PAPERS AND ORIGINALS

Resistance to chenodeoxycholic acid (CDCA) treatment in obese patients with gall stones*

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Summary and conclusions

In most patients with radiolucent gall stones who were given chenodeoxycholic acid (CDCA) in doses of 13-15 mg/kg body weight/day the bile became unsaturated in cholesterol, and their gall stones dissolved. The patients whose stones did not dissolve were significantly heavier and fatter than the responders, which suggested that obese patients might be "resistant" to the effects of CDCA. To test this hypothesis, 32 consecutive patients presenting for medical treatment of gall stones had their ideal body weight (IBW) and estimated body fat mass calculated. The eight most obese and the eight least obese patients were then selected, and their fasting bile lipid responses to CDCA 13-15 mg/kg/day were measured. The very obese patients were also given larger doses, and any changes in bile lipid composition were studied in relation to subsequent gall-stone dissolution.

Before treatment the obese patients had a higher mean biliary cholesterol saturation index than the non-obese patients, and this difference was maintained during treatment with the normal dose of CDCA: the bile in the obese patients remained supersaturated while that in the non-obese became unsaturated with cholesterol. When the obese patients were given larger doses of CDCA their bile ultimately became unsaturated in cholesterol. Gall stones dissolved partially or completely in five of the eight non-obese patients after 6-18 months of 13-15 mg CDCA/kg/day, but none of the obese patients showed any response after comparable periods of treatment with this standard dose. With increased doses and unsaturated bile, however, three of the obese patients showed partial gall-stone dissolution after 3-12 months' treatment and one showed complete gall-stone dissolution after three years' treatment.

These results suggest that when giving CDCA to patients with gall stones, larger than normal doses (some 18-20 mg/kg/day) should be prescribed. Alternatively the lipid composition of the patients' bile should be monitored by duodenal intubation and the CDCA dose increased until the bile becomes unsaturated in cholesterol.

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Introduction

Oral chenodeoxycholic acid (CDCA) dissolves cholesterol-rich gall stones by reducing biliary cholesterol secretion[1 2] and by changing fasting gall-bladder bile from being supersaturated to being unsaturated in cholesterol.[3 4] We have shown that reproducible changes in the lipid composition of bile-rich duodenal fluid develop within one month of starting treatment,[5] and that these changes enable one to identify reasonably accurately the patients whose gall stones will dissolve.[4] Thus, by ensuring early in the course of treatment that CDCA has produced an unsaturated "bile," one may prevent months or even years of ineffective treatment of individual patients.

One of the aims of those studying the bile lipid response to treatment is to establish a uniform dose of CDCA which will reliably produce unsaturated bile in all patients. If this were possible there would be no need for duodenal intubation, which is uncomfortable for patients and time-consuming and expensive for the investigator. Furthermore, with more widespread use of CDCA, it would clearly be impracticable for family practitioners, and indeed for most hospital-based physicians and surgeons, to measure routinely biliary cholesterol saturation in all patients undergoing medical treatment for gall stones. If we are to abandon analysis of bile lipids in the management of these patients, however, we need to identify any "resistant" patients who might not respond predictably to chemotherapy.

In 1975 we showed that 13-15 mg of CDCA/kg body weight/day consistently produced unsaturated bile.[4] But an analysis of

our more recent results[6] showed that the bile of some patients who were given this dose remained supersaturated with cholesterol and their gall stones did not dissolve (fig 1). In retrospect we found that these non-responders were not only heavier than the responders (whose gall stones dissolved) but also that they had a significantly greater percentage ideal body weight (table I). This suggested that obese patients might be resistant to the effects of CDCA on biliary cholesterol saturation.

TABLE I—*Analysis of results[6] in 20 patients whose gall stones dissolved during treatment with CDCA (responders) and in 19 patients whose gall-stone size remained unchanged despite a minimum of 12 months' treatment with 13-15 mg CDCA/kg/day (non-responders)*

	Responders	Non-responders (treated >12 months)	P value
No of patients	20	19	
Absolute dose (mg/day)	856±44	1046±53	<0·02
Body weight (kg)	60·4±2·7	74·8±3·7	<0·005
Dose related to weight (mg/kg/day)	14·3±0·7	14·2±0·7	NS
% Ideal body weight	108±2·8	128±6·9	<0·02

