Ursodeoxycholic Acid in the Treatment of Cholesterol Cholelithiasis
Part II

WILLIAM H. BACHRACH, MD and ALAN F. HOFMANN, MD

RESULTS OF CLINICAL TRIALS

Effectiveness

Dissolution of Gallstones. In almost every report of treatment of patients with cholesterol gallstones with UDCA, the calculation of the success rate is based on the sum of the complete and partial dissolutions. In this review, only complete disappearance of the gallstones is accepted as a successful result, since reduction of size during treatment does not guarantee that continued treatment will result in complete dissolution. Data from publications which do not distinguish between partial and complete dissolution in presenting the rate of successful treatment are therefore not included in the tabulations. Furthermore, some of the authors display their data in a way which makes it impossible to understand their results. This is attributable in no small measure to changes of dosage during the trial instead of continuing with a given dose in a given patient.

Where the dose is stated in mg/kg/day, it was certainly not prescribed that way. The investigators prescribed the number of tablets or capsules to be taken daily, then calculated the dose on a weight basis.

The smallest number of patients in any series was 12 (140), the largest 106 (145), the latter a multicenter study. The total number of patients entered in all series (Table 18) was 852, of whom 128 (15%) dropped out. Drop-outs are defined in this review as those patients who chose not to continue or who were withdrawn from the trial for any reason, including cholecystectomy, before it could be determined whether or not the stones could be dissolved. Uncooperative subjects comprised 2/3 of the drop-outs; the remaining 1/3 were withdrawn by the investigator for medical or surgical indications other than cholecystectomy, or because of signs and/or symptoms indicating the need for cholecystectomy.

A total of 724 patients (85% of those entering the trial) continued in treatment, but since many of them had been receiving the drug for only a few months at the time of the reports the data are of limited validity. The dosage of UDCA varied widely, ranging from 150 to 1000 mg/day, or, where the dose was calculated on the basis of body weight, from 3 to 15 mg/kg/day. The majority of the patients had been treated for 12 months or less, with a dissolution rate of 18%; for the relatively few patients treated more than 12 months the rate was 28%. Among 161 patients in whom duration of treatment was not specified the dissolution rate was also 28%. The overall success rate was approximately 20% of those who continued in treatment, 17% of those who entered the studies.

Among the three reports in which a placebo control was included (Table 19), the disappearance rate in patients receiving the placebo was 1/42 (2.4%) while the rate for those receiving UDCA was 23/115 (20%), clearly a highly significant difference.

When the data are analyzed to take into account the dose of UDCA (Table 20) and the size of the gallstones (Table 21), criteria for improving the effectiveness of the therapy become apparent. Regardless of the size of the stones (Table 20), the dissolution rate (12%) in patients receiving 150–250 mg/day was doubled in patients receiving 450–600 mg/day. There were too few patients to make the difference statistically significant, and too few patients receiving a higher dose to make the compari-

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From the Gastroenterology Section, Baylor College of Medicine, Houston, Texas and the Division of Gastroenterology, Universtiy of California Medical Center, San Diego, California.

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Address for reprint requests: Dr. William H. Bachrach, 6565 Fannin B-503, Houston, Texas 77030.

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son meaningful. In the results reported by investigators who calculated the dose on a weight basis, a dose–response effect is, paradoxically, less apparent.

When the size of the gallstones is considered without regard to the dose, a clear size–response relationship emerges (Table 21). In patients with stones larger than 10 mm in diameter, the success rate was only 9%, which was approximately half the rate (17%) in those with stones 5–10 mm, and 1/3 the rate (31%) for stones less than 5 mm. However, the difference is statistically significant only between the latter two stone sizes.

Despite the paucity of data, an attempt was made to relate the success rate to the size of the stones, the dose of UDCA, and the duration of treatment (Table 22). A trend emerges from this analysis suggesting that patients with stones less than 5 mm in diameter have a 30% chance of their gallstones disappearing within one year, many of these within 6 months, on dosages of 600 mg/day and often less. However, since more than 1/3 of the patients were Japanese, a 600-mg dose could well be equivalent to 12 mg/kg/day or more, which is not a small dose for this drug.

People with stones 5–10 mm in diameter are not likely to be liberated from the stones within 6 months, but beyond that time, and mostly within a year, they can expect an 18% prospect of success. Finally, with stones more than 10 mm in diameter, any dissolution which might occur will require more than 6 months, probably more than a year in those cases in which the stones will ultimately dissolve, and the expected success rate is of the order of 1 in 10.

In the experience of Möckel (197), the time required for dissolution can generally be predicted from the size of the stones, as follows:

Size of stones	Duration to dissolution (months)
Pinhead	2–3
Rice kernel	4–8
Pea	6–12
Cherry seed	9–12
Bean	10–15
Hazelnut	12–18
Cherry	12–24

Kajiyama et al (144) proposed yet another criterion for predicting the probable result of treatment. They observed gallstone dissolution (partial or complete) in 7/28 (25%) of normolipidemic patients and 13/25 (52%) in hyperlipidemics (types IIa, IIb, IV) treated with 300 mg/day (5–7.5 mg/kg/day) of either CDCA or UDCA. A factor contributing to the higher success rate may have been the relative incidence of floating stones, 7/28 (25%) in the normolipidemics, 11/25 (44%) in the hyperlipidemics, although the difference is not statistically significant.

