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Effects of ursodeoxycholic acid treatment on nutrition and liver function in patients with cystic fibrosis and longstanding cholestasis

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Abstract

The prevalence of biliary and hepatic diseases is increasing in patients with cystic fibrosis as more of them reach adult life. There is no effective treatment or method of preventing cholestasis in cystic fibrosis, although beneficial effects have been ascribed to the tertiary bile acid, ursodeoxycholate, in other forms of chronic cholestasis. We evaluated prospectively the effects of a six month course of ursodeoxycholate (15–20 mg/kg per day) in eight, mostly adult, patients with cystic fibrosis and chronic cholestasis. Bile acid treatment improved inflammatory activity (average decrease in alanine aminotransferase, 60%, $p<0.005$) and cholestasis (alkaline phosphatase, 47%; $p<0.01$) in all patients. Quantitative liver function, measured by 45 minute sulphobromophthalein retention and by the ^{14}C-aminopyrine breath test, improved in all patients while galactose elimination capacity showed a slight decrease. Patients' nutritional state improved as evidenced by a 1·8 kg weight gain and an increase in muscle mass suggested by a 26% increase in 24 hour urinary creatinine excretion. Steatorrhea was not affected by bile acid treatment. Ursodeoxycholic acid may be beneficial in the treatment of chronic cholestasis in cystic fibrosis by improving liver function and also the patient's nutritional state.

Cystic fibrosis is the most common lethal homozygous genetic disease in white races with an estimated prevalence of 1 in 2000 live births.[1] Mean survival has increased from 14 years in 1969 to 23 years in 1982, mostly as a result of aggressive pulmonary treatment programmes and improvements in nutrition.[2] With increasing age, hepatobiliary problems become more frequent. Thus, the incidence of clinically evident cirrhosis ranges from 0·5 to 8% in children and from 5 to 20% in adolescents and young adults.[3] Gasking *et al* recently showed distal biliary tract abnormalities in 96% of adults with cystic fibrosis.[4]

Recent reports have shown that ursodeoxycholic acid, a tertiary bile salt with potent choleretic properties, has a beneficial effect on cholestasis in primary biliary cirrhosis[5] and improves the nutritional state in patients with biliary atresia.[6]

We prospectively evaluated the effect of ursodeoxycholic acid treatment on the hepatic function and nutritional state of eight patients with cystic fibrosis and chronic cholestasis.

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Materials and methods

Subjects were selected from patients followed at the Cystic Fibrosis Centre of Berne University's Children's Hospital according to the following criteria:

(1) Cystic fibrosis documented by typical pulmonary and digestive symptoms and raised sweat chloride values.

(2) Chronic cholestasis manifested by raised liver enzyme activities over at least one year, associated with abnormal ultrasound scan appearances of liver size, liver surface, and homogeneity of the parenchyma.

(3) Absence of surgically treatable obstruction as a cause of cholestasis shown by ultrasound scan or hepatobiliary scintigraphy with ^{99m}Tc-labeled N-(2,6-diethyl-3-iodo-phenylcarbamoylmethyl)-iminodiacetate, or both.

From 1987 to 1988, nine patients fulfilled the above criteria, eight of whom have completed a six month's course of treatment that forms the basis of this report. The study was described to each patient and his or her parents and informed consent was obtained. The study had been approved by the ethics committee of the University of Berne.

During the week before starting the ursodeoxycholic acid treatment, patients underwent complete physical examination and conventional liver tests including determination of transaminases, alkaline phosphatase, 5'-nucleotidase, serum bilirubin, serum bile acids, plasma proteins, cholesterol, and triglycerides. Three day stool collection and 24 hour urine collection were performed under home diet to evaluate steatorrhea and creatinine excretion, respectively.

Liver function was quantitated by determining galactose elimination capacity according to Tygstrup,[7] by the aminopyrine breath test after intravenous administration of ^{14}C-aminopyrine as already described,[8] and by fractional sulphobromophthalein clearance.[9] Permission was not given to perform the galactose elimination and aminopyrine test in one patient (YH). Fasting serum bile acids were measured using a commercial radioimmunoassay with a cross reactivity for ursodeoxycholic acid of 90% (Becton and Dickinson). All other laboratory determinations were done with routine autoanalyser methods.

After the initial investigations, patients were given ursodeoxycholate, 15–20 mg/kg per day orally, in four divided doses. During the study, no changes in pancreatic enzyme substitution or nutritional supplements were allowed. Conventional liver tests were undertaken every four to six weeks. After completion of six months'

TABLE I *Characteristics of cystic fibrosis patients with chronic cholestasis*

Patient	*Sex*	*Age (yrs)*	*Failure to thrive*	*Symptoms*
SM	F	24	+	Dig
YH	M	10	−	Pulm, Dig
HV	F	22	−	Dig
ZU	M	12	+	Dig
StM	F	22	++	Pulm, Dig
GA	M	21	−	Dig
EV	M	18	++	Pulm, Dig
PM	M	20	++	Dig

Dig=digestive; Pulm=pulmonary.

treatment, the measurements described above were repeated.

