Dissolution of gall stones with an ursodeoxycholic acid menthol preparation: a controlled prospective double blind trial

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SUMMARY In a controlled prospective double blind trial patients with cholesterol gall bladder stones are treated with ursodeoxycholic acid (group A: UDCA 11.1 mg/kg per day; n=16) and Ursomenth respectively (group B: a mixture of UDCA/menthol: 4.75 mg/kg per day each; n=17). With same stone number and size (10-12 mm) there is a complete dissolution rate in group A of 38%, and of 53% in group B within 15-16.9 months. The response rate (complete+partial dissolution) amounted to 75% and 76% respectively. In group A there is one case of stone calcification, in group B none. Both preparations are free of unwanted effects. This suggests that the cyclic monoterpene menthol enhances the effect of UDCA and is of comparable effect to a mixture of six different terpenes used in former times.

In 1979 Bell and Doran¹ reported the treatment of 24 patients with cholesterol stones of the gall bladder and the bile ducts with Rowachol^{(R)*}, one capsule/10 kg/day. After six to 12 months the stones had dissolved in four patients partially and in three patients completely. In 1981² the same group reported on Rowachol treatment of 13 patients with bile duct stones. In eight of 13 patients the concretions had vanished. In 1984 the authors³ administered Rowachol (one capsule twice daily) plus 7.0-10.5 mg/kg/day chenodeoxycholic acid (CDCA) to 29 patients with gall stones. After two years the stones were completely dissolved in 15 patients. Finally in 1985 the same group⁴ reported on the treatment of 19 patients with common bile duct stones with Rowachol and 15 patients with the combination Rowachol and CDCA (CDCA: 3.8-16.6 mg/kg/day; n=11) or ursodeoxycholic acid (UDCA: 4.5-7.1 mg/kg/day; n=4). In the first group eight of 19, in the second group 11 of 15 patients

became stone free. Perhaps Rowachol may even dissolve calcified cholesterol stones.⁵

Rowachol is a mixture of six cyclic monoterpenes: menthol, menthone, pinene, borneol, camphene and cineol.⁶ From the first stone dissolution with Rowachol by Sarreither in 1955 (Sarreither W, *Medizinische Monatsschrift* 1955; 9:97 cited according to ref 6) until today all patients were treated either with this mixture alone or in combination with CDCA and only four patients with UDCA. None of the studies were undertaken in double blind form.

Therefore we carried out the following investigations that should elucidate three questions: (1) Can the cholelitholytic effect of terpenes be corroborated in a controlled prospective double blind study? (2) Is the combination of menthol with UDCA as effective as the combination of six terpenes with CDCA? (3) Is the mixture of six terpenes necessary or will the use of menthol do?

STUDY DESIGN

The study was done as a controlled prospective double-blind trial for 24 months. Forty patients with symptomatic radiolucent gall stones were admitted in two groups of 20 patients each. Patient selection was done by sonography, plain gall bladder radiograph

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Table 1 Data on all patients allocated to group A (UDCA)

n	Sex	Age (years)	Height (cm)	Weight (kg)	Overweight (De Broca)	Stones	
						n	Size of the biggest stone (mm)
1	F	61	158	63	27.8%	1	8
2	F	73	154	85	85.2%	20	6
3	F	53	170	70	17.6%	1	15
4	F	62	170	73	22.7%	2	15
6	F	74	162	67	27.1%	10	11
8	F	35	156	65	36.5%	2	7
10	F	45	170	65	9.2%	2	15
12	F	59	160	68	33.3%	10	5
13	F	77	157	64	31.9%	15	10
14	M	60	172	85	31.2%	3	6
15	M	55	179	85	19.5%	1	12
18	F	31	164	120	120.6%	3	15
20	M	67	172	75	15.7%	1	5
21	F	31	168	74	17.6%	1	15
22	F	29	174	119	89.2%	3	15
29	F	34	183	73	3.5%	10	5
31	F	46	158	78	58.2%	6	15
33	M	38	168	75	22.5%	8	7
35	F	50	172	63	2.9%	1	6
39	M	52	185	105	37.2%	6	7
Mean	F : 15	51.6	167.6	78.6	35.47%	5.3	10.0
	M: 5						