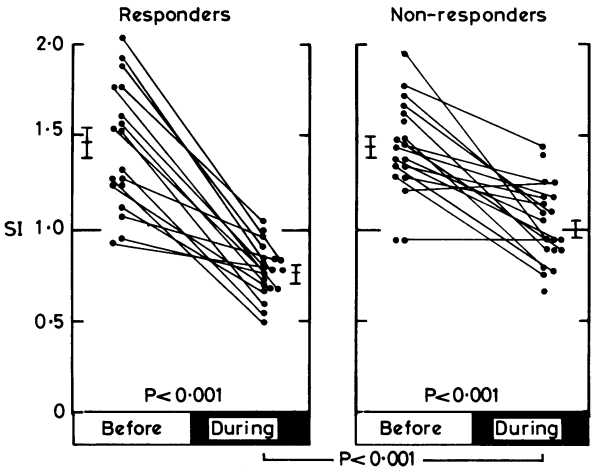

FIG 1—Cholesterol saturation index (SI)[18] of bile-rich duodenal fluid (according to limits of cholesterol solubility in bile as defined by Hegardt and Dam[19]) measured before and during CDCA treatment in patients who responded with complete gall-stone dissolution and those who did not respond after at least 12 months' treatment with 13-15 mg CDCA/kg/day. Mean values ±SE of mean are also shown (see table I).

To test this hypothesis we measured the lipid composition of bile-rich, duodenal fluid before and after the usual recommended dose of CDCA (13-15 mg/kg/day)[4] in two groups of patients with gall stones—those who were unequivocally obese and those who were not. We also studied the effect of larger than normal doses of CDCA (up to 20 mg/kg/day) on the cholesterol saturation of bile in the obese group. These changes in bile lipid composition were then related to the effects of long-term treatment on gall stone dissolution.

Patients and methods

Thirty-two consecutive patients with radiolucent gall stones who were accepted for treatment with CDCA were graded according to their percentage ideal body weight, as determined from measurements of height and weight, estimation of frame size, and reference to Metropolitan Life Insurance Tables.[7] The top quartile of these patients (n=8), all of whom had an ideal body weight over 125% of normal (mean (±SE of mean) 152±10·8%; see table II), formed the obese group. At the other end of the obese/non-obese range eight patients whose weight was less than 103% ideal body weight (mean 97±1·6%; table II) formed the non-obese group. As a further index of the degree of obesity, total body fat was estimated in seven of the eight obese patients and in five of the non-obese, with a formula based on height and on measurements of skinfold thickness at three different sites.[8]

Patients with other disorders known to affect lipid composition, such as diabetes mellitus[9] or hyperlipidaemia,[10] were excluded. Only one patient took oral contraceptives (which are also thought to influence adversely the cholesterol saturation of bile[11]) and then only for a short period early in her CDCA treatment. None of the patients showed any significant change in body weight during the study, again of importance since weight reduction per se can modify bile lipid composition.[12 13]

There were eight women in the obese group compared with seven women and one man in the non-obese quartile. The ages of these two groups were comparable. All patients had radiolucent, presumed cholesterol-rich gall stones, and all had functioning gall bladders which opacified during oral cholecystography and contracted in response to a fatty meal.

TABLE II—*Clinical details, indices of obesity, and dose of CDCA in the eight most and least obese patients with gall stones*

Case No	Age and sex	Height (cm)	Weight* (kg)	% Ideal body weight	Body fat mass (kg)	Standard CDCA dose (per day)		High CDCA dose (per day)	
						Dose (mg)	Dose/body weight (mg/kg)	Dose (mg)	Dose/body weight (mg/kg)
				Obese patients					
1	36 F	160	68	126	30·5	875	12·9	1250	18·4
2	38 F	173	86	130	38·0	1250	14·5	1750	20·4
3	47 F	152	72	133		1000	13·9		
4	47 F	168	79	136	31·8	1250	15·9	1500	19·0
5	59 F	163	77	143	34·8	1000	13·0		
6	38 F	168	94	157	40·1	1000	10·6	1750	18·6
7	56 F	182	78	177	25·1	1125	14·4	1500	19·2
8	41 F	159	118	215	33·2	1500	12·7	1875	15·9
Mean±SE of mean	45·3±3·0	162±2·7	84±5·6	152±10·8	33·4±1·88	1125±71	13·4±0·56	1604±94	18·6±0·61
				Non-obese patients					
9	52 F	160	43	88	14·5	625	14·5		
10	62 F	167	52	95	12·3	750	14·4		
11	43 F	168	56	97		500	8·9		
12	26 F	168	56	97		750	13·4		
13	47 F	163	51	100		750	14·7		
14	45 F	177	63	100	17·8	1000	15·9		
15	55 F	165	54	100	13·8	750	13·9		
16	36 M	169	65	102	17·8	1000	15·4		
Mean±SE of mean	45·8±4·0	167±2·0	55·0±2·4	97·4±1·6	15·2±1·1	766±60	13·9±0·79		

