

CHENO AND URSO COMPARED AND CONTRASTED

R. HERMON DOWLING

Gastroenterology Unit. Department of Medicine. Guy's Hospital and Medical School. London, SE1 9RT

SUMMARY

UDCA was introduced as a gallstone dissolving agent some 5 years after CDCA. Experience with urso is, therefore, more limited but the initial 5-7 years of clinical investigation for CDCA have been condensed into a mere 1-2 years for UDCA. As a result, there is now a substantial data base on which to compare the two agents. With careful patient selection, efficacy is high and comparable for both bile acids but UDCA depresses HMGCoAR activity (at least in our experience), reduces biliary cholesterol secretion, desaturates fasting duodenal bile, and dissolves cholesterol gallstones at 50-66% of the CDCA dose. It is almost free from medium-range (up to 3 years) side-effects and, cost apart, UDCA is likely to replace CDCA as the medical treatment of choice for gallstones.

RESUMO

COMPARAÇÃO DOS ÁCIDOS URSODESOXICÓLICO E QUENODESOXICÓLICO NA TERAPÊUTICA DA LITÍASE BILIAR

O ácido ursodesoxicólico foi apontado como eficaz na dissolução dos cálculos biliares 5 anos após a introdução do ácido quenodesoxicólico para o mesmo fim. A experiência com o AUDC é, portanto, mais reduzida embora os 5-7 anos de investigação sobre o AQDC tenham sido condensados em apenas 1-2 anos no respeitante à investigação sobre o AUDC. Em consequência, existem já presentemente dados que permitem comparar estas duas drogas. A eficácia de ambos os ácidos biliares, num grupo de doentes devidamente seleccionados, é elevada e sobreponível mas o AUDC define a actividade da HMGCoAR (pelo menos na nossa experiência), reduz a secreção de colesterol na bilis, provoca dessaturação da bilis duodenal e dissolve os cálculos biliares numa dose de 50-66% da habitualmente necessária para a terapêutica com AUDC. É praticamente isento de efeitos colaterais a médio prazo (até 3 anos) e, não atendendo ao custo, poderá em breve destronar o AQDC no tratamento médico de eleição para os cálculos biliares.

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INTRODUCTION

This paper presents a *state of the art* or update on the medical treatment of gallstones and based on the results of comparative studies, reviews what is known about dose, efficacy¹⁻³, mechanism of action, collateral benefits, symptoms and side-effects of CDCA and UDCA therapy.

DOSE

1. Bile Lipids

With comparable doses (15 mg kg⁻¹ day⁻¹) UDCA reduces the relative molar concentration of biliary cholesterol^{4,5} (moles %), the fasting biliary cholesterol saturation index^{4,5} (uncorrected for the amount of UDCA present⁶) and biliary cholesterol secretion⁷ more effectively than CDCA. (Table 1).

With different doses, UDCA achieves the same effect as CDCA⁸ at 50-66% of the CDCA dose, 7.5-10 mg UDCA kg⁻¹ day⁻¹ having an equivalent effect on the above variables as 12-15 mg CDCA kg⁻¹ day⁻¹. (Table 1).

Dose response studies have shown a significant negative linear correlation between fasting biliary cholesterol saturation indices (SI's) and the dose of CDCA^{9,10} in mg kg⁻¹ but for UDCA, although it is still possible to derive such a relationship when pre-treatment (0 mg UDCA) values are included⁸, this is no longer seen when (1) the Carey correction⁶ is applied and (2) only post-treatment SI values are plotted.^{11,11a}

When SI is plotted against UDCA dose (mg/kg) in individual patients given multiple doses, a curvi-linear relationship is seen (convex downwards) with a plateau effect suggesting that once bile becomes desaturated, no further benefit may accrue from increasing the UDCA dose.¹² This observation is supported by preliminary results on gallstone

dissolution from some UDCA studies where optimum efficacy was seen using 7-10 mg UDCA/kg with no further increment in efficacy using larger UDCA doses.¹³ (Table 1).

2. GALLSTONE DISSOLUTION

In patients responding to treatment with partial or complete gallstone dissolution, the dose of CDCA found to produce this response is again approximately 12-15 mg kg⁻¹ and of UDCA about 7-8 mg kg⁻¹ day⁻¹ (Table 1).

TABLE 1

DOSE AND EFFICACY: SUMMARY OF PUBLISHED RESULTS

1. Different doses give same effect

- (a) Desaturation of fasting duodenal bile with: —
12-15 mg CDCA kg⁻¹ day⁻¹
7-10 mg UDCA kg⁻¹ day⁻¹
- (b) Gallstone dissolution — maximum efficacy (partial and complete gallstone dissolution)
— at 6 months approx. 70%
— at 12 months approx. 80%

Dose: 12-15 mg CDCA kg⁻¹ day⁻¹
7-10 mg UDCA kg⁻¹ day⁻¹

2. Same doses give better effect

- (a) **Fasting duodenal bile**
Approx. 15 mg bile acid kg⁻¹ day⁻¹ gives post-treatment SI's of:
CDCA — approx. 0.8; UDCA — approx. 0.6
(Stiehl et al 1978)⁴
- (b) **Steady-state bile lipis secretion**
Cholesterol secretion reduced more with UDCA than CDCA
(von Bergmann et al 1979).⁷

3. Not yet proven: —

with equimolar doses:

— more rapid gallstone dissolution	}	with UDCA
— more effective gallstone dissolution		than CDCA

