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Efficacy and Indications of Ursodeoxycholic Acid Treatment for Dissolving Gallstones

A Multicenter Double-Blind Trial

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The cholelitholytic action of ursodeoxycholic acid (UDCA) was investigated by a double-blind clinical trial. The trial started with 151 subjects all confirmed by radiographic examination as having radiolucent gallstones in a functioning gallbladder. The subjects were divided into three groups receiving 600 mg/day of UDCA, 150 mg/day of UDCA, and placebo (lactose) per day, respectively. Seventy-nine cases were classed as dropouts or were excluded due to incomplete follow-up or inadequate patient selection, and the data on the remaining 72 cases were analyzed. After 6-12 mo of treatment, dissolution or decrease in size or number of stones occurred in 10 of the 29 cases in the 600 mg/day group (34.5%), 4 of 23 cases in the 150 mg/day group (17.4%), and 1 of 20 cases in the control group (5.0%). For those cases with noncalcified, less than 15 mm in diameter, and floating stones, efficacy increased to 83.3% in the 600 mg/day group. Lithogenic index of bile defined by Thomas and Hofmann became unsaturated after treatment in the 600 mg/day group. Neither diarrhea nor hepatic toxicity was noted. The results indicate that UDCA is a safe and effective litholytic agent.

Ursodeoxycholic acid (UDCA) is the principal bile acid of bear bile. Bear bile has been used in Japan for many years as a folk medicine to treat dyspepsia or biliary colic.

In 1972, Danzinger et al.[1] reported that oral administration of chenodeoxycholic acid (CDCA) was effective in dissolving cholesterol gallstones. Ursodeoxycholic acid is the 7β-hydroxy epimer of CDCA, and large amounts have been detected in the bile of some subjects treated with CDCA.[2] This indicates that it is also a litholytic agent. Sugata et al.[3] also suggested it in their retrospective study on cases with gallstone disappearance. Makino et al.[4] were the first in 1975 to demonstrate in open clinical trial that UDCA is an effective gallstone dissolving agent.

In order to gain additional information on the efficacy and safety of high and low doses of UDCA for the dissolution of gallstones, we undertook a double-blind clinical trial using inactive placebo and daily doses of 150 mg/day and 600 mg/day of UDCA.

Method

Subjects

The 151 subjects (57 men and 94 women) were patients in 21 hospitals who had been confirmed by radio-

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Table 1. Clinical Data of Patients Studied

Group	Total	Male	Female	Age	Height (cm)	Weight (kg)[a]
Control	45	15	30	51.0 ± 9.4	155.8 ± 8.8	56.0 ± 9.7
UDCA 150 mg/day	54	18	36	51.2 ± 11.4	155.9 ± 7.6	56.4 ± 7.5
UDCA 600 mg/day	52	24	28	51.8 ± 12.2	158.8 ± 9.8	57.4 ± 9.6

Mean ± SD. [a] After treatment, body weight was not changed significantly in each group.

graphic examination as having asymptomatic radiolucent gallstones with and without calcification in well-visualized gallbladders. None of the subjects had liver disease, cholecystitis, pancreatitis, or peptic ulcer or had suffered an attack of biliary colic within 1 mo before the study. Pregnant women and women of child-bearing age were excluded. Dietary calories, cholesterol, and fiber were not specifically limited.

Treatment

Patients were allocated randomly to three treatment groups receiving 600 mg of UDCA (52 cases), 150 mg of UDCA (54 cases), and placebo (lactose, 45 cases) per day in three equal doses after meals.

Concurrent use of drugs that might affect the lithogenicity of bile such as sex hormones, antihyperlipidemic drugs, barbiturates, or cholagogues was prohibited.

Number, sex, age, body weight, and height distribution among three groups was well-balanced ($P > 0.10$) (Table 1).

The UDCA was supplied by Tokyo Tanabe Co., Ltd. (Tokyo, Japan). It was 98.5% plus pure with a lithocholic acid content of not more than 0.1% as determined by gas-liquid chromatography and thin-layer chromatography.

The medications prepared as 100 mg and 25 mg tablets were identical with placebo as to color, size, and taste. They were prepacked for each individual patient.