All data are expressed as mean (SD). Values before treatment and after six months of ursodeoxycholic treatment were compared using the paired student's *t* test.[10] A value of $p<0.05$ was considered statistically significant.

Results

The patient characteristics at entry into the study are given in Table I; mean age at entry into the study was 18·0 (5·1) years (range 10–25). All patients had hepatomegaly and five had splenomegaly. Four patients had experienced variceal bleeding, three of whom required distal portocaval shunting. Five patients showed failure to thrive (Table I).

Serum biochemistry in the patients before treatment is given in Table II. Total bilirubin and fasting serum bile salts were abnormal in five and seven patients respectively. Total plasma proteins were normal in all patients but serum albumin was low in six. In spite of vitamin K substitution, prothrombin time was normal in one patient only. In contrast with other forms of cholestasis, serum lipid values were normal. Steatorrhoea was present in all patients under adequate enzyme substitution.

During treatment with ursodeoxycholic acid, serum aspartate aminotransferase and alanine aminotransferase activities (Fig 1) and the cholestatic enzymes (Fig 2) were significantly decreased in all patients. The time course of this improvement is shown by the evolution of 5'-nucleotidase, whose activity is influenced by neither age nor growth (Fig 3). The improvement was obtained within the first six weeks of treatment, thereafter values stabilised at a lower level. The other enzymes showed similar patterns.

TABLE II *Biochemical data before treatment with ursodeoxycholic acid*

	Normal range	*Mean (SD)*	*Range*
Serum bilirubin (μmol/l)	1·7–21·5	48·0 (55·0)	7–153
Serum bile salts (μmol/l)	<6	25·2 (24·7)	4–70
AST (GOT) (IU/l)	11·0–38·0	148·0 (79·2)	52–266
ALT (GPT) (IU/l)	10·0–39·0	157·0 (74·9)	84–256
Alkaline phosphatase (IU/l)	36–108*	946·4 (531·7)	415–2220
Glutamyltranspeptidase (IU/l)	11–64	492·4 (400·5)	139–153
5'-nucleotidase (IU/l)	0–18	114·3 (106·5)	24–370
Serum albumin (g/l)	32–52	28·9 (4·8)	21–36
Prothrombin time (Quick; %)	70–130	58 (11)	40–84
Cholesterol (mmol/l)	3·0–6·1	4·0 (1·4)	2·2–5·3
Triglycerides (mmol/l)	0·4–2	0·8 (0·4)	0·4–1·6
Faecal fat (g/day)	<5	47 (21)	10–72

*For 3–15 years: 108–345 IU/l.
AST=aspartate aminotransferase; ALT=alamine aminotransferase; GOT=glutamic oxalo-acetic transaminase; GPT=glutamic pyruvic transaminase.

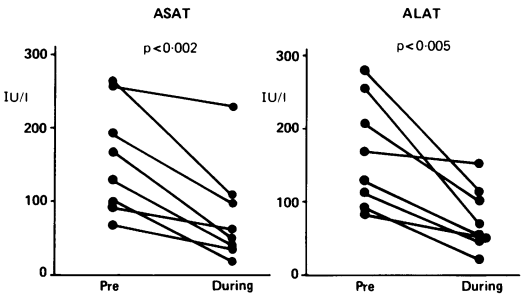

Figure 1: Effect of ursodeoxycholate treatment on serum aspartate transaminase (ASAT) and alanine aminotransferase (ALAT) activities. The activities of the transaminases decreased by 52% ($p<0.005$) and 61% ($p<0.001$), respectively.

The serum bilirubin concentration was abnormal in five patients before treatment and decreased by an average of 46% in these patients; overall the difference was not statistically significant (Fig 4). Serum bile salt values averaged 28 (15) and 15 (10) μmol/l before and after treatment respectively (NS). They fell in those patients whose values were appreciably raised before treatment and increased in those with lower values. The effects of ursodeoxycholic acid treatment on quantitative liver function tests are shown in Figure 5. Galactose elimination capacity decreased significantly from 6·6 (0·9) to 5·7 (1·4) mg/kg per minute ($p<0.05$). In contrast, microsomal capacity measured by the aminopyrine breath test increased in all seven patients in whom it had been measured ($p<0.02$). Similarly, 45 minute retention of sulphobromophthalein improved in all eight patients (Fig 4). In some patients this was due to an improvement in k_1, reflecting uptake (0·102 (0·040) *v* 0·111 (0·037) l/minute) while in others k_2, reflecting biliary excretion, was mainly affected (0·011 (0·014) *v* 0·014 (0·010) l/minute). Due to this divergent effect, neither change in the elimination rate constants reached statistical significance.