4. Cost

- (a) **per unit weight of bile acid**
UDCA 50-100% more expensive than CDCA (? long-term 10% more expensive)
- (b) **per effective dose**
CDCA and UDCA comparable (if bedtime dose gives increased efficacy, dose and cost reduced for: —
— CDCA and UDCA (Maudgal et al 1979)⁹⁹
— ? not for UDCA (Sugata et al 1980)¹⁰⁰

EFFICACY

1. PATIENT SELECTION AND MANAGEMENT

The efficacy of medical treatment for gallstones with both bile acids depends on careful patient selection, the best results being found in nonobese patients with radiolucent stones measuring < 15 mm in diameter in functioning gallbladders¹. Large Stones respond less well to treatment and take longer to dissolve. Obese patients require greater than normal bile acid doses (even when calculated per unit body weight).² They respond marginally better to weight reduction, with constant capsule dose, than to weight maintenance with increased numbers of capsules.³

2. IMPORTANCE OF STANDARDISING CRITERIA USED TO DEFINE EFFICACY

Efficacy also depends on the criteria used to define the response to treatment and the extent to which these have been controlled by various authors when reporting their results, differs considerably making comparison of efficacy findings from different centres difficult or impossible.

For example, if an asymptomatic gallstone patient starts treatment with UDCA, remains well but defaults from follow-up at 5 months just before her first post-treatment cholecystogram, we have no way of knowing whether or not the x-ray would have shown partial or complete gallstone dissolution. Should the results in such a patient be included in the total when calculating efficacy?

Accepting that the efficacy numerator should be based on the number of patients showing gallstone dissolution, should the denominator be based on the total number of patients starting treatment or on the number of patients completing, say, 6 months treatment with a follow-up x-ray? Where a patient stops treatment because of complications of bile acid therapy, few would argue that they should be listed as treatment failures. Equally, when patients stop treatment because of complications from their gallstones (rather than complications of the treatment itself), one could argue that this should still be recorded as a treatment failure — even if such complications might have occurred with equal or greater frequency in the absence of bile acid therapy. But what about the poorly motivated patient who starts treatment only to stop in a desultory fashion after a few weeks or months before any post-treatment x-rays have been carried out? It is debatable whether or not such patients should be classified as treatment failures so influencing the denominator in the efficacy equations. Until some uniform standards are agreed, when reporting our results we must state precisely which criteria are used — perhaps giving efficacy figures both with and without *drop-outs*. In view of the imprecision in defining **partial** gallstone dissolution, ultimately efficacy figures must be based on **complete** gallstone dissolution only.

3. OVERALL RESULTS WITH CDCA

Since 1977, all newly-referred gallstone patients accepted for medical treatment at Guy's Hospital have been given UDCA rather than CDCA. As a result, sufficient time has now elapsed for us to determine the final outcome of treatment in patients who started CDCA between 1971 and 1976. We are now left with only 2 patient groups — those who stopped treatment (for whatever reason) and those

whose gallstones dissolved completely. We no longer have patients awaiting their first follow-up x-ray, patients continuing treatment with, as yet, no radiological evidence of response and none with partial but, as yet, incomplete gallstone dissolution. Of 125 patients with radiolucent gallstone in functioning gallbladders who started CDCA, we have seen complete gallstone dissolution in 47 (38%).¹⁴ The remaining 78 patients stopped treatment — many within the first few weeks of starting therapy.

4. RETROSPECTIVE COMPARISON OF CDCA AND UDCA IN SELECTED PATIENTS

In a retrospective comparison in comparable groups of patients ideally suited for medical treatment (non-obese patients with radiolucent gallstones less than 15 mm diameter in functioning gallbladders), the maximum efficacy for partial or complete gallstone dissolution in patients completing 6 months treatment was broadly similar for both bile acids 66% for UDCA and 81% for CDCA.¹² In those completing 12 months treatment, the maximum cumulative efficacy was 80% with both bile acids. The corresponding figures for complete gallstone dissolution in patients completing one year's treatment were 27% for UDCA and 49% for CDCA. (Table 1).

5. OVERALL RESULTS WITH UDCA

By 1980 we had treated a total of 56 patients with UDCA and, in addition to the highly selected patients in the comparative study (see above) the overall group (which still represents a partially selected population of gallstone patients) included obese patients and those with large (greater than 15 mm in diameter) radiolucent stones.¹² From the total of 56 patients, 11 continue treatment and remain well but have not yet completed their first post-treatment x-ray at 6 months. They are not, therefore, included in the denominator for calculating efficacy. Of the remaining 45 patients, after 6-36 months' treatment, so far 19 have shown partial and 10 complete gallstone dissolution, 8 have stopped treatment and 8 have, as yet, shown no response. This gives a complete gallstone dissolution rate of 22% and a complete plus partial gallstone dissolution rate of 64% (including in the denominator all patients withdrawing from treatment). The corresponding figures for partial or complete dissolution increased from 56% at 6 months to 73% at 12 months and 76% at 18 months (cumulative efficacy — that is including results in patients who had previously shown complete gallstone dissolution).

If the results in the 8 patients who withdrew from treatment are excluded, the **maximum** cumulative efficacy recorded was 94% for partial or complete gallstone dissolution and 48% for complete gallstone dissolution alone.

MECHANISM OF ACTION

Both bile acids decrease biliary cholesterol secretion and desaturate fasting duodenal bile (again ignoring correction factors⁶ for UDCA-rich bile). Having said that, the precise mechanism whereby CDCA and UDCA work is unknown. Probably as a result of this ignorance, many theories have emerged which are summarised in Tables 4-8 and below.