Table 2 Data on all patients allocated to group B (Ursomenth)

n	Sex	Age (years)	Height (cm)	Weight (kg)	Overweight (De Broca)	Stones	
						n	Size of the biggest stone (mm)
5	F	45	160	77	51%	4	15
7	F	48	162	55	1.5%	6	8
9	F	45	161	70	34.8%	2	9
11	F	40	153	58	28.7%	5	14
16	F	69	153	74	64.3%	10	12
17	F	42	170	66	10.9%	8	13
19	F	17	164	60	10.3%	10	10
23	F	62	163	69	8.7%	8	14
24	M	40	166	78	31.3%	2	7
25	F	34	160	65	27.4%	1	13
26	M	57	172	100	54.3%	1	15
27	F	33	160	70	37.2%	10	6
28	F	36	154	90	96.01%	7	15
30	M	63	172	85	31.2%	5	8
32	F	63	172	78	27.4%	2	10
34	F	61	168	60	3.8%	10	6
36	F	52	150	63	48.2%	2	8
37	F	51	170	61	2.5%	7	8
38	F	38	166	64	14.1%	1	9
40	F	55	152	62	40.3%	2	13
Mean	F : 17	47.6	162.4	70.3	31.2%	5.1	10.7
	M: 3						

and oral or intravenous cholecystography. The patients' allocation to group A and B and the assessment of the results were done by the Institut für Medizinische Datenverarbeitung, Grebenhain, FRG. The study was approved by our local ethics committee. All patients gave written consent to participation. Sex, age, size, weight, and stone number of groups A and B are given in Tables 1 and 2.

Group A received UDCA as monotherapy. Group B received Ursomenth, a combination of 100 mg UDCA and 100 mg menthol in one capsule. Both UDCA and menthol are registered in the German AMG (AMG 76); their purity corresponded to the requirements of the DAB8†. Ursomenth was packed in gastric juice resistant soft gelatinous capsules (Scherer, FRG). All preparations were provided by the company Steiner & Co, Deutsche Arzneimittelgesellschaft, Berlin, FRG.

Patients weighing less than 50 kg received two capsules UDCA of 250 mg or Ursomenth at bedtime. From 50–75 kg we gave one capsule at noon, two capsules at bedtime. In cases of 75–100 kg body weight we gave one capsule at noon and three capsules at bedtime. Cases of 100–125 kg received one capsule at noon and four at bedtime. The mean UDCA dosage amounted to 11.1 mg/kg per day; the

mean Ursomenth dosage was 9.6 mg/kg per day. This corresponds to 4.8 mg UDCA+4.8 mg menthol/kg per day. Only complete and not partial dissolution was considered as therapeutic success.

The patients were first examined by sonography, radiology, and laboratory tests (BSR, WBC, RBC, SGOT, SGPT, GGT, AP, bilirubin, albumin, total protein, BUN, creatinine, triglycerides, cholesterol, uric acid, potassium, calcium, sodium, chloride, fasting glucose). Follow up: every six months ultrasound sonography of upper abdomen, every two months the aforementioned laboratory tests were done.

Results

In group A four patients dropped out, in group B three dropped out which meant that seven patients wished to leave the study without any contraindications. Hence 33 patients fulfilled all the study requirements (group A: 16; group B: 17) and were treated.

Group A (treated patients) comprised four men and 12 women. Group B comprised two men and 15 women. The mean age of group A was 48.8 years and of group B 48.6 years. The mean body weight of group A was 79.7 kg and of group B 68.5 kg. The mean stone number of group A was 4.2 and of group B 4.7. The mean stone size in group A was 9.6 mm

†Neither the Ames test nor the DNA repair test (National Cancer Institute, USA) gave any indication of carcinogenic effect.

