Effect of ursodeoxycholic acid treatment on ileal absorption of bile acids in man as determined by the SeHCAT test

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Abstract

The effects of ursodeoxycholic acid on ileal absorption of bile acids and on serum bile acid and lipoprotein concentrations were studied. Eight healthy subjects were investigated. The γ emitting bile acid analogue, SeHCAT, was given orally and its fractional catabolic rate and seven day retention were assessed by repeated external counting over the upper abdomen during the next seven days. Ursodeoxycholic acid was then given orally at a dose of 15 mg/kg/day for three weeks and the study was repeated during treatment. The fractional catabolic rate increased by 64% (mean (SD), 0.333 (0.159) *v* 0.203 (0.061)/day; $p < 0.05$) and seven day retention decreased by 44% (15 (10) *v* 27 (10)%, $p < 0.001$), indicating bile acid malabsorption. Total serum cholesterol fell from 5.79 (1.22) to 5.50 (1.18) mmol/l ($p = 0.05$), while serum ursodeoxycholic acid increased 22 fold (7.87 (2.67) *v* 0.34 (0.24) μ mol/l, $p < 0.001$). Five of the subjects continued taking 30 mg/kg/day of ursodeoxycholic acid for one week and showed an increase in fractional catabolic rate of 81% (0.300 (0.091) *v* 0.166 (0.037)/day; $p < 0.05$) and a fall in seven day retention of 50% (16 (12) *v* 32 (8)%, $p < 0.01$). There were significant reductions in total cholesterol (5.36 (1.71) *v* 6.08 (1.47) mmol/l; $p < 0.05$) and low density lipoprotein cholesterol (3.70 (1.33) *v* 4.58 (1.16) mmol/l; $p < 0.05$). The results support the concept that ursodeoxycholic acid treatment interferes with the absorption of endogenous bile acids, and emphasise the beneficial effects of this treatment on lipoprotein concentrations in man.

The primary bile acids, cholic acid and chenodeoxycholic acid, are formed from cholesterol in the liver and stored in the gall bladder in the fasting state.¹ In response to a meal, bile acids are excreted into the intestine where they contribute to the efficient absorption of dietary fat and cholesterol. The secondary bile acids, deoxycholic acid and lithocholic acid, are the result of dehydroxylation of cholic acid and chenodeoxycholic acid by intestinal bacteria. The reabsorption of bile acids is very efficient, particularly because of active uptake in the distal ileum. The synthesis of bile acids is regulated by a homeostatic mechanism in which bile acids returning to the liver from the intestine inhibit their own synthesis.² The demand for hepatic cholesterol increases where bile acid synthesis is stimulated, and this is met by an increased cholesterol synthesis as well as by an increased expression of

the low density lipoprotein receptors.³ Thus, disturbances in bile acid kinetics may influence low density lipoprotein catabolism in several clinical situations.

Ursodeoxycholic acid, which is the 7 β epimer of chenodeoxycholic acid, is a minor constituent of the normal bile pool acid in man.⁴ Its clinical use has become important in the treatment of cholesterol gall stones,⁴ primary biliary cirrhosis,⁵ and sclerosing cholangitis.⁶ Oral administration of ursodeoxycholic acid makes the bile unsaturated with cholesterol because of reduced cholesterol secretion.^{4,7,8} In contrast to treatment with chenodeoxycholic acid, the synthesis of primary bile acids is not suppressed during ursodeoxycholic acid treatment.^{7,9} When ursodeoxycholic acid becomes the major bile acid secreted, the absorption of dietary and biliary cholesterol is reduced through the decreased micellar solubilisation power of this bile acid.^{10,11} Finally, there may be competition between ursodeoxycholic acid and the other bile acids for the intestinal bile acid transport system.⁹

Bile acid absorption can now be determined by using ⁷⁵Selenium homocholic acid taurine (⁷⁵SeHCAT), a synthetic analogue of the natural conjugated bile acid taurocholic acid with the γ emitter ⁷⁵Se in the side chain.^{12,13} It has been shown in previous studies that SeHCAT behaves like the natural bile acid with regard to enterohepatic cycling, hepatic handling, active absorption from the terminal ileum, faecal excretion, and overall turnover in the enterohepatic circulation.¹²⁻¹⁶ The only difference is that SeHCAT undergoes negligible deconjugation by colonic bacteria.