*Patient lightly clothed.

DOSE OF CDCA, BILE SAMPLING, AND BILE LIPID ANALYSIS

Before starting treatment samples of bile-rich fluid were aspirated from the duodenum after intravenous administration of cholecystokinin (75 units of CCK, either Pancreozymin or Karolinska Institute CCK, Stockholm, Sweden). Initially all but two patients received about 13-15 mg CDCA/kg/day, and after at least one month's treatment[5] "bile" was again collected for estimating bile acids, phospholipids, and cholesterol and for calculating the resulting biliary cholesterol saturation index (see below).

Bile lipids were analysed as described,[14] except for cholesterol, which was measured by an enzymatic method.[15] Because of possible technical errors that may arise when analysing dilute bile,[16] samples with bile acid concentrations of <20 mmol/l were arbitrarily considered to be insufficiently "bile-rich" for accurate interpretation. The cholesterol saturation of bile was expressed as the saturation index,[17] based on the lithogenic index of Metzger *et al*[18] and the criteria for cholesterol solubility in bile of Hegardt and Dam.[19]

If after a month (or more) of treatment bile remained supersaturated with cholesterol the dose of CDCA was increased by 3-6 mg/kg/day, and after a further month's treatment bile-rich duodenal fluid was again collected for analysis as described above.

Results

ASSESSMENT OF DEGREE OF OBESITY

Most of the patients in the top quartile of the ideal body weight spectrum (table II) were well above 125% of ideal body weight, and three, whose weight was over 150%, were clinically grossly obese. Six of these eight patients had a calculated body fat mass of over 30 kg. Conversely, among the patients in the other three quartiles (under 125% ideal body weight) there was only one with a body fat mass over 30 kg.

In the non-obese quartile (table II) all the patients, except one, were within $\pm 5\%$ of their ideal body weights. Five of the eight had skinfold thickness measured and their body fat mass calculated on the basis of this. Although two of the five had a body fat mass of almost 18 kg, this level was still much lower than that of the obese group and the mean value ($\pm$SE of mean) of $15{\cdot}2 \pm 1{\cdot}1$ kg was significantly less ($t = 8{\cdot}355$; $P < 0{\cdot}001$) than that of the obese quartile ($33{\cdot}4 \pm 1{\cdot}9$ kg).

Of the remaining 16 patients who were graded as intermediate between obese and non-obese, there were only four with a body fat mass of under 18 kg.

DOSE OF CDCA AND BILE LIPID RESPONSE TO TREATMENT

The results in table II show that even though both groups were initially given the same daily standard dose of CDCA per kg body weight the obese patients were receiving significantly higher absolute doses ($P < 0{\cdot}005$), since, as well as being obese, they were about the same height as the non-obese patients and therefore, on average, 53% heavier ($P < 0{\cdot}001$).

Before treatment the mean biliary cholesterol saturation index in the obese patients ($1{\cdot}73 \pm 0{\cdot}15$) was higher than that in the non-obese patients ($1{\cdot}40 \pm 0{\cdot}13$), but, mainly because of the scatter of results about the mean, this difference was not statistically significant (fig 2). During treatment with 13-15 mg CDCA/kg/day bile remained supersaturated in the obese patients, in whom the mean post-treatment saturation index of $1{\cdot}11 \pm 0{\cdot}08$ was significantly higher than that in the non-obese group ($0{\cdot}81 \pm 0{\cdot}07$; $P < 0{\cdot}02$). For this reason the CDCA dose in the obese group was increased to reach an ultimate mean of $18{\cdot}6 \pm 0{\cdot}6$ mg/kg/day or an absolute dose of 1604 ± 94 mg/day, which, in some patients, was over three times that given to the non-obese patients. As a result bile became unsaturated in every case, the mean index in the six obese patients who were given the higher CDCA doses falling to $0{\cdot}87 \pm 0{\cdot}07$ (fig 2).