The treatment with bile acid or placebo was continued at least 6 mo and not longer than 12 mo. Even if the stones disappeared in less than 6 mo, treatment was continued up to at least 6 mo for further observation.

The trial began in March, 1975 and ended at the end of August, 1976. The drug code was held by the controller during the trial. When the key code was opened, of the beginning 151 cases at entry, 58 cases (16 cases from 600 mg, 26 from 150 mg, and 16 from control) were judged as dropouts because of long-term (1 mo or more) absence from medication or because of lack of the patient response to follow-up. An additional 21 cases (7 cases from 600 mg, 5 from 150 mg, and 9 from control) were excluded because of choledocholithiasis or insufficient x-ray films. There was no significant difference between the three groups in distribution of analyzed cases as well as dropouts and excluded cases ($P > 0.10$). The average treatment period was about 9 mo in all three groups (294 ± 14 days in the 600 mg group, 296 ± 16 in the 150 mg group, and 279 ± 16 days in control group).

The 72 cases that were analyzed showed no group-to-group inequality with respect to sex, age, body weight, height, treatment period, stone size, presence or absence of calcification, and flotation and complications in each item ($P > 0.10$). The mean doses administered were 10.5 mg/kg/day and 2.7 mg/kg/day in the 600 mg and 150 mg groups, respectively.

Evaluation of Efficacy

Oral or intravenous cholecystography was performed before the trial, at intervals of 3 mo during treatment and after the trial. A standardized cholecystographic technique was not used, but the same technique and conditions were employed in each hospital throughout the study.

First of all, the controller checked the four members of the x-ray film interpreting committee as to reproducibility of judgment individually and the coincidence of judgment collectively with respect to the characteristics and

Table 2. Dissolving Effect of UDCA on Radiolucent Gallstones in a Functioning Gallbladder

	Success		Unsuccess		
Group	Dissolved	Diminished	Unchanged	Enlarged	Fisher's method
Control	1/20	0/20	18/20	1/20	
	(5.0%)		(95.0%)		
UDCA 150 mg/day	2/23	2/23	19/23	0/23	
	(17.4%)		(82.6%)		
UDCA 600 mg/day	7/29	3/29	19/29	0/29	
	(34.5%)		(65.5%)		

	Control	150 mg	600 mg
Control		NS	[a]
150 mg			NS
600 mg			

Numerator shows number of patients judged and denominator shows number of patients in each group. Statistical comparison of "success" vs. "unsuccess" for the three groups was made. NS = no significant difference. [a] $P < 0.05$.

Table 3. Influence of Duration of UDCA Treatment on Gallstone Dissolution

Group	0–3 mo		3–6 mo	
	Dissolved	Diminished	Dissolved	Diminished
Control	0/20	1/20	0/20	1/20
	(5.0%)		(5.0%)	
UDCA 150 mg/day	0/23	0/23	1/23	1/23
	(0.0%)		(8.7%)	
UDCA 600 mg/day	0/29	3/29	3/29	7/29
	(10.3%)		(34.5%)	
Fisher's method	Control: NS; 150 mg: NS; 600 mg: NS		Control: NS; 150 mg: [a]; 600 mg: [a]	

Numerator shows number of patients judged and denominator shows number of patients in each group. Statistical comparison of "success" ("dissolved" plus "diminished") vs. "unsuccess" ("unchanged" plus "enlarged") for the three groups was made, although only "success" cases were tabulated. NS = no significant difference. [a] $P < 0.05$.

changes of gallstones. The reliability of the judgment proved to be more than 85%, so the controller recognized the judgment by the committee to be reliable.

Then, each cholecystogram was interpreted by each committee member. Committee members were not informed of the patient's code. Gallstone size was recorded as the maximum diameter of the largest stone in x-ray film. All cholecystograms which were obtained on follow-up visits were compared with those obtained at the beginning of the trial and judged as "dissolved," "diminished," "unchanged," or "enlarged." "Dissolved" meant disappearance of gallstones, "diminished" indicated more than 40% reduction in size and/or number of gallstones, "unchanged" meant no change in size and/or number, whereas "enlarged" indicated more than 40% increase in size and/or number.

When the stones disappeared, the patient was given the same medication for another month, and cholecystography was performed to confirm the gallstone disappearance.