Table 3 Results of UDCA treatment (group A; n=16)

n	UDCA (mg/kg/day)	Stones (n/mm)	Dissolution time (months)
4	10.3	2/15	24
14	11.8	3/6	6
20	10.0	1/5	18
22	10.5	3/15	24
29	10.3	10/5	6
35	11.9	1/6	12
Mean	10.8	3.3/8.7	15.0
1	11.9	1/8	Partial dissolution
6	11.2	10/11	Partial dissolution
8	11.5	2/7	1 calcification, 1 dissolved
10	11.5	2/15	Partial dissolution
12	11.5	10/5	—
18	10.4	3/15	—
21	10.1	1/15	Partial dissolution
31	12.8	3/15	Partial dissolution
33	10.0	8/7	—
39	11.9	6/7	—
Mean	11.3	4.6/10.5	—

Mean UDCA dosage: 11.1 mg/kg/day; complete dissolution: 6/16 (38%); partial dissolution: 6/16 (37%); response rate: 75%; mean treatment time until dissolution: 15.0 months.

and in group B 10.5 mm. Thus groups A and B were well matched (Tables 1 and 2).

In group A stones dissolved completely in six of 16 patients (37.5%) and partially in another six of 16 (37.5%). In group B there was complete dissolution in nine of 17 patients (53%) and partial dissolution in four of 17 (23%). This difference is statistically not significant. One patient from group B had to be withdrawn in the 18th month of treatment because of colic. He was considered as a non-responder. In group A UDCA responders had approximately the same stone number as non-responders but stones of the non-responders were some 2 mm larger than those of the responders. In group B stone number was the same in responders and non-responders too but the stone size of non-responders was larger (Tables 3 and 4). When groups A and B are compared with respect to the stones dissolved, in the Ursomenth group we dissolved rather more and larger stones than in the UDCA group. In group A one patient experienced stone calcification after one of his two stones had completely dissolved. In group B there was no stone calcification. The mean treatment time amounted to 15 months in group A and 16.9 months in group B. The differences between stone size and number and dissolution time are not significant in groups A and B. That means that Ursomenth had dissolved the same number and equally large stones in the same time as UDCA. Complete and partial dissolution, individual UDCA/menthol dosage and treatment time are given in Tables 3 and 4.

Table 4 Results of ursomenth treatment (group B; n=17)

n	Ursomenth (UDCA/menthol: mg/kg/day)	Stones (n/mm)	Dissolution time (months)
7	5.5	6/8	6
17	4.5	8/13	24
27	4.3	10/6	24
30	4.7	5/8	20
32	5.1	2/10	24
36	4.8	2/8	8
37	4.9	7/8	14
38	4.7	1/9	8
40	4.8	2/13	24
Mean	4.8/4.8	4.8/9.2	16.9
5	5.2	4/15	Partial dissolution
9	4.3	2/9	—
11	5.2	5/14	Partial dissolution
16	4.0	10/12	—
23	4.3	8/14	Partial dissolution
24	5.2	2/7	—
25	4.6	1/13	Even resistant to MTBE
28	4.7	7/15	Withdrawal after 18 months; partial dissolution
Mean	4.7/4.7	4.9/12.4	—

Mean UDCA/menthol dosage: 4.8 mg/kg/day; complete dissolution: 9/17 (53%); partial dissolution: 4/17 (23%); response rate: 76%; mean treatment time until dissolution: 16.9 months.

Both types of medication were free from unwanted effects. Laboratory tests were comparable in all groups. Apart from colic we noticed a rise in SGOT, SGPT, AP, or GGT of short duration. In almost all patients complaints decreased considerably and disappeared completely in the end. In group B one patient developed severe colic, he underwent surgery, and was classified as a non-responder.

Discussion

Ursomenth induced in 53% of those patients treated complete stone dissolution, UDCA in 38%. When the percentage of partial stone dissolution is added – which we did not consider as therapeutic success – then the response rate in group A amounted to 75% and in group B to 76%. In other words the result is almost identical for both types of medication. It is unlikely that the Ursomenth result can be ascribed to the UDCA portion in Ursomenth alone. This would mean that 4.8 mg UDCA/kg per day corresponded to the 2.3-fold higher dosage of 11 mg UDCA/kg/day. The Franco-Belgian study group^{7,8} has shown, however, that already a UDCA dosage of 8.4 mg/kg/day can significantly improve the dissolution rate compared with the half dosage of 4.2 mg/kg/day.⁷ This is in keeping with results of Dowling *et al*⁹ who showed in 55 responders that the optimal dosage is 9.6