GALL STONE DISSOLUTION

None of the obese patients showed any evidence of gall-stone dissolution after a mean of $10 \pm 1{\cdot}7$ (range 3-18) months of treatment with the 13-15 mg/kg dose, but three (cases 2, 4, and 6 in table II) showed partial gall-stone dissolution after 12, 3, and 12 months' treatment respectively with the higher CDCA doses, while a fourth (case 8; by far the most obese), who had shown partial gall-stone dissolution after six months' high-dose treatment went on to show complete gall-stone dissolution after 30 months' treatment with 16·3-18·5 mg/kg/day. Of the remaining patients in the obese group one developed cholecystitis after three months' high-dose CDCA and underwent cholecystectomy while three opted for elective cholecystectomy when there had been no radiological evidence of gall-stone dissolution after 6, 18, and 18 months' treatment with increased CDCA doses.

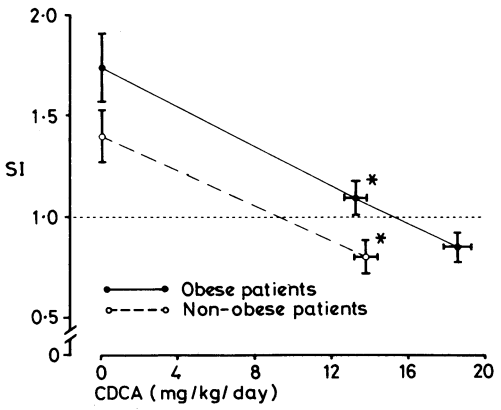

FIG 2—Mean bile lipid composition (expressed as biliary cholesterol saturation index (SI) according to the criteria of Hegardt and Dam[19]) for the two groups of patients. Sloping lines join the mean data points for the two groups of patients; they do not indicate regression lines. *$P < 0{\cdot}02$. Because of fixed CDCA capsule size (125 mg) it was not possible to give both groups of patients identical standard doses (13-15 mg/kg/day).

Gall stones in four of the eight patients in the non-obese group dissolved completely after 6, 12, 18, and 18 months' treatment, while a further patient showed partial dissolution after six months' treatment with the standard dose. The remaining three patients showed no response after two years' CDCA treatment. One of these (case 9) was shown to have calculi with radio-opaque rims (an exception to the rule that we no longer accept patients with radio-opaque calculi for chemotherapy); one (case 15) was referred for elective cholecystectomy when radiolucent, non-cholesterol, "pigment" stones were found; while the third, who refused surgery, proved to be a non-obese resistant patient (case 16).[20]

Discussion

Our results show that when obese patients with gall stones are given CDCA in doses that effectively produce unsaturated bile in the non-obese their bile remains supersaturated with cholesterol. Theoretically gall stones would not be expected to dissolve in these circumstances: such patients may, therefore, be regarded as "resistant" to CDCA. Nevertheless, the bile of the obese patients we studied eventually became unsaturated when the dose of CDCA increased beyond the usual recommended range of 13-15 mg/kg/day.

Ultimately the response to CDCA treatment must be judged not on the results of bile lipid analysis but on gall-stone dissolution rates. Although we studied only a few patients, our results in terms of gall-stone dissolution broadly support the concept that the bile lipid response to CDCA is a valuable predictor of subsequent gall-stone dissolution. Five of the eight non-obese patients responded to 6-18 months' treatment with the standard CDCA dose with partial or complete dissolution of their gall stones. In contrast, none of the obese patients showed any change in gall-stone size on the standard dose, although when they too achieved an unsaturated bile on the higher CDCA doses four showed evidence of gall-stone dissolution.