1. ACUTE EFFECT OF CDCA AND UDCA ON BILIARY LIPID TRANSPORT — THE SCHERSTÉN EFFECT

Lindblad and Scherstén first showed, in post-cholecystectomy T-tube patients, that when the bile was rendered markedly supersaturated in cholesterol by biliary diversion, acute replacement of the endogenous bile acid pool with exogenous, intraduodenal CDCA could enrich the bile with CDCA and desaturate the bile in cholesterol, within a few hours.¹⁵ The same group subsequently confirmed this *exchange transfusion* phenomenon with UDCA.¹⁶ Recently, however, when Sama et al¹⁷ and Gilmore and Hofmann¹⁸ carried out similar studies in the United States, although they confirmed the acute desaturating effect of UDCA they could not do so with CDCA. (Table 2).

This acute effect may be due to a *membrane-leeching* action of the bile acid selectively removing phospholipids and cholesterol from the canalicular membrane of the hepatocyte or from the lipid membrane of other intracellular organelles. Based on studies in bile fistula Rhesus monkeys^{19,4}, such a mechanism was first proposed many years ago by Small. Proof that CDCA or UDCA can pick up and transport relatively more phospholipids and relatively less cholesterol than other bile acids as they transverse the cell and the canalicular membrane is, as yet, wanting.

2. SUB-ACUTE AND CHRONIC EFFECTS OF CDCA AND UDCA ON BILIARY LIPID TRANSPORT (Table 2).

With *conventional* bile acid treatment of gallstone patients, CDCA displaces the endogenous bile acids gradually. After starting 13-15 mg CDCA kg⁻¹ day⁻¹ by mouth, it usually takes 4-6 weeks before bile becomes fully enriched with cheno and unsaturated in cholesterol.¹⁹ However, by deliberately aspirating as much of the endogenous bile acid pool as possible during the first duodenal intubation, it is possible to truncate or *concertina* the CDCA enrichment and biliary cholesterol desaturation processes to 4 days — as opposed to 4 weeks.²⁰ Similar studies have yet to be carried out with UDCA. Whether or not this represents a different mechanism of action from the membrane-leeching effect described above, is an open question.

3. INHIBITION OF HEPATIC CHOLESTEROGENESIS

At least 5 laboratories have shown that CDCA treatment inhibits the activities of hepatic HMGCoA reductase²¹⁻²⁵, the rate-limiting enzyme in cholesterologenesis. However, the effects of UDCA on this enzyme are controversial. Maton et al²³ found a comparable reduction in hepatic HMGCoAR activity in liver biopsies from patients treated with UDCA as in those given CDCA but at half to two-thirds the CDCA dose. Salen and colleagues²⁶ confirmed that UDCA also inhibits this enzyme and while Einarsson et al also found a 25% reduction in mean enzyme activity during ursotherapy, this difference was not statistically significant.²⁵ In contrast, Carulli et al²⁴ found a significant **increase** in HMGCoAR activity in liver biopsies from gallstone patients treated with UDCA for only 8 days. The same authors have not re-examined this enzyme activity after more prolonged ursotherapy. (Table 2).

For several reasons, the attractively simple hypothesis that inhibition of hepatic cholesterol synthesis might explain the reduction in biliary cholesterol secretion, is unlikely to explain completely the mechanism of action of CDCA

* The total now numbers 100 patients given 106 courses of UDCA treatment.¹⁴

TABLE 2

MECHANISMS OF ACTION — SUMMARY OF PUBLISHED RESULTS

1. Desaturation of fasting duodenal bile

— acute effect: (2-3 hours)
CDCA and UDCA (Scherstén et al)^{15,16}
UDCA only (Sama et al)¹⁷
(Gilmore & Hofmann)¹⁸

— sub-acute effect: (4 days)
CDCA only (Iser et al 1980)²⁰

— chronic effect: (> 4-6 weeks)
CDCA) Approximately 20 studies
UDCA)

2. Reduction in biliary cholesterol secretion

CDCA — Northfield et al 1975¹⁰¹
— Adler et al 1975¹⁰²
— Reuben et al 1980¹⁰³

CDCA and UDCA — (von Bergmann et al 1979)⁷
— (Roda et al 1980)¹⁰⁴

3. Hepatic cholesterologenesis

HMG CoA reductase activity reduced:
CDCA + + and UDCA + + (Maton et al)²³
(Salen et al)²⁶
CDCA + + and UDCA — (Carulli et al)²⁴
CDCA + + and UDCA ± (25% ↓ NS)
(Einarsson et al)²⁵

4. Cholesterol absorption

unchanged — Tangedahl et al (1979)³⁸
Roda et al (1980)¹⁰⁵
Mok et al (1980)³⁹
Larusso and Thistle (1980)⁴¹

reduced — Ponz de Leon et al (1979)³³, (1980)³⁴

Conclusion: Unlike to explain mechanism of action of CDCA and UDCA

5. Possible related effects

(i) Differential inhibition of endogenous bile acid synthesis

— with CDCA: primary BA synthesis reduced + +
(Danzinger et al 1973)⁴²
— with UDCA: primary BA synthesis reduced ±
(Williams et al 1979)⁴³

(ii) Intestinal bacterial degradation to lithocholate

— more rapid and complete for CDCA than UDCA (Federowski et al 1977)⁴⁴
— therefore more exogenous UDCA than CDCA remains available for absorption and therapeutic effect

(iii) Equilibrium cholesterol solubility

reduced in UDCA-enriched bile compared to CDCA-rich bile or bile of mixed bile acid composition (Carey 1978)⁶