This investigation was undertaken to study the effect of treatment with ursodeoxycholic acid on endogenous bile acid absorption using the SeHCAT technique. A detailed study was performed simultaneously on the effects on plasma lipoprotein values and serum bile acid composition.

Methods

SUBJECTS

This study comprised eight healthy normolipidaemic volunteers with relative body weight $< 120\%$ (Table I). All of them took 15 mg/kg/day of ursodeoxycholic acid and five of them later continued with 30 mg/kg/day. After a basal clinical and laboratory evaluation excluding heart, kidney, thyroid, liver disease, and diabetes, they were followed closely as outpatients and allowed to continue their normal diet. Informed consent was obtained from each sub-

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TABLE I Basal data on the subjects

Subject no/sex	Age (yrs)	Body weight	
		kg	Relative (%) [*]
1/M	44	90	120
2/M	36	64	88
3/M	34	81	103
4/M	31	56	81
5/M	48	75	88
6/M	31	74	82
7/M	40	94	108
8/F	29	58	91

$$^* \text{Relative body weight} = \frac{\text{body weight (kg)}}{\text{Height (cm)} - 100} \times 100\%$$

ject, and the ethical aspects of the study were approved by the Ethical Committee of the Karolinska Institute, Stockholm.

EXPERIMENTAL PROCEDURE

Basal data obtained before the start of ursodeoxycholic acid treatment included fasting blood samples for serum lipid, lipoprotein, and bile acids concentrations.

SeHCAT (10 μ Ci, Amersham International) was given orally with a drink of water following the technique described by Thaysen¹³ and Delhez *et al.*¹⁴ The initial count rate (100% value) was measured three hours after the intake of isotope (day 0), with the subject lying in supine and prone position under an uncollimated gamma camera (Porta Camera, General Electric, Nuclear Medical ApS, Denmark). The distance from the bed to the gamma camera crystal was maintained at 75 cm and the crystal (Na I) was centred over the middle of the xiphoid-umbilical line. The count rate in a 25% window centred around the 265 and 280 KeV photon peaks of ⁷⁵Se was measured. The measurements, which took 10 minutes (five minutes each position), were repeated on days 2, 4, and 7 after the administration of the capsule. The background activity was subtracted and correction was made for the decay of the isotope. The geometric means of the counts measured in the anterior and posterior positions were plotted in a logarithmic-linear graph. An exponential function was fitted to the data points using the method of least squares. The $T_{1/2}$ – that is the time when the abdominal retention of the SeHCAT was reduced to 50% of initial, was calculated from the curve, as well as the fractional catabolic rate defined as $\ln 2/T_{1/2}$.

After completing the SeHCAT test the sub-

jects were given ursodeoxycholic acid (Ursofalk, Dr Falk GmbH & Co, Germany, purity >99%) in a dose of 15 mg/kg/day for three weeks. Fasting blood samples (obtained 12–14 hours after intake) were then collected again, and the SeHCAT test was repeated. The treatment was continued during the studies. After completing the second SeHCAT test, five of the subjects increased the dose of ursodeoxycholic acid to 30 mg/kg/day in order to load further the bile acid transport system. Fasting blood samples were collected after one week, and the SeHCAT test was repeated during continued 'high dose' treatment.