TABLE 18. OVERALL RESULTS OF TREATMENT OF PATIENTS WITH RADIOLUCENT GALLSTONES

Source				*Procedure*							
						Drop-outs				*Daily dose*	
Investigator	*Ref*	*Country**	*Yr. 19-*	*Product†*	*No. entered*	*Lost to FU*	*Med ind*	*GB surg*	*Rx contd*	*grams*	*mg/kg*
Okumura	215	J	77	U	89	15		7	67	0.45	
Nakagawa	202	J	77	U	55	11			44	0.15–.6	
Weis	310	G	78	F	33	2		2	29		5–15
Bazzoli	25	I	79	–	40	2		1	37		3–15
Gasbarrini	91	I	79	–	35			1	34		9
Salvioli	258	I	79	Z	50	4		3	43		6.6–15
Ciravegna	58	I	79	–	76	8			68		10–15
Chirone	57	I	79	–	20				20		7–15
Iwamura	146	J	80	U	12				12	0.3–.6	
Sugata	280	J	80	U	83				83		6–12
Kameda	145	J	80	U	106	42	12		52	0.15–.6	
Williams**	313	E	80	D	45			6	39		5–15
Polli	232	I	80	–	78			1	77		5–12
Allesandrini	3	I	80	D	76	5	3	3	65		5–12
Salen	251	U	80	U	21				21	0.25–1.0	
Delmont	71	F	80	–	33				33		5–10
Total					852	89	15	24	724		
Percent						10	2	3	85		
							15				

TABLE 18. *Continued*

Therapeutic effects									
On gallstones				*On symptoms*					
Disappearance of stones (mo)						*Adverse effects*			
0–12	*12*	*Not spec*	*Rate*	*Better*	*Worse*	*Diarrhea*	*Other*	*Abn LFTs*	*Abn Bx*
12/58		4/16	16/89	26/35	1/35	4/74	1/35‡	0/74	
5/31			5/55			0/44		0/44	
	7/23		7/33		3/23	0/23		0/23	
9/32			9/40	19/40		2/37		0/32	
2/34			2/35			3/35	3/35§	0/35	
		14/50	14/50			0/43		0/43	
5/68			5/76			3/76		0/76	
5/20			5/20						
		2/12	2/12	3/7		1/12		0/12	
		25/83	25/83			4/83	3/83¶	0/83	
9/52			9/106			3/106		0/40	
7/21	1/6		8/45	5/5		1/38		0/38	0/5
14/79			14/78	74/78		0/78		0/78	
10/65			10/76			0/65		0/65	
7/21			7/21	14/20		0/21		0/21	
10/33			10/33			0/33		0/33	
95/514	8/29	45/161	148/852	141/185	4/58	21/768	7/153	0/697	0/5
18	28	28	17	76	7	3	5	0	0

*J = Japan E = England G = Germany I = Italy U = United States.
†U = URSO (Tokyo Tanabe); F = URSOFALK (Dr. Falk, Freiburg); D = DEURSIL (Gipharmex, Italy); Z = ZAMBON (S.p.A., Italy).
‡Constipation.
§Acute pancreatitis (1), allergic reaction, unspecified (1), bradycardia (1).
¶Itching.
**Includes data from Maton et al.

These observations could not be confirmed by Bateson et al (20) nor could they (16) identify any patients' characteristics or pretreatment biliary lipid analyses predictive of gallstone dissolution.

On theoretical grounds it would be reasonable to predict that in all patients in whom cholesterol desaturation of bile results from treatment with UDCA, radiolucent gallstones will dissolve. This has not, however, been the case, even when the Carey correction factor (45) has been applied (16) as a measure for distinguishing apparent from actual desaturation.

While some investigators (16, 191, 234, 316) have not found the Carey factor relevant to the prediction of gallstone dissolution, others profess to find it a significant contribution in that direction. Podda and his associates (229) reported that after two months of treatment with a dose of 10 mg/kg/day, UDCA induced a mean reduction of 50% in the cholesterol saturation index versus a 27% reduction with CDCA in the same dosage; with application of the Carey factor the cholesterol-desaturating effect of UDCA was approximately the same as that of CDCA. The relevance of this exercise to the predictability of gallstone dissolution was assumed but not documented. The same applies to the experiments of Marteau and associates (186); biliary fistula subjects receiving single doses of 1, 2, or 3 g UDCA showed a greater reduction in the molar percentages of cholesterol in the bile than did those receiving CDCA. With application of the Carey factor, the saturation index was the same with UDCA as with CDCA. Among 26 patients treated with UDCA by Zuin et al (323) for one year, bile was unsaturated with cholesterol as calculated by both the Hegardt and Dam (118) and the Carey

TABLE 19. RESULTS OF PLACEBO-CONTROLLED STUDIES OF UDCA THERAPY

			Dissolution rate	
Author	*Ref*	*Duration*	*Placebo*	*UDCA*
Bazzoli	25	3 mo	0/09	9/32
Nakagawa	202	6 mo	0/13	5/31
Kameda	145	6 mo	1/20	9/52
Total			1/42	23/115
			$P < 0.01$	

TABLE 20. RELATION OF DOSE TO DISSOLUTION IN PATIENTS TREATED UP TO ONE YEAR

		Dissolution rate per dose in mg/day				
Author	*Ref*	*150–250*	*450*	*600*	*1000*	*Total*
Okumura	215		16/67			16/67
Nakagawa	202	3/16		2/15		5/31
Kameda	145	2/23		7/29		9/52
Salen	251	1/11			6/10	7/21
Total		6/50	16/67	9/44	6/10	37/121
Percent		12	24	20	60	22
			Dissolution rate per dose in mg/kg/day			
			3–6	*10–12*	*15*	*Total*
Weis	310		1/6	4/11	2/6	7/23
Bazzoli	25		3/16	3/8	3/8	9/32
Polli	232		5/36	9/42		14/78
Ciravegna	58			4/25	7/32	11/57
Total			9/58	20/86	12/46	41/200
Percent			16	23	28	20

indices in almost all of those who responded with the dissolution of stones, while only according to the Carey index did the bile remain supersaturated in the majority of nonresponders. In summary, the evidence for the clinical applicability of any index of biliary cholesterol saturation for the individual patient remains tenuous, and the place of the Carey factor is not established.

The dissolution effectiveness indicated in the foregoing review is the minimal rate because (a) the investigators were experimenting with a wide range of doses; (b) some of the patients had not been in treatment long enough to have a 6-month radiographic follow-up; and (c) fully one third of the patients were Japanese, in whom the percentage of pigment stones is much higher than in the other populations studied (121).