(iv) Cholesterol dissolution rate

slower in UDCA-enriched solutions than in CDCA or mixed bile acid solutions (Igimi & Carey 1980)⁴⁸
Carey correction reduces predictive value of on-treatment SI (Williams et al 1979)¹¹
Carey correction improves predictive value of on-treatment SI (Zuin et al 1980)⁴⁵

and UDCA. First, we know from recent studies in animals by Dietschy and colleagues²⁷ that hepatic cholesterol synthesis accounts for only 18% (approximately) of normal biliary cholesterol secretion. Secondly, the same investigators have questioned the validity of measuring HMGCoAR activity *in vitro* under V_{max} conditions and of extrapolating from the findings to hepatic cholesterol synthesis *in vivo*.²⁸ Certainly other methods of measuring cholesterol synthesis do not always yield the same pattern of results.²⁸ Thirdly, although Key et al²⁸, found a significant linear relationship between hepatic HMGCoAR activity and biliary cholesterol secretion in *untreated* gallstone patients, they were unable to confirm this observation in patients treated with CDCA.³⁰ We too, found no relationship between these two variables.³¹ Finally, although the liver is the major site for total body cholesterologenesis, many other tissues synthesise this sterol.³² Measurement of hepatic HMGCoAR activity, therefore, cannot tell us the whole story about overall cholesterol synthesis. Besides, the HMGCoAR theory ignores the contributions of HDL cholesterol and chylomicron remnant cholesterol as sources of biliary cholesterol secretion. (Table 2).

4. THE EFFECT OF CDCA AND UDCA ON INTESTINAL CHOLESTEROL ABSORPTION

Although Ponz de Leon and colleagues have shown convincingly that both CDCA³³ and UDCA³⁴ significantly reduce intestinal cholesterol absorption — at least as measured by their technique — it now seems unlikely that this phenomenon can explain how cheno and urso desaturate bile with cholesterol.³⁵

The Modena group themselves have gone on to show that deoxycholic and (DCA) feeding also depresses intestinal cholesterol and, as is well known, it does not desaturate bile — if anything DCA increases biliary cholesterol saturation.³⁵ Furthermore, Ponz de Leon's results are controversial.³⁶ Using different methods, several other groups have found that CDCA and UDCA apparently have no effect on intestinal cholesterol absorption.³⁷⁻⁴¹ Why different methods used in different laboratories should yield such contradictory results is unknown but for the reasons already stated, the cholesterol absorption theory is no longer fashionable as an explanation for cheno and urso's ability to desaturate bile and to dissolve cholesterol gallstones. (Table 2).

5. POSSIBLE RELATED EFFECTS OF CDCA AND UDCA

(a) Endogenous bile acid synthesis

CDCA and UDCA have differing inhibitory effects on primary bile acid (cholic acid) synthesis*.

* Because of metabolic inter-conversion between CDCA and UDCA it is difficult, if not impossible, to measure CDCA synthesis during cheno — or ursotherapy.

CDCA markedly inhibits cholic acid synthesis⁴²; UDCA has a lesser effect.⁴³ The significance of this finding in relation to biliary cholesterol desaturation and to gallstone dissolution is also uncertain. (Table 2).

(b) Speed of bacterial degradation of the ingested bile acids to lithocholic acid

In the test tube, Fedorowski and colleagues have shown that the bacterial 7α dehydroxylation of CDCA to form lithocholate by a mixed faecal flora is more rapid and complete than the 7β dehydroxylation of UDCA.⁴⁴ Again it is difficult to extrapolate the results of this study to guessing what might happen *in vivo* but the authors⁴⁴ have suggested that more undergraded exogenous bile acid would remain available for absorption and therapeutic effect during ursotherapy than during treatment with CDCA. (Table 2).

(c) Equilibrium cholesterol solubility and cholesterol dissolution rate

From the elegant *in vitro* studies by Carey and colleagues⁶, we know that equilibrium, cholesterol solubility is reduced in UDCA-enriched bile* when compared with CDCA-rich bile or bile of mixed bile acid compositions*. Indeed, based on these findings, Carey suggested that it was necessary to apply a correction factor (calculated from the percentage of UDCA conjugates in bile and from the bile acid glycine: taurine ratio) when calculating biliary cholesterol saturation indices in patients being treated with UDCA. This correction factor lowers the estimated limit of equilibrium cholesterol solubility and, in effect, increases the calculated on-treatment SI so that the higher the UDCA dose, the higher the percentage of UDCA conjugates in bile and the greater the corrected SI indices.

Although one group of investigations found that the Carey correction did improve the predictive value of measuring on-treatment SI's⁴⁵, this was certainly not our experience¹¹ nor that of others.^{11a} We found that *before* applying the Carey correction, provided that we included the pre-treatment results ($\text{Omg UDCA kg}^{-1} \text{ day}^{-1}$), there was a significant linear relationship between SI and the dose of UDCA in $\text{mg kg}^{-1} \text{ day}^{-1}$: patients given $>10 \text{ mg UDCA kg}^{-1} \text{ day}^{-1}$ invariably had unsaturated post-treatment fasting duodenal bile and, as in patients treated with CDCA, the uncorrected, on-treatment SI was of useful predictive value in determining which patients would subsequently respond with gallstone dissolution. *After* applying the correction factor, the linear relationship between SI and the dose of UDCA no longer held true. Those given high ($>10 \text{ mg kg}^{-1} \text{ day}^{-1}$) doses of UDCA have supersaturated bile (if the

Carey correction is applied) but despite this, many still dissolved their gallstones.¹¹