While these findings help to explain why bile remained supersaturated with cholesterol despite the standard dose of CDCA in about half of our non-responding patients (fig 1), they do not explain why in the other half the gall stones failed to dissolve even after one year's treatment, which produced an

unsaturated bile. One possible explanation is that the gall stones, although radiolucent, were non-cholesterol. So far out of a total of 120 patients with radiolucent gall stones in functioning gall bladders treated with CDCA we have seen only six patients who were ultimately found at operation to have typical "pigment" stones or debris. On analysis these stones all contained less than 10% cholesterol by weight. In practice, therefore, this problem occurred only rarely, which was fortunate since some 15-20% of radiolucent stones may be non-cholesterol in type.[21 22]

The criteria for assessing the degree of obesity in this study were based primarily on ideal body weight measurements calculated from reference tables.[7] This simple classification proved adequate since it separated the top and bottom quartiles of patients from either end of the obese/non-obese range, without overlap. Had we used another criterion for assessing obesity, that of body fat mass,[8] the top quartile of our 32 patients would have differed in only two cases. Although the same degree of correlation between the percentage ideal body weight and body fat mass was not found at the non-obese end of the scale, regardless of the method used, these patients were, none the less, significantly less obese.

The reason why obese patients with gall stones are resistant to the effects of normal doses of CDCA on biliary cholesterol saturation and therefore need higher CDCA doses per kg to achieve unsaturated bile is uncertain. One possible explanation is based on the finding that CDCA may reduce biliary cholesterol secretion by inhibiting hydroxymethylglutaryl-Co enzyme A reductase (HMGCoAR),[23] which controls hepatic cholesterol synthesis. Recently the activity of this enzyme has been shown to correlate with biliary cholesterol secretion,[24] and, since obese patients secrete more cholesterol in their bile than the non-obese,[25 26] the activity of this enzyme might well be higher in obese patients. Although there have been no estimates of HMGCoAR in obesity to confirm or refute this idea, such studies are in progress in our laboratory. If HMGCoAR activity is indeed higher in obese patients with gall stones than in patients with cholelithiasis alone this might explain why obese patients need the higher doses of CDCA.

Since this study was completed we have gone on to show that resistance to CDCA (judged by persistence of supersaturated bile despite not just the standard dose but even doses of 19-22 mg/kg/day, producing 72-96% CDCA in biliary bile acids[20 27]) may occur rarely in non-obese as well as in obese patients (case 16). And, in keeping with the postulated mechanism for this resistance, one obese patient who subsequently had an operation was shown to have unsuppressed HMGCoAR levels in an operative liver biopsy specimen despite receiving 22 mg CDCA/kg/day.[20 27]

The illustration in fig 2 is not meant to indicate that there are necessarily separate and parallel regression lines for the two groups of patients, correlating the pre- and post-treatment saturation indices with the daily doses of CDCA in mg/kg. But we have shown that when no attempt is made to segregate obese from non-obese patients there is a significant linear relationship between these two variables.[28] Since the obese and non-obese patients studied here were drawn from a total of 32 consecutive patients presenting for medical treatment, one might have expected that it would have been possible to relate the bile lipid response on different doses of CDCA to the degree of obesity. But because of our current policy of starting all patients on 13-15 mg CDCA/kg/day there was an insufficient scatter of dose levels (plotted on the abcissa of fig 2) to obtain such a correlation.

When faced with treating obese patients with gall stones medically there are three possible courses of action if one chooses not to monitor the bile lipid response to CDCA: (*a*) increasing the dose of CDCA without attempting to reduce body weight, which usually, but not always,[20 27] produces unsaturated bile; (*b*) maintaining the dose of CDCA and reducing weight by diet; or (*c*) combining both these measures. For health reasons it would seem logical to advise weight reduction, particularly because CDCA is more likely to cause unacceptable diarrhoea if large doses are prescribed, since the diarrhoea of CDCA treatment is dose-related.[28] But obese patients are often resistant to blandishments about weight reduction by diet, and the results of one study suggest that bile that is already supersaturated as a result of obesity becomes even more supersaturated during active weight reduction by diet,[25] possibly because tissue cholesterol is mobilised independently of hepatic HMGCoAR and is then secreted in excess into the bile. We are studying both these potential courses of therapeutic action. Our preliminary results suggest that in most obese patients with gall stones weight reduction alone reduces[13] (rather than increases[25]) the saturation of bile with cholesterol, which should therefore potentiate the effects of normal doses of CDCA on bile lipid composition.

On the basis of our results we suggest that whenever possible obese patients undergoing medical treatment for gall stones should lose weight. Sustained weight loss is, however, notoriously difficult to achieve and we therefore recommend that the response of the bile lipids to CDCA therapy should be monitored in all obese patients if prolonged and ineffective treatment is to be avoided.

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Requests for reprints should be addressed to Professor R Hermon Dowling.

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