Clinical Chemistry

Liver function tests (serum bilirubin, SGOT, SGPT, Alk-Pase, LAP, γ-GTP, zinc turbidity test, thymol turbidity test, and ICG clearance test), hemogram (erythrocyte, leucocyte, hemoglobin, and reticulocyte counts), and urine (albumin, glucose, urobilinogen, bilirubin, and sediment) were examined by conventional methods before the trial, in the 2nd and 4th wk and afterwards at intervals of 4 wk during treatment.

Bile Analysis

Duodenal bile rich fluid was collected before and 6 mo after treatment from willing patients. Ten, 13, and 8 specimens in the 600 mg, 150 mg, and control groups, respectively, were collected by duodenal intubation after an overnight fasting. Gallbladder was contracted by duodenal infusion of 25% magnesium sulphate solution. Specimens were kept frozen until analysis. Determination of bile acid composition was made by the method of Okawa et al.[5] Cholesterol and phospholipids were determined by the method of Naka[6] and Chen et al.,[7] respectively. The biliary cholesterol saturation was calculated using the equation of Thomas and Hofmann,[8] and the limit of the cholesterol solubility was as defined by Hegardt and Dam.[9]

Statistics

Data was analyzed by the controller using a nonparametric method. Background was analyzed by the χ^2 test. Fisher's method was applied to the judgment of

Table 4. Dissolving Effect of UDCA on Noncalcified Gallstones

Group	Success		Unsuccess		Fisher's method
	Dissolved	Diminished	Unchanged	Enlarged	
Control	1/15	0/15	14/15	0/15	
	(6.7%)		(93.3%)		
UDCA 150 mg/day	2/16	1/16	13/16	0/16	Control: NS; 150 mg: [a]; 600 mg: NS
	(18.8%)		(81.2%)		
UDCA 600 mg/day	7/24	3/24	14/24	0/24	
	(41.7%)		(58.3%)		

Numerator shows number of patients judged and denominator shows number of patients in each group. Statistical comparison of "success" vs. "unsuccess" for the three groups was made. NS = no significant difference. [a] $P < 0.05$.

Table 5. Dissolving Effect of UDCA in Relation to Size of Gallstones

Group	$d \leqq 5$ (S)		$5 < d \leqq 15$ (M)		$15 < d$ (L)		Fisher's method
	Dissolved	Diminished	Dissolved	Diminished	Dissolved	Diminished	
Control	1/5	0/5	0/7	0/7	0/8	0/8	S: NS; M: NS; L: NS
	(20.0%)		(0.0%)		(0.0%)		
UDCA 150 mg/day	2/5	0/5	0/9	2/9	0/9	0/9	S: NS; M: NS; L: NS
	(40.0%)		(22.2%)		(0.0%)		
UDCA 600 mg/day	5/7	1/7	2/16	2/16	0/6	0/6	S: [a]; M: [b]; L: NS
	(85.7%)		(25.0%)		(0.0%)		

The "d" indicates the maximum diameter of the largest gallstones in millimeters. Numerator shows number of patients judged and denominator shows number of patients in each group. Statistical comparison of "success" ("dissolved" plus "diminished") vs. "unsuccess" ("unchanged" plus "enlarged") among "S" ($d \leqq 5$), "M" ($5 < d \leqq 15$), and "L" ($15 < d$) for each group was made, although only "success" cases were tabulated. NS = no significant difference. [a] $P < 0.05$. [b] $P < 0.01$.

cholecystograms. Results of the bile analysis and clinical chemistry were compared before and after treatment using Student's *t*-test.

Results

Efficacy

Gallstones disappeared in 7 and decreased in size and number in 3 of the 29 cases in the 600 mg/day treatment group, giving a success rate of 34.5%. In the 23 cases of the 150 mg/day treatment group, stones disappeared in 2 and diminished in size and number in 2, a success rate of 17.4%. Gallstones disappeared in 1 of the 20 cases in the control group. There was a significant difference ($P < 0.05$) in efficacy between the 600 mg/day and control groups, but not between the control and 150 mg/day groups and between the 150 mg/day and 600 mg/day groups (Table 2).