Apart from the unlikely possibility that Carey was wrong, there seem to be two possible explanations for this paradox. First, the advantage of a marked reduction in hepatic biliary cholesterol secretion induced by ursotherapy (which is greater than that seen with a comparable dose of CDCA⁷) might outweigh the disadvantage of reduced equilibrium cholesterol solubility once the bile has left the liver. Secondly, based on controversial findings by Cussler and Evans⁴⁶, it seemed possible that more rapid cholesterol dissolution in UDCA-rich bile could offset the limitations of reduced equilibrium cholesterol solubility. Indeed, Mufson et al⁴⁷ showed several years ago that it might take up to 10 days for anhydrous cholesterol to reach a true equilibrium in model bile solutions. Even if the time required to reach equilibrium is much shorter for the *physiological* form of cholesterol found in bile and gallstones (cholesterol monohydrate), taking perhaps ten hours rather than ten days, is this relevant in the treatment of gallstone patients where bile is continuously flushing in and out of the gallbladder during the day?

The problem was further complicated when Igimi and Carey⁴⁸ and Hisadome et al^{48a} clearly showed that not only equilibrium cholesterol solubility but also the *speed* of cholesterol dissolution was slower in UDCA-rich bile than in bile of mixed bile acid composition — particularly in the absence of phospholipids — yet another reason why UDCA should *not* dissolve gallstone even though the results of clinical studies from around the world clearly suggested the contrary. A satisfactory explanation for this confusing situation may, at last, be emerging. Corrigan and Higuchi⁴⁹ have recently shown that UDCA-rich *simulated bile* dissolves cholesterol not by forming micelles but by non-micellar, mesophase solubilisation — the formation of lecithin-cholesterol liquid crystals at the liquid-solid interface of the gallstone surface.* It may well be, therefore, that cheno and urso dissolve cholesterol gallstone by completely different mechanisms — cheno by forming classical mixed micelles of cholesterol, lecithin and bile acids — and urso by forming liquid crystals (which may subsequently be transformed into conventional micelles not by UDCA itself but by the residual 50% of other bile acids — including CDCA and cholic acid — which remain in bile during ursotherapy). The quantitative significance of this non-micellar, mesophase solubilisation of cholesterol has yet to be determined in man. But assuming it is important, until we can measure the non-micellar contribution, these new observations not only invalidate measurement of SI's by the traditional method but it also completely negates the clinical usefulness of applying the Carey correction. (Table 2).

* Even with high UDCA doses, the UDCA conjugates seldom exceed 55-60% of the total biliary bile acids: during chenotherapy, CDCA conjugates may account for < 90% of the biliary bile acid total.

* This finding was subsequently confirmed by Carey and colleagues.

MEASUREMENT OF SATURATION INDICES DURING CDCA AND UDCA THERAPY

Does this mean that until one can quantitate the meso-phase contribution, we should ignore a decade of results based on the saturation or lithogenic indices of Admirand and Small⁵⁰, Hegardt and Dam⁵¹, Holzbach et al⁵², Carey and Small⁵³ and others — all of whose limits of cholesterol solubility were based on equilibrium values and ignored both the speed (or rate) of cholesterol dissolution and non-micellar solubilisation? Indeed, considering that SI's ignore the kinetics of cholesterol dissolution, it is amazing that they were of any practical use. The fact remains that measurement of SI's has been of enormous clinical value. For example, it was based on Thistle and Schoenfield's original observation⁵⁴ that CDCA desaturated fasting duodenal bile that CDCA was first used to treat gallstone patients. The initial doseresponse studies both with CDCA^{9,10} and UDCA⁸ were based on SI's. Furthermore, many, but not all, investigators find that measurement of on-treatment SI's, 4-6 weeks after starting therapy, provides a useful guide about the choice of dose, the response to treatment and the chances of subsequent gallstone dissolution. Measurement of SI's during treatment taught us that obese patients respond poorly to the usual recommended doses of CDCA² and that a small group of CDCA-treated patients are apparently *resistant* to CDCA in that they do not desaturate their bile despite having 70-90% CDCA conjugates in their biliary bile acids.⁵⁵

Measurement of SI's may also help to identify patients with radiolucent, non-cholesterol stones.^{55a} Even though there is a considerable overlap in SI results between controls and patients with radiolucent, presumed cholesterol-rich gallstones, most patients with untreated cholesterol stones have either saturated or supersaturated fasting duodenal bile and the presence of unsaturated bile before treatment should make one suspicious about the 15-20% chance of radiolucent non-cholesterol stones.^{56,57}

In summary, ignoring the disputed role of inhibitors of crystal formation⁵⁸, there are 4 other components of cholesterol solubility in bile — the speed of dissolution and equilibrium solubility of cholesterol in micellar solutions and the kinetics of dissolution and the maximum solubility of cholesterol in mesophase, liquid crystals (non-micellar solubilisation).^{*} Traditional measurement of SI relies on only one of these four components. Yet before we too readily espouse *the new theory*, we must still bridge the gap between physical chemistry studied in the test tube and the pragmatic, but hopefully critical application of these observations, to clinical science.