BIOCHEMICAL ANALYSIS

Serum lipoproteins

Cholesterol and triglyceride concentrations were determined with automated enzymatic techniques (Boehringer Mannheim Test Combination Cholesterol and Triglycerides, respectively). Serum lipoprotein analysis was performed by a combination of ultracentrifugation and precipitation.¹⁷

Serum bile acids

Serum together with added internal standards (³H₃-cholic acid, ³H₃-chenodeoxycholic acid, ³H₃-deoxycholic acid, and ³H₃-ursodeoxycholic acid) was subjected to hydrolysis, acidification, and methylation. The methylated extracts were silylated and analysed by gas chromatography mass spectrometry with an NERMAG R10-10H Quadropol instrument equipped with a multiple ion detector unit. Details of the method have been described elsewhere.¹⁸

STATISTICAL ANALYSIS

The results are expressed as mean (SD) values. The statistical significance of differences was evaluated by Student's paired *t* test.

Results

Giving ursodeoxycholic acid at a dose of 15 mg/kg/day resulted in increased excretion of SeHCAT in all subjects (Table II). The mean fractional catabolic rate increased by 64%, from 0.203 (0.061) to 0.333 (0.159)/day (mean (SD);

TABLE II Effect of treatment with ursodeoxycholic acid (UDCA) on fractional catabolic rate (FCR) (/day) and $T_{1/2}$ (days) of SeHCAT

Subject no	Basal			UDCA treatment, 15 mg/kg/day			UDCA treatment, 30 mg/kg/day		
	FCR	$T_{1/2}$	Retention at day 7 (%)	FCR	$T_{1/2}$	Retention at day 7 (%)	FCR	$T_{1/2}$	Retention at day 7 (%)
1	0.162	4.27	32	0.196	3.53	25	0.283	2.45	16
2	0.144	4.80	37	0.274	2.53	25	0.354	1.96	9
3	0.183	3.79	28	0.328	2.11	10	0.343	2.02	9
4	0.218	3.18	22	0.279	2.48	14	0.371	1.87	8
5	0.122	5.68	43	0.192	3.61	27	0.149	4.65	36
6	0.303	2.29	13	0.693	1.00	<1			
7	0.242	2.86	19	0.385	1.80	8			
8	0.250	2.77	18	0.318	2.18	10			
Mean (SD)									
(1–8)	0.203 (0.061)	3.70 (1.15)	27 (10)	0.333 (0.159)*	2.41 (0.86)†	15 (10)‡			
(1–5)	0.166 (0.037)	4.34 (0.96)	32 (8)	0.254 (0.059)	2.85 (0.68)†	20 (8)	0.300 (0.091)*	2.59 (1.17)†	16 (12)†

**p* < 0.05; †*p* < 0.01; ‡*p* < 0.001 compared with basal value.

TABLE III Effects of ursodeoxycholic acid (UDCA) on serum bile acids (values mean (SD))

Bile acids	Basal ($\mu\text{mol/l}$)	UDCA ($\mu\text{mol/l}$)
(a) 8 Patients, UDCA 15 mg/kg/day		
Cholic acid	0.75 (0.59)	0.73 (0.32)
Chenodeoxycholic acid	1.71 (0.84)	1.71 (0.50)
Deoxycholic acid	0.81 (0.46)	0.66 (0.36)
Ursodeoxycholic acid	0.34 (0.24)	7.87 (2.67)†
(b) 5 Patients, UDCA 30 mg/kg/day		
Cholic acid	0.95 (0.69)	0.68 (0.53)
Chenodeoxycholic acid	1.90 (1.03)	2.18 (2.38)
Deoxycholic acid	0.93 (0.51)	0.85 (0.90)
Ursodeoxycholic acid	0.27 (0.24)	11.37 (4.13)*

* $p < 0.005$, † $p < 0.001$ v basal values.

TABLE IV Effect of ursodeoxycholic acid treatment (UDCA) on plasma lipid concentrations (values mean (SD))