In those subjects that responded to treatment, a change in gallstone size and number was seen after 3 mo. In 3–6 mo, UDCA-treatment showed effectiveness in 34.5% of those on 600 mg/day, 8.7% of those on 150 mg/day, and 5.0% of those on placebo. Earlier response was observed in the 600 mg/day group than in the 150 mg/day group ($P < 0.05$) or control group ($P < 0.05$), respectively, but there was no significant difference between the 150 mg/day and control groups (Table 3). If the stones disappeared within 6 mo, disappearance was confirmed by re-x-ray after 1 mo.

Efficacy of UDCA was examined in terms of stone characteristics. With noncalcified (radiolucent) stones, the success rates were 41.7%, 18.8%, and 6.7% in the 600 mg/day, 150 mg/day, and the placebo groups, respectively, and there was a significant difference ($P < 0.05$) between the 600 mg/day and the placebo group (Table 4). Only 1 subject with calcified gallstones who received 150 mg/day showed a decrease in stone size and number.

UDCA-treatment (600 mg/day) was most effective in subjects with stones that measured less than 5 mm in diameter. Such gallstones disappeared in 5

Table 6. Dissolving Effect of UDCA on Floating and Nonfloating Gallstones

Group	Floating stones		Nonfloating stones		Fisher's method
	Dissolved	Diminished	Dissolved	Diminished	
Control	1/6	0/6	0/13	0/13	NS
	(16.7%)		(0.0%)		
UDCA 150 mg/day	2/8	2/8	0/14	0/14	[b]
	(50.0%)		(0.0%)		
UDCA 600 mg/day	3/7	2/7	3/20	1/20	[a]
	(71.4%)		(20.0%)		

Numerator shows number of patients judged and denominator shows number of patients in each group. Statistical comparison of "success" ("dissolved" plus "diminished") vs. "unsuccess" ("unchanged" plus "enlarged") among floating stones and nonfloating stones for each group was made, although only "success" cases were tabulated. In this Table, 2 cases from 600 mg/day group and each 1 case from 150 mg/day and control groups were excluded because the flotation of gallstones could not be confirmed. NS = no significant difference. [a] $P < 0.05$. [b] $P < 0.01$.

Table 7. Dissolving Effect of UDCA on Noncalcified, Less than 15 mm and Floating Stones

Group	Success		Unsuccess		Fisher's method
	Dissolved	Diminished	Unchanged	Enlarged	
Control	1/6	0/6	5/6	0/6	
	(16.7%)		(83.3%)		Control: NS; 150 mg: ^{a}; 600 mg: NS
UDCA 150 mg/day	2/7	1/7	4/7	0/7	
	(42.9%)		(57.1%)		
UDCA 600 mg/day	3/6	2/6	1/6	0/6	
	(83.3%)		(16.7%)		

Numerator shows number of patients judged and denominator shows number of patients in each group. Statistical comparison of "success" vs. "unsuccess" for the three groups was made. NS = no significant difference. ^{a} $P < 0.05$.

cases, diminished in 1, and were unchanged in 1. In 16 cases with stones that measured from 5 to 15 mm, gallstones disappeared in 2 and diminished in 2. No improvement was seen when stone size exceeded 15 mm. The efficacy of UDCA 600 mg was significantly different between less than 5 mm and from 5 to 15 mm ($P < 0.05$) or exceeding 15 mm ($P < 0.01$). Therefore, the size of stones was also found to be an important factor for determining the efficacy of the treatment (Table 5).

In subjects with floating stones which are especially rich in cholesterol,UDCA-treatment was effective in 71.4% on 600 mg/day, 50.0% on 150 mg/day, and in 16.7% on placebo (Table 6). When stones did not float, treatment was less effective in the 600 mg/day group; only 4 of 20 with nonfloating stones showed improvement ($P < 0.05$).

When all factors which affected efficacy were considered together, improvement rate was considerably increased: 83.3% on 600 mg/day and 42.9% on 150 mg/day, if stones were less than 15 mm, noncalcified, and floated (Table 7).