The effect of the treatment on nutritional status is shown in Table III. Body weight increased by a mean of 1·8 kg per patient ($p<0.0001$). An increase in muscle mass was suggested by an increase of 26% in 24 hour urine creatinine excretion ($p<0.05$). This effect was also seen when creatininuria was expressed as the creatinine/height index, averaging 34·0 (9·8) and 45·8 (13·4) μmol/day per cm before and after six months of treatment, respectively ($p<0.05$). In contrast, steatorrhoea was not affected. Both

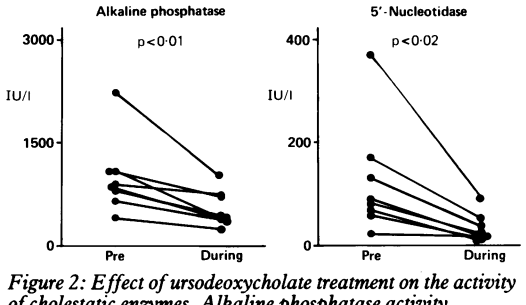

Figure 2: Effect of ursodeoxycholate treatment on the activity of cholestatic enzymes. Alkaline phosphatase activity decreased by 46% ($p<0.01$) and 5'-nucleotidase activity by 73% ($p<0.02$).

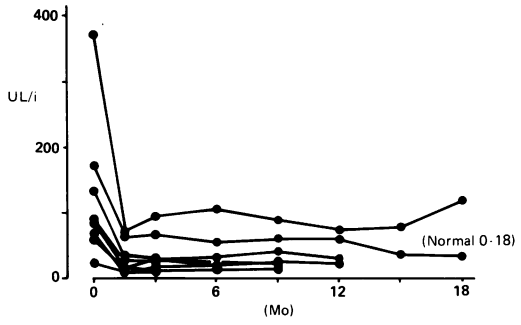

Figure 3: Time course of 5'-nucleotidase activity during treatment with ursodeoxycholate. The major effect occurred during the first six weeks of treatment, thereafter the activity reached a lower plateau. The activity of 5'-nucleotidase is independent of age and bone growth.

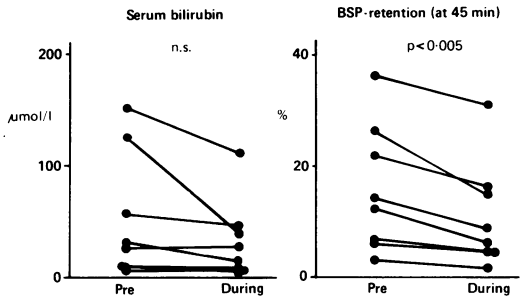

Figure 4: Effect of ursodeoxycholate treatment on biliary excretory function. Although the bilirubin concentration decreased by 46% in those patients in whom it was raised before treatment, ursodeoxycholate had no significant effect in the whole group. Sulphobromophthalein (BSP) retention at 45 minutes showed an average improvement of 5%, all patients improving during ursodeoxycholate treatment (p<0·005).

serum cholesterol and triglyceride values decreased, but only the latter reached statistical significance (Table III). The serum albumin concentration showed a small insignificant increase but the prothrombin time ratio, measured as the Quick value, increased significantly in all patients and remained abnormal in two patients only. Vitamin K substitution was not changed during the trial. While serum vitamin A values were not affected (281 (342) *v* 342 (222) IU/l; NS), serum vitamin E increased from 3·0 (2·8) to 8·2 (3·6) mg/l (p<0·05).

Ursodeoxycholate was well tolerated in this trial – no side effects, and in particular no change in bowel habits, were reported.

Discussion

In the past 20 years a dramatic improvement in life expectancy has been achieved in patients with cystic fibrosis, mainly due to effective pulmonary treatment.[2] During the same time, severe hepatic disease in cystic fibrosis has increased from 4 to 20%.[3 11-15] In a recent study, biliary tract abnormalities were detected in 96% of adult patients with cystic fibrosis.[4] Thus, the hepatic disease may become life-limiting in some adult patients.

Liver disease in cystic fibrosis is thought to be primarily caused by the accumulation of inspissated bile in the interhepatic ducts, leading to secondary biliary cirrhosis.[16] Alternatively, accumulation of potentially toxic bile acids, such as lithocholic and chenodeoxycholic acid, have been implicated in the pathogenesis of biliary cirrhosis.[17] Both pathophysiological possibilities provide a rationale for treatment with choleretic bile acids – inspissation of bile may be inhibited by keeping the bile ducts patent or accumulation of toxic bile acids may be prevented by replacing the bile acid pool with less toxic bile acids, or both.