Lipids	Basal (mmol/l)	UDCA (mmol/l)
(a) 8 Patients, UDCA 15 mg/kg/day		
Total cholesterol	5.79 (1.22)	5.50 (1.18)*
Triglycerides	1.26 (0.87)	1.26 (0.60)
VLDL cholesterol	0.50 (0.37)	0.52 (0.33)
LDL cholesterol	4.24 (1.02)	3.84 (0.94)
HDL cholesterol	1.06 (0.27)	1.15 (0.39)
VLDL triglycerides	0.74 (0.68)	0.69 (0.57)
(b) 5 Patients, UDCA 30 mg/kg/day		
Total cholesterol	6.08 (1.47)	5.36 (1.71)†
Triglycerides	1.40 (1.04)	1.06 (0.48)
VLDL cholesterol	0.52 (0.43)	0.52 (0.22)
LDL cholesterol	4.58 (1.16)	3.70 (1.33)†
HDL cholesterol	1.00 (0.25)	1.12 (0.44)
VLDL triglycerides	0.80 (0.78)	0.58 (0.36)

*Significantly different from basal value, $p = 0.05$; † $p < 0.05$.
VLDL=very low density lipoprotein; LDL=low density lipoprotein; HDL=high density lipoprotein.

$p < 0.05$), and the $T_{1/2}$ decreased from 3.70 (1.15) to 2.41 (0.86) days ($p < 0.05$). In the five subjects who continued taking the 'high' dose of ursodeoxycholic acid, there was a still more pronounced increase in the fractional catabolic rate compared with basal values (0.300 (0.091) v 0.166 (0.037)/day, $p < 0.05$). Accordingly, the $T_{1/2}$ decreased from 4.34 (0.96) to 2.59 (1.17) days ($p < 0.005$). The seven day retention of SeHCAT (%) was reduced from 27 (10) to 15 (10)% ($p < 0.001$) during the 15 mg/kg/day dose, while with the 'high' dose it fell from 32 (8) to 16 (12)% ($p < 0.01$).

Serum bile acid analysis during ursodeoxycholic acid administration showed a significant increase in the ursodeoxycholic acid concentration (7.87 (2.67) v 0.34 (0.24) $\mu\text{mol/l}$; $p < 0.001$) and an even greater one during 'high' dose treatment (11.34 (4.13) v 0.27 (0.24) $\mu\text{mol/l}$; $p < 0.005$), while there was no significant change in the concentrations of the other bile acids (Table III).

During treatment with 15 mg/kg/day, the only significant change in plasma lipids was a decrease in the total cholesterol concentration from 5.79 (1.22) to 5.50 (1.18) mmol/l ($p = 0.05$), reflecting a (non-significant) reduction of the concentration of low density lipoprotein cholesterol from 4.24 (1.02) to 3.84 (0.94) mmol/l (Table IV). During 'high' dose ursodeoxycholic acid administration there was a further significant decrease from the basal values in the total cholesterol concentration (from 6.08 (1.47) to 5.36 (1.71) mmol/l; $p < 0.05$) and low density lipoprotein cholesterol (from 4.58 (1.16) to 3.7 (1.33) mmol/l; $p < 0.05$). There were no significant changes in total or very low density lipoprotein triglycerides or very low

density or high density lipoprotein cholesterol during treatment at either dosage.

Discussion

Several distinct effects of ursodeoxycholic acid on bile acid and cholesterol metabolism in normolipidaemic humans are evident from the present study. Firstly, we could show directly a dose related interaction with the absorption of SeHCAT, indicating competitive inhibition of the intestinal uptake of this radiolabelled bile acid analogue. Since SeHCAT has very similar physiological properties to taurocholic acid, a disturbance of its reabsorption should reflect interaction with the active transport system in the terminal ileum. A tendency for an increased fractional catabolic rate of radiolabelled cholic acid during ursodeoxycholic acid treatment has also been observed during kinetic studies in humans,⁹ but the present approach should give a more sensitive detection since SeHCAT is stable and does not undergo deconjugation by colonic bacteria.¹⁶

Although the molecular properties of the intestinal bile acid carrier are not yet known in detail, physiological studies have indicated that the transport system has a preference for trihydroxy bile acids and that it is working relatively close to saturation under physiological conditions.¹⁹ An increased load of exogenous ursodeoxycholic acid should thus preferentially interfere with the enterohepatic circulation of cholic acid. In accordance with this contention, the excretion of cholic acid was increased somewhat more than that of chenodeoxycholic acid during short term administration of ursodeoxycholic acid to patients with ileostomy.²⁰ Such an exclusion of cholic acid (and chenodeoxycholic acid) from the enterohepatic circulation would result in reduced amounts of primary bile acids being returned to the liver via the portal venous circulation. Since ursodeoxycholic acid does not seem to suppress bile acid synthesis^{7,21} or the activity of its rate limiting enzyme, cholesterol 7 α -hydroxylase,²² such treatment would result in an increase in bile acid production in order to maintain the pool sizes of these bile acids.