Biliary Lipid Composition

Biliary bile acid composition is shown in Table 8. The UDCA fraction increased significantly in proportion to the dose of UDCA administered. In the 150 mg group, UDCA fraction increased from 3.5% to 18.9% ($P < 0.001$) and in the 600 mg group, from 2.4% to 43.2 ($P < 0.001$), respectively. Significant difference in increase of UDCA fraction was found between high and low doses of UDCA ($P < 0.001$). With respect to lithocholic acid, it increased slightly in the three groups, but these changes were not significant among them. After treatment, satura-

Table 8. Effects of Various Doses of UDCA on Biliary Bile Acid Composition

Group	Bile acid	Cases	Before	After[b]	Statistics[a]
Control	Cholic acid	8	34.6 ± 1.3	37.6 ± 3.5[f]	CA: Control: ^{d}; 150 mg: ^{d}; 600 mg: ^{c}
	Deoxycholic acid		16.8 ± 5.0	20.5 ± 5.0[f]	
	Chenodeoxycholic acid		44.3 ± 5.1	37.8 ± 3.7[f]	
	Lithocholic acid		0.4 ± 0.2	1.2 ± 0.4[f]	
	Ursodeoxycholic acid		3.9 ± 1.4	2.9 ± 0.6[f]	DCA: Control: NS; 150 mg: ^{d}; 600 mg: NS
UDCA 150 mg/day	Cholic acid	13	32.8 ± 2.6	24.8 ± 1.8[e]	CDCA: Control: NS; 150 mg: ^{c}; 600 mg: NS
	Deoxycholic acid		24.3 ± 5.8	20.5 ± 3.4[f]	
	Chenodeoxycholic acid		38.1 ± 2.9	33.0 ± 2.9[d]	
	Lithocholic acid		1.3 ± 0.5	2.8 ± 0.5[c]	
	Ursodeoxycholic acid		3.5 ± 1.5	18.9 ± 1.6[e]	LCA: Control: NS; 150 mg: NS; 600 mg: NS
UDCA 600 mg/day	Cholic acid	10	31.8 ± 2.8	16.2 ± 1.3[e]	UDCA: Control: ^{e}; 150 mg: ^{e}; 600 mg: ^{e}
	Deoxycholic acid		25.9 ± 4.7	13.4 ± 2.3[c]	
	Chenodeoxycholic acid		39.5 ± 4.5	25.9 ± 2.2[d]	
	Lithocholic acid		0.4 ± 0.2	1.4 ± 0.3[f]	
	Ursodeoxycholic acid		2.4 ± 0.9	43.1 ± 3.1[e]	

Mean ± SD. Figures show molar percent of each bile acid in total bile acid. CA = cholic acid. DCA = deoxycholic acid. CDCA = chenodeoxycholic acid. LCA = lithocholic acid. UDCA = ursodeoxycholic acid. ^{a} Statistical comparison for the three groups after treatment was made. ^{b} Statistical comparison for individual bile acid between before and after treatment was made. ^{c} $P < 0.05$. ^{d} $P < 0.01$. ^{e} $P < 0.01$. ^{f} No significant difference. NS = no significant difference.

Table 9. Effect of Various Doses of UDCA on Saturation Index of Bile

Group	Cases	Before	After	Statistics
Control	8	1.32 ± 0.16	1.44 ± 0.09	NS
UDCA 150 mg/day	13	1.42 ± 0.13	1.07 ± 0.07	[a]
UDCA 600 mg/day	10	1.36 ± 0.12	0.78 ± 0.10	[b]

Results are expressed as a saturation index defined by Thomas and Hofman[8] before and after 6 mo treatment. Comparison was made between before and after treatment in each group. NS = no significant difference. [a] $P < 0.10$. [b] $P < 0.05$.

tion index defined by Thomas and Hofmann[8] fell significantly ($P < 0.05$) and bile became unsaturated only in the 600 mg/day group (Table 9).

Side Effects

Out of the 151 cases which started the trial, side effects were seen in 3 of 52 cases (5.8%) in the 600 mg group, 2 of 54 cases (3.7%) in the 150 mg group, and 3 of 45 cases (6.7%) in the control group. The difference was not statistically significant among the groups. The major side effect was diarrhea which was experienced by 3 subjects who received 600 mg/day. However, the diarrhea was just transient and the stools normalized without discontinuing the treatment. No significant body weight change was observed during treatment in all three groups.

Clinical chemistry showed no significant change in serum cholesterol and triglyceride between before and after treatment in all groups, also hematology and urinalysis revealed no abnormality in any case.