PROVEN SIDE EFFECTS

1. DIARRHOEA

As far as the patient is concerned, the only consistently reported side-effect of CDCA treatment is diarrhoea. It is dose-related and usually transient, often occurring during the first weeks of treatment until tolerance is acquired —

possibly as a result of colonic adaptation^{59,60} after which the diarrhoea tends to disappear spontaneously. In some patients, however, it occurs sporadically throughout the period of treatment but only rarely does it persist to such an extent that the patient cannot tolerate the normal prescribed CDCA dose.¹⁴ It affects 30-60% CDCA treated patients at some time during therapy. In contrast, urso seldom causes diarrhoea, most investigators reporting no change of bowel habit in their patients treated with UDCA.^{8,61}

The reasons for the marked difference in the incidence of diarrhoea in patients treated with CDCA and UDCA have often been reviewed before and need not be restated here. Suffice to say that in low concentrations (1 — 5 mM), dihydroxy bile acids with two α OH groups (such as CDCA and deoxycholic acid) inhibit water and electrolyte transport in the colon⁶² and may increase colonic motility⁶³ while bile acids with one α and one β OH group (such as UDCA) do not. However, Caspary has shown, by colonic perfusion studies in animals that even UDCA has a slight *cathartic* effect⁶⁴ and in keeping with this observation, a low (1-2%) incidence of diarrhoea has been reported in some patients given UDCA¹³. (Table 3).

TABLE 3

PROVEN SIDE EFFECTS — SUMMARY OF PUBLISHED RESULTS

Diarrhoea

Dose-related; usually transient; occasionally persistent; occasional intermittent

Affects: —

30-60% of CDCA treated patients

0- 2% of UDCA treated patients

In colon

- | | |
|---|-------------------------|
| — CDCA markedly affects water, electrolyte and oxalate absorption (Chadwick et al 1977) ⁶² | } clinical
relevance |
| — UDCA minimally affects water, electrolyte and oxalate absorption (Caspary et al 1980) ⁶⁴ | |

Hypertransaminasaemia

Dose-related; usually transient; usually modest; no associated changes in liver histology.

Affects:

approximately 30% CDCA-treated patients

1% UDCA-treated patients

CDCA *toxic* to cultured human hepatocytes + +

UDCA *toxic* to cultured human hepatocytes±
(Nakayama et al 1980)⁷⁰

* It could be argued that liquid-crystalline mesophase formation is simply an intermediate step in the solubilisation of cholesterol from solid crystalline material to aqueous phase micellar solution.

A detailed discussion of the possible mechanisms whereby CDCA inhibits colonic water and electrolyte absorption is also beyond the scope of this review but the results of recent studies in experimental animals from our own unit have clarified two points. First, some sulphated bile acid is excreted in the stools of gallstone patients both before and during bile acid treatment^{65,65a}. The amount of BA sulphates present in faeces is the net result of hepatic sulphation and colonic bacterial desulphation. Sulphation seems to project the colon against the cathartic effect of the dihydroxy bile acids. When perfused through the large bowel at concentrations ranging from 5-15 mM, the 3-monosulphates of CDCA and deoxycholic acid did not affect water and electrolyte transport in the rat.⁶⁶ Secondly, although perfusion of rat colon with dihydroxy bile acids stimulated huge increases in the amount of the prostaglandin E₂ (PGE₂) appearing in the perfusion effluent, and although perfusion with PGE₂ itself in pharmacological doses also inhibited colonic water and electrolyte transport, the *cathartic* effect of CDCA and UDCA could not be prevented by pre-treatment with the prostaglandin synthesis inhibitor, indomethacin.⁶⁷ It seems probable, therefore that prostaglandins are **not** the major mediators of bile acid-induced diarrhoea. It also seems unlikely that gallstone patients developing diarrhoea during chenotherapy will benefit from treatment with prostaglandin synthesis inhibitors such as indomethacin.

2. HYPERTRANSAMINASAEMIA

Although diarrhoea is the side-effect, of CDCA which troubles patients most and which is one of the major reasons for recommending UDCA in preference to CDCA in terms of patient acceptability, compliance and the chances of the patient continuing treatment, hypertransaminasaemia in patients given CDCA has not yet been satisfactorily explained. Again, it is dose-related, mostly transient and usually modest — seldom exceeding 2-3 times the upper limit of normal.⁹ The raised transaminase levels usually return to normal spontaneously, even with the continuation of treatment. They may be related to the variable capacity of the human liver to sulphate and excrete the potentially hepatotoxic bacterial metabolite of CDCA-lithocholic acid. Indeed, Schoenfield and colleagues have shown recently that there is a rough correlation between the frequency of hypertransaminasaemia and the *sulphation fraction* — a numerical index of the degree of sulphation of a bolus IV injection of exogenous¹⁴ C-lithocholat across the liver.⁶⁸

As with diarrhoea, there is again a striking difference between CDCA and UDCA in the frequency of this side-effect. CDCA causes raises serum transaminase levels in about one-third of gallstone patients treated with this bile acid⁶⁹: the incidence during UDCA therapy is 0-2%.¹³ The reason for this striking difference is again not known but Nakayama and colleagues have recently shown that CDCA is markedly *toxic* to cultured human hepatocytes while UDCA has only minimal effects on cultured liver cells⁷⁰. The significance of this finding in relation to *intact man* is unknown but it is worth re-emphasising that the hypertransaminasaemia of CDCA therapy is **NOT** associated with consistent changes in the light or electron microscopic appearance of the liver.⁶⁹ In gallstone patients biopsied before, and at different times during, chenotherapy, the incidence of mi-

nor changes in liver architecture was the same before and during treatment. In gallstone patients treated for up to 4 years with doses up to 20 mg CDCA kg⁻¹ day⁻¹. there has, as yet, been no evidence of hepatotoxicity* but the mechanism for the raised serum transaminase levels awaits a satisfactory explanation. (Table 3).

POSSIBLE SIDE-EFFECTS

The effects of both bile acids on triglyceride metabolism are discussed below (see collateral benefits).