A second new finding in this study emerges from the determination of individual serum bile acid concentrations (Table III). In agreement with previous studies,¹⁸ the administration of 15 mg/kg/day of ursodeoxycholic acid leads to a large increase in the serum concentration of this bile acid, whereas there were no significant changes in the concentrations of cholic acid, chenodeoxycholic acid, or deoxycholic acid. This indicates that despite the increased loss of endogenous bile acid during ursodeoxycholic acid therapy, the pool sizes of these bile acids were maintained. This concept could now be extended to treatment with large amounts of ursodeoxycholic acid (30 mg/kg/day), where still no changes in serum bile acid concentrations could be observed, despite a more than 40 fold increase in ursodeoxycholic acid serum concentrations. It should be noted that all these measurements refer to the fasting state, and that a reduced return of bile acids may be present postprandially, as has recently been shown

during cholestyramine treatment.²³ The data in this study are thus in agreement with the concept of a stimulated bile acid production during ursodeoxycholic acid treatment, and such an effect could at least partially explain why the secretion rate of cholesterol into bile is reduced.⁷⁻⁹

A third finding was a dose related decrease in plasma total and low density lipoprotein cholesterol concentrations (Table IV). A cholesterol lowering effect of ursodeoxycholic acid has been noted in some previous studies,^{24,25} but this is not a universal finding.⁴ The effect is in clear contrast to observations during chenodeoxycholic acid therapy, where low density lipoprotein cholesterol and the low:high density lipoprotein ratios are frequently increased.²⁶⁻²⁸ It is reasonable to assume that the difference between the two bile acids relates to their differing effects on hepatic cholesterol metabolism. Thus, chenodeoxycholic acid is known to suppress drastically bile acid biosynthesis,^{7,29} mediated via down regulation of the cholesterol 7 α -hydroxylase.²² This in turn creates a decreased hepatic demand for cholesterol, resulting in reduced activity of HMG CoA reductase³⁰ as well as a tendency for reduced low density lipoprotein receptor expression.³¹ The latter effect is probably the explanation for the approximately 10% increase in low density lipoprotein cholesterol which has been reported.²⁶⁻²⁸ On the other hand, as discussed above, ursodeoxycholic acid slightly increases the activity of cholesterol 7 α -hydroxylase²² and bile acid production rate.^{7,21} This would lead to an increased hepatic demand for cholesterol, reflected in an unchanged or slightly stimulated activity of HMG CoA reductase.^{24,32} It is reasonable to assume that the low density lipoprotein receptor expression is stimulated, and such a phenomenon could well explain the decrease in low density lipoprotein cholesterol concentrations, particularly since there is no evidence of an effect on the very low density lipoprotein production rate.⁹ Another mechanism that is probably operative during ursodeoxycholic acid therapy is a reduced absorption of dietary and biliary cholesterol because of the reduced capacity to form micelles.^{10,11,17,33}

In conclusion, treatment with ursodeoxycholic acid results in a dose dependent reduction of intestinal bile acid reabsorption. The unchanged serum concentrations of cholic acid, chenodeoxycholic acid, and deoxycholic acid indicate a stimulated bile acid production rate with unchanged pools. In addition, ursodeoxycholic acid treatment is associated with lowering of total and low density lipoprotein cholesterol, hypothetically as the result of stimulation of low density lipoprotein receptor expression secondary to an increased hepatic cholesterol demand. Compared with chenodeoxycholic acid, this effect on lipoprotein concentrations should be an advantage during long term treatment in gall stone disease.

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