Mean value of liver function tests before and after treatment were compared with those patients who received UDCA for more than 6 mo. They were all within normal range. There was no significant changes during and after the administration of UDCA.

Transient elevation of serum transaminases was observed in 2 subjects in the 600 mg/day group (SGOT 63, SGPT 125; SGOT 205, SGPT 131), and in 1 subject each in the 150 mg/day (SCOT 282, SGPT 240) and control groups (SGOT 45, SGPT 121), but the abnormalities were corrected without discontinuing administration of the drug.

Discussion

Indication and Dose Effect

In the present trial, cholelitholytic action of UDCA in humans was confirmed as was true with CDCA.[10] Our results are in good agreement with those of Nakagawa et al.[11] who showed the complete dissolution of gallstones in 8 of 31 cases (25.8%) treated with either 150 mg or 600 mg per day of UDCA for 6 mo.

In evaluating the reason why stones dissolve, the spontaneous disappearance of stones from the gallbladder must be considered. However, the lack of stone disappearance during placebo treatment is similar to that reported by Kameda et al.[12] or Wolpers.[13] Thus, gallstones rarely spontaneously disappear.

The administration of 600 mg/day was almost equivalent to 10 mg/kg body weight in our subjects which was the same dose suggested as optimum by Maton et al.[14] who also showed a significant correlation between the saturation index of the bile and dose administered. Statistically, our results could not demonstrate that there was positive correlation between the dose ingested and the efficacy or between the dose and the desaturation of bile. However, the higher dose seemed to be more effective than the lower dose considering the overall efficacy (Table 2), tendency of earlier response (Table 3), or desaturation of bile (lithogenic index fell down below 1.0 only in 600 mg group).

During treatment with low and high dose of UDCA, no complications such as passage of stones into cystic duct or common duct were observed.

Diarrhea

Loose bowel movements were observed in 3 of 52 subjects who were treated with 600 mg/day (5.8%). However, they occurred transiently and were corrected during the continued administration of the bile acid. In contrast, Ohno et al.[15] have reported that diarrhea occurred in 26% of the subjects treated with the daily dose of 500 mg/day of CDCA. Therefore, loose bowel movements occurred less frequently with UDCA than with CDCA. Similar findings that UDCA did not cause diarrhea in humans were reported by Debongnie and Phillips.[16] Colonic perfusion studies in rabbits carried out by Chadwick et al.[17] demonstrated that CDCA markedly increased the water secretion and permeability of the colon, whereas UDCA had virtually no such effects.

Hepatotoxicity

Elevations of SGOT and SGPT were observed transiently in 4 of the 151 subjects who started the

trial. The mechanism of the elevated serum transaminases by UDCA is unknown. Liver histology was not examined in our study. Bile analysis in the groups treated with UDCA did not reveal any marked increase of lithocholic acid. Intestinal anaerobic bacteria 7-dehydroxylate both CDCA and UDCA to form lithocholic acid. However, less lithocholic acid is formed during incubation with intestinal bacteria with UDCA than with CDCA.[18] In rhesus monkeys, Fedorowski et al.[19] investigated the effects of UDCA and CDCA (40 and 100 mg/kg/day) feeding on hepatic function and showed that the liver function and morphology were normal during UDCA treatment and it was not accompanied by a rise in lithocholic acid in bile. In contrast, these doses of CDCA produced serious hepatic dysfunction and liver lesions in the monkeys and lithocholic acid levels rose substantially in the bile.

Mechanism of Dissolution

Salen et al.[2] observed that UDCA was increased in the bile of some subjects who received CDCA. They postulated that UDCA might play a role in dissolution of gallstones during CDCA treatment.

Like CDCA, the administration of UDCA caused the cholesterol saturation in the bile to fall. The mechanism of this effect is not known. However, preliminary studies[14,19] noted that UDCA, like CDCA, inhibited hepatic HMG-CoA reductase activity, which suggested that UDCA acted by suppressing hepatic cholesterol synthesis.

Since UDCA is a poor solubilizer of cholesterol,[20,21] it may be possible that UDCA also reduces intestinal cholesterol absorption which in turn may affect cholesterol secretion from the liver. However, much remains to be studied.

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