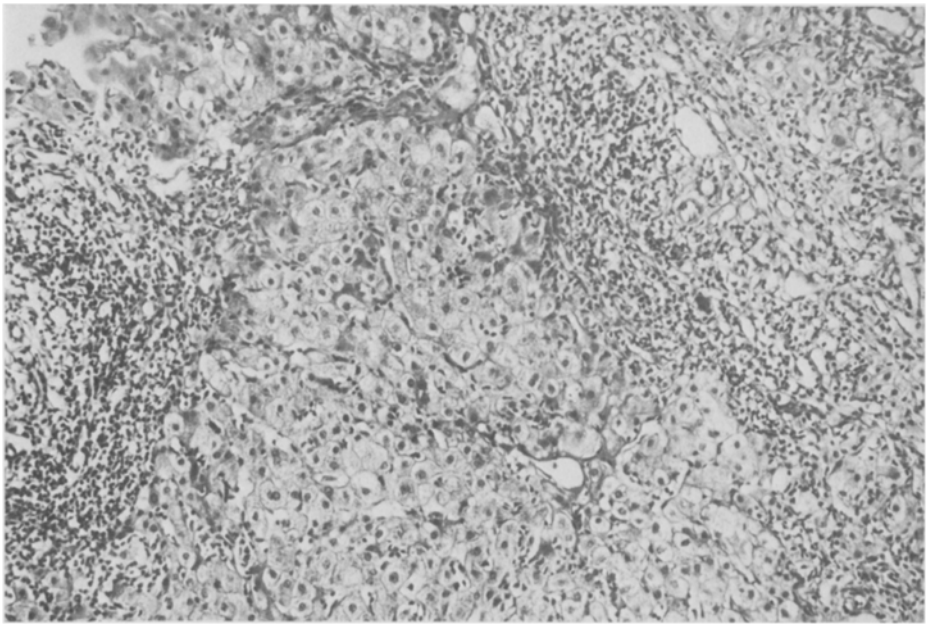

Fig 2. Patient 6 (five months before onset of UDCA-treatment): Chronic active hepatitis with inflammatory cell infiltration in the portal tracts, septa, and adjacent hepatic lobules with perilobular parenchymal degeneration and necrosis (piecemeal necrosis) (H&E, 100×).

patient 6, the piecemeal necroses were no longer detectable, at least, deterioration was not observed. A concrement recurred in patient 6 about six months after the end of UDCA therapy. The other patients have remained free of recurrence for the 18–24 months since treatment ended. The untreated controls showed no change in laboratory parameters. This time no liver samples were taken.

TABLE 5. MORPHOLOGIC FINDINGS IN FOUR PATIENTS WITH CAH BUT WITHOUT UDCA TREATMENT BEFORE AND AT END OF STUDY*

	Patient			
	7	*8*	*9*	*10*
Laparoscopy				
Red spotted color	++	++ (+)	+	
Faded lobular limitation	+	+ (+)	+	+
Subcapsular vessels	+	+++ (+++)	+	
Capsular fibrosis	0	0 (+)	0	++
Flat cicatrices	0	0 (0)	0	0
Pathology				
Piecemeal necrosis	+	++ (++)	+	+
Portal infiltration	++	+++ (++)	++	+
Kupffer cell proliferation	+	+ (0)	0	0

*Examination at the end of the study in parentheses. + = visible; ++ = marked; +++ = excessive.

DISCUSSION

Gallstones are found in about 10–20% of the population of western Europe and the United States (6–8), but only in 18–50% are they symptomatic (9–11). The frequency of complications is said to be greater with gallstones and concurrent hepatitis (12, 13). Thus, the treating physician is occasionally confronted by the question of what to do with patients with chronic liver disease and symptomatic gallstones. Surgery involves risks and the possibility of anesthetic injury; chemical stone dissolution involves the risk of drug-induced liver injury.

Cholecystectomy is a low-risk operation (14, 15). Figures for patients with concurrent chronic active

TABLE 6. STONE SIZE, DOSAGE, AND RESULTS OF UDCA TREATMENT

	Patient					
	1	*2*	*3*	*4*	*5*	*6*
Gallstone						
Number	3	1	2	4	2	1
Size (mm)	13	20	4	12	4	5
UDCA treatment						
Dose (mg/kg/day)	11.9	10.7	7.8	10.9	8.8	8.0
Period (month)	18	3	5	16	14	20
Dissolution	+	0	+	+	+	+

TABLE 7. STONE NUMBER AND SIZE IN PATIENTS WITH CAH BUT WITHOUT UDCA TREATMENT*

	Patient			
	7	8	9	10
Number	1	1	4	2
Size (mm)	3	4	12	10

*Ultrasound at the end of the study: no stone disappearance.

hepatitis are not available except for cirrhosis (16, 17). But since cholecystectomy is not a curative therapy for gallstones, and stones recur in the biliary tract in 5–10% of cases, patients must later submit themselves to a second operation having a higher incidence of complications and mortality.

For these reasons, attempted therapy with UDCA appeared to us worthy of investigation. It has certainly been reported that CDCA leads to transient rises in transaminases in about 30% of cases, but no corresponding morphological findings in the liver attributable with certainty to chenic acid have been made (18–22). However, irrespective of these clinical observations, oral administration of chenic acid to monkeys and rats can lead to liver lesions (23–31). Rhesus monkeys are incapable of adequate sulfating of lithocholic acid, which is hepatotoxic (32). However, in humans, sulfation of 60–80% of the LCA produced is an adequate detoxification system (33, 34).

It is clear from all the investigations on ursodeoxycholic acid hitherto published that in patients it does not lead to a significant rise in transaminases or other side effects as does chenic acid (35). Investigations in laboratory animals yielded different results. In rats even high UDCA doses produced no morphological alterations (26, 36–38). In rhesus monkeys, UDCA induced abnormalities of liver function and structure; after termination of the treatment, restitution was incomplete (31). Minor alterations were demonstrated in rabbits (39). It was supposed that the difference between the two bile acids in man was that UDCA is converted into LCA in the intestine to a lesser extent than is CDCA (40–42), but this again appears doubtful after investigations by Bazzoli et al (43). It is possible that the lack of side effects can be attributed to the dose of UDCA necessary to dissolve gallstones being lower, or the finding that UDCA suppresses the synthesis of cholic acid, and thus the formation of deoxycholic acid (DCA), to a lesser extent than does CDCA. However, the concentration of DCA appears to correlate inversely with the LCA concentration in the stool (44). Finally, it may be mentioned that LCA may perhaps be less well absorbed in the colon on therapy with UDCA than with CDCA (45).

These data and earlier observations by Maton et al (46) that UDCA can lead to a decrease in γ-GT and alkaline phosphatase encouraged us to attempt therapy with UDCA: dissolution of the stone occurred in five of the six patients, and four of the five patients have remained free of recurrence hitherto. No deterioration of CAH was observed.

Whether the fall of GOT and GPT during UDCA treatment was spontaneous or the result of the therapy cannot be determined. A spontaneous decrease of laboratory parameters is rather unlikely, since in all patients there was an at least 20-month pretreatment period during which the parameters were consistently elevated. It was only with UDCA that they decreased, and after end of treatment there was a rise again. In the four untreated patients laboratory values showed the usual fluctuations.

Further studies using UCDA in patients with CAH will be necessary to establish if UCDA is beneficial and safe in this group of patients.

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