The effects of both CDCA and UDCA on cholesterol metabolism has been studied repeatedly and until recently, no significant differences were found in fasting serum cholesterol^{10,71,72} levels nor in cholesterol pool sizes^{73,74} between patients studied before and those studied during treatment. Despite the original *armchair prediction* that by feeding an exogenous bile acid one might inhibit endogenous bile acid synthesis with a resultant accumulation of precursor cholesterol to cause hypercholesterolaemia⁷⁵, this did not seem to happen in practice.* It seemed that the inhibitory effect of CDCA on 7 α hydroxylase activity (rate-limiting for bile acid synthesis) was, fortunately, balanced by a corresponding inhibition of HMGCoAR activity (rate-limiting for cholesterol synthesis). But UDCA seems to inhibit cholic acid synthesis **less** than CDCA⁴³ and in some studies, at least, it inhibits HMGCoAR **more** efficiently than cheno.²³ Might there not, after all, be a difference between the two

TABLE 4

POSSIBLE SIDE EFFECTS — SUMMARY OF PUBLISHED RESULTS

Total serum cholesterol

Fasting serum cholesterol
— no change (Bell et al)⁷¹
with CDCA (Thistle and Hofmann 1973)¹⁰⁵
(James et al 1975)⁷⁹
or UDCA (Williams et al 1980)⁹⁵
Cholesterol pool size
— no change (Pedersen et al 1974)⁷⁴
(Hoffman et al 1974)⁷³

Lipoprotein cholesterol

LDL cholesterol increased
— CDCA (Leijd et al 1980)⁷⁶
(Thistle et al 1978)^{76a}
HDL cholesterol lowered — CDCA
HDL cholesterol increased — UDCA
(von Bergmann and Leiss 1980)⁷⁷
No change in lipoprotein cholesterol
— UDCA (Williams et al 1980)⁹⁵

* This review was written before the results of the U.S. National Cooperative Gallstone Study were published (Ann. Int. Med. 1981, 95) — see the Editorial Comment on the NCGS elsewhere in this issue.

* Again this review does not include the results of the United States NCGS studies which are discussed in the accompanying Editorial.

bile acids in their effects on cholesterol metabolism? Three recent reports raise a frisson of doubt. Leijd et al⁷⁶ and Thistle et al^{76a} found an increase in LDL cholesterol levels during CDCA therapy whilst von Bergmann and Leiss⁷⁷ found that CDCA and UDCA had differing effects on HDL cholesterol. When measured at the end of a one day, secretion/perfusion study (using a liquid formula meal which, in theory, could have acutely affected the serum lipid results) they found that CDCA lowered the levels of the potentially beneficial HDL cholesterol while UDCA raised them. These results suggest that more studies on the effects of CDCA and UDCA on lipoprotein metabolism are required. To date, the evidence that CDCA may have deleterious effects is minimal but the limited data available again point in favour of UDCA as the medical treatment of choice for patients with gallstones. (Table 4).

COLLATERAL BENEFITS

1. Non-specific dyspepsia and biliary pain

For decades, if not for centuries, clinicians have described the occurrence of vague dyspeptic symptoms — such as post-prandial epigastric discomfort bloating, heartburn, belching and dietary fat intolerance — in association with gallstones. These symptoms are non-specific occurring also in patients with hiatus hernia, peptic ulcer and even with the spastic colon. What is more, they cannot be accurately quantified and there are no objective markers to support the subjective complaints. Little is known about their pathophysiology. Small wonder, therefore, that these complaints have attracted relatively little scientific attention. Despite this, many uncontrolled studies have reported a reduction in non-specific dyspepsia during treatment with both CDCA^{78,79} and UDCA.⁸ These claims are obviously subject to a placebo bias and healthy scepticism about such collateral benefits can only be allayed by *proof* from well designed, double-blind trials. To date, there have been three such studies, all of which support the suggestion that bile acids do indeed reduce dyspeptic symptoms. The first two were both short-term studies (14 days) from Italy in which Frigerio et al⁸⁰ and Polli⁸¹ et al showed that although there was indeed a strong placebo effect in relieving the gallstone-associated dyspepsia there was a significantly greater benefit with UDCA. The third, as yet unpublished study, was presented at the VIth International Bile Acid Meeting in Freiburg by Fisher on behalf of the Canadian National Gallstone Study Group. In a much longer (2 years) double-blind study he too found a significantly greater reduction in dyspeptic symptoms when gallstone patients were given CDCA than was found with placebo.⁸² (Table 5).

The mechanism whereby bile acids relieve dyspepsia is unknown but preliminary results from our unit⁸³ lend support to the following working hypothesis. We postulated that the dyspeptic symptoms were due to duodenogastric reflux with bile acid mediated gastritis and that at prevailing gastric luminal pH, only the taurine conjugated bile acids (which normally account for 25-33% of the total) would remain in solution, ionised and capable of mediating tissue damage and the production of symptoms. During treatment with CDCA or UDCA, we know that glycine conjugated bile acids predominate and we suggested that even if the degree of reflux remained unchanged, the glycine conjugates would displace the potentially *gastrotoxic* taurine conjugates and that the ratio of precipitated: soluble intragastric bile acids would increase. To date, this theory has been tested

TABLE 5

COLLATERAL BENEFITS — SUMMARY OF PUBLISHED STUDIES

1. Non-specific dyspepsia and biliary pain

- comparable benefit in long-term uncontrolled studies
- short-term benefit confirmed for UDCA in double-blind study (Frigerio et al 1979)⁸⁰
- long-term benefit confirmed for CDCA in double-blind study (Fischer et al 1980)⁸²