Ursodeoxycholic acid, a hydrophilic bile salt that occurs in a proportion of 1–2% in normal human bile,[18] is virtually free of hepatotoxicity.[19 20] In animal experiments it induces a bicarbonate-rich choleresis.[21] It reduces ductular proliferation and portal inflammation in bile duct-ligated hamsters[22] and protects against bile salt-induced cholestasis.[23] In our trial, ursodeoxycholate improved microsomal function, as measured by the aminopyrine breath test,[8] as well as excretory function, as measured by sulphobromophthalein elimination.[9] In contrast, functional liver cell mass, estimated by the galactose elimination capacity,[7] showed a slight but statistically significant deterioration. Whether this reflects progression of the hepatic disease or toxicity of ursodeoxycholate, or both, cannot be stated definitively at present. We have not observed a consistent decrease in galactose elimination capacity in patients with other cholestatic diseases (unpublished observation) favouring the explanation that this decrease represents the natural history of the disease rather than toxicity.

The beneficial effects of ursodeoxycholate treatment on partial aspects of hepatic function seen in our study could be the result of ursodeoxycholate's choleretic properties or the described decrease in chenodeoxycholic acid synthesis, or both.[24] A similar beneficial effect of ursodeoxycholate on liver function has been

TABLE III *Effect of six months' treatment with ursodeoxycholate on different nutritional parameters (mean (SD))*

	Before	*At 6 mths*	*Difference*	*p*
Body weight (kg)	42·1 (11·6)	43·9 (11·9)	1·8 (0·5)	<0·0001
Body mass index (kg/m²)	17·4 (2·4)	18·1 (2·5)	0·6 (0·4)	<0·005
Creatininuria (mmol/day)	5·1 (1·5)	6·9 (2·0)	1·1 (0·9)	<0·05
Faecal fat (g/day)	47 (21)	45 (22)	−2 (23)	NS
Serum cholesterol (mmol/l)	4·0 (1·4)	3·5 (0·7)	−0·7 (0·9)	NS
Serum triglycerides (mmol/l)	0·8 (0·4)	0·7 (0·3)	−0·1 (0·2)	<0·05
Serum albumin (g/l)	28·9 (4·8)	30·5 (4·3)	1·6 (2·3)	NS
Prothrombin time (Quick; %)	58 (11)	66 (7)	8 (8)	<0·05

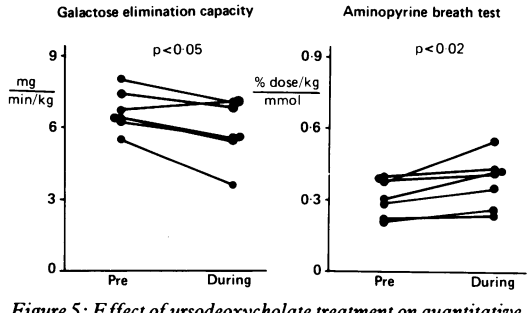

Figure 5: Effect of ursodeoxycholate treatment on quantitative liver function in cystic fibrosis with chronic cholestasis. While galactose elimination capacity, a measure of the functional hepatocellular mass, decreased in 6 of 7 patients (p<0·05), microsomal reserve, as assessed by the aminopyrine breath test, showed an improvement in all patients tested (p<0·02). One patient (YH) was not tested.

observed in patients with primary biliary cirrhosis.[5]

The most important effect clinically could be the improvement in nutritional status, which is notoriously difficult to achieve in cystic fibrosis.[1,2] A similar effect has been described in a child with biliary atresia whose nutritional status did not permit liver transplantation but in whom surgery was possible after a short course of ursodeoxycholate treatment.[6] The increase in body weight was clearly not due to simple growth as six of our patients were postpubertal. This contention is supported by the improvement in serum prothrombin time in spite of unchanged vitamin K substitution and a slight increase in visceral proteins such as albumin. The increase in body mass index and creatinine excretion suggests an increased muscular mass, but formal anthropometric studies will be needed to support this hypothesis.

The mechanism(s) of this improvement in nutritional status remains to be explained. It could be related to an improvement in liver function or to alkalinisation of duodenal pH by the bicarbonate-rich choleresis induced by ursodeoxycholate, or both.[21] It is clearly not the result of an improvement in fat absorption since faecal fat excretion was unchanged. Moreover, a decrease in cholesterol absorption during ursodeoxycholate treatment has been described in normal volunteers,[18] and this is also documented by the decrease in serum cholesterol and triglycerides in our study.

Our results suggest that ursodeoxycholate has a beneficial effect on hepatic function and nutritional status in adult patients with cystic fibrosis and chronic cholestasis. Longterm studies will be needed to determine whether this form of treatment also affects survival or whether it can delay the onset of hepatic dysfunction which may limit life expectancy as the age of these patients increases, or both.

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