Table 5 Studies showing dose dependency of gall stone dissolution with UDCA

Reference	Patients (n)	Stone size (mm)	UDCA dose (mg/kg/day)	Complete dissolution (%)
Salen <i>et al</i> (1980) ¹⁰	10	<15	3.6	10
	10	<15	14.3	60
Tokyo Coop. Study Group (1980) ¹¹	23	<5 to >15	2.7	8.7
	29	<5 to >15	10.5	24.1
	5	<5	2.7	40.0
	7	<5	10.5	71.4
	9	5–15	2.7	0.0
	16	5–15	10.5	12.5
	7	Floating	2.7	28.6
	6	Floating	10.5	50.0
Inter-Hospital Clinical Research Group (1981) ¹²	36	<15	5–6	13.9
	42	<15	10–12	28.6
Podda <i>et al</i> (1982) ¹³	24	<20	4.0	8.3
	24	<20	8.0	12.5
	23	<20	12.0	21.7
Franco-Belgian Study Group (1983) ⁷	34	No data	2.1	29.4*
	37		4.2	37.8*
	38		8.4	52.5*
	41		16.3	48.8*

*Complete plus partial dissolution.

mg/kg/day and in 29 non-responders that a dosage of 7.2 mg/kg/day is already suboptimal. Other authors consider 8 mg/kg/day to be the optimal dosage;⁷ 4.2 mg/kg/day are considered suboptimal. Further studies which confirm these results are given in Table 5.^{7,10–13} Because we procured the same or even better results with 4.8 mg UDCA as with a 2.3-fold higher dosage, this suggests an enhancing effect of menthol.

In the UDCA group we observed stone calcification in one patient, none in the Ursomenth group. Unfortunately, to date we are not sure whether stone calcification under UDCA is dose dependent.¹⁴ Should this be the case, then Ursomenth would represent a preparation preventing stone calcification. Investigations of Ellis *et al*⁵ would support this possibility where the terpene mixture of Rowachol even produced diminishing of calcified concretions. As Neuberger and Grauer¹⁵ showed in 1951, menthol secreted into bile in the form of glucuronide obviously improves the solubility of calcium carbonate and phosphate.

Our study suggests that terpenes have an adjuvant effect in stone dissolution with UDCA, that the effect of UDCA is comparable with that of CDCA³ in a combination preparation and that it is obviously not necessary to use a mixture of terpenes. The terpene menthol had the same effect as the Rowachol mixture.

The mode of action of terpenes has not been definitively clarified. In 1976 Kodama *et al* showed¹⁶ that the monoterpene d-limonene lowered the ratio

bile acids and phospholipids to cholesterol in rats. In 1979 Doran *et al*¹⁷ reported that the terpene mixture Rowachol in a low dosage will lower the cholesterol concentration in bile but increase in high dosage. Finally in 1980 Clegg *et al*¹⁸ showed that the terpenes menthol and cineol inhibit HMG-CoA reductase by 70%, borneol and menthone by 50% and that the terpenes pinene and camphene are without effect. As of the four effective terpenes in Rowachol cineol is present only in 2%, borneol in 5%, menthone in 6% but menthol in 32% concentration,⁶ the effect of Rowachol should be predominantly caused by menthol. This should explain why we have seen the same effect with Ursomenth as with Rowachol. Doran *et al*¹⁷ have reduced the cholesterol concentration with a total menthol dosage of 192 mg/day. In a dosage of 512 mg/day they noticed a rise. We administered 331 mg menthol per day with Ursomenth and therefore we could speculate whether the amount of menthol in Ursomenth could not be reduced.

Furthermore, Rowachol has a choleretic effect and it is said to be a non-specific enzyme inducer.¹⁹ Igimi *et al* and ourselves^{20,21} reported that the terpenes d-limonene and cineol would dissolve cholesterol stones *in vitro* too and thus the effect described by Clegg *et al*¹⁸ for terpenes on HMG-CoA reductase is obviously not their only effect.

Whether the UDCA/menthol mixture will achieve an equally favourable dissolution rate in larger stones as UDCA monotherapy still has to be investigated in a considerably larger number of patients. The promising results discussed here in stones of an average of 10–12 mm suggest at least that UDCA/menthol might be useful for recurrence prophylaxis. Stone recurrence after UDCA treatment is found in 20–50%^{22,23} and therefore a cheap preparation for longterm treatment is needed without unwanted effects.

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