It is known that some of the cases showing diminution in the size of the gallstones at the time the results were published have since gone to complete dissolution. Bazzoli et al (25) observed 5 complete and 13 partial dissolutions in 36 patients at the end of 3 months; at the end of 6 months there were 9 complete and 14 partial dissolutions in 32 patients. Calculated on the basis of the total of 40 patients entered, the success rate increased from 5/40 (12.5%) at 3 months to 9/40 (22.5%) at 6 months. In patients receiving the higher dose (10–15 mg/kg/day) the dissolution rate reported by Salen's group (Table 17) was 33%; the rate on longer treatment at the high dose became 75% (296). In the preliminary report of Ciravegna et al (58), there were 5/68 dissolutions with 12 months; in the final report (42), 13 dissolutions occurred among 57 patients treated at least 6 months. Leuschner (172) claims a dissolution rate of 85% in properly selected subjects.

The minimal effective dose is a matter of some difference of opinion. Francavilla et al (86) reported 3/12 complete and 6/12 partial (predictive of eventual complete disappearance) dissolutions after 6 months on a single bedtime dose of 600 mg. Leuschner et al (172) achieved impressive results (85% success) with a dose of 11.5 mg/kg/day, which is in the same range as that (750 mg/day) considered by Bateson et al (21) to be the lowest dose likely to be effective. According to Stiehl (273), pushing the dose above 13 mg/kg/day is counterproductive because beyond that level the bile becomes supersaturated.

Czygan et al (67), motivated by reports (228, 229, 278) that a combination of UDCA with CDCA lowers the cholesterol saturation index more than either alone, undertook a clinical trial of a combination of 7.0 mg/kg of UDCA and 8.3 mg/kg of CDCA. They found the combination to be at least as effective as UDCA alone. The putative advantages of the combination would be (a) reduction of the side effects of conventional dosage with CDCA and (b) a 25% reduction in the cost of UDCA therapy alone.

Whatever the rate of success of therapy with UDCA, the best results seem to be achieved in patients with small (5-mm diameter or less) radiolucent gallstones on a dose of 8–10 mg/kg/day for up to 12 months.

TABLE 21. RELATION OF SIZE OF GALLSTONES TO INCIDENCE OF DISSOLUTION

		Dissolution rate per stone diameter in mm				
Author	*Ref*	*<5*	*5–10*	*>10*	*Other*	*Total*
Okumura	215	6/18	6/22	4/34		16/74
Nakagawa	202	5/8	3/10	0/9		8/27
Weis	310				7/10*	7/10
Bazzoli	25	3/11	2/19	0/6		5/36
Kameda	145	7/12	2/25†			9/37
Salen	251	0/4	5/9	2/8		7/21
Polli‡	232	9/26	4/32	1/20		14/78
Alessandrini	3	4/30	1/22	1/13		6/65
Subtotal		34/109	23/139	8/90		
		<5 mm				
		0.05 5–10 mm				
		0.001 NS	>10 mm			
Total						72/348
Percent						21

*Stones less than 15 mm in diameter. Author compared only the less-than-15-mm size with the greater-than-15-mm. In the latter category there were 11 patients, no complete dissolutions.
†Stones 5–15 mm grouped together.
‡Divided stone sizes into <4, 4–10, and 11–15 mm.

The only adverse symptomatic effect has been an infrequent case of diarrhea, rarely requiring interruption of therapy or even reduction of dose.

Calcification in Previously Radiolucent Stones. Gallstone calcification with consequent arrest of the dissolution process occurred after 6–12 months of treatment with UDCA in 5/54 cases reported by Bateson et al (18) and after 30–40 months in 5/53 cases treated by Tint et al (296). In the latter series, the incidence of calcification was not related to number or size of gallstones or to dosage. Since calcium salts of bile acids are likely to be radiolucent, calcification appearing on gallstones is probably calcium carbonate or calcium phosphate.

Batta et al (23) suggest that this complication may be avoided by administering TUDCA instead of the unconjugated compound; in five patients treated for one month with TUDCA, 1000 mg/day, 40% of the UDCA in the bile was taurine-conjugated in contrast to the 5% taurine conjugation in patients receiving unconjugated UDCA. They speculate that the more polar taurine conjugate would improve gallstone dissolution, and, as predicted by Carey and Igimi (44), circumvent calcification of the stones.

In view of the fact that in the National Cooperative Gallstone Study (264) calcification of gallstones occurred equally (7%) among patients receiving CDCA or placebo, it is not yet possible to state whether calcification occurs more frequently in patients receiving UDCA than in untreated or CDCA-treated gallstone bearers.

Postdissolution Recurrence. Although the true incidence of recurrence after termination of successful treatment has not yet been established, it is already amply clear that the rate will be quite substantial. This disquieting forecast is based on reports that recurrence was observed in 2 of 8 (250) and in 3 of 25 (280) UDCA-treated patients. The tendency to recurrence is not related to age, body weight, size or number of stones, dose or duration of treatment, or degree of lowering of cholesterol saturation index (250) but does appear to be sex-related in that recurrence is proportionately more frequent in females (250). It is likely that recurrence is preventable by continuation of treatment after dissolution has occurred, but the dose required has not been established; only one recurrence ensued in ten patients receiving small postdissolution dosage (100–150 mg/day) for a period of up to two years (280).

Symptoms of Gallstone Disease. In the clinical trials of dissolution of gallstones, information on the effect of UDCA on symptoms ascribed to the gallstones and/or associated cholecystitis is interesting but, in the absence of controls, unconvincing. Since biliary colic was generally not recorded separately from noncolicky abdominal pain, all of the symptoms (those attributable to migrating calculi, nonspecific pain, and dyspepsia not attributable to concomitant gastrointestinal disorders) are lumped together in the analysis of the overall results of treatment (Table 18). Among patients who were symptomatic at the outset, improvement was re-

ported in 76%. In 7% symptoms either occurred for the first time during treatment, or if present beforehand, became more severe. Among the three placebo-controlled studies (Table 19) only one recorded the effect on symptoms, with the following results:

	Before treatment		After 3 months treatment	
	Dyspepsia	Colic	Dyspepsia	Colic
Placebo	10/10 (100%)	6/10 (60%)	6/10 (60%)	1/10 (10%)
UDCA	35/40 (88%)	26/40 (65%)	14/37 (38%)	3/37 (8%)

These data constitute an eloquent testimonial to the therapeutic effects of placebos. So also do the results of a multicenter placebo-controlled double-blind trial (87) designed to evaluate the effectiveness of UDCA in the treatment of pain and of dyspepsia "associated with different biliary tract disorders such as cholecystitis, gallstones, biliary dyskinesia." How these diagnoses were made, except for gallstones, is not stated. "Pain" was defined as right upper abdominal noncolicky pain associated with dyspepsia. The diagnosis of dyspepsia was based on complaints of "postprandial fullness or headache, abnormally frequent belching, pyrosis and acid regurgitations, epigastric pain and meteorism or flatulence." UDCA (150 mg) or an identical-appearing placebo capsule were given morning and evening for two weeks. The trial was completed by 661 patients. Satisfactory improvement (very good, good, moderate—the terms were not defined) of pain was achieved in 80% of subjects receiving UDCA, 49% of those receiving the placebo. For dyspepsia the results were 85% and 53%, respectively. Statistically, the difference between UDCA and placebo was highly significant. The report deserves serious attention in that it confirms the impression derived from uncontrolled studies by a number of investigators (191, 296, 298) and particularly since the results have been confirmed in a smaller controlled study (231). Campa (41) suggests, on the basis of studies of the effect of UDCA on biliary tract dynamics, that the salutary effect of UDCA in dyspeptic patients may be a result of "correction of a possible hypertonic biliary dyskinesia." The results of experiments by Meredith et al (196) suggest to them that the improvement in dyspepsia may be attributed to a modification of the composition, physical chemistry, and solubility of bile acid refluxed from the duodenum into the stomach.

Choledocholithiasis. In a review of the management of common duct stones, Thistle (290) points out that UDCA given orally may be of value in cases where other measures are contraindicated or unsuccessful.

Safety

As has been explained in the review of the literature on the pharmacology of UDCA, this and all bile acids are confined to the enterohepatic circulation except for the amount which spills over into the systemic circulation. Therefore, potentially adverse effects are to be sought in the liver, the gut, and the blood. Also, because of the interrelationship of bile acids and lipid metabolism, particular attention has been directed to the levels of cholesterol and triglycerides in the serum.

Effect on the Liver. Considering that migration of gallstones may cause transient obstruction with consequent shedding of enzymes from hepatocytes into the blood, it is indeed remarkable how rarely such signs of hepatic injury have emerged in the

TABLE 22. RELATION OF GALLSTONE SIZE, DURATION OF TREATMENT, AND DOSE OF UDCA TO INCIDENCE OF COMPLETE DISSOLUTION OF STONES

					Less than 5 mm							
					Up to 6 months				*More than 6 months*			
Investigator	*Ref*	*Country**	*Yr.*	*Product†*	*<300*	*450*	*600*	*1000*	*<300*	*450*	*600*	*1000*
Okumura	215	J	1977	U		1/3				5/15		
Nakagawa	202	J	1977	U					2/4		2/4	
Bazzoli‡	25	I	1979	D	2/5		1/4	0/2				
Iwamura	140	J	1980	U							2/12	
Kameda§	145	J	1980	U	1/5		3/7		1/4		2/4	
Salen	251	U	1980	U					0/3			0/1
Polli	232	I	1980	—		4/11		5/15				
Total					3/10	5/14	4/11	5/17	3/11	5/15	6/20	0/1
					8/24		9/28		8/26		6/21	
Percent					33		32		30.8		28.6	

TABLE 22. *Continued*

5–10 mm								*More than 10 mm*							
Up to 6 months				*More than 6 months*				*Up to 6 months*				*More than 6 months*			
<300	*450*	*600*	*1000*	*<300*	*450*	*600*	*1000*	*<300*	*450*	*600*	*1000*	*<300*	*450*	*600*	*1000*
	1/4				5/18				0/2				4/32		
				1/8		0/2						0/4		0/9	
0/11		0/3	2/5					0/2		0/2	0/2				
						0/10								0/10	
0/9		0/16		0/9		2/16									
				1/3			4/6					0/4			2/3
0/20	1/4	0/19	2/5	2/20	5/18	2/28	4/6	0/2	0/2	0/2	0/2	0/8	4/32	0/19	2/3
1/24		2/24		7/38		6/34		0/4		0/4		4/40		2/22	
4.2		8.3		18.4		17.6		0		0		10.0		9.1	

*J = Japan; U = United States; I = Italy.
†U = URSO (Tokyo Tanabe); D = Deursil 150 (Gipharmex, Italy).
‡Doses were in mg/kg/day, here included under the nearest appropriate column
§Stones classified 5 or less, 5–15, and 15 or larger. The 5 to 15-mm stones are here included under 5–10 column.

clinical trials with UDCA. Most of the investigators (3, 25, 40, 91, 140, 145, 215, 232, 257, 310) state, without presenting their data, that there were no, or only occasional, sustained elevations in the serum levels of enzymes of hepatic origin in patients under treatment for up to 2 years. Only a few have supplied the actual figures (Table 15) for a total of about 120 patients.

The results of only one series (191) suggest a pharmacological effect, possible salutary rather than harmful, on the liver; the serum GGT before treatment averaged 47 units, while in patients receiving doses of 5–15 mg/kg/day, the values were approximately one half to one third the control level. Changes in the alkaline phosphatase were in the same direction, although not to the same degree. Since the average AST (SGOT) in these patients did not change, the diminishing release into the blood of the enzymes associated with cholestasis may be an indication that UDCA facilitates the passage of these enzymes from the cell into the bile canaliculi.

Among 151 patients in the clinical trial conducted by the Tokyo Cooperative Gallstone Study Group (145), transient elevations of transaminases were observed in two subjects receiving 600 mg/day, in one subject receiving 150 mg/day, and in one patient receiving placebo; these abnormalities reverted to normal without interruption of treatment. A similar transient effect was reported by Iwamura (140) in 2 of 12 patients taking 300–600 mg/day.

Altogether, in the published clinical trials comprising some 850 patients, no evidence of liver injury clearly attributable to UDCA has been forthcoming. Liver tissue was obtained (314) in only five patients; no abnormalities were identified by light microscopy. The need for a great deal more information on hepatic morphology, especially as examined by the electron microscope, is obvious. Until such information becomes available one can only assume, from the results of biochemical tests, that UDCA has no hepatotoxic effect. Assumption, however, is not a sufficient basis for considering a drug safe for the market place.

Effect on Bowel Function. The relatively innocuous effect of orally administered UDCA on the intestinal tract was illustrated in a cross-over double-blind trial (305) carried out to compare the effect of CDCA and UDCA on bowel habit in 24 subjects on doses of 15 mg/kg day. Fifteen of the 24 subjects experienced diarrhea while on CDCA, and three of these had diarrhea of only slight degree when treated with UDCA. The nine patients who had no diarrhea on CDCA were free of that symptom on UDCA, whereas among the 21 patients who had no adverse effect of UDCA, 12 experienced diarrhea with CDCA. The three patients with a slight diarrhea while taking UDCA experienced a more intense diarrhea while taking CDCA. These differences were statistically highly significant.

Variations in the incidence of diarrhea are illustrated by the following: among 768 patients in the published clinical trials in which attention was paid to the occurrence of diarrhea (Table 18), this symptom was completely absent in seven of the trials comprising a total of 247 patients. The incidence in

two of the reports (25, 215) was 5.4%, in another (91) 9%. The overall incidence was of the order of 3%. Even this low figure overstates the problem since almost without exception the authors of papers reporting occurrence of diarrhea took pains to emphasize that it was transient, not severe, and resolved spontaneously without reduction of dose. The fact is that in the published trials diarrhea was rarely a problem with UDCA therapy. In the experience of Bateson (14), for example, the dose of drug had to be reduced because of persistent diarrhea in 14/74 patients treated with CDCA versus 0/37 in patients treated with UDCA. In another report from Bateson's group (16), one of 20 patients experienced diarrhea and vomiting which remitted promptly on discontinuation of therapy; the patient was apparently not rechallenged with the drug to verify that the reaction was UDCA-related.

Hematology. Results of blood counts, tests of hemolysis, and biochemical tests (other than cholesterol and triglycerides) are provided in only one of the published reports. Statements have been made that treatment with UDCA produced no changes in blood counts (140, 145), hemolysis (140, 215), or "routine" blood tests (140). Bateson et al (16) presented data showing an increase in platelet counts.

Serum Lipids. Among the 16 clinical trials, data on the effects of treatment on serum cholesterol and triglycerides were provided in seven. It is clear that serum cholesterol was not affected (Table 13). In only two series (258, 315) was there a statistically significant lowering of serum triglycerides (Table 14). In two others (191, 202) there was a trend in that direction, but the number of patients was very small. Whether this would prove to be significant if more subjects were studied remains speculative.

Development of Acute Cholecystitis. The concern has frequently been voiced that the reduction in the size of gallstones during dissolution treatment poses a risk for migration of the stones into the cystic duct, with resulting acute cholecystitis. A major finding in the National Cooperative Gallstone Study (264) was that the incidence of cholecystectomy was no greater in patients whose gallstones were dissolving than in those whose gallstones were not. The same should reasonably apply to patients receiving UDCA.

Other Effects. Adverse effects other than diarrhea (Table 18, column 20), noted in only three of the 16 clinical trials, consisted of three cases of itching and one each of constipation, acute pancreatitis, allergic reaction of unspecified type, and bradycardia. Acute pancreatitis, the only potentially serious condition among those listed, is almost certainly a complication of the gallstone disease rather than an effect of the medication.

Summary. The results of the clinical trials reported in the literature leave little doubt that UDCA is a safe drug for the treatment of gallstones. Effectiveness for the primary indication, as reported in the literature, is unimpressive. Nevertheless, the results of ongoing studies yet to be published in full do provide a basis for predicting that an acceptable dissolution rate can be achieved by limiting treatment to patients in whom therapy is most likely to succeed. Selection of such patients, and more accurate assessment of the endpoint of therapy, will be further facilitated as methods are improved for evaluating the functional status of the gallbladder (306) and the types of gallstones (74, 177), and for verifying that dissolution is indeed complete (267). In the meantime, clinicians undertaking treatment with UDCA should be aware of the limitations of this therapy.

LIMITATIONS OF TREATMENT WITH UDCA

1. UDCA is not a wonder drug. It will not dissolve the calculi in every patient with cholecystolithiasis. It will not dissolve pigment stones, therefore it will not dissolve all radiolucent stones. It will not even dissolve all cholesterol stones, even though this is the primary indication for UDCA therapy. It will not dissolve stones containing calcium, therefore UDCA therapy is contraindicated if the stones have a radioopaque component.

2. Since UDCA therapy is expensive, it should be administered only in cases in which there is high probability, not merely a possibility, that the stones are dissolvable.

3. A patient who has had frequent attacks of biliary colic should not be treated with UDCA unless there is a compelling contraindication to surgery.

Since no information is available on the safety or effectiveness of UDCA during pregnancy, this drug should not be given to women who can become pregnant during the course of therapy. UDCA should not be given to patients with evidence of bile duct obstruction.

Other relative or absolute contraindications to UDCA have not been defined. Since UDCA and its conjugates do not damage the gastric mucosal barri-

er (178), it is permissible to give UDCA to patients with peptic ulcer disease.

4. The first requirement in determining whether a gallstone patient is a promising candidate for UDCA therapy is a technically satisfactory cholecystogram. The cholecystogram must provide information regarding gallbladder function and the presence, size, and composition of the calculi.

A gallbladder which is poorly opacified and does not contract well after stimulation by a meal or cholecystokinin indicates a poor prognosis for gallstone dissolution.

Gas bubbles in the hepatic flexure of the colon overlying the gallbladder should not be mistaken for radiolucent calculi within the gallbladder.

Stones larger than 10 mm in longest cross-section are not likely to dissolve within any reasonable time. Unless there is a contraindication to cholecystectomy, UDCA therapy should not be offered to the patient.

If the stones are within the prescribed size limit, it is important not to overlook deposits of calcium within or enveloping the gallstones. The films should not be over-penetrated; a "soft" x-ray technique is preferable (108).

5. Having established that the gallbladder functions well, that the stones are not an artifact, that they are small enough, and that they do not contain calcium, the next step is to ascertain whether they are made up predominantly of cholesterol. The radiographic diagnosis is, in this respect, not entirely reliable, but if the stones are shown to be completely radiolucent, small and smoothly rounded, they are almost certainly cholesterol stones (28, 303, 318). If UDCA therapy is reserved for patients with such gallstones, the success rate will exceed 50% and may be as high as 80%.

6. Therapy should be initiated at a dose of 10 mg/kg/day, which usually amounts to 750 mg, given as 250 mg after breakfast, 500 mg after the evening meal.

7. The first follow-up filming (or ultrasound scanning in patients sensitive to iodine) should be obtained in 6 months. At this first follow-up, the stones will have disappeared in about 25% of the patients. In those not dissolved, the degree of change in size of the gallstones at 6 months has been reported (22, 314) to be predictive of eventual response to dissolution therapy. This is a helpful generalization, but judgment is required in applying it in the individual case. If there is obvious reduction in the size of the stones in 6 months, UDCA therapy should, of course, be continued.

If there is no reduction in the size of the stones, therapy should be discontinued if (a) the patient has been taking the medication regularly as prescribed and there is no contraindication to cholecystectomy; and (b) the patient has not been taking the medication regularly and cannot be relied upon to follow the regimen.

Therapy should be continued if (a) cholecystectomy is contraindicated in a patient who has taken the medication regularly; and (b) a previously uncooperative but repentant patient promises to start adhering to the regimen.

8. Experience with various brands of UDCA in more than 1000 patients indicates that all biochemical and hematological parameters have remained unchanged during treatment. However, the conservative physician may prefer to determine the transaminase levels before and after one month of treatment.

9. Further imaging of the gallbladder should be performed at 6-month intervals. Therapy should be continued, as long as progressive reduction in size is demonstrable, until the stones disappear completely. If at any further follow-up interval the process of dissolution appears to be arrested, an additional 6-month follow-up cholecystogram should be obtained before abandoning therapy. In the event of complete disappearance of the stones, treatment should be continued at full dosage for 3 months and another imaging performed to confirm the absence of calculi.

10. Once the gallstones are dissolved, the clinician has three options. He can (a) keep the patient on a maintenance dose of 250 mg at bedtime for a stipulated period, eg, 6 months or 1 year, (b) keep the patient on a maintenance dose indefinitely, or (c) discontinue therapy entirely. The tendency for gallstones to recur after complete dissolution provides the rationale for maintenance therapy. On the other hand, three considerations militate against maintenance therapy: (a) in at least 60% of cases, gallstones do not recur during a 2-year postdissolution follow-up (280, 291); (b) recurrent stones dissolve much more quickly than the original stones; (c) some observations suggest that a low-cholesterol diet or the addition of bran to the diet diminishes the likelihood of recurrence. Avoidance of excess body weight is very important. Thus routine maintenance therapy imposes continuing expense on many people who do not need it. It is less costly to

prescribe measures which help forestall supersaturation of bile and to retreat only those patients in whom gallstones recur.

WHITHER UDCA?

Considering its limitations, the question arises whether UDCA is a major therapeutic contribution.

Many authorities believe it is. Leuschner (172) for example, points out that in West Germany six million people have gallstones; 65,000 cholecystectomies are performed annually. He finds that 20–30%, ie, at least 1,200,000 of the gallstone carriers, are legitimate candidates for dissolution therapy; based on at least a 60% dissolution rate in his (172) and others' (197, 296) experience, success could be anticipated in 720,000 patients. Allowing for a 20% recurrence rate, a long-term medical cure would be expected in 576,000. In Leuschner's opinion, these are conservative figures. With strict adherence to the selection criteria outlined above, he (172) and Möckel (197) achieve dissolution in 80% of their patients on a dose of 10 mg/kg/day. The ultimate recurrence rate is not known, but it is likely to be of the order of 50%. But even then, the annual or biennial eradication of gallstones without removing the gallbladder in 360,000 of the six million afflicted would surely be a significant achievement; if gallbladders can be freed of stones at a rate of 5–10 times the annual incidence of gallstone disease, the prevalence must decrease dramatically.

On the other hand, those who are unimpressed with dissolution therapy (139, 168, 195) are influenced primarily by the dismal results obtained with CDCA in the National Cooperative Gallstone Study (264), especially in view of (a) the long and burdensome follow-up (periodic blood tests and imagings of the gallbladder), (b) the drop-out rate, (c) the expense (which approximates or exceeds that of cholecystectomy), (d) the side effects (diarrhea, transaminasemia, elevation of serum LDL), (e) the length of time required for complete dissolution, (f) the need for surveillance after dissolution to detect recurrences, and (g) the substantial recurrence rate. Thus, a number of respected authorities continue to view the prospects for medical dissolution therapy with the same skepticism as those expressed in 1972 by Isselbacher (138), and in 1975 by Haubrich, (116) who wrote: "Can we dissolve gallstones? Yes, but right now the best way probably is to perform a cholecystectomy and put the stones in a beaker of ethyl ether."

The results of the National Cooperative Gallstone Study (264) are not a valid basis for judging the effectiveness of dissolution therapy; the dosages used were inadequate. The evidence reviewed herein indicates that in properly selected cases, which in the United States would comprise approximately three million gallstone bearers, complete dissolution of stones with UDCA therapy in a dose of 8–10 mg/kg will occur in at least 50% of cases. This can be achieved with minimal blood testing (since UDCA is rarely a cause of hepatic injury), with fewer drop-outs (since the drug is virtually free of side effects), and in an acceptable (6–12 months) period of treatment. Calcification of radiolucent stones during treatment occurs in 10% of UDCA-treated patients, which may not be much higher than the incidence of spontaneous calcification. The Achilles heel of UDCA therapy is the potential recurrence rate. There is no reason to assume that the incidence of recurrence after UDCA treatment

TABLE 23. SUMMARY OF REPORTS COMPARING URSODEOXYCHOLIC ACID (UDCA) AND CHENODEOXYCHOLIC ACID (CDCA)*

Author	*Ref*	*Experimental model*	*Effects compared*	*Results*	*Clinical implication favors*		
					UDCA	*CDCA*	*No difference*
I. Physical chemistry							
Igimi	135		1. Solubility at intestinal pH	UDCA less soluble, may be less well absorbed		X	
			2. Solubility at colonic pH	UDCA less likely to cause diarrhea	X		
Montet	200		Surface tension of monomolecular films	Surface tension lowered better with CDCA		X	
Hisadome	125		C solubilizing capacity	UDCA–lecithin micelle solubilizes less C		X	
Park	221		Gallstone dissolution *in vitro*	Equally rapid in "urso-rich" and "cheno-rich" bile			X

TABLE 23. *Continued*

Author	Ref	Experimental model	Effects compared	Results	Clinical implication favors UDCA	CDCA	No difference
Carey	44		Deposition of Ca on gallstones during R_x	More likely with GUDCA than with GCDCA		X	
Mazer	193		Size of micelles	UDCA forms smaller micelles, solubilizes lecithin much less effectively		X	
II. Pharmacology							
A. Metabolism							
Hardison	109	Rat	T_m	Much higher with UDCA	X		
Götz	98	Isolated liver cells	Uptake of bile acids	Both concentrated 100-fold			X
Marigold	185	Human	Extraction by the liver	UDCA less efficiently extracted		X	
von Bergmann	32	Human	Hepatic secretion of bile acids	Same increase with both			X
Roda	247	Human	Bile acid pool size	Unchanged with both			X
Bazzoli	26	Human	Formation of LCA in the colon	Same amount formed by both			X
Fedorowski	82	Human	Production of LCA by colonic flora	More rapid with CDCA than with UDCA	X		
Salvioli	257	Human	Formation of LCA by bacterial enzymes	Less formed from UDCA	X		
Sarva	262	Rhesus monkey	Lithocholate in bile	Increased with both			X
Bazzoli	24	Rhesus monkey	Lithocholate in bile and serum	Increased with both			X
Stiehl	276	Human	Biliary lithocholate	LCA and LCA sulfate lower with UDCA	X		
Fedorowski	83	Rhesus monkey	Lithocholate in bile	Elevated with CDCA only	X		
Kurtz	159	Rat	Bile acids in small intestinal wall	LCA higher after CDCA	X		
Stiehl	276	Human	Serum bile acid concentrations	LCA higher with CDCA	X		
B. Pharmacological Effects							
1. Liver							
Hatanaka	113	Cell-free extracts of yeast	Inhibition of conversion of acetate to C	UDCA twice as effective	X		
Gilmore	93	Dog	Choleresis	Induced by both			X
Yanaura	320	Dog	Choleresis	Induced by both			X
Gilmore	93	Dog	Canalicular permeability	Unchanged by both			X
Yamatake	319	Dog	Intraportal injection on portal blood flow and liver tissue blood flow	Diminished by CDCA only	X		
Carulli	51	Human	Hepatic HMGCoAR activity	Decreased by CDCA, increased by UDCA		X	
Maton	191	Human	Hepatic HMGCoAR activity	Reduced by both			X
Carulli	51	Human	Hepatic 7α-hydroxylase activity	Not significantly different			X
Carulli	51	Human	Hepatic microsomal C content	Significant decrease with UDCA only	X		
Thistle	292	Human	Suppression of synthesis of CA	More suppression with CDCA		X	
Gilmore	93	Dog	Hepatic C secretion	Induced by both			X
Marteau	186	Human	C content of bile	Decreased more effectively with UDCA	X		
Stiehl	278	Human	C content of bile	Decreased more effectively with UDCA	X		
Gilmore	94	Human	C content of bile, C saturation	UDCA lowers both more effectively	X		

TABLE 23. *Continued*

Author	*Ref*	*Experimental model*	*Effects compared*	*Results*	*Clinical implication favors*		
					UDCA	*CDCA*	*No difference*
Williams	314	Human	Desaturation of bile	Achieved with lower dose of UDCA	X		
Kajiyama	144	Human	Lithogenic index in hyperlipidemics	Equally reduced with both			X
Thistle	292	Human	C saturation index	UDCA unsaturates bile at a lower dose	X		
von Bergmann	32	Human	Lithogenic index of hepatic bile	Comparable decrease with both			X
Stiehl	276	Human	Biliary C saturation	Significantly lower with UDCA	X		
Gilmore	93	Dog	Hepatic PL secretion	Induced by both			X
von Bergmann	32	Human	Hepatic PL secretion	Greater increase with CDCA			
Horak	130	Isolated baboon liver	Biliary lipid secretion	C increased by both, PL by UDCA only	X		
Gurantz	102	Hamster	Biliary lipid secretion	Increased secretion of C with both			X
Roda	248	Human	C and PL secretion in bile	UDCA lowered C, increased PL more effectively	X		
Pearlman	224	Hamster	Gallstone prevention on gallstone-inducing diet	Gallstones prevented by both			X
2. Intestine							
Caspary	53	Rat	Absorption of water and sodium from ileum and colon	UDCA produced much less inhibition	X		
Gordon	97	Rat	Movement of water and sodium in isolated loop of cecum	Increased secretion with CDCA only	X		
Rahban	240	Rabbit	Secretion into ileal and colonic loops	Increased secretion with CDCA only	X		
Chadwick	55	Rabbit	Absorptive function and permeability of colon	Only CDCA induced net water secretion and increased permeability	X		
Debongnie	70	Human	Water and sodium absorption in the colon	Reduced by CDCA only	X		
Reynier	245	Mouse	Absorption of C	Less with UDCA	X		
Reynier	244	Rat	Uptake of C by everted jejunal sacs	Much less from UDCA	X		
Ponz de Leon	235	Human	Absorption of C	Both decreased			X
LaRusso	166	Human	Absorption of C	No effect with either			X
Roda	246	Human	Absorption of C	No effect with either			X
Walker	307	Rat	Absorption of bile acid conjugates in ileum and colon	Equal with both			X
Nakamura	204	Hamster	Glucose absorption by everted intestine	Inhibited by CDCA only	X		
Kurtz	159	Rat	Absorption of digitoxin	Delayed by CDCA only	X		
Rahban	240	Rabbit	Nucleotides in colonic mucosa	Changes with CDCA only	X		
Caciagli	38	Human	Nucleotides in colonic mucosa	CDCA increases cAMP and cGMP, UDCA only cAMP	X		
C. Toxicology							
1. Liver							
Kimura	150	Human hepatocytes	Morphology	CDCA more toxic	X		
Nakayama	206	Human hepatocytes	Morphology	CDCA more toxic	X		
Dancygier	68	Rat	Liver cell proliferation	More severe with CDCA	X		
Leuschner	176	Rat	Ultrastructure	Severe damage with CDCA only	X		

TABLE 23. *Continued*

Author	*Ref*	*Experimental model*	*Effects compared*	*Results*	*Clinical implication favors*		
					UDCA	*CDCA*	*No difference*
Fedorowski	83	Rhesus monkey	Ultrastructure	Injury with CDCA only	X		
Sarva	262	Rhesus monkey	Ultrastructure	Injury with both			X
Celle	54	Pregnant rat	Ultrastructure	Injury with both at highest dose			X
Wolfson	317	Rabbit	Morphology	Both toxic to liver			X
Kimura	150	Human hepatocytes	LDH activity	Greater increase with CDCA	X		
Hatoff	114	Rat hepatocytes	Accumulation of APT	UDCA induced less cholestatic effect	X		
Nakayama	162	Human hepatocytes	Release of hepatic enzymes	Much greater with CDCA	X		
Schölmerich	265	Isolated hepatocytes	Release of enzymes	With CDCA only	X		
Hatoff	115	Rat	Release of APT when bile duct was obstructed	Induced by CDCA only	X		
Wolfson	317	Rabbit	Blood levels of hepatic enzymes	Elevated by both			X
Fedorowski	83	Rhesus monkey	Release of hepatic enzymes	With CDCA only	X		
Sarva	262	Rhesus monkey	Release of hepatic enzymes	With both			X
Iwamura	140	Human	Release of hepatic enzymes	Less frequent with UDCA	X		
Williams	314	Human	Release of hepatic enzymes	With CDCA only	X		
2. Gastrointestinal tract							
Lillemoe	178	Dog	Effect of taurine conjugates on gastric mucosal barrier	Damage more severe with TCDCA	X		
Gordon	97	Rat	Mucosal alterations	With CDCA only	X		
Czygan	65	Rat	Cocarcinogenicity in DMH induced colon carcinoma	Both equally cocarcinogenic			X
Chadwick	55	Rabbit	Morphology of colon	Loss of epithelial cells after CDCA only	X		
3. Other							
Celle	54	Rat	Embryotoxicity	Statistically significant after CDCA only	X		
B. Clinical aspects							
1. Therapeutic effects							
Iwamura	140	Human	Gallstone dissolution	Similar with both			X
Polli	186	Human	Gallstone dissolution	UDCA effective in lower dose	X		
Williams	314	Human	Gallstone dissolution	UDCA effective in lower dose	X		
Leuschner	175	Human	Gallstone dissolution	UDCA effective in lower dose	X		
Polli	232	Human	Dyspepsia/pain	Improved equally with both			X
Williams	314	Human	Biliary colic and dyspepsia	Improved equally with both			X
2. Effect on blood lipids							
von Bergmann	32	Human	HDL cholesterol	CDCA decreased, UDCA increased	X		
Thistle	293	Human	HDL cholesterol	Same increase with both			X
			VLDL cholesterol	No change with either			X
			LDL cholesterol	Decreased with UDCA only	X		
Carulli	50	Human	HDL cholesterol	Increased after CDCA only		X	

TABLE 23. *Continued*

Author	*Ref*	*Experimental model*	*Effects compared*	*Results*	*Clinical implication favors*		
					UDCA	*CDCA*	*No difference*
Williams	314	Human	Triglycerides	Decreased with UDCA only	X		
von Bergmann	32	Human	Triglycerides	Decreased with CDCA only		X	
Carulli	50	Human	Triglycerides	Decreased with CDCA only		X	
Bateson	15	Human	Hypertriglyceridemia	Decreased with CDCA only		X	
Chirone	57	Human	Hypertriglyceridemia	Decreased with CDCA only		X	
von Bergmann	32	Human	Atherogenic index	CDCA increased, UDCA decreased slightly	X		
3. Side effects							
Bateson	14	Human	Diarrhea	With CDCA only	X		
Polli	232	Human	Diarrhea	With CDCA only	X		
Williams	314	Human	Diarrhea	With CDCA only	X		
Volpi	305	Human	Diarrhea	Much more frequent with CDCA	X		
Iwamura	140	Human	Diarrhea	Less frequent with UDCA	X		
Ruppin	250	Human	Postdissolution recurrence of stones	Less frequent with UDCA	X		

*C = cholesterol; PL = phospholipid; APT = alkaline phosphatase.

will be less than that after CDCA treatment, which in one series amounted to 70% in 5 years after dissolution.

When bile acid therapy is discontinued, bile returns to its supersaturated state, reestablishing the conditions which led to the formation of gallstones in the first place. It is therefore logical to expect that a commitment to UDCA therapy is a life-long commitment. With a low-risk, curative operation available, it is no wonder that many observers doubt that UDCA therapy is worthwhile.

COMPARISON OF UDCA AND CDCA

With the emergence of UDCA as an alternative to CDCA for the dissolution of gallstones, it was inevitable that studies should be undertaken to compare the properties of the two compounds. The resulting literature is so extensive that it is more conveniently summarized in tabular rather than in discussion form. In many of these reports (Table 23) the authors drew conclusions regarding the clinical implications of their findings, ie, whether the results suggested that one or the other of the two bile acids would be safer or more effective, or both, in the treatment of cholesterol cholelithiasis. Where such conclusions were not stated by the authors but could be reasonably inferred from their findings, we have made the appropriate entry in the column "Clinical Implication Favors . . .". It will be seen that in most instances the experimental observations favor UDCA. However, this does not relieve the clinician of the responsibility for individualizing the patient with regard to the selection of UDCA or CDCA for an attempt at gallstone dissolution. In a chronically constipated person, for example, it may be preferable to start therapy with CDCA; if it is well tolerated, as it is in the great majority of patients, the fact that it is much less expensive would make CDCA the bile acid of choice for initiating therapy (195).

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