2. Post-ileectomy gallstones

- CDCA treatment aggravates diarrhoea
- UDCA may reduce diarrhoea and steatorrhea (Cox et al 1978)⁸⁶ (LaRusso et al 1979)⁸⁷
- dissolves radiolucent cholesterol-rich stones (LaRusso et al 1979)⁸⁷

3. Hypotriglyceridaemic effect

- (a) In previously normolipidaemic patients
 - 10-30% reduction in fasting VLDL-triglyceride levels (inconsistent findings — ? transient)
 - inhibition in triglyceride synthesis (Begemann 1978)⁹³ (Angelin et al 1978)⁹⁴
 - both CDCA and UDCA (Bell et al 1973⁷¹, Williams et al 1979⁹⁵)
 - CDCA only (Angelin et al 1978⁹⁴, von Bergmann and Leiss 1980⁷⁷)
- (b) In previously hypertriglyceridaemic patients (Type IV)
 - more consistent effect than in normotriglyceridaemics (up to 50% reduction)
 - ? CDCA and UDCA comparable
 - inadequate information (Williams et al 1980)⁹⁵
 - CDCA alone (Types IIa and IV)
 - (Carulli et al 1980)⁹⁷
 - (Angelin et al 1980)⁹⁴
 - (Camarri et al 1980)⁹⁸

only in open studies and while the initial results are encouraging⁸³, we must await the results of a double-blind cross-over study before the theory can be fully accepted.

The relief of biliary pain during treatment with CDCA and UDCA has been studied even less. As a phenomenon, it is open to the same criticisms as those applied to the relief of dyspepsia. How do we define biliary pain or colic? How do we know that episodic epigastric and/or right upper quadrant pain is necessarily arising in the biliary tree and that it is due to the gallstones? Despite these valid objections, uncontrolled observations again suggest that treatment with both bile acids reduces the frequency and severity of biliary pain — irrespective of whether or not the gallstones have been dissolved.⁷⁸ Support for these claims also comes from two short-term, double-blind studies from Italy^{80,81} where a significantly greater reduction in biliary pain was seen with UDCA than with placebo. Although helpful, these studies are of limited value because of their short duration. *Classical* biliary colic is unpredictable in its frequency and severity. Some untreated gallstone patients, for example, may only have 2 or 3 attacks during the course of a year. In such cases, long-term double-blind trials would seem mandatory to prove the point. Furthermore, the mechanism for the production of biliary colic badly needs mo-

re scientific scrutiny — perhaps with dynamic studies of gallbladder motor function before and during bile acid treatment in relation to hormonal and neuronal control of gallbladder filling and emptying.

2. POST-ILEECTOMY GALLSTONES

It has been known since 1965 that patients with bile acid deficiency and steatorrhea secondary to ileal resection respond badly to bile acid replacement therapy.⁸⁴ In the absence of an active ileal bile acid transport mechanism, exogenous di-alpha-hydroxy bile acids (such as CDCA), when given as treatment simply spill into the colon and aggravate the diarrhoea. The fact that UDCA, when perfused directly into the human colon, did not affect water and electrolyte transport⁸⁵ led Cox, Chadwick and van Berge Henegouwen⁸⁶ to feed large amounts of this bile acid (up to 4g per day) to ilectomised patients which significantly diminished both the degree of diarrhoea and the magnitude of steatorrhea. About the same time, LaRusso and Thistle⁸⁷ showed that high-dose UDCA could desaturate fasting duodenal bile in such patients. Urso, therefore, but not cheno, offers the possibility of dissolving cholesterol-rich gallstones in ileectomy patients. These patients have at least a three-fold increase in the incidence of gallstones when compared to matched controls^{88,89} (Table 5).

3. HYPOTRIGLYCERIDAEMIC EFFECT

Since the original observation in 1973 that CDCA reduces fasting serum triglyceride levels in both normo and hypertriglyceridaemic gallstone patients⁷¹, many^{73,90,93} but not all⁹¹, investigators have confirmed this effect. The mean reduction in fasting serum triglyceride levels is in the order of 10-30% but the magnitude of change has varied from 0-50% in different studies. It has also been suggested that the effect may be transient and that with time the serum triglycerides may *escape* from the beneficial effect of CDCA.⁹² The mechanism for this hypotriglyceridaemic effect of cheno seems to be due to a reduction in triglyceride synthesis⁹³ which Angelin et al⁹⁴ have shown correlates linearly (at least in type IV hyperlipoproteinaemic patients who do not have gallstones) with cholic acid synthesis. If Angelin's observations also apply to gallstone patients, since UDCA depresses cholic acid synthesis less than CDCA, one might expect that UDCA would have a lesser effect on fasting serum triglycerides. Here the evidence is conflicting. Williams et al⁹⁵ found that in normolipidaemic gallstone patients, UDCA had a comparable triglyceride lowering effect to that seen with CDCA. It was dose-dependent, occurred within the first 3 months of treatment, and was sustained for at least 1 year. The reduction in serum total triglycerides was entirely due to a fall in the VLDL fraction. However, other investigators have found different results both in patients who had previously been normotriglyceridaemic^{77,96} and in those who had been hypertriglyceridaemic before bile acid therapy.⁹⁶⁻⁹⁸

Thus, although the weight of evidence favours CDCA rather than UDCA in terms of this collateral, and admittedly minor, benefit of therapy, more studies are needed with both bile acids to resolve the existing conflict of opinion about the comparative efficacy of CDCA and UDCA in lowering fasting serum triglycerides. (Table 5).

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Address for reprints: R. Hermon Dowling
Gastroenterology unit
Department of Medicine
Guy's Hospital and Medical School
London, SE1